

Single Technology Appraisal

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

Contents:

The following documents are made available to stakeholders:

- 1. Comments on the Draft Guidance from CSL Behring**
 - a. Company DG Comments
 - b. HCP consensus document
- 2. Consultee and commentator comments on the Draft Guidance from:**
 - a. Hereditary Angioedema UK
 - b. British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)
 - c. Royal College of Pathologists
 - d. NHS England (Immunology and Allergy Clinical Reference Group)
 - e. Takeda
- 3. Comments on the Draft Guidance received through the NICE website**
- 4. External Assessment Group critique of company comments on the Draft Guidance**

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

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

Consultation on the draft guidance document – deadline for comments: 5pm on Wednesday 23 July 2025. Please submit via NICE Docs.

	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>CSL Behring</p>
<p>Disclosure</p>	<p>N/A</p>

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<p>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]</p> <p>Please state:</p> <ul style="list-style-type: none"> • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased. 	
<p>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>N/A</p>
<p>Name of commentator person completing form:</p>	<p>██████████</p>
<p>Comment number</p>	<p>Comments</p> <p>Insert each comment in a new row.</p> <p>Do not paste other tables into this table, because your comments could get lost – type directly into this table.</p>
<p>Overall</p>	<p>Executive summary</p> <p>CSL Behring appreciates the opportunity to provide additional evidence to address the uncertainties noted by the committee in the draft guidance consultation (DGC).</p> <p>In this response, we provide further information regarding the following key points:</p>

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	<ul style="list-style-type: none"> • Recently received individual patient-level data (IPD) from Elbashir et al. (2024), updated cost-effectiveness analyses (see section 3.10 and Appendix) • Clinical consensus statement signed by 8 clinical HAE experts in the UK (see sections 3.1, 3.2, 3.3, 3.13 and 3.20) • Cost-effectiveness analysis utilising baseline attack rate aligned with berotralstat TA738 (see section 3.18) <p>General overview response:</p> <p>Has all of the relevant evidence been taken into account?</p> <p>No, since the IPD from Elbashir et al. (2024) has become available after the first assessment committee meeting (ACM1) on the 11th of June. The appropriate interpretation of the Elbashir et al. (2024) poster was a crucial driver of uncertainty identified by the committee, and the main source of divergence of opinion between CSL Behring and EAG on Key Issue 4. Utilising Elbashir et al. (2024) IPD to obtain the estimate of berotralstat efficacy for responder patients resolves both the committee's uncertainty concerns, as well as makes the previous disagreement between CSL Behring and EAG on the correct interpretation of Elbashir et al. (2024) poster a moot point. The results of the Elbashir et al. (2024) IPD analysis are provided in Section 3.10 and the appendix.</p> <p>While (aside from the aforementioned IPD analyses) all the other submitted evidence is acknowledged by the committee, CSL Behring believes the evidence has not been fully utilised, and in places accurately described, to the extent the company deems appropriate. Further details on this are discussed throughout the document.</p> <p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p> <p>Most of the summaries of clinical and cost-effectiveness are reasonable interpretation of the evidence, as they have been agreed by the committee, EAG and CSL Behring. However, there are four points which require particular attention, due to their importance to the cost-effectiveness results and the disagreement in interpretation between key stakeholders:</p> <ol style="list-style-type: none"> 1. The clinical benefit and differentiation of garadacimab, making it a step-change in the management of HAE, which is discussed in Sections 3.2, 3.6 and 3.20 2. The effectiveness of berotralstat in responders population, which is covered in Section 3.10,
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	<p>3. The utilisation of baseline attack rate aligned with berotralstat TA738, discussed in Section 3.18</p> <p>4. The interpretation of the Nordenfelt et al. (2014) attack coefficient, addressed in Section 3.12.</p> <p>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>CSL Behring remain committed to collaborating with NICE, NHS England and all other health system partners to ensure that eligible patients with HAE have more choice in how their condition is managed. In particular, we are keen to support NICE in achieving its Principle 6: use evidence that is relevant reliable and robust, by ensuring that the best available and scientifically selected evidence is used for the decision making.</p> <p>Could any of the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology? Could any of the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?</p> <p>CSL Behring agrees with the committee’s summary on the difficulties associated with accessing any HAE LTP options due to the current NHS treatment algorithm, particularly for those experiencing severe/laryngeal but infrequent attacks and for younger people. CSL Behring is not aware of any specific adverse impacts that this preliminary recommendation may have on people with a particular disability or disabilities. Please see CSL Behring’s comments on section 3.19 for further comments.</p>
1	<p>Why the committee made these recommendations</p> <p>Section 1 of the report states that “<i>indirect comparisons suggest that garadacimab is clinically effective compared with berotralstat, C1-INHs or lanadelumab.</i>”</p> <p>CSL Behring’s response: CSL Behring believes that the current wording does not present the full scope of comparative benefit of garadacimab treatment. More details on this are provided in section 3.6.</p>
2	<p>Information about garadacimab</p> <p>In Section 2.1, the marketing authorisation indication is introduced as ‘<i>Garadacimab (Andembry, CSL Behring) is indicated for ‘routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older’.</i></p>

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	<p>CSL Behring’s response: CSL Behring would like to request the inclusion of a trademark symbol with the branded name of garadacimab (i.e. Andembry®).</p>
3.1	<p>Details of the condition</p> <p>In section 3.1 it is written that “<i>clinical experts explained that quality of life with uncontrolled hereditary angioedema is similar to that for other long-term chronic conditions, like uncontrolled type 2 diabetes</i>”.</p> <p>CSL Behring’s response: CSL Behring would like to make clear that this was not a sentiment that was put forward by a clinical expert during ACM1, but rather a comparison made by the health economics representative for the EAG during a discussion in ACM1. In this discussion, the EAG health economics representative suggested that it was theoretically possible for the company’s model to show quality of life in individuals experiencing ≥ 2 attacks per week that is similar to that of oncology appraisals. Based on this, the EAG felt that this was not reasonable and suggested that their approach of modelling the disease was more appropriate as it showed quality of life similar to that of an uncontrolled diabetes patient.</p> <p>CSL Behring would like to request that this comparison in the Guidance will be reassessed for the following reasons:</p> <ul style="list-style-type: none"> • The supporting evidence for these claims has not been shown to the company or committee (before, during or after ACM1) and the claims are not verifiable • These claims were not supported by clinical experts in the meeting • A clinical consensus statement, signed by eight clinical experts in the UK, states that it is not appropriate to consider the impacts of HAE on quality of life to be the same or similar to those of other conditions.¹ • The company believes that it sets a dangerous precedent to compare the burden of disease measured in one condition to that observed in another unrelated condition. We would contend that this risks arbitrarily limiting the individualised differences between the burden felt between patients with different diseases, instead of letting the published quality of life data speak for itself. <p>As such, CSL Behring kindly request that this section is either reworded to be made more reflective of the committee meeting discussion or removed on the basis of factual accuracy.</p>
3.2	<p>Preventive treatment options</p>

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	<p>Section 3.2 states that, as per NHS England's HAE treatment algorithm, lanadelumab <i>"can be used by people 2 years and over."</i></p> <p>CSL Behring's response: As per the CHMP, the indication of lanadelumab was changed in 2023 which resulted in the medication to be licensed for those ≥ 2 years of age rather than ≥ 12 years of age.² While this updated indication has indeed been reflected in the recently published NHSE HAE treatment algorithm,³ CSL Behring would like to highlight that, as per the NICE guidance for TA606, lanadelumab remains recommended for those ≥ 12 years of age.⁴</p> <p>For full clarity, CSL Behring would like to highlight that the UK SmPC outlines different posology for 2–12 year-olds compared to ≥ 12 year olds, with the recommended dosage and dose adjustments being based on body weight in 2–12 year-olds.⁵ However, since the model is focused on those aged ≥ 12 years old, these changes do not impact on the EAG or company base cases.</p> <p>Section 3.2 also states that <i>"the committee felt that it had not heard that garadacimab was a step change in managing hereditary angioedema."</i></p> <p>CSL Behring's response: The company believe that evidence of a step-change has been seen before, during and after the committee meeting.</p> <ul style="list-style-type: none"> • Before the meeting: Please note the following statement from section 3.4.1.8 of the EAG report: <i>"The EAG's preferred NMA found garadacimab, lanadelumab (every two weeks), and SC Berinert (outside of the NICE scope), to have a [REDACTED] berotralstat for the efficacy outcomes reported, with [REDACTED] of the proportion of attack-free patients, where uncertainty of the estimates was demonstrated by the wide and overlapping credible intervals"</i>. • During the meeting: Beyond clinical benefit, an important perspective shared during the meeting was the benefit to patient autonomy that garadacimab is likely to confer. As can be read in the patient information leaflet, the autoinjector may be stored at room temperature (up to 25 °C) for a single period of up to two months, but not beyond the expiry date. The HAE UK representative indicated this would lift key restrictions on patients including those on travel, work, school, visiting family and leisure. • After the meeting: The draft guidance provides evidence that garadacimab is indeed a step-change in the management of hereditary angioedema. Section 3.6 refers to a published company NMA by Walsh
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	<p>et al. (2025),⁶ concluding that “overall, garadacimab was ranked as the most effective treatment among all comparators assessed”. Moreover, Section 3.18 states that “for people having ≥ 2 attacks per week, garadacimab was more effective and less costly than the comparators, in the company and EAG base-cases and applying committee’s preferred assumptions. So, garadacimab dominated in all scenarios.”</p> <p>Additionally, a clinical consensus statement was signed by eight clinical experts in the UK, which states that “garadacimab represents an important development in the prophylactic treatment of HAE attacks” and that, notwithstanding clinical effectiveness, “garadacimab provides potential benefits to patients, particularly those experiencing < 2 attacks per week, that represent a step-change in their care”.¹</p> <p>Summary: CSL Behring would like to point out that, since different treatment options are available for patients with different attack rates, the impact of the availability of garadacimab would be differently characterised for patients with different attack rates. As stated in the draft guidance Section 3.3: “The committee understood that in UK clinical practice, berotralstat is stopped if the number of attacks per month does not reduce by at least 50% after 3 months. Because berotralstat does not work well for everyone, there is a particular need for an alternative treatment option for people having 2 or more attacks per month (compared with 2 attacks per week, for which there are more available treatments)”. As such, CSL Behring believes that garadacimab would indeed be a step-change in the management of HAE for patients with ≥ 2 attacks per month, particularly for those with < 2 attacks per week.</p>
3.3	<p>Positioning of garadacimab</p> <p>Section 3.3 states that ‘the company submission positioned garadacimab as an alternative to berotralstat, C1-INHs or lanadelumab for hereditary angioedema in people 12 years and over with 2 or more attacks per month’ and indicated that ‘C1-INHs or lanadelumab were modelled for people having 2 or more attacks per week’.</p> <p>CSL Behring’s response: CSL Behring believes that, in this context, the use of ‘IV C1-INHs’ is more appropriate than ‘C1-INHs’, since the comparison with SC C1-INHs is outside of the NICE scope.</p> <p>The positioning of garadacimab is explored in Section 3.3, which states that “The company [...] suggested that people having garadacimab at first line would not have berotralstat at second line. But, the EAG’s clinical experts</p>

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	<p><i>explained that people might switch their first-line treatment between berotralstat and garadacimab, because of side effects or lack of efficacy.”</i></p> <p>CSL Behring’s response: This summary of the positioning of garadacimab was raised as factually inaccurate during the committee meeting. In that instance, it referred to the same claim as made on a slide entitled “Key issue 1: Uncertainty around treatment pathway for HAE (1/2)”. We would request that this is removed to better reflect the company’s positioning of garadacimab. With the company, EAG, committee, NHSE and clinical expert signatories to a consensus statement¹ all in agreement that the company positioning is appropriate, we believe this statement may read as potentially confusing.</p> <p>Section 3.3 further states that <i>“the committee concluded that the company’s proposed positioning of garadacimab and its comparators, which were determined by attack frequency, was appropriate.”</i> and that <i>“it also concluded that the EAG’s exploration of second-line garadacimab after berotralstat, compared with no preventive treatment, was reasonable to consider.”</i></p> <p>CSL Behring’s response: We are reassured by the agreement between the EAG, committee, NHSE and clinical experts forming a consensus that the company’s positioning is appropriate. Further sequencing is out of scope, in terms of both methods and comparators used, and has not been explored in other appraisals in HAE where it would have been feasible.</p> <p>Section 3.3 of the report also states: “Clinical experts advised that if both berotralstat and garadacimab were available, they would likely try berotralstat first because it is an effective oral treatment”.</p> <p>CSL Behring’s response: CSL Behring recalls the clinicians emphasising the need for a patient-centric approach that reflects product efficacy, method of administration, side-effects and cost-effectiveness. While one expert indicated that some patients may prefer to try oral treatment first, they clearly indicated that it will be highly patient-specific and should reflect patient choice. As such, CSL Behring would like to request that this nuanced perspective is taken into account.</p>
3.4	VANGUARD trial

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	<p>Section 3.4 states that the intention-to-treat population (ITT) was “<i>people who had 1 or more attack per month over the 6-month treatment period.</i>”</p> <p>CSL Behring’s response: CSL Behring would like to clarify that, as per the VANGUARD CSR and the CS, the ITT consisted of HAE-1/2 patients who have experienced ≥ 3 HAE attacks during the 3 months before screening, experienced ≥ 1 attack per month in the study run-in period and received treatment with either garadacimab or placebo during the 6-month treatment period. As such, the committee’s interpretation of the intention-to-treat population is not fully accurate.</p>
3.5	<p>Clinical effectiveness results</p> <p>Thank you. No further comment, CSL Behring agrees with the committee’s summary.</p>
3.6	<p>Indirect treatment comparison</p> <p>Section 3.6 stated that “<i>after technical engagement, the company and EAG both preferred the NMA of phase 3 placebo-controlled trials of garadacimab (VANGUARD), berotralstat (ApeX-2 and ApeX-J), lanadelumab (HELP-03, with every 2 week and every 4 week dosing) and the C1-INH Berinert (COMPACT).</i>”</p> <p>CSL Behring’s response: Since any comparisons with SC C1-INHs are not in the NICE scope, CSL Behring believes that the removal of C1-INH Berinert (COMPACT) and mention of the sensitivity analysis performed with Cinryze is more appropriate in this section. If the removal of C1-INH Berinert (COMPACT) is not deemed appropriate by the committee, CSL Behring would kindly suggest the addition of “(not deemed a comparator for this submission)” for completeness. The company would like to kindly remind the committee to pull through any changes into the conclusions drawn from the ITCs (sections 3.6 and 1)</p> <p>Section 3.6 also stated that the committee “<i>also concluded that, based on these analyses, garadacimab is clinically effective compared with berotralstat, C1-INHs or lanadelumab.</i>”</p> <p>CSL Behring’s response: CSL Behring would like to clarify the conclusions of the indirect treatment comparisons (ITCs) since the current wording does not present the full scope of benefit. The ITCs show that garadacimab is clinically [REDACTED] than berotralstat and IV C1-INHs and [REDACTED] lanadelumab. This is also portrayed earlier in Section 3.6 by the committee, when they indicate that “<i>overall, garadacimab was ranked as the most effective treatment among</i></p>

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	<p><i>all comparators assessed, with lanadelumab every 2 weeks or subcutaneous C1-INH ranked second'</i></p> <p>Moreover, this conclusion aligns with those drawn in the EAG report, which states that the EAG's preferred ITC (FE NMA with phase 2 trial removed) shows that:</p> <ul style="list-style-type: none"> garadacimab is [REDACTED] than berotralstat in preventing HAE attacks while being [REDACTED] and leading to [REDACTED] HRQoL outcomes garadacimab is similarly effective to lanadelumab Q2W in preventing HAE attacks while being [REDACTED] and leading to [REDACTED] numerical HRQoL outcomes than lanadelumab although estimates for this analysis are considered highly uncertain by the EAG, garadacimab was reported to be [REDACTED] than IV C1-INHs <p>Finally, the draft guidance does not include the sensitivity analysis done with the IV C1-INH Cinryze. CSL Behring believes that, in this context, the mention of this sensitivity analysis and the exclusion of SC C1-INHs (or reiteration that these are not deemed a comparator) is more appropriate, since the comparison with SC C1-INHs is out of the NICE scope.</p>
3.7	<p>Company's overall model structure</p> <p>Thank you. No further comment, CSL Behring agrees with the committee's summary.</p>
3.8	<p>Tunnel states</p> <p>Section 3.8 states <i>'The EAG noted that in VANGUARD, the most significant impact on health-related quality of life occurred within the first month of treatment.'</i></p> <p>CSL Behring's response: CSL Behring notes that, while the statement accurately records a claim made by the EAG on page 102 of its report, the evidential basis for this claim appears uncertain, and later comments by the EAG during the appraisal suggest a different position. Overall, the company would welcome further consideration towards the importance of attack-free periods, highlighted in international guidelines and in section 3.1 of the draft guidance, point at the second committee meeting.</p> <p>CSL Behring is also concerned about the differing standards applied to the assessment of tunnel states. In reaching the above conclusion, the EAG appears to rely chiefly on visual inspection of graphical AE-QoL data from VANGUARD. However, when the company presented AE-QoL regression</p>

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	<p>analyses that supported the validity of tunnel states, the EAG responded that “<i>the AE-QoL regression results could not be used to make inferences about the magnitude of the effect in relation to EQ-5D</i>” (p. 18 of the EAG review of the technical-engagement response).</p> <p>In effect, AE-QoL data have been used to question, but not to support, the use of tunnel states. CSL Behring would like to request a balanced appraisal of the available evidence.</p> <p>For completeness, please see the statement made by the EAG referred to earlier “<i>AE-QoL, as measured within the VANGUARD... suggests to the EAG that tunnel states are unlikely to be required to capture HRQoL improvements after an attack. (EQ-5D scores were not collected with enough granularity to determine the monthly impact immediately after an attack.)</i>” p.102 of the EAG report</p>
3.9	<p>Berotrastat’s longer-term effectiveness and stopping rule</p> <p>Thank you. No further comment, CSL Behring agrees with the committee’s summary.</p>
3.10	<p>Evidence for modelling berotrastat’s longer-term effectiveness</p> <p>Section 3.10 states, ‘<i>The company used this evidence to estimate the proportion of study participants whose hereditary angioedema responded to berotrastat and could continue treatment [...]. The EAG emphasised that it recognised the difficulties faced by the company in not having access to effectiveness data on response to berotrastat. The company and EAG both contacted the Elbashir et al. study authors to understand the data better.</i>’</p> <p>CSL Behring’s response: CSL Behring would like to thank the authors of the Elbashir et al. (2024) study for sharing the anonymised, individual patient level, real-world berotrastat audit data. The company has full confidence that this new IPD is key in resolving the issue of the efficacy of berotrastat responders. The analysis of the IPD by CSL Behring followed the preferred methodology previously outlined by the EAG (specified in the joint communication to the Elbashir et al. (2024) authors), as described in the Appendix to this DGC response form.</p> <p>Below analyses of garadacimab versus berotrastat use the committee’s preferences as a base and use the different arms of the real-world berotrastat audit data as specified by the EAG. The company considers the responder population of Arm 2 the most relevant for decision making, as it pertains to the berotrastat responders’ population of interest.</p> <ul style="list-style-type: none"> • Arm 1 (patients who started berotrastat before the TA738 recommendation in October 2021)

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	<ul style="list-style-type: none"> ○ Incremental costs: [REDACTED] ○ Incremental quality-adjusted life years (QALYs): [REDACTED] ○ Incremental cost-effectiveness ratio (ICER): Dominating • Arm 2 (patients who achieved a 50% or more reduction in attack rates at month 3) <ul style="list-style-type: none"> ○ Incremental costs: [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating • Arm 3 (patients who did not achieve a 50% or more reduction in attack rates at month 3, but continued treatment nonetheless) <ul style="list-style-type: none"> ○ Incremental costs: [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating • Current committee preference <ul style="list-style-type: none"> ○ Incremental costs: [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating <p>Section 3.10 states, “The EAG explored using Elbashir et al. in a scenario analysis, but implemented the data differently to the company. A clinical expert in the committee meeting was also a contributor on the Elbashir et al. study. They confirmed that the EAG’s assumption that the attack rate ratio (month 3 to 24) compared people who continued treatment with all study participants, including people who stopped treatment (for any reason), was correct. They also explained that in people who started berotralstat before the stopping rule was introduced, treatment response continued to improve after the first 3 months of berotralstat treatment. There was then a levelling of response seen by 8 to 12 months.”</p> <p>CSL Behring’s response: As presented above, CSL Behring has provided additional analyses derived from IPD kindly shared by the authors from Elbashir et al. (2024), which should help resolve any interpretational uncertainties associated with the poster. The company trusts that the</p>
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	<p>IPD-based results inform a more precise assessment, removing the further need for the deliberation on this point.</p> <p>Section 3.10 states <i>‘The committee noted that the design of the Elbashir et al. study was not well aligned with the way the company used the data’</i>.</p> <p>CSL Behring’s response: CSL Behring acknowledges the committee’s observation but considers that its use of the Elbashir et al. study remains consistent with the study’s design. The methods section of the study reports: <i>“A questionnaire was distributed to all interested UK immunology centres to collect anonymised retrospective data, including demographics, frequency of HAE attacks, ... Data were collected for multiple time points: at baseline (three months pre-treatment) and at multiple intervals post-treatment initiation (3, 6, 12, 18, and 24 months).”</i>⁷</p> <p>The company used the data on frequency of HAE attacks across multiple timepoints to estimate the attack rate reductions for berotralstat, which is aligned to the design of the study.</p> <p>Section 3.10 also states <i>‘The EAG noted that the company’s updated approach disregarded the NMA for garadacimab and comparators after month 3 and was therefore a naive comparison’</i></p> <p>CSL Behring’s response: The CSL Behring’s updated approach continues to use the NMA for estimating attack rates for garadacimab, lanadelumab Q2W, lanadelumab Q4W, IV C1-INHs.</p> <p>As explained in Section 3.9, the EAG noted that the NMA can only consider a pooled population of responders and non-responders because this distinction was not made in the berotralstat trials. This fact makes the NMA unsuitable for estimating the attack rates for berotralstat responders.</p> <p>Additionally, the company’s updated approach did not disregard the NMA for berotralstat. The company followed the NICE manual on indirect comparisons and network meta-analyses (3.4.11) as it is written: <i>“When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate.”</i>⁸</p> <p>Given the NMA is not appropriate for estimating attack rates for berotralstat responders, the company used the next best available source for estimating these attack rates, which is in line with NICE methods and guidance.</p>
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	<p>Moreover, Section 3.10 states that <i>“It stated that using the EAG’s scenario based on the Elbashir et al. study gave results between the preferred attack rate of the company (best case) and EAG (worst case)”</i>.</p> <p>CSL Behring’s response: CSL Behring notes that both clinical experts at the committee meeting advised that the so-called “worst-case” scenario was not clinically realistic. Accordingly, describing the company’s analysis as a “best-case”, the EAG base case as a “worst-case”, and the EAG Elbashir scenario as intermediate may give a misleading impression of the underlying evidence. CSL Behring suggests revising this wording to align with the expert feedback provided.</p>
3.11	<p>Lanadelumab dose switching</p> <p>CSL Behring would like to rectify the following minor errors identified in Section 3.11</p> <ul style="list-style-type: none"> • The Dorr et al. (2021) study mentioned in the paragraph is from 2023 - Dorr AD, Chopra C, Coulter TI, Dempster J, Dziadzio M, El-Shanawany T, et al. Lanadelumab for the prevention of hereditary angioedema attacks: A real-world UK audit. <i>Allergy</i>. 2023;78(5):1369-71.⁹ • The company aligned with the EAG assumption that switching to lanadelumab Q4W would occur over a period of 6-months (Table 3 of the technical engagement response form) • The Magerl et al. (2024) study was conducted in France, Greece and Austria, in addition to Germany.¹⁰
3.12	<p>Patient utilities for having an attack</p> <p>Section 3.12 states <i>‘The EAG explained that there was ambiguity in Nordenfelt et al. (2014) about the way attack disutility was calculated. This was whether the decrement for ‘attacks in past cycle’ meant in the previous 28 days or the previous year.’</i></p> <p>CSL Behring’s response: CSL Behring would like to clarify the apparent ambiguity in the way attack disutility was calculated. Table 24 of the company submission reports the use of attack disutility directly from the Nordenfelt et al. (2014) study, in the same way as TA606⁴ (Table 43) and TA738¹² (Table 29, BioCryst used the average attack disutility)</p> <p>The issue that this section brings to attention is the interpretation of -0.0043 ‘per attack’ coefficient reported in Nordenfelt et al. (2014), p.187. This</p>

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	<p>coefficient was used in the calculation of baseline utility values for garadacimab, TA606 and TA738, and not attack disutility.</p> <p>Regarding the issue if the number of attacks used in calculating the attacks disutility should be summed up over 28 days or the previous year, CSL Behring would like the committee to account for the following statement made by Nordenfelt et al. (2014), which points to the annual interpretation of the attack coefficient.</p> <p>“The 103 patients that reported an EQ5D today score were split into three subgroups defined by reported annual attack frequency; 0 –14 attacks per year (n=84), 15–29 attacks per year (n=8), and ≥30 attacks per year (n=11).” p.187</p> <p>Section 3.12 states that <i>‘the EAG clarified after the meeting that its updated base case presented to committee assumed attacks in the previous 28 days, as the company had done.’</i></p> <p>CSL Behring’s response:</p> <p>Response: CSL Behring would welcome further clarification on the rationale for the EAG’s recent change in position regarding this assumption. The company observes that the revision was made only after CSL Behring had aligned its assumption with the EAG’s earlier preference, in accordance with the Chair’s request; the assumption was then reconsidered and its validity questioned. The EAG had maintained the same stance on this point for almost six months across multiple appraisal milestones, including the EAG report, economic model, response to technical engagement and the model used during technical engagement.</p> <p>CSL Behring notes that, in the course of aligning with the EAG, the company identified and transparently corrected an error in the EAG’s implementation of the coefficient, which in turn improved the estimated cost-effectiveness of garadacimab. As this was the only change introduced, and the scientific rationale underlying the EAG’s original position otherwise appears unchanged, CSL Behring would appreciate clarification of the basis for revising the base-case assumption.</p> <p>CSL Behring remains committed to working collaboratively with the committee, NICE and the EAG to ensure that its submission accurately reflects the scientific evidence. The company is nevertheless concerned that the current process may not fully capture the value that garadacimab brings to patients and would welcome further dialogue to address this.</p>
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	<p>Section 3.12 states <i>‘The EAG explained that when it tested both scenarios, assuming attacks in the previous year gave negative utility values, which it did not consider credible.’</i></p> <p>CSL Behring’s response:</p> <p>CSL Behring has stress-tested this assumption across several versions of the model: the original company submission, the model used by the EAG during technical engagement and the latest version incorporating post-meeting updates. Only the latter two reflect the committee’s evolving preferred assumptions, and in neither case did wide-ranging scenario tests generate negative utility values. While negative utilities did arise in the earliest model (and only in the most extreme scenarios), it should be noted that that version assumed a one-week attack duration and applying the committee-preferred duration of 3.13 days removed this issue. Due to the above, we do not believe that negative utilities can be achieved in the current version of the model by using the annual attack coefficient.</p> <p>The company would greatly appreciate clarity with respect to this, particularly since, due to this false assertion, the annual coefficient assumption is no longer part of the committee’s preferred assumptions, despite forming part of the chair’s offered actions.</p>
3.13	<p>Patient utilities for being attack-free</p> <p>Section 3.13 states <i>‘The EAG advised there was some double counting of health-related quality of life because of the separate elements of the impact of treatment on attacks and freedom from attacks.’</i></p> <p>CSL Behring’s response: CSL Behring appreciates the committee’s attention to the potential for double counting health-related quality-of-life (HRQoL) benefits. The company would like to clarify that the model treats two distinct, non-overlapping aspects of HRQoL:</p> <ol style="list-style-type: none"> 1. Burden of individual attacks: the physical and emotional impact of managing and recovering from debilitating HAE attacks. 2. Psychological benefit of attack-free periods: the reduction in fear and anxiety when patients remain free from attacks. <p>In addition to patient representatives and clinical experts stressing the importance of both dimensions during the committee meeting, the below mathematical formulae demonstrate that there is no double-counting by using tunnel states:</p>

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	<ol style="list-style-type: none"> Baseline utility (based on Nordenfelt et al. (2014)) = $0.825 - 0.02205 \times \text{age} - 0.0043 \times \text{attacks}$ (attacks in the previous annum) Month 1 tunnel state utility = Baseline utility + $(1/6) \times \text{Gain}$ Gain (from baseline to general population utility if the patient goes six-months without an attack) = General population utility – Baseline utility Month 1 tunnel state utility expanded = $(0.825 - 0.02205 \times \text{age} - 0.0043 \times \text{attacks}) + (1/6) \times \text{General population utility} - (1/6) \times (0.825 - 0.02205 \times \text{age} - 0.0043 \times \text{attacks})$ Month 1 tunnel state utility simplified = $(1/6) \times \text{General population utility} + (5/6) \times (0.825 - 0.02205 \times \text{age} - 0.0043 \times \text{attacks})$ Month 1 tunnel state utility simplified = $(1/6) \times \text{General population utility} + (5/6) \times (\text{Baseline utility})$ <p>From the equivalent equations (4), (5) and (6), it is clear there is no double added benefit of a patient progressing from the baseline to month 1 of the tunnel states, which represents one month without having an attack. The utility experienced in this tunnel state is simply the first step along a linear progression to improved quality of life, should the patient continue to remain without attacks. Since the ‘attacks’ coefficient is applied to the number of attacks experienced by the <i>cohort</i>, and not the individual patient, there is no added or double counted benefit because of the tunnels.</p> <p>Section 3.13 also states <i>‘They added that improvement in attack severity is also important, although this was not compared between treatments in the model.’</i></p> <p>CSL Behring’s response: CSL Behring notes the committee’s emphasis on improvements in attack severity. In the company’s base-case model, treatment-specific differences in attack severity are reflected through a naïve comparison of the available evidence. By contrast, the EAG analysis assumes that all comparators share garadacimab’s severity profile. The company believes that retaining treatment-specific severity estimates provides a more accurate reflection of clinical outcomes.</p> <p>Section 3.13 also states <i>‘The EAG explained that in its preferred approach, utility was only a function of time spent attack free based on the number of attacks in the previous year. People with 6 to 12 months of attack freedom</i></p>
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	<p><i>in the EAG model accrued a utility value close to the general population. The committee decided that it preferred the EAG's simpler modelling approach that linked quality of life to time spent attack free based on the number of previous attacks.'</i></p> <p>CSL Behring's response: Eight clinical experts who signed the clinical consensus statement showed agreement with both the company and the committee by stating that it is reasonable to assume that a patient's quality of life gradually improves over the duration that they are attack-free.¹ The tunnel states in the company's model are designed to capture this link between quality of life and time spent attack-free based on number of attacks.</p> <p>Additionally, CSL Behring notes that the EAG has not provided a scientific rationale for selecting a 12-month period of attack freedom as the point at which patients attain utilities approaching those of the general population. During technical engagement, the company submitted four independent sources indicating that quality-of-life gains are realised after approximately six months of sustained attack freedom — a view also endorsed by clinical experts at the committee meeting. CSL Behring therefore suggests that a six-month period may more accurately capture the benefits observed in clinical practice.</p>
3.14	<p>Carer utilities</p> <p>Section 3.14 states <i>'The EAG noted that the size of the carer utility decrement (0.145) was large compared with decrements used in previous submissions for hereditary angioedema'</i></p> <p>CSL Behring's response: CSL Behring would like to clarify that the EAG has cited the unscaled caregiver disutility value (0.145), which could be misleading. In the company's model this decrement is adjusted for the duration of HAE attacks requiring caregiver assistance, resulting in an effective value approximately nine-fold smaller. Accordingly, the caregiver disutility applied in the model is in line with those used in previous HAE submissions and should not be considered unusually large.</p> <p>This statement uses a similar rationale to that stated elsewhere in the draft guidance, where the EAG compare quality of life in HAE to other conditions. Whilst the company have concerns about this approach, we also feel this view is not being consistently applied. When deciding an appropriate size for the quality of life impact on carers in HAE, the EAG refer to a range seen in TSD 9. However, their favoured source of evidence found no relationship between specific diseases and the impact on carers. We feel the reference of comparison has then been changed by the EAG from the range provided in TSD 9, wherein every appraisal utilised a disease-specific source of elicited carer burden.</p>

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	<p>Section 3.14 states <i>‘The committee concluded that it preferred the EAG’s approach for including carer utilities in the model, including assuming 1 carer per household.’</i></p> <p>CSL Behring’s response: CSL Behring would like to clarify that they have aligned with the EAG on this assumption during the technical engagement process.</p>
3.15	<p>Severity</p> <p>Thank you. No further comment, CSL Behring agrees with the committee’s summary.</p>
3.16	<p>Committee’s preferred assumptions</p> <p>Please see the comments on Section 3.14 regarding the number of carers.</p>
3.17	<p>Acceptable incremental cost-effectiveness ratio</p> <p>CSL Behring agrees with the committee’s summary and thanks the committee for acknowledging the difficulties in evidence generation for HAE because of its rarity, and acknowledging the unmet need, particularly for people with an attack frequency below eligibility criteria for the ≥ 2 attacks per week subgroup.</p> <p>CSL Behring would, however, like to note two areas where it believes the residual uncertainty is lower than implied:</p> <ul style="list-style-type: none"> • <i>‘there was no evidence from trials directly comparing garadacimab with C1-INHs or lanadelumab’</i> – Key Issue 2 concerning the indirect treatment comparisons has now been addressed, such that the absence of head-to-head trials with C1-INHs or lanadelumab should not introduce material additional uncertainty • <i>‘in the assumptions that needed to be made about lanadelumab dose switching’</i> – Applying the committee’s preferred dose-switch approach led to garadacimab dominating lanadelumab in the cost-effectiveness analyses <p>CSL Behring suggests that these points are taken into account when characterising the overall uncertainty in the evidence base.</p>
3.18	<p>Cost-effectiveness estimates</p>

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	<p>Section 3.18 states <i>‘For the comparison with berotralstat for people having 2 or more attacks per month [...] the EAG’s deterministic base-case ICER for garadacimab was substantially higher than £30,000 per QALY gained.’</i></p> <p>CSL Behring’s response: In an effort to align the comparisons made across TAs and reduce the uncertainty in decision making, the company would like to propose a scenario analysis with the baseline number of attack rates being valued at 3.1 attacks per month (as per the APeX study and TA738). The cost-effectiveness of garadacimab for the comparison with berotralstat for people having ≥ 2 attacks per month significantly improves with the committee-preferred assumptions with Arm 2 of the berotralstat real-world audit data (See Section 3.10). In summary:</p> <ul style="list-style-type: none"> • Incremental costs: [REDACTED] • Incremental QALYs: [REDACTED] • ICER: Dominating <p>Additionally, and in line with previous appraisals, CSL Behring would like to present the cost-effectiveness results across the possible attack rates in the ≥ 2 attacks per month range, taking into account the committee-preferred assumptions and Arm 2 of the berotralstat real-world audit data:</p> <ul style="list-style-type: none"> • <u>3 attacks/month</u> <ul style="list-style-type: none"> ○ Incremental costs: - [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating • <u>4 attacks/month</u> <ul style="list-style-type: none"> ○ Incremental costs: - [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating • <u>5 attacks/month</u> <ul style="list-style-type: none"> ○ Incremental costs: - [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating • <u>6 attacks/month</u> <ul style="list-style-type: none"> ○ Incremental costs: - [REDACTED] ○ Incremental QALYs: [REDACTED]
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	<ul style="list-style-type: none"> ○ ICER: Dominating • 7 attacks/month <ul style="list-style-type: none"> ○ Incremental costs: - [REDACTED] ○ Incremental QALYs: [REDACTED] ○ ICER: Dominating <p>It should be noted that the baseline number of attacks of patients in Arm 2 of the berotralstat real-world audit data is [REDACTED], which suggests the VANGUARD baseline number of attacks is conservative for garadacimab's cost-effectiveness.</p> <p>Section 3.18 also states '<i>For the comparison with [IV] C1-INHs or lanadelumab for people having 2 or more attacks per week, garadacimab was more effective and less costly than the comparators, in the company and EAG base-cases and applying committee's preferred assumptions. So, garadacimab dominated in all scenarios.</i>'</p> <p>CSL Behring's response: CSL Behring formally adopted dual base cases for the ≥2 attacks per month and ≥2 attacks per week subgroups during technical engagement. Given the committee's conclusion that garadacimab is cost-effective in the ≥2 attacks per week subgroup, CSL Behring would like to understand the rationale for not recommending garadacimab for this group of patients experiencing more frequent attacks.</p>
3.19	<p>Equality</p> <p>When discussing reasons for younger people having less access to LTP options, section 3.19 states "<i>Attack frequency: 2 or more attacks per month (berotralstat) or 2 or more attacks per week (C1-INHs and lanadelumab)</i>" as one of these reasons. Similarly, the section states that "<i>the committee was also aware that some religious groups may be unwilling to have blood product-derived treatments, such as C1-INHs</i>" and that "<i>it also noted that both garadacimab and lanadelumab are alternatives to C1-INHs that are not derived from human plasma.</i>"</p> <p>CSL Behring's response: Since only the IV formulations of C1-INHs are recommended by the NHS commissioning policy and the NHS treatment algorithm,³ and the comparison with SC C1-INHs is out of the NICE scope, CSL Behring kindly suggest that the use of 'IV C1-INHs' as being more appropriate here.</p>
3.20	Uncaptured benefits

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	<p>Section 3.20 states that the committee “<i>did not identify additional benefits of garadacimab not captured in the economic modelling and concluded that all benefits of garadacimab had already been taken into account.</i>”</p> <p>CSL Behring’s response: CSL Behring would like to kindly remind the committee of the following two benefits of garadacimab that the company believes are currently not captured in the economic model:</p> <ul style="list-style-type: none"> • While it is understood that patients generally favour home administration due to cost and time savings, improved flexibility and fewer hospital visits, some patients have difficulty achieving consistent and successful self-injection due to poor manual dexterity or experience anxiety at the prospect of self-injection.¹³ These factors can reduce patients’ medication adherence and overall experience. Garadacimab is administered subcutaneously via an autoinjector pen which administers 200 mg of garadacimab into subcutaneous tissue and requires no skin pinching, offering a more straightforward method of self-administration compared to existing subcutaneous (pre-filled syringe) options such as lanadelumab.^{5,14} This well-designed autoinjector may help improve patients’ self-injection confidence and medication adherence compared with the subcutaneous administration with a pre-filled syringe.¹³ • As per the garadacimab PIL,¹⁵ the garadacimab autoinjector may be stored at room temperature (up to 25°C) for a single period of up to 2 months, but not beyond the expiry date. As mentioned in Section 3.2, the HAE UK representative at ACM1 indicated that this would lift key restrictions on patients in terms of travelling to work, school, visiting family and for leisure purposes. It was mentioned that this would have a large impact on daily life and quality of life. <p>The additional benefit that these aspects offer to patients are endorsed by the eight UK clinicians who signed the clinical consensus statement, which states that “<i>garadacimab administration is through a pre-filled autoinjector pen which may be stored at room temperature for a period of up to two months. This additional flexibility, when combined with the advantages of attack freedom, is likely to confer important benefits to the lives of patients, in terms of quality of life and achieving progress towards the ambition of international guidelines to normalise their lives.</i>”¹</p>
3.21	<p>Recommendation</p> <p>Thank you. No further comment, CSL Behring agrees with the committee’s summary.</p>

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4	<p>Evaluation committee meeting members and NICE project team</p> <p>Thank you. No further comment, CSL Behring agrees with the committee's summary.</p>
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the [NICE Health Technology Evaluation Manual](#) (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as '[REDACTED]' in turquoise, and all information submitted as '[REDACTED]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix

Anonymised, individual patient level, real-world berotralstat audit data from the authors of the Elbashir et al. (2024) study.

This appendix expands on the methodology used to assess the anonymised, individual patient level, real-world berotralstat audit data from the Elbashir et al. (2024) study, and presents the associated results. This data is based on retrospective data from 18 immunology centers around the United Kingdom, from the period of 2019 to mid-2024, providing critical evidence on the attack rates of berotralstat patients.

Methodology

The analysis of the individual patient-level data (IPD) by the company followed the preferred methodology previously outlined by the EAG (specified in joint communication to the Elbashir et al. (2024) authors, drafted 25 March 2025). In short, CSL Behring have:

- Used the full follow-up time horizon, not restricting to months 0–24.
- Assessed analysis Arms for patients who had ≥ 2 attacks per month at baseline:
 - Arm 1 - All patients who initiated treatment before the introduction of the stopping rule in October 2021.
 - Arm 2 - Only patients who achieved a 50% reduction in attack rate at month 3 (the data allowed the direct identification of these patients)
 - Arm 3 - All patients who did not achieve a 50% attack rate reduction at month 3, but nonetheless continued treatment
- If patients discontinue due to safety events or efficacy, their data was censored from the analysis from that point onwards.
- For each arm and at each timepoint, the following data was provided in a tabulated manner: the sample size, mean and standard error for the attack rate reductions, and number of patients that discontinue due to loss of response and safety events.

The dataset contained inputs for 164 patients, which is the same as the Elbashir et al. (2024) poster. [REDACTED] were removed from the analysis because they did not have data on baseline attack rate data, so their relative reduction in attack rates from baseline cannot be calculated. Table 1, Table 2, and Table 3 below provide the summary outcomes for the analysis Arms 1, 2 and 3 respectively.

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Results

Patients in Arm 1 achieved

[REDACTED]

Whilst this group contains patients who have been on treatment the longest, Arm 2 has a higher sample size informing the later periods of the analysis so there is little value in Arm 1 informing long-term outcomes specifically.

Patients in Arm 2 are by definition the best responding cohort of the analysis, with attack rate reductions ranging from [REDACTED]. These efficacy outcomes are

[REDACTED]

Patients in Arm 3 did not have a 50% reduction in attack rates 3 months after starting treatment but continued treatment, managed to achieve on average [REDACTED] reduction in attack rates [REDACTED]. Overall, this arm shows

[REDACTED]

Table 1. Efficacy and discontinuation outcomes (Arm 1, real-world berotralstat audit data)

Arm 1	3 months after	3–6 months after	6–12 months	12–18 months	18–24 months
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	starting bero	starting bero	after starting bero	after starting bero	after starting bero
HAE attack rate reduction from baseline					
n	■	■	■	■	■
Mean	■	■	■	■	■
SE	■	■	■	■	■
Reasons for discontinuation					
Efficacy	■	■	■	■	■
Safety	■	■	■	■	■
Efficacy and Safety	■	■	■	■	■
Other*	■	■	■	■	■

Abbreviations: bero, berotralstat; HAE, hereditary angioedema; SE, standard error.

*Other defined as 'not efficacy, safety, or efficacy and safety'. ■ patient(s) discontinuing in month 24 or beyond due to ■

Table 2. Efficacy and discontinuation outcomes (Arm 2, real-world berotralstat audit data)

Arm 2	3 months after starting bero	3–6 months after starting bero	6–12 months after starting bero	12–18 months after starting bero	18–24 months after starting bero
HAE attack rate reduction from baseline					
n	■	■	■	■	■
Mean	■	■	■	■	■
SE	■	■	■	■	■
Reasons for discontinuation					
Efficacy	■	■	■	■	■
Safety	■	■	■	■	■
Efficacy and Safety	■	■	■	■	■
Other*	■	■	■	■	■

Abbreviations: bero, berotralstat; HAE, hereditary angioedema; SE, standard error.

*Other defined as 'not efficacy, safety, or efficacy and safety'. ■ patient(s) discontinuing in month 24 or beyond due to ■

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

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Table 3. Efficacy and discontinuation outcomes (Arm 3, real-world berotralstat audit data)

Arm 3	3 months after starting bero	3 to 6 months after starting bero	6 to 12 months after starting bero	12 to 18 months after starting bero	18 to 24 months after starting bero
HAE attack rate reduction from baseline					
n	■	■	■	■	■
Mean	■	■	■	■	■
SE	■	■	■	■	■
Reasons for discontinuation					
Efficacy	■	■	■	■	■
Safety	■	■	■	■	■
Efficacy and Safety	■	■	■	■	■
Other*	■	■	■	■	■

Abbreviations: bero, berotralstat; HAE, hereditary angioedema; SE, standard error.

*Other defined as 'not efficacy, safety, or efficacy and safety'.

Email heading: Clinical consensus statement – CSL Behring – NICE ID6394 garadacimab – request for engagement

UK Clinician Statement

As healthcare professionals with experience in the treatment of hereditary angioedema (HAE) in the UK, we collectively endorse the integration of garadacimab into the patient care pathway. Current commissioning criteria¹ based on attack frequency are too simplistic and leave many patients underserved and without access to effective, licensed prophylactic treatment. Garadacimab represents an important development in the prophylactic treatment of hereditary angioedema attacks. In the VANGUARD study² the majority of patients (61.5%) were attack free at the end of the study period (182 days) and durability of this effect was demonstrated in the phase-3 OLE³ after a median exposure of 13.8 months with 60% of garadacimab patients being attack free.

Notwithstanding clinical effectiveness, garadacimab provides potential benefits to patients, particularly those experiencing <2 attacks per week, that represent a step-change in their care. Namely, garadacimab administration is through a pre-filled autoinjector pen which may be stored at room temperature for a period of up to two months. This additional flexibility, when combined with the advantages of attack freedom, is likely to confer important benefits to the lives of patients, in terms of quality of life and achieving progress towards the ambition of international guidelines to normalise their lives⁴.

The HAE patients that we treat suffer from a rare genetic disease, the inflammatory attacks of which are episodic, unpredictable and at times disfiguring and debilitating. As well as this physical burden of an ongoing attack, individuals with this condition are also burdened by the anticipatory anxiety and post-traumatic stress associated with awaiting the next attack and recovering from the last. Thus, the longer the attack free period, the greater the clinically meaningful impact on their quality of life compared to the total number of non-consecutive attack-free days. It is reasonable to assume that this improvement in quality of life would accumulate gradually over months, as individuals overcome these anxieties the longer they remain free from attacks.

In many cases, the care rendered to individuals with HAE is delivered by an individual who also has the condition. In such cases, the condition management of the carer/recipient of care are connected whereby they can influence and induce each other's attacks. To best characterise and elicit the impact on quality of life on carers and patients, we believe that it is most appropriate to consult sources of evidence which have directly elicited their quality of life when living with/caring for those with HAE. We do not believe it is appropriate to consider that carers or patients in HAE experience the same or similar quality of life impact as might be observed in other conditions.

We welcome garadacimab as an alternative treatment to berotralstat for those experiencing ≥ 2 HAE attacks per month, and an alternative treatment to IV C1-INHs and lanadelumab for those experiencing ≥ 2 HAE attacks per week. We also support the stakeholder feedback provided by the NHSE Specialised Immunology and Allergy Clinical Reference group that the company's proposed positioning is consistent with the clinical commissioning algorithm and accurately reflects the current treatment landscape. Our patients, individuals with a historically underserved rare disease associated with a high emotional and physical burden, deserve the best care possible. As clinicians, we strongly advocate for the adoption of this technology into NHS care.

Consent to be named:

If you agree with the above statement, please indicate so with the provision of the details requested in the below table.

Name	Role	Hospital	Trust
	Consultant Immunologist		
	Consultant Immunologist		
	Consultant Immunologist		
	Consultant Immunologist		
	Consultant Immunologist		
	Nurse Consultant		
Anonymous Allergy and Immunology Nurse Consultant			
Anonymous Consultant Immunologist			

References:

1. NHSE, 2025. Commissioned treatment options for patients with Hereditary Angioedema secondary to C1 esterase inhibitor deficiency (HAE-C1-INH) Accessed via: <https://www.england.nhs.uk/wp-content/uploads/2025/02/hereditary-amd-acquired-angioedema-algorithms.pdf>
2. Craig et al, 2023. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Accessed via: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)00350-1/abstract](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00350-1/abstract)
3. Reshef et al, 2025. Long-term safety and efficacy of garadacimab for preventing hereditary angioedema attacks: Phase 3 open-label extension study. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/39370961/>
4. The international WAO/ EAACI guideline for the management of hereditary angioedema – The 2021 revision and update. Accessed via: https://hub.eaaci.org/resources_guidelines/the-international-wao-eaaci-guideline-for-the-management-of-hereditary-angioedema-the-2021-revision-and-update/

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

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	<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>
<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Hereditary Angioedema UK</p>

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<p>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>None</p>
<p>Name of commentator person completing form:</p>	<p>██████████</p>
<p>Comment number</p>	<p>Comments</p> <p>Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.</p>
<p>Example 1</p>	<p>We are concerned that this recommendation may imply that</p>
<p>1</p>	<p>The discontinuation of Berotralstat has no correlation whatsoever to the unmet need of another LTP requirement. Berotralstat does not suit every patient. Every HAE Patient is different.</p>

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2	Current NICE commissioning guidance for Lanadelumab, Berotralstat and C1-INH is based on frequency of attack and not on severity. Patients not achieving the required commissioned guidance are left with only C1-INH: Garadacimab would be their only other option to invasive IV treatment. Berotralstat does not suit every patient. Lanadelumab does not suit every patient. Every HAE patient is different.
3	Quality of life is NOT taken into account in NICE commissioning guidance because only frequency and not severity of attack is considered. An attack can last 1 to 4 days with prolonged after-attack severe fatigue and flu-like symptoms. A patient having two attacks per month each lasting 7-8 days before complete resolution, surely has a severely impacted Quality of Life, as does a patient who has two attacks per week that last 2 days before complete resolution. Every HAE patient is different.
4	No treatment currently available is a 'cure' for Hereditary Angioedema. LTP treatments give patients an expectation AND realisation of reduced attacks, BUT on-demand treatment will always be needed in case of a breakthrough attack. Breakthrough attacks can be caused by trauma, heightened anxiety, pregnancy, illness etc. LTP treatment is absolutely the way forward for every patient but every patient must be considered individually. Every HAE patient is different.
5	The unmet need is for an LTP that sits in terms of guidance alongside Berotralstat and Lanadelumab AS WELL AS being another option for patients with an attack rate of less than 2 per month. Some patients who have less than two attacks per months have very severe attacks which can currently according to the algorithm only be treated by C1-INH: there is no other LTP option. According to the algorithm if a patient is on Berotralstat and shows either an increase in attack OR not a 50% or greater reduction in attacks then only Lanadelumab or C1-INH are the options. Every HAE patient is different.
6	For patients in the 12 to 25 year age gap, Garadacimab fulfils the unmet need of a suitable LTP that can be easily administered at home. This age group – and in particular female patients with pubescent fluctuation of oestrogen – can much more easily manage their attacks by being on an easier to administer sub-cut LTP and not be again reliant on the only other LTP Lanadelumab for which they may not meet the current attack frequency guidance. This greatly enhances Quality of Life for this particular age group in education. Every HAE patient is different.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the [NICE Health Technology Evaluation Manual](#) (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)</p>

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	Total BioCryst UK Limited 78,484.00
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	
Comment number	Comments
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2	Following on from comment #1, it would be helpful to know if garadacimab is cost effective compared to no treatment in patients with 2 or more attacks per month.
3	We note on page 9 that clinical experts advised they would like to try berotralstat first if both garadacimab and berotralstat were available. We would point out that in the wider clinical community, there is a body of clinical experts that would take the view that if both were available, garadacimab would be preferable to berotralstat given the available data on efficacy and tolerability. Additionally, guidelines and clinical experts also indicate that the decision of which one to use should be a shared decision making process with the patient, to determine which is most appropriate for the individual patient.
4	On page 13/14, we note that the EAG preferred to assume that after month 3, berotralstat had the same efficacy as lanadelumab dosed every 2 weeks. This assumption is not something we recognised in clinical practice. Lanadelumab overall tends to be more effective than berotralstat, with lower rates of discontinuation due to ineffectiveness. Lanadelumab also has higher attack-free rates. This is true even though lanadelumab is restricted to a group of patients with more severe disease than the berotralstat population.
5	On page 14, we note that clinical expert advice was that patients who responded to berotralstat could continue to respond very well. Although, this is true for individual patients, when taken in totality, although real world data is limited, our clinical impressions is that the group of patients that respond to lanadelumab overall tend to have a better response compared to the group of patients

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	that continue on berotralstat. Again, it should be noted that lanadelumab is restricted to a group of patients with extremely severe disease compared to berotralstat. We understand that further analysis of the Elbashir data is happening, which should help contribute to this.
6	On page 14, we note that the EAG preferred approach of using lanadelumab efficacy as a proxy for berotralstat. As above, we would contend that this is not appropriate, as there is no good data to indicate that this is true, especially in the UK given the inherent differences in disease severity in these two groups. Equivalency between lanadelumab and berotralstat is therefore not borne out in our clinical experience.
7	On page 17, we note the EAG assumption that lanadelumab switching to every 4 weeks would occur instantaneously at 12 months based on real world study in Germany. This is not clinical practice in the UK, and patients on lanadelumab would gradually transition from every 2 weeks to every 4 weeks if stable, rather than instantaneously at 12 months. Additionally, German practice is not the same as in the UK, and access to lanadelumab in Germany is not restricted by the attack frequency criteria that exists in the UK, resulting in patients in Germany having lower baseline attack rates than UK patients as seen in the INTEGRATED study (Magerl et al. 2025)
8	On page 17, we note that the EAG prefer to assume equal efficacy of lanadelumab every 4 weeks compared to every 2 weeks. Although some patients will be able to extend the dosing to interval to every 4 weeks, not all patients are able to do this (typically <50% in UK data) and efficacy will drop in some patients who are extended to intervals longer than 2 weeks, even though they were previously stable on lanadelumab every 2 weeks.

Insert extra rows as needed

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<p>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>none</p>
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3	We note on page 9 that clinical experts advised they would like to try berotralstat first if both garadacimab and berotralstat were available. We would point out that in the wider clinical community, there is a body of clinical experts that would take the view that if both were available, garadacimab would be preferable to berotralstat given the available data on efficacy and tolerability. Additionally, guidelines and clinical experts also indicate that the decision of which one to use should be a shared decision making process with the patient, to determine which is most appropriate for the individual patient.
4	On page 13/14, we note that the EAG preferred to assume that after month 3, berotralstat had the same efficacy as lanadelumab dosed every 2 weeks. This assumption is not something we recognised in clinical practice. Lanadelumab overall tends to be more effective than berotralstat, with lower rates of discontinuation due to ineffectiveness. Lanadelumab also has higher attack-free rates. This is true even though lanadelumab is restricted to a group of patients with more severe disease than the berotralstat population.
5	On page 14, we note that clinical expert advice was that patients who responded to berotralstat could continue to respond very well. Although, this is true for individual patients, when taken in totality, although real world data is limited, our clinical impressions is that the group of patients that respond to lanadelumab overall tend to have a better response compared to the group of patients that continue on berotralstat. Again, it should be noted that lanadelumab is restricted to a group of patients with extremely severe disease compared to berotralstat. We understand that further analysis of the Elbashir data is happening, which should help contribute to this.
6	On page 14, we note that the EAG preferred approach of using lanadelumab efficacy as a proxy for berotralstat. As above, we would contend that this is not appropriate, as there is no good data to indicate that this is true, especially in the UK given the inherent differences in disease severity in these two groups. Equivalency between lanadelumab and berotralstat is therefore not borne out in our clinical experience.
7	On page 17, we note the EAG assumption that lanadelumab switching to every 4 weeks would occur instantaneously at 12 months based on real world study in Germany. This is not clinical practice in the UK, and patients on lanadelumab would gradually transition from every 2 weeks to every 4 weeks if stable, rather than instantaneously at 12 months. Additionally, German practice is not the same as in the UK, and access to lanadelumab in Germany is not restricted by the attack frequency criteria that exists in the UK, resulting in patients in Germany having lower baseline attack rates than UK patients as seen in the INTEGRATED study (Magerl et al. 2025)
8	On page 17, we note that the EAG prefer to assume equal efficacy of lanadelumab every 4 weeks compared to every 2 weeks. Although some patients will be able to extend the dosing to interval to every 4 weeks, not all patients are able to do this (typically <50% in UK data) and efficacy will drop in some patients who are extended to intervals longer than 2 weeks, even though they were previously stable on lanadelumab every 2 weeks.

Insert extra rows as needed

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Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Immunology and Allergy Clinical Reference Group, NHS England</p>

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<p>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>N/A</p>
<p>Name of commentator person completing form:</p>	<p>[REDACTED]</p>
<p>Comment number</p>	<p>Comments</p> <p>Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.</p>
<p>Example 1</p>	<p>We are concerned that this recommendation may imply that</p>
<p>1</p>	<p>The premise for therapy appears to have become confused alongside the financial assessment. Given the relative efficacy (low to moderate) of Berotralstat and its side effect profile and the need for daily therapy, we are not convinced that a majority of physicians would recommend Berotralstat</p>

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	over Garadacimab were either to be options for first line therapy. It is desirable that either/or options should be available.
2	We are concerned that the cost-benefit of Lanadelumab has been overestimated or the true cost of 55% of patients remaining on Lanadelumab fortnightly should be considered which is the current overall NHS burden for Lanadelumab and consistent with previous trial data and real-world data. Fortnightly lanadelumab would not have made the cost per QALY threshold for commissioning to be advised.
3	Although not explored here, the 12 – 16 yr age group appear to have more recognised side effects of Berotralstat than older patients. Garadacimab would offer a more equitable treatment option and we are concerned that failure to commission Garadacimab would adversely affect the adolescent population and at a time of their life when school milestones with high stakes exams may be a significant factor in increasing attack frequency.
4	
5	
6	

Insert extra rows as needed

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<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Takeda UK</p>

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<p>Name of commentator person completing form:</p>	<p>[REDACTED]</p>
<p>Comment number</p>	<p>Comments</p> <p>Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.</p>
<p>1</p>	<p>Takeda would like to provide some clarification regarding an inaccurate statement made on page 7 of the draft guidance consultation document: '<i>It noted that garadacimab is a self-injected treatment that is more portable than some others like lanadelumab because it does not need refrigeration.</i>' However, as per Section 6.4 of the Summary of Product Characteristics (SmPC)¹,</p>

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	<p><u>garadacimab must be stored in a refrigerator</u> (2°C - 8°C), but may (as per Section 6.3) be stored 'at room temperature (up to 25 °C) for a single period of up to 2 months'.</p> <p>Furthermore, lanadelumab, as per the Summary of Product Characteristics², must also be stored in a refrigerator (2°C - 8°C), but 'may be stored below 25°C for a single period of 14 days'. Takeda suggests that NICE clarify the wording to align with both products Summary of Product Characteristics to avoid any confusion or misinterpretations.</p> <p>1. Summary of Product Characteristics, Andembry 200 mg Solution for injection in pre-filled pen, last updated March 2025. Available at: https://www.medicines.org.uk/emc/product/100625/smpc</p> <p>2. Summary of Product Characteristics, TAKHZYRO 300 mg solution for injection in pre-filled syringe, last updated July 2025. Available at: https://www.medicines.org.uk/emc/product/12051/smpc</p>
2	<p>As a second point of clarification, on page 11 of the draft guidance consultation document, it is stated that: from Walsh et al 2025¹, '<i>overall, garadacimab was ranked as the most effective treatment among all comparators assessed, with lanadelumab every 2 weeks or subcutaneous C1-INH ranked second.</i>'</p> <p>From figure 7 and 8 of this publication, despite being ranked overall as the most effective treatment in terms of time-normalized number of hereditary angioedema attacks, garadacimab failed to show a statistically significant benefit over lanadelumab dosed every 2 weeks and HAEG 60 BIW subcutaneous C1-INH (60 IU/kg twice weekly) was ranked the third, not the second, most effective treatment.¹</p> <p>To avoid any misinterpretation of the current statement, Takeda suggests that NICE explicitly state the lack of statistical significance against lanadelumab dosed every 2 weeks, as this indicates there is not sufficient evidence to demonstrate a difference in effect between the two treatments. Furthermore, NICE should correct that subcutaneous C1-INHs were ranked the third most effective treatment in this network meta-analysis (NMA).</p> <p>Takeda suggest new wording to the effect of, 'In this network meta-analysis, overall garadacimab was ranked as the most effective treatment among all comparators assessed although statistical significance was not demonstrated over lanadelumab dosed every 2 weeks, ranked second, with subcutaneous C1-INHs ranked third.'</p> <p>1. Walsh S, Bartlett M, Salvo-Halloran EM, et al. Network Meta-Analysis of Pharmacological Therapies for Long-Term Prophylactic Treatment of Patients with Hereditary Angioedema. Drugs R D. 2025;25(2):161-178. doi:10.1007/s40268-025-00511-y</p>

Insert extra rows as needed

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Single Technology Appraisal

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]

Comments on the draft guidance received through the NICE website

Name	
Organisation	No
Conflict	No
Comments on the DG:	
<ul style="list-style-type: none">Has all of the relevant evidence been taken into account? <p>I do not know if the unpublished data by Elbashir has been taking into account. I have included details of relevance in my comment. Also see comment for detail</p> <ul style="list-style-type: none">Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? <p>I do not believe so - see comment</p> <ul style="list-style-type: none">Are the recommendations sound and a suitable basis for guidance to the NHS? <p>No - see comment</p> <ul style="list-style-type: none">Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? <p>No</p> <ul style="list-style-type: none">Comment on Section 1: Recommendations, 1.1 <p>I would like to strongly state that there remains a significant unmet need in HAE patients who have <2 attacks per week. Although berotralstat is available for this group of patients, data from Elbashir (pending publication / poster presented at BSI-CIPN 2024) indicates that one third of them do not continue on berotralstat due to lack of efficacy or unacceptable side effects. Apart from berotralstat, there is no other licensed or commissioned therapies in this group of patients.</p>	

It would be helpful to know if garadacimab is cost effective compared to no treatment in patients with 2 or more attacks per month

I note (page 9) that a clinical expert advised they would like to try berotralstat first if both garadacimab and berotralstat were available. I would point out that international guidelines and other clinical experts would suggest that the decision on which treatment to use should be a shared decision with the patient.

On page 13/14, the EAG preferred to assume that after month 3, berotralstat had the same efficacy as lanadelumab dosed every 2 weeks.

This assumption is not something recognised in clinical practice.

Lanadelumab tends to be more effective than berotralstat, with lower rates of discontinuation due to ineffectiveness.

On page 14, clinical expert advice was that patients who responded to berotralstat could continue to respond very well. This may be true for individual patients, but patients treated with lanadelumab tend to have a better response. In this regard lanadelumab efficacy cannot be used as a proxy for berotralstat efficacy, particularly in the UK due to the distinct differences in the patient baseline characteristics in those able to access lanadelumab versus those able to access berotralstat (disease at baseline is much more severe in the lanadelumab treated group). There is therefore no equivalence between lanadelumab and berotralstat and this assumption cannot be made.

On page 17, the EAG assumes that lanadelumab switching to every 4 weeks occurs at 12 months (based on real world study in Germany). This is not clinical practice in the UK, and patients on lanadelumab would gradually transition from every 2 weeks to every 4 weeks if stable, rather than at 12 months. German practice is not the same as in the UK, and access to lanadelumab in Germany is not restricted by the attack frequency criteria making the German population not equivalent to the UK population.

There is also an assumption that lanadelumab every 2 weeks is equally effective as lanadelumab every 4 weeks. This is not confirmed in clinical practice where a proportion of patients are controlled on lanadelumab every 2 weeks but not when the interval is extended.



Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394] A Single Technology Appraisal

EAG Review of company and other stakeholders' response to Draft Guidance

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR170269.
Declared competing interests of the authors	None
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG), and the clinical expert advice provided by Dr Mike Tarzi (from University Hospitals Sussex NHS Foundation Trust) and Dr Patrick Yong (from Frimley Health NHS Foundation Trust).



University
of Exeter

1. INTRODUCTION

The purpose of this document is to respond to points raised by stakeholders ahead of the second committee meeting. The sections of the report are split according to the issues referred to and address stakeholder comments in response to each issue. Responses have only been provided where comments related to unresolved issues which may require Committee discussion or directly to the work of the External Assessment Group. Updated economic analyses are then presented based upon the company's PAS, which remains the same as the PAS from the first Appraisal Committee Meeting.

An additional cPAS appendix has been produced for Committee members to be viewed alongside this document. It contains updated economic analyses with all relevant price discounts applied.

2. EAG RESPONSE

2.1. Modelling the effectiveness of berotralstat

- **Key issue #4 in original EAG report**
- **Section 3.10 in draft guidance document**

NICE guidance states that berotralstat has a stopping rule that requires patients to discontinue treatment if they do not achieve a reduction in HAE attack rate greater than 50% by month 3. Data from clinical trials that included berotralstat did not incorporate this stopping rule.¹ Attempts were made to use data from a real-world study, presented in a poster by Elbashir et al. (2024),² to model the attack rate for patients who responded at month 3. These attempts were hampered by limitations in the way these data were reported in the poster.

The authors of the Elbashir et al. study have since shared the individual patient level data with the company. The EAG would like to thank the authors for providing these data. The company have used the data to model the attack rate amongst patients who achieve a response on berotralstat by month 3. The EAG consider that the way in which the company have conducted this analysis, from month 3 onwards is consistent with the individual patient data. The results are, however, slightly worse for berotralstat than the ITT analysis, i.e. using the data from the NMA without adjusting for the stopping rule. This does not hold face validity as allowing only responders to continue treatment would not be expected to reduce the effectiveness of berotralstat. The EAG therefore prefers to use the ITT analysis from the NMA to represent a realistic lower bound for the effectiveness of berotralstat. The EAG maintains that this provides a conservative estimate of the effectiveness of berotralstat as it is clear from TA738 that the company assumed increased effectiveness versus an ITT analysis and that this was accepted by the Committee.

The EAG considers that the implausible conclusion derived from using the individual patient level data from the Elbashir study is primarily driven by the nature of the data (real-world study). This data is different to all of the other effectiveness data used within the model, which are taken from clinical trials. The EAG also note that the baseline attack rate in the Elbashir cohort is considerably higher than the VANGUARD and APEX trials. The EAG therefore consider that using real-world data for only one treatment increases the risk of bias. It is possible that if real world studies were conducted for the other treatments, the results would also be worse than

those in the clinical trials. This could be caused by several issues, including eligibility criteria for clinical trials, reduced baseline attack rates and increased monitoring.

There is an additional point of disagreement between the EAG approach and the company approach to modelling the attack rate for berotralstat patients, which relates to the period between Month 0 and Month 3. The company continues to argue that the efficacy of berotralstat should not be anchored to garadacimab.

As the EAG argued previously, comparators were considered likely to have a more similar attack profile to garadacimab than no prophylaxis. The company did not present attack rates per cycle for placebo. Consequently, even if the EAG had wanted to anchor relative effectiveness to placebo, these data were not available in the submission (Table 1 in Appendix R only presented information for garadacimab). It was suspected that this change alone would have a minor impact on cost-effectiveness, though this was not something the company appears to have tested.

The company in the latest version of the model have applied the relative attack rate reduction from the NMA to the baseline attack rate in the clinical trials. This could only be considered appropriate if the same method was implemented for garadacimab. Anchoring relative effectiveness estimates from an NMA to different treatments per the current modelling approach is likely to yield biased results. This change alone has a modest impact, reducing the total cost of berotralstat from [REDACTED] to [REDACTED] and the QALYs from [REDACTED] to [REDACTED].

The EAG therefore present the following analyses for Committee decision making:

- ITT analysis: plausible lower bound of berotralstat effectiveness with the stopping rule
- Assuming equal effectiveness between berotralstat responders and lanadelumab Q2W: this provides an optimistic assessment of berotralstat effectiveness
- EAG amended scenario using the Elbashir data using the NMA for the first 3 months: the EAG does not consider this plausible as this assumes that effectiveness without the stopping rule is worse than with it, however, it is presented for completeness

2.2. The calculation of patient utilities

- **Key issue #6 in original EAG report**
- **Sections 3.8 and 3.12 in draft guidance document**

The company raised two key issues related to patient utilities:

1. The company sought again to defend the use of tunnel states for utilities
2. The company argued that the most plausible interpretation of the Nordenfelt (2014)³ attack coefficient is that it relates to the annual attack rate, rather than the monthly attack rate.

2.2.1. Tunnel States (section 3.8 in draft guidance)

The company continues to argue that tunnel states should be implemented such that patients who remain attack free for 6 months converge linearly on the utility for the general population. The EAG does not support this assumption.

The EAG previously requested data that could be used to confirm or deny the hypothesis that patients converge on general patient quality of life and could be used to inform the rate at which patients converge on the general population. As the company indicate in their response, they were not able to provide suitable data from the trials. The company raised the following objection in their response to the ACD:

'CSL Behring is also concerned about the differing standards applied to the assessment of tunnel states. In reaching the above conclusion, the EAG appears to rely chiefly on visual inspection of graphical AE-QoL data from VANGUARD. However, when the company presented AE-QoL regression analyses that supported the validity of tunnel states, the EAG responded that "the AE-QoL regression results could not be used to make inferences about the magnitude of the effect in relation to EQ-5D" (p. 18 of the EAG review of the technical-engagement response).

In effect, AE-QoL data have been used to question, but not to support, the use of tunnel states. CSL Behring would like to request a balanced appraisal of the available evidence.'

The EAG acknowledges the company's concerns and would like to clarify that the additional analyses were requested to see whether these data could be used to implement tunnel states, by giving an indication of the way in which an average patient's utility evolves over 6 months of attack freedom. However, this was not possible as the sample size was only meaningful for less than 2 months of attack freedom and 6 months of attack freedom (See Technical Engagement report). This meant it wasn't possible to assess how patient's utility evolved over a 6-month period.

The company also stated the following in their response to the ACD:

'CSL Behring appreciates the committee's attention to the potential for double counting health-related quality-of-life (HRQoL) benefits. The company would like to clarify that the model treats two distinct, non-overlapping aspects of HRQoL:

- 1. Burden of individual attacks: the physical and emotional impact of managing and recovering from debilitating HAE attacks.*
- 2. Psychological benefit of attack-free periods: the reduction in fear and anxiety when patients remain free from attacks.'*

The EAG would like to clarify that the Nordenfelt attack coefficient adequately accounts for the psychological benefit of attack free periods as it includes a coefficient that, the EAG believes, represents the benefits of a month of attack freedom. To implement tunnel states, when no data are available on the benefits of 6 months of attack freedom compared with more than a month of attack freedom, would risk double counting. The same point would apply, even if the Nordenfelt attack coefficient related to annual attack rate.

The EAG is of the opinion that there is already a risk of double counting. The Nordenfelt study included a regression that assessed the relationship between the number of attacks the patient had experienced in the previous month and their utility. This means that the coefficient for one month of attack freedom will likely already incorporate both the psychological benefit of attack free periods and some of the burden of individual attacks. Attacks are now assumed to impact patient utility for 3.13 days, because of a decision taken by the committee, further suggesting that the impact of the attacks themselves will impact the coefficient included in the Nordenfelt study. To incorporate tunnel states on top of this would only add to the risk of double counting.

The EAG further notes that, in the updated company base case, where tunnel states are not applied for utilities and the Nordenfelt coefficient is assumed to apply to monthly attacks, patient quality of life already converges on the general population.

As the EAG stated previously:

'The EAG has implemented the Nordenfelt regression differently from the way in which it was implemented in the company's model. The amended implementation implies substantially higher patient utility values as we assume an intercept of 1. Therefore, for

patients with no previous attacks, utilities are calculated only based upon age.' (EAG FAC response)

The company has accepted the implementation of the EAG's interpretation of the intercept in the Nordenfelt paper, which means that implementing tunnel states has no impact (as well as being inappropriate in the EAG's view). This is demonstrated by the following results:

- In the **old company base case**, in month 12, patients in the garadacimab arm who have not had an attack for 12 months achieve a utility value that is [REDACTED] lower than the general population utility ([REDACTED] versus [REDACTED]), due to adverse events.
- In the **new company base case**, in month 12, patients in the garadacimab arm who have not had an attack for 12 months achieve a utility value that is [REDACTED] lower than the general population utility ([REDACTED] vs [REDACTED]), due to adverse events. In month 6, the difference is the same.
- In the **new EAG base case**, in month 12, patients in the garadacimab arm who have not had an attack for 12 months achieve a utility value that is [REDACTED] lower than the general population utility ([REDACTED] vs [REDACTED]), due to adverse events. In month 6, the difference is the same.

This shows that the introduction of utility tunnel states has a negligible impact.

Finally, the company stated that:

'Additionally, CSL Behring notes that the EAG has not provided a scientific rationale for selecting a 12-month period of attack freedom as the point at which patients attain utilities approaching those of the general population.'

The EAG chose 12 months as a point of comparison. The above analysis now also includes the results at 6 months of attack freedom.

2.2.2. Implementation of Nordenfelt (section 3.12 in draft guidance)

The company continue to argue that the coefficient contained within the Nordenfelt paper applies to annual attack rate and not monthly attack rate. The EAG continues to acknowledge that the paper is unclear but believes, on the balance of the evidence available, that monthly attack rate is the more likely interpretation. The EAG attempted to contact the authors of the paper to clarify this uncertainty but did not receive a response.

(The company have highlighted some inconsistencies in documentation during this Technology Appraisal, where the EAG have sometimes reversed the labelling of these two options [annual attack rate vs monthly attack rate]. The EAG acknowledged these inconsistencies following the first committee meeting and have attempted to ensure complete clarity from that point onwards.)

The EAG acknowledges that the wording in the paper may suggest that annual attack rate is the more logical interpretation. This would support the company's preferred assumption. However, upon analysing the data, the EAG became convinced that the modelled health state utilities are implausibly low (and in some cases negative) when the coefficient is assumed to apply to annual attacks. The EAG therefore believes it is more plausible to assume that the coefficient relates to the monthly attack rate.

The company stated that:

'CSL Behring has stress tested this assumption across several versions of the model: the original company submission, the model used by the EAG during technical engagement and the latest version incorporating post meeting updates. Only the latter two reflect the committee's evolving preferred assumptions, and in neither case did wide ranging scenario tests generate negative utility values. While negative utilities did arise in the earliest model (and only in the most extreme scenarios), it should be noted that that version assumed a one week attack duration and applying the committee preferred duration of 3.13 days removed this issue. Due to the above, we do not believe that negative utilities can be achieved in the current version of the model by using the annual attack coefficient.'

'The company would greatly appreciate clarity with respect to this, particularly since, due to this false assertion, the annual coefficient assumption is no longer part of the committee's preferred assumptions, despite forming part of the chair's offered actions.'

Table 1 provides a comparison of the modelled health state utility values across the different comparators and different sets of assumptions. Using the company's preferred assumptions would result in negative utility values for an untreated 50-year old patients with 2 or more attacks per week. The EAG considers this implausible.

Table 1: Comparison of company and EAG modelled utility for an average 50-year-old patient just under 10-year post baseline, by treatment

	≥2 attacks per month			≥2 attacks per week		
	New company base case (Annual attacks)	New company base case (Monthly attacks)	New EAG base case (Monthly attacks)	New company base case (Annual attacks)	New company base case (Monthly attacks)	New EAG base case (Monthly attacks)
Garadacimab	■	■	■	■	■	■
Berotralstat	■	■	■	■	■	■
Lanadelumab	■	■	■	■	■	■
Cinryze	■	■	■	■	■	■
No prophylaxis	■	■	■	■	■	■

Note: These values were calculated by multiplying the utility value in the model engines in the cycle at 10 years, by 13

The EAG raised the implausibly low utility estimates in the committee meeting. The Company raised an objection to the written summary of this discussion.

'In section 3.1 it is written that "clinical experts explained that quality of life with uncontrolled hereditary angioedema is similar to that for other long-term chronic conditions, like uncontrolled type 2 diabetes".

CSL Behring's response: *CSL Behring would like to make clear that this was not a sentiment that was put forward by a clinical expert during ACM1, but rather a comparison made by the health economics representative for the EAG during a discussion in ACM1. In this discussion, the EAG health economics representative suggested that it was theoretically possible for the company's model to show quality of life in individuals experiencing ≥2 attacks per week that is similar to that of oncology appraisals.*

The supporting evidence for these claims has not been shown to the company or committee (before, during or after ACM1) and the claims are not verifiable'

The EAG does not agree with the company's recollection of the discussion. Rather, the EAG maintains that it was the clinical expert who made the comparison between quality of life in HAE and uncontrolled type 2 diabetes. The EAG then pointed out, at the discussion, that the

company modelled utility values for no prophylaxis would be comparable to those for cancer patients receiving palliative care (see for example the case studies included in the NICE TSD evaluating the potential impact of using the EQ-5D-5L⁴) and that the utility values from the EAG analysis and Banerji et al EQ-5D mappings were more similar to what would be expected for uncontrolled type 2 diabetes, to help the clinicians and Committee assess their clinical face validity.

Studies are available which provide utility estimates across a range of health conditions to aid comparison. In a recent example of such a paper, Falk Hvidberg et al. (2023),⁵ patients with Type II diabetes have a utility value of around 0.7 (Table 2 in study). One of the lowest utility values reported in the table is for patients with 'systemic atrophies primarily affecting the central nervous system and other degenerative diseases', who have an average utility value of 0.475.

In summary, the EAG does not consider that the utility values using an annual decrement have face validity, and therefore prefer to use a monthly decrement in our base case. Although this may not align with the implied time period in the Nordenfelt paper, it is consistent with prior appraisals and does not produce health state utilities worse than death. The EAG considers that some of the issues with the application of an annual decrement from the Nordenfelt paper may come from double counting of the impacts of attacks on quality of life during and after attacks. Production of more robust data to inform the quality of life of people with HAE during and after an attack is a key area where additional research is required to inform future decision making.

2.3. Baseline attack rate

- **Not reported as a key issue in original EAG report**
- **Section 3.18 in draft guidance document**

In the original submission, baseline attack rates were taken from the garadacimab trial (VANGUARD). In the two or more attacks per month population, this gave a baseline attack rate of ■ attacks per 28 days, with ■ attacks per 28 days requiring adjunct therapy. The company's response includes scenario analysis in which the baseline attack rate has been amended to match TA738.

'In an effort to align the comparisons made across TAs and reduce the uncertainty in decision making, the company would like to propose a scenario analysis with the baseline number of attack rates being valued at 3.1 attacks per month (as per the APeX study and TA738). The cost-effectiveness of garadacimab for the comparison with

berotralstat for people having ≥ 2 attacks per month significantly improves with the committee-preferred assumptions with Arm 2 of the berotralstat real-world audit data (See Section 3.10).'

The company has highlighted the high baseline attack rate in Arm 2 of the company's post-hoc analysis of the Elbashir study to justify this.

'It should be noted that the baseline number of attacks of patients in Arm 2 of the berotralstat real-world audit data is [REDACTED], which suggests the VANGUARD baseline number of attacks is conservative for garadacimab's cost-effectiveness.'

The EAG do not agree with the logic of picking a higher baseline attack rate from a different trial. However, the EAG do agree that implementing a baseline attack rate in line with the population in which garadacimab would be used (and berotralstat is already used) in the UK is justified.

In response, the EAG has implemented the baseline attack rate from the Elbashir paper. The EAG views this as the best available source of evidence as it is a real-world study set in the UK, whereas the previous estimate was taken from a clinical trial which may not have been representative of clinical practice in the UK. Restricting the analysis to Arm 2 would not be appropriate, as this only includes patients who respond at month 3. Rather, the relevant patient group is all patients at baseline, regardless of whether they go on to achieve a response.

The EAG conducted this analysis using the subgroup of patients in the two or more attacks per month population who began treatment following the positive reimbursement decision. This gives a baseline attack rate of [REDACTED]. The number of attacks requiring adjunct therapy was calculated using the ratio between total attacks and attacks requiring adjunct therapy from the trial data [REDACTED]). The EAG note that this provides a more favourable estimate of cost-effectiveness than the company's original amendment. Nevertheless, the EAG consider this to be more representative of practice. This change increases the QALY benefit for garadacimab compared with berotralstat from [REDACTED] to [REDACTED].

2.4. Minor issues

DG	Minor issue	Response
CSL Behring		
3.13	<i>'CSL Behring's response: CSL Behring notes the committee's emphasis on improvements in attack severity. In the company's base-case model, treatment-specific differences in attack severity are reflected through a naïve comparison of the available evidence. By contrast, the EAG analysis assumes that all comparators share garadacimab's severity profile. The company believes that retaining treatment-specific severity estimates provides a more accurate reflection of clinical outcomes.'</i>	<p>The EAG report explained that attack severity was graded differently across the different trials, meaning that it was not possible to compare attack severity across the different treatments in a meaningful way.</p> <p><i>'From the details provided in the CS and at the clarification stage (A16), it was notable to the EAG that attacks graded as mild in VANGUARD/CSL312_2001 could potentially be graded as moderate in HELP (lanadelumab trial). The severity grading used in APeX-2 was detailed in the NICE appraisal of berotralstat [ID1624].⁶ The company (BioCryst Pharmaceuticals) stated that the severity of attack outcomes in the APeX-2 trial were self-diagnosed and subject to individual level biases, reducing the validity of the data. BioCryst was so concerned that they instead used more objective measures in the appraisal rather than the self-reported severity of attacks.'</i> (EAG report)</p> <p><i>'The EAG considered the NMA for number of moderate and/or severe HAE attacks to be subject to considerable uncertainty due to the inconsistency in the definitions of attack severity used in the trials. The EAG noted that the proportion of patients experiencing laryngeal attacks – where the definition is most similar – is consistent across trials (1%-2%), and that the NMA showed that each active treatment demonstrated a statistically significant reduction in people's moderate to severe attacks in comparison to placebo. Therefore, given the uncertainty related to the NMA outcome, the EAG base case used the severity distribution data from VANGUARD for garadacimab for all active treatments.'</i> (EAG report)</p>
3.14	<i>'CSL Behring's response: CSL Behring would like to clarify that the EAG has cited the unscaled caregiver disutility value (0.145), which could be misleading. In the company's model this decrement is adjusted for the duration of HAE attacks requiring caregiver assistance, resulting in an effective value approximately nine-fold smaller. Accordingly, the caregiver disutility applied in the model is in line with those used in previous HAE</i>	<p>The EAG does not agree with the company's summary of the evidence. TA606 states the following:</p> <p><i>'However, as no utility data exists which seeks to quantify the impact of HAE on caregivers, or how treatment with lanadelumab may lead to improvements in their quality of life, it was not possible to formally capture this as part of the analysis.'</i>⁷</p>

DG	Minor issue	Response
	<i>submissions and should not be considered unusually large.'</i>	TA738 states that utility values were taken from a time-trade off (TTO) study, but the values are redacted. ⁶ Further, the EAG would like to reiterate that whether to include carer utility values and their size has a very limited impact on cost-effectiveness and has already been explored extensively in sensitivity analysis.
3.20	<i>'CSL Behring's response: 'While it is understood that patients generally favour home administration due to cost and time savings, improved flexibility and fewer hospital visits, some patients have difficulty achieving consistent and successful self-injection due to poor manual dexterity or experience anxiety at the prospect of self-injection.⁸ These factors can reduce patients' medication adherence and overall experience. Garadacimab is administered subcutaneously via an autoinjector pen which administers 200 mg of garadacimab into subcutaneous tissue and requires no skin pinching, offering a more straightforward method of self-administration compared to existing subcutaneous (pre-filled syringe) options such as lanadelumab.^{9,10} This well-designed autoinjector may help improve patients' self-injection confidence and medication adherence compared with the subcutaneous administration with a pre-filled syringe.⁸'</i>	The disutility associated with sub-cutaneous injection has a very minor impact on cost-effectiveness. The company did not present any evidence to inform a different decrement associated with the garadacimab auto injector, so the EAG does not believe there are sufficient grounds to assume a different impact.
3.3	<p>The positioning of garadacimab is explored in Section 3.3, which states that <i>"The company [...] suggested that people having garadacimab at first line would not have berotralstat at second line. But, the EAG's clinical experts explained that people might switch their first-line treatment between berotralstat and garadacimab, because of side effects or lack of efficacy."</i></p> <p>CSL Behring's response: <i>'This summary of the positioning of garadacimab was raised as factually inaccurate during the committee meeting. In that instance, it referred to the same claim as made on a slide entitled "Key issue 1: Uncertainty around treatment pathway for HAE (1/2)". We would request</i></p>	<p>At the technical engagement stage the company stated in <i>Issue 1: Uncertainty around the treatment pathway for people with HAE</i>: "Limiting garadacimab to a first- or second-line treatment option at ≥ 2 attacks per month, rather than simply as an alternative to berotralstat, would limit the treatment options for patients if they decide to choose garadacimab as their first option since they will not be able to receive berotralstat as a second-line option according to the EAG's treatment pathway."</p> <p>Therefore, the EAG reject the claim that this was a factual inaccuracy. The EAG reiterate that there are two possible positions for garadacimab for those experiencing ≥ 2 attacks per month. It could be an alternative to berotralstat first-line where, as stated by the EAG's clinical experts, people might switch their first-line treatment between berotralstat and garadacimab. Alternatively, it could be second-line in people for whom berotralstat has failed.</p>

DG	Minor issue	Response
	<i>that this is removed to better reflect the company's positioning of garadacimab. With the company, EAG, committee, NHSE and clinical expert signatories to a consensus statement¹¹ all in agreement that the company positioning is appropriate, we believe this statement may read as potentially confusing.'</i>	
Other respondents		
	<p>British Society for Immunology Clinical Immunology</p> <p><i>On page 17, we note that the EAG prefer to assume equal efficacy of lanadelumab every 4 weeks compared to every 2 weeks. Although some patients will be able to extend the dosing to interval to every 4 weeks, not all patients are able to do this (typically <50% in UK data) and efficacy will drop in some patients who are extended to intervals longer than 2 weeks, even though they were previously stable on lanadelumab every 2 weeks.</i></p> <p>British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)</p> <p><i>On page 17, we note the EAG assumption that lanadelumab switching to every 4 weeks would occur instantaneously at 12 months based on real world study in Germany. This is not clinical practice in the UK, and patients on lanadelumab would gradually transition from every 2 weeks to every 4 weeks if stable, rather than instantaneously at 12 months. Additionally, German practice is not the same as in the UK, and access to lanadelumab in Germany is not restricted by the attack frequency criteria that exists in the UK, resulting in patients in Germany having lower baseline attack rates than UK patients as seen in the INTEGRATED study (Magerl et al. 2025)</i></p> <p>Tomaz Garcez</p>	<p>The EAG notes that it has received several similar comments on the efficacy of the lanadelumab Q4W regime and the proportion of patients expected to switch from Q2W to Q4W.</p> <p>The proportion of patients assumed to switch to the Q4W dose was informed by the Dorr et al. (2022)¹² real world study. This is believed to be the best available evidence – it is in line with the assumptions used in previous technology appraisals and the company have not provided alternative evidence.</p> <p>Some stakeholders commented on the timing of switch – specifically at whether it's more appropriate to assume all patients switch at the end of the first year, or they switch gradually over the first year. Both have been tested as part of sensitivity analysis. Both have a minimal impact on cost-effectiveness (See technical engagement response).</p> <p>Some stakeholders have further commented that patients who responded to the Q2W regime may not achieve the same level of response on the Q4W dosing regime. The EAG's position, based upon clinical expert input to the EAG, is that patients who do not maintain their response would move back onto Q2W. The proportion of patients receiving the Q4W treatment regime, and its effectiveness, therefore represents the net effect at a population level of patients moving on and off the Q4W dosing regime over time. Data are not available to support more sophisticated modelling of patients switching between the Q4W and Q2W doses and their associated attack rates.</p>

DG	Minor issue	Response
	<p><i>On page 17, the EAG assumes that lanadelumab switching to every 4 weeks occurs at 12 months (based on real world study in Germany). This is not clinical practice in the UK, and patients on lanadelumab would gradually transition from every 2 weeks to every 4 weeks if stable, rather than at 12 months. German practice is not the same as in the UK, and access to lanadelumab in Germany is not restricted by the attack frequency criteria making the German population not equivalent to the UK population.</i></p> <p><i>There is also an assumption that lanadelumab every 2 weeks is equally effective as lanadelumab every 4 weeks. This is not confirmed in clinical practice where a proportion of patients are controlled on lanadelumab every 2 weeks but not when the interval is extended.</i></p> <p>Dr Patrick Yong for The Royal College of Pathologists</p> <p><i>On page 17, we note the EAG assumption that lanadelumab switching to every 4 weeks would occur instantaneously at 12 months based on real world study in Germany. This is not clinical practice in the UK, and patients on lanadelumab would gradually transition from every 2 weeks to every 4 weeks if stable, rather than instantaneously at 12 months. Additionally, German practice is not the same as in the UK, and access to lanadelumab in Germany is not restricted by the attack frequency criteria that exists in the UK, resulting in patients in Germany having lower baseline attack rates than UK patients as seen in the INTEGRATED study (Magerl et al. 2025)</i></p>	
	<p>Immunology and Allergy Clinical Reference Group, NHS England</p> <p><i>'We are concerned that the cost-benefit of Lanadelumab has been overestimated or the true cost</i></p>	<p>The proportion of patients assumed to switch to the Q4W does was informed by the Dorr et al. (2022)¹² real world study. This is believed to be the best available evidence – it is in line with the assumptions used in previous</p>

DG	Minor issue	Response
	<i>of 55% of patients remaining on Lanadelumab fortnightly should be considered which is the current overall NHS burden for Lanadelumab and consistent with previous trial data and real-world data. Fortnightly lanadelumab would not have made the cost per QALY threshold for commissioning to be advised.'</i>	<p>technology appraisals and the company have not provided alternative evidence.</p> <p>The cost-effectiveness of lanadelumab has been assessed assuming that a proportion of patients remain on the Q2W regime and a proportion of patients switch to the Q4W regime, which is appropriate.</p>
	<p>Tomaz Garcez</p> <p><i>It would be helpful to know if garadacimab is cost effective compared to no treatment in patients with 2 or more attacks per month</i></p> <p>Dr Patrick Yong for The Royal College of Pathologists</p> <p><i>Following on from comment #1, it would be helpful to know if garadacimab is cost effective compared to no treatment in patients with 2 or more attacks per month.</i></p>	<p>The EAG assessed the cost-effectiveness of garadacimab compared with no treatment within the technical engagement response. Garadacimab was found</p> <p>[REDACTED]</p>

3. EAG RESPONSE TO CHANGES TO THE COMPANY'S COST EFFECTIVENESS ESTIMATES

The EAG accepts that a longer attack length is preferred by the committee than in the EAG's previous base case. The EAG corrected the company's PAS in the Excel file from [REDACTED] to [REDACTED] in line with previous communications, before producing economic analysis results. Results for all other comparators are presented using their list price.

The EAG does not agree with the company's assumption that the berotralstat attack rate for months 0-3 should be anchored against on-demand treatment (placebo). Rather, the EAG maintains its assumption that the berotralstat attack rate should be anchored to garadacimab (as for all other comparators), using the relative attack rate data from the NMA.

The EAG present the following analyses for Committee decision making in relation to the berotralstat stopping rule:

- ITT analysis: plausible lower bound of berotralstat effectiveness with the stopping rule
- Assuming equal effectiveness between berotralstat responders and lanadelumab Q2W: this provides an optimistic assessment of berotralstat effectiveness
- EAG amended scenario using the Elbashir data using the NMA for the first 3 months: the EAG does not consider this plausible as this assumes that effectiveness without the stopping rule is worse than with it, however, it is presented for completeness

The EAG has made one further change, which is to implement the baseline attack rate from the Elbashir paper, restricted to patients in the two or more attacks per month population, who began treatment following the positive reimbursement decision. This gives a baseline attack rate of [REDACTED].

Table 2, Table 3 and Table 4, below, compare the new company base case with the updated EAG analyses. A series of relevant scenarios are also presented, which are referenced in the main text. Scenarios were run using a deterministic base case, due to the time needed and the fact that the probabilistic results are closely aligned with the deterministic results.

The EAG included a scenario assuming that the attack coefficient in Nordenfelt was annual instead of monthly. The EAG noted that using these assumptions in the ≥ 2 attacks per week

population resulted in negative utilities in the no prophylaxis arm. The EAG therefore do not believe this scenario is credible, but the company have argued that they support this assumption, so it is included to provide context.

No prophylaxis has been included as a comparator in the company base case and EAG base case, to enable triangulation and as the Committee considered this to be a relevant comparator in the ≥ 2 attacks per month population.

3.1. ≥ 2 attacks per month

Table 2: Exploratory analyses undertaken by the EAG

Preferred assumption	Comparator	Costs	QALYs	Incremental costs	Incremental QALYs	Cost per QALY gained
New company base case (baseline attack rate: ≥ 2)	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
New company base case (Elbashir baseline attacks: ≥ 2)	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
New company base case (berotrastat 0-3 anchored to garadacimab)	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
New company base case (berotrastat ITT analysis)	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
New EAG base case: ITT analysis for stopping rule effectiveness	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
New EAG base case: Elbashir stopping rule effectiveness	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
New EAG base case: berotrastat and lanadelumab same effectiveness from Month 3	No Prophylaxis	£1,000	0.00	£0	0.00	£0
	Garadacimab	£1,000	0.00	£1,000	0.00	£1,000
	Berotrastat	£1,000	0.00	£1,000	0.00	£1,000
	No Prophylaxis	£1,000	0.00	£0	0.00	£0

Preferred assumption	Comparator	Costs	QALYs	Incremental costs	Incremental QALYs	Cost per QALY gained
New EAG base case (Nordenfelt coefficient annual, bero ITT analysis)	Garadacimab					
	Berotrastat					
New EAG probabilistic base case	Garadacimab					
	Berotrastat					

Abbreviations: EAG, External Assessment Group; ITT, Intention-To Treat; QALY, quality-adjusted life year.

Table 3: Altered positioning of garadacimab (corrected ICER) in the ≥ 2 attacks per month population

	Treatment	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG base case ICER	Berotrastat					
	Garadacimab					
Altered positioning	Berotrastat then no prophylaxis					
	Berotrastat then garadacimab					

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

3.2. ≥ 2 attacks per week

Table 4: Exploratory analyses undertaken by the EAG

Preferred assumption	Comparator	Costs	QALYs	Cost per QALY gained
New company base case = New EAG base case	Garadacimab			
	Cinryze			
	Berineret			
	Lanadelumab			
New EAG base case (Nordenfelt coefficient annual)	Garadacimab			
	Cinryze			
	Berineret			
	Lanadelumab			

Abbreviations: EAG, External Assessment Group; QALY, quality-adjusted life year.

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