NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using garadacimab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- 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 recommendations sound and a suitable basis for guidance to the NHS?
- 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: June 2025

Note that this document is not NICE's final guidance on garadacimab. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using garadacimab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 23 July 2025
- Second evaluation committee meeting: 12 August 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

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

1.2 This recommendation is not intended to affect treatment with garadacimab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

What this means in practice

Garadacimab is not required to be funded in the NHS in England to prevent recurrent attacks of hereditary angioedema in people 12 years and over. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that garadacimab is value for money in this population.

Why the committee made these recommendations

Usual treatment for recurrent attacks of hereditary angioedema in people 12 years and over is long-term preventive treatment with berotralstat, C1-esterase inhibitors (C1-INHs) or lanadelumab.

Clinical trial evidence shows that garadacimab reduces the number of hereditary angioedema attacks and increases the likelihood of freedom from attacks compared with placebo. Indirect comparisons suggest that garadacimab is clinically effective compared with berotralstat, C1-INHs or lanadelumab.

There are uncertainties with some of the assumptions used in the economic model, including:

- how usual treatment is used in NHS clinical practice, such as:
  - how well berotralstat works for people who continue treatment after 3 months
  - the timing and proportion of people switching to less-frequent lanadelumab dosing
- how recurrent attacks of hereditary angioedema affect quality of life.

The cost-effectiveness estimates for garadacimab are also uncertain. But the most likely estimates are much higher than what NICE considers an acceptable use of NHS resources. So, garadacimab should not be used.

2 Information about garadacimab

Marketing authorisation indication

2.1 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for garadacimab.

Price

2.3 The list price of garadacimab for subcutaneous injection by pre-filled pen is confidential until published by the Department for Health and Social Care.

2.4 The company has a commercial arrangement, which would have applied if garadacimab had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for CSL Behring will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by CSL Behring, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Unmet need

Details of the condition

3.1 Hereditary angioedema is a rare genetic disorder. Almost all cases are caused by a mutation affecting the C1-esterase inhibitor (C1-INH) gene, known as type 1 or type 2 hereditary angioedema. Hereditary angioedema affects at least 1 in 59,000 people the UK and usually develops between the ages of 8 and 12 years. Hereditary angioedema is a chronic condition involving recurrent unpredictable attacks of swelling in areas of the skin and submucosal tissue. The swelling may happen in the fingers and toes, face, mouth, abdomen, genitalia, gut or airway, and can cause severe pain. Swelling of the airway (laryngeal attacks) can be life threatening. Patient and clinical experts explained that swelling develops quickly over a few hours but can take days or up to a week to go. After an attack, people feel drained with flu-like symptoms and extreme fatigue.

The clinical experts explained that attacks should be treated with on-demand treatment as soon they happen. They advised that the aim of preventive treatment is to reduce the number and severity of attacks. Patient and clinical experts emphasised that people with hereditary angioedema particularly value freedom from attacks. This is because of the severe anxiety of anticipating future attacks, which diminishes with time since the last attack. They advised that although people on existing treatments could have no attacks, breakthrough attacks can occur

because hereditary angioedema is very unpredictable. These are often caused by stressful life events, such as exams, surgery, a car crash, bereavement or giving birth. Attacks may become more pronounced when there are changes in hormone levels, particularly oestrogen, during puberty and menopause. People can also have long periods with more frequent or more severe attacks, which have a significant impact on quality of life and are associated with extreme anxiety. 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. Hereditary angioedema can disrupt education and affect the choice of college, university and career, and can also make traveling for work and leisure extremely challenging. They noted the impact in young people (aged 12 to 17 years) and explained that painful abdominal or facial attacks can lead to stigma and stop people from going out. The committee recognised that hereditary angioedema can be severe and debilitating, and the unpredictability of attacks causes considerable anticipatory anxiety for people with the condition. It understood that the condition varies greatly between different people, so treatment is highly individualised. It also noted that people with well-controlled attacks can still have breakthrough attacks and these are a significant source of worry. The committee concluded that there is an unmet need for additional effective treatment options to prevent recurrent attacks of hereditary angioedema.

Clinical management

Preventive treatment options

3.2 In NHS England's algorithm of commissioned treatment options for hereditary and acquired angioedema secondary to C1-INH deficiency (PDF only) eligibility for long-term preventive treatment is defined by attack frequency:

- People having 2 or more attacks per month can have berotralstat. This is a daily oral treatment that can be used by people 12 years and over.

- People having 2 or more attacks per week despite oral treatments can have:
  - lanadelumab, which is given as a subcutaneous injection every 2 to 4 weeks and can be used by people 2 years and over, or
  - human-plasma-derived C1-INHs, which are given by slow intravenous injection or infusion approximately every few days or weekly and can be used by all ages.
- People having fewer than 2 attacks per month can have on-demand treatment only.

The company presented evidence from a panel of 59 UK healthcare professionals, which reported that eligibility criteria for preventive treatment based only on attack frequency are too simplistic. It also reported that the criteria disadvantage people who would benefit substantially from long-term preventive treatment but are unable to access it because they do not meet the attack frequency criteria. Stakeholder submissions stated that children and young people are likely to have a lower attack frequency than adults. So they may not meet the attack frequency criteria for preventive treatments but can still be significantly affected by the condition. They noted that severity of attacks, which can vary, is not captured in eligibility criteria for preventive treatment. The committee noted that some people have difficulty swallowing tablets, so alternatives to oral treatment are valuable. It noted that garadacimab is a self-injected treatment that is more portable than some others like lanadelumab because it does not need refrigeration. This gives people with the condition more flexibility to travel with medicine and more freedom of choice. The committee felt that it had not heard that garadacimab was a step change in managing hereditary angioedema. It concluded that people with hereditary angioedema and healthcare professionals would welcome an additional preventive treatment option to improve treatment choice.

Positioning of garadacimab

3.3 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. At technical engagement, the company clarified that the comparator being modelled differed by attack frequency:

- berotralstat was modelled for people having 2 or more attacks per month
- C1-INHs or lanadelumab were modelled for people having 2 or more attacks per week.

The EAG agreed with this positioning of garadacimab and the comparators. It also suggested that line of treatment should be explored for people having 2 or more attacks per month, for whom alternative preventive options are most needed. This is because berotralstat is the only preventive treatment option. The EAG explored positioning garadacimab as a first-line option instead of berotralstat or as a second-line option after berotralstat compared with no preventive treatment. The company noted that no preventive treatment was not a comparator in the final scope and 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. The EAG explained that because there was limited data for people continuing berotralstat after 3 months, the indirect comparison with berotralstat is highly uncertain (see sections 3.9 and 3.10). They noted that in the trial, garadacimab was compared with placebo, so comparing garadacimab with no preventive treatment in the model would provide a less uncertain, direct comparison. Berotralstat had shown cost effectiveness compared with best supportive care (with no preventive treatment) in NICE's technology appraisal guidance on berotralstat for preventing recurrent attacks of hereditary angioedema (from here TA738). So, if

garadacimab also demonstrated cost effectiveness compared with no preventive treatment, this could reduce the uncertainty about the indirect comparison of garadacimab and berotralstat. 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). So, the committee decided that exploring second-line garadacimab compared with no preventive treatment was reasonable. Clinical experts advised that if both berotralstat and garadacimab were available, they would likely try berotralstat first because it is an effective oral treatment. The committee was aware that some people have difficulty swallowing tablets, so may prefer less-frequent self-injected medicines. The committee concluded that the company's proposed positioning of garadacimab and its comparators, which were determined by attack frequency, was appropriate. It also concluded that the EAG's exploration of second-line garadacimab after berotralstat, compared with no preventive treatment, was reasonable to consider.

Clinical effectiveness

VANGUARD trial

3.4 The clinical-effectiveness evidence for garadacimab is from VANGUARD. This is a phase 3, randomised, double-blind, placebo-controlled trial. It compared garadacimab (200 mg by subcutaneous injection, every 4 weeks) with placebo in 64 people 12 years and over with type 1 or 2 hereditary angioedema. Participants could not use any other preventive treatment during the trial. The intention-to-treat population was people who had 1 or more attack per month over the 6-month treatment period. The primary outcome was the time-normalised number of hereditary angioedema attacks during the 6-month treatment period. The committee

was aware that the trial was small and did not include people in the UK. The EAG noted the eligibility criteria of 3 or more attacks during the 3 months before screening, which was not specified in the NICE scope. The committee recalled that the company positioning of garadacimab was for people having more frequent attacks (2 or more per month). The clinical experts noted that there was no experience of using garadacimab in the UK. So, there was uncertainty about how it compared with other preventive treatments used in UK clinical practice. The committee concluded that the trial results were likely to be generalisable to people in the UK having recurrent attacks of hereditary angioedema. But this was associated with some uncertainty because people in the trial had a lower minimum frequency of attacks than those who might be eligible for garadacimab in UK clinical practice.

Clinical-effectiveness results

3.5 The mean age in VANGUARD was 41 years and almost 60% of participants had a history of laryngeal attacks. In the 3 months before screening, attacks most commonly occurred in the abdomen and extremities (hands, feet). The mean number of hereditary angioedema attacks during the 6-month treatment period was 0.3 per month with garadacimab compared with 2 per month with placebo. This was equivalent to an 86.5% reduction in mean number of attacks per month with garadacimab. During the trial, 61.5% in the garadacimab arm had freedom from attacks, compared with 0% in the placebo arm. Garadacimab reduced the mean number of moderate or severe hereditary angioedema attacks per month by 90% compared with placebo. The company reported a post-hoc analysis of longer-term effectiveness from pooled results of VANGUARD and an open-label phase 3 study. It noted that the efficacy of garadacimab in reducing the time-normalised number of attacks from baseline was maintained beyond the randomised 6-month treatment period of VANGUARD. There was also no evidence of waning of treatment effect after more than 2 years of treatment. It suggested this reduced the uncertainty associated with the relatively short treatment

period in VANGUARD. The committee noted that it would have liked to have seen results from a phase 3 trial that compared garadacimab with standard care treatments. It concluded that the clinical evidence suggested garadacimab was more effective than placebo at reducing the number of hereditary angioedema attacks.

Indirect treatment comparison

3.6 There is a lack of direct evidence comparing garadacimab with berotralstat, C1-INHs or lanadelumab. So, the company did indirect treatment comparisons. Its preferred approach was a fixed-effect network meta-analysis (NMA) of trials in people aged 12 years and over with hereditary angioedema. 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). The company considered the treatment effect estimates produced by the NMA to be confidential so they cannot be reported here. The committee noted that it had reviewed the NMA results, which were presented for several hereditary angioedema efficacy outcomes and for adverse events. It noted that time-normalised number of attacks was the key efficacy outcome used in the company's model (see section 3.7). It was also aware of a similar fixed-effect NMA that included the phase 2 and phase 3 trials of garadacimab that was published by Walsh et al. (2025). This stated that, overall, garadacimab was ranked as the most effective treatment among all comparators assessed, with lanadelumab every 2 weeks or subcutaneous C1-INH ranked second. The committee concluded that the treatment effect estimates provided in the company's fixed-effect NMA of phase 3 trials were suitable for decision making. It also concluded that, based on these analyses, garadacimab is clinically effective compared with berotralstat, C1-INHs or lanadelumab.

Economic model

Company's overall model structure

3.7 The company submitted a cohort-based Markov model. It had 3 primary health states (alive with an attack, alive without an attack, and dead) with 6 tunnel states (see section 3.8). Hereditary angioedema attack severity could be mild, moderate, severe non-laryngeal or severe laryngeal. The company explained that severe non-laryngeal or laryngeal attacks were modelled separately because of differences in resource use. Cycle length was 28 days without half-cycle correction and the model had a lifetime horizon (60 years). For each treatment in the model, the rate ratio of time-normalised number of hereditary angioedema attacks from the indirect treatment comparison was applied to the mean number of attacks per month from the VANGUARD placebo arm. This modelled the number of attacks per cycle for each treatment. Background mortality for use within the economic model was based on UK life tables from the Office of National Statistics (2024). Disease-specific mortality was not considered for garadacimab or comparators in the model. Both costs and outcomes were discounted at 3.5% annually, as per the NICE reference case. The EAG agreed with the company's overall approach, except for the tunnel states (see section 3.8). The committee concluded that the company's overall model structure with 3 primary health states was acceptable for decision making.

Tunnel states

3.8 The company's model health state 'alive without an attack' included 6 tunnel states. These included people who had not had an attack in successive cycles and tracked the amount of time since the previous hereditary angioedema attack. The tunnel states captured improvement in quality of life over this period as well as resource use. The EAG noted that adding tunnel states was the main difference between the company's model and previous models evaluated in NICE's technology appraisal guidance on lanadelumab for preventing recurrent attacks of hereditary

angioedema (from here TA606) and TA738. The company suggested at technical engagement that using tunnel states was justified. This is because attack freedom is a key concern for people with hereditary angioedema, given the spontaneous, unpredictable and debilitating nature of the condition. It added that evidence from garadacimab trials, including VANGUARD, confirmed the relationship between quality of life and time since last attack. The EAG noted that in VANGUARD, the most significant impact on health-related quality of life occurred within the first month of treatment. So, tunnel states are unlikely to be needed to capture health-related quality-of-life improvements after an attack (see section 3.13). The committee noted that the company's use of tunnel states was a different approach from those used in previous technology appraisals.

Berotralstat's longer-term effectiveness and stopping rule

3.9 In UK clinical practice, berotralstat is stopped if the number of hereditary angioedema attacks is not reduced by at least 50% after 3 months from starting treatment. Clinical experts advised that the berotralstat stopping rule is applied in clinical practice but added that there may not be another preventive treatment that can be offered afterwards. The committee noted that the berotralstat stopping rule was not implemented in the ApeX trials. Also, data from TA738 on the impact of the stopping rule on berotralstat's effectiveness was considered confidential by the company that makes berotralstat. So, the company needed to make assumptions about what the efficacy (average attack rate) would be in people continuing berotralstat after 3 months (such as those whose hereditary angioedema responded to berotralstat treatment).

In its original submission, the company extrapolated the NMA data for the average attack rate up to month 3 to those remaining on berotralstat after month 3. The EAG explained that because this approach used data on what would be response and non-response to berotralstat in clinical practice, berotralstat efficacy was being underestimated in the longer term. The EAG preferred a different approach, which was to assume that

after month 3, berotralstat had the same efficacy as lanadelumab dosed every 2 weeks. The EAG explained that its preferred approach was based on clinical expert advice that hereditary angioedema that responded to berotralstat can continue to respond very well. In response to clarification questions, the company also provided a scenario based on real-world evidence on long-term use of berotralstat, presented in a poster by Elbashir et al. (2024; see section 3.10). At technical engagement, the company disagreed with the EAG's preferred approach of using lanadelumab efficacy as a proxy for berotralstat. It argued this was based on weak evidence of clinical expert opinion and was not justified given the higher likelihood of attack freedom seen in lanadelumab studies compared with berotralstat studies. Clinical experts noted that it was difficult to compare lanadelumab and berotralstat efficacy because they were used in different populations characterised by different frequency of attacks. They reiterated that there was no 'one-size-fits-all' approach for treating hereditary angioedema. Some people find their condition responds very well to 1 treatment, but not all treatments work for everyone. The committee decided that the lack of longer-term data on berotralstat, including around the stopping rule, introduced high uncertainty into the modelling of berotralstat's longer-term effectiveness.

Evidence for modelling berotralstat's longer-term effectiveness

3.10 At technical engagement, the company updated its approach to modelling berotralstat's longer-term effectiveness (see section 3.9). This used real-world evidence on clinical effectiveness and patient-reported outcomes from a clinical audit of long-term preventive use (up to 24 months) of berotralstat (Elbashir et al. 2024; poster presentation). The company noted that the study included 18 UK immunology centres and included a more people (n=164) than the pivotal phase 3 trial of berotralstat. The company used this evidence to estimate the proportion of study participants whose hereditary angioedema responded to berotralstat and could continue treatment. It then used the average attack rate in these participants between month 12 and 24 and applied it after month 3 to

people continuing berotralstat in the model. The EAG emphasised that it recognised the difficulties faced by the company in not having access to effectiveness data on response to berotralstat. The company and EAG both contacted the Elbashir et al. study authors to understand the data better. On balance, the EAG thought that the limitations with the small amount of data available in the Elbashir et al. poster were too great to use it in its base case. The limitations included that:

- little information was provided on the study methods
- the population or subpopulation included in figures showing key data were unclear
- some people in the study started berotralstat before the stopping rule was introduced, so the study was likely to underestimate berotralstat efficacy
- treatment stopping occurred for mixed reasons (stopping rule and other reasons) and there was a lack of information on its timing.

The committee noted that the design of the Elbashir et al. study was not well aligned with the way the company used the data. The company stated that the Elbashir et al. study was the best available source on berotralstat responder efficacy, because it had a large sample size and was specific to NHS clinical practice. It explained that most of the study participants started berotralstat after the stopping rule was introduced. 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. The EAG maintained its approach, which assumed that after month 3 berotralstat had the same efficacy as lanadelumab dosed every 2 weeks (see section 3.9).

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. They noted that this differed from a typical peak response to lanadelumab, which was seen within approximately 74 days (Dorr et al. 2021). The clinical expert said that further details of the Elbashir et al. study would be published soon but were not available for committee consideration at the first meeting. The EAG noted that the modelled hereditary angioedema attack rate had a large impact on the cost-effectiveness estimate for garadacimab compared with berotralstat. 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). Taking into account evidence from the company, EAG and clinical experts at the meeting, the committee decided that it was not appropriate to assume berotralstat had the same efficacy as lanadelumab (EAG base case). It also decided that the limited data from the Elbashir et al. study could be used in the modelling. This is because it was from the largest real-world study of berotralstat in the UK. It noted that the EAG's scenario implementation of the data was supported by a clinical expert who had worked on the Elbashir et al. study. So, it concluded that it preferred the EAG's scenario based on the Elbashir et al. poster for modelling berotralstat long-term effectiveness and stopping. It also concluded this approach was highly uncertain.

Lanadelumab dose switching

3.11 The committee noted that the starting dose for lanadelumab is 300 mg every 2 weeks. This can be reduced to every 4 weeks in people whose condition is stable and attack free, especially those with low body weight. In TA606 it was assumed that 77% of people taking lanadelumab

switched to every 4 weeks dosing after 1 year. In the company and EAG's preferred model it was assumed that 45% of people having lanadelumab switched to every 4 weeks dosing based on Dorr et al. (2021). The company assumed that dose switching from every 2 weeks to every 4 weeks occurred linearly across cycles over a 12-month period. To estimate the effectiveness of lanadelumab every 4 weeks, the company used the 3-arm HELP-03 trial, which included an arm in which people started lanadelumab at a dosage of 300 mg every 4 weeks. The EAG disagreed that switching to every 4 weeks dosing would be gradual and instead preferred to assume it occurred instantaneously at 12 months. This was based on a real-world study in Germany by Magerl et al. (2024). The EAG also preferred to assume equal efficacy of lanadelumab every 4 weeks and lanadelumab every 2 weeks. It advised that this seemed to be a reasonable assumption because dose switching would occur in people whose condition was stable and attack free and overall this stability and attack freedom would continue with less-frequent dosing. The committee noted that the company's approach likely underestimated lanadelumab efficacy. This was because it assumed the level of response is lower for lanadelumab every 4 weeks than lanadelumab every 2 weeks. So, by then also assuming switching was gradual, and started earlier, this benefitted the garadacimab arm in the model. The committee concluded it preferred the EAG's assumptions for lanadelumab dose switching.

Utility values

Patient utilities for having an attack

3.12 The company used Nordenfelt et al. (2014), a Swedish registry study to estimate the impact of hereditary angioedema attacks on health-related quality of life. The committee noted this was the same source as used in TA738 (berotralstat) and TA606 (lanadelumab). This provided utility values for an attack and for being attack free based on EQ-5D-5L data. The utility value in the attack health state was derived from the baseline utility value (calculated by an equation in Nordenfelt et al. 2014) minus the

hereditary angioedema attacks disutility (and other technology-specific disutilities). 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. The EAG report stated that attacks in the previous year was perhaps the more logical interpretation of the wording in the paper and assumed this in its original base case. It noted that the company had assumed it was attacks in the previous 28 days. So the EAG had initially disagreed with the company about how attack disutility was calculated. But, 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. 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. The committee decided it had not seen these disutility values and would like to see further explanation and justification of the company's and EAG's preferred approaches for the second committee meeting.

The company assumed the impact of an attack on health-related quality of life lasted 3.13 days (Lumry et al. 2010). The company suggested that the impact of an attack should capture both physical and psychological acute effects. The committee recalled that patient and clinical experts explained that it can take up to a week to recover from the effects of an attack (see section 3.1). The EAG preferred to use a shorter duration of health-related quality-of-life impact for an attack, which was the same as the duration of an attack in VANGUARD. The attack duration cannot be reported here because the company considers it to be confidential. The committee decided that it preferred that company's assumption that the impact lasted on average 3.13 days. It concluded that it would like to see further explanation and justification of the company's and EAG's preferred approaches for calculating attack disutility for the second committee

meeting. It also concluded that impact of an attack should last 3.13 days (as assumed by the company).

Patient utilities for being attack free

3.13 The EAG noted that the company's modelling assumed that health-related quality of life was dependent on time spent attack free, as well as the direct impact of attacks on health-related quality of life. This is because freedom from attacks is stipulated in hereditary angioedema treatment guidelines. The EAG explained that in the company's 6-cycle tunnel states (see section 3.8), for each cycle a person remained attack free, they had a 0.031 utility gain compared with the previous attack-free cycle. In the company model, the value of the individual tunnel state (see section 3.8) was a function of linear progression from the baseline utility value (based on Nordenfelt et al. 2014 [see section 3.12]) to the upper utility estimate value. People who remained attack free for all 6 cycles reached the maximum utility, which was the same as full health for the general population. 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. The EAG preferred to assume that the benefit from attack freedom would be incurred within the first month after an attack through the application of the Nordenfelt et al. (2014) equation (without tunnel states). It noted that both company's and EAG's clinical experts disagreed with the company's assumption that quality of life would return to that of the general population. This is because of the lingering fear or anticipatory anxiety about the next attack. Patient and clinical experts in the meeting noted that anticipatory anxiety and mental health effects were important considerations for the health-related quality of life of people with hereditary angioedema.

The committee noted that the company's approach using tunnel states implied there was a cycle-by-cycle linear relationship between time spent attack free and improvement in health-related quality of life. It was unsure that the improvement would be linear, particularly because there was so

much individual variation in the impact of the condition. Patient and clinical experts advised that long periods of time being attack free would lead to large improvements in health-related quality of life. Clinical experts explained that even after being attack free for 6 months, a breakthrough attack (see section 3.1) would lead to a large reduction in health-related quality of life. It would also cause a loss of all attack-free utility. They added that improvement in attack severity is also important, although this was not compared between treatments in the model. 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 in the EAG model accrued a utility value close to the general population.

The committee decided that there was uncertainty associated with the company's use of tunnel states for estimating attack-free utility. This included potential double counting of the impact of attacks on health-related quality of life and the implied linear relationship between time spent attack free and improvement in health-related quality of life. It also did not accept the company's assumption that being attack free for 6 months led to a utility value that was the same as full health for 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. It was satisfied the EAG's overall approach captured a health-related quality-of-life benefit for having freedom from attacks. It concluded that the EAG's approach to modelling utility for being attack free (without using tunnel states) should be used in decision making.

Carer utilities

3.14 The committee understood that hereditary angioedema could affect more than 1 person in a family, such as a parent and their child. It noted that the caring role could swap between family members depending on who was having an attack. The company included a disutility for carers of people

with recurrent attacks of hereditary angioedema in the model. The company estimated 1.46 carers per household. This could not be verified by the EAG, so it applied 1 carer per household in its base case. The company estimated carer disutility for each attack using carer utilities reported by Lo et al. (2022), which were based on vignettes specifically designed to describe the hereditary angioedema context. The EAG noted that this did not align with the NICE reference case. Also, it was uncertain whether these vignettes might be too sensitive to hereditary angioedema, potentially leading to an overestimation of the disutility associated with the condition. 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. The EAG identified a study by Pennington et al. (2024), which used the SF-6D to measure utilities from the UK Household Longitudinal Study. It estimated carer disutility to be 0.0123 for every 0.1 patient disutility in its base case. The committee decided that it was reasonable for carer disutility to be included in the model. But this was likely to be overestimated using the company's approach. The committee concluded that it preferred the EAG's approach for including carer utilities in the model, including assuming 1 carer per household.

Severity

3.15 NICE's methods for conditions with a high degree of severity did not apply to this evaluation.

Cost-effectiveness estimates

Committees preferred assumptions

3.16 The committee concluded that the cost-effectiveness modelling for garadacimab compared with standard care preventive treatments was uncertain (see section 3.17). It agreed with the company's overall model structure for decision making (see section 3.7) but not the company's use of tunnel states for estimating health-related quality of life (see section 3.8

and section 3.13). The committee was also able to determine some preferred assumptions, which were:

- the EAG's scenario based on the Elbashir et al. (2014) poster for modelling berotralstat long-term effectiveness and stopping (see section 3.10), although this was highly uncertain
- the EAG's modelling of lanadelumab dose switching (see section 3.11)
- the EAG's modelling of patient utility without using tunnel states, but that the duration of health-related quality-of-life impact of an attack should be the company's preferred 3.13 days (see sections 3.12 and section 3.13), but it asked the company and EAG to provide more information on the attack disutility values that they assumed
- the EAG's approach for including carer utilities in the model, including assuming 1 carer per household (see section 3.14).

Acceptable incremental cost-effectiveness ratio

3.17 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- there was no evidence from trials directly comparing garadacimab with berotralstat, C1-INHs or lanadelumab (see section 3.6)
- in the assumptions that needed to be made about berotralstat longer-term effectiveness and stopping treatment, in relation to the stopping rule applied in NHS clinical practice (see sections 3.9 and section 3.10)
- in the assumptions that needed to be made about lanadelumab dose switching (see section 3.11)

- in patient utilities (see sections 3.12 and section 3.13).

The committee also recognised:

- the difficulties in evidence generation for hereditary angioedema because it is a rare disease
- the unmet need, particularly for people with an attack frequency below eligibility criteria for lanadelumab.

The committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Cost-effectiveness estimates

3.18 Because of confidential commercial arrangements for garadacimab, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. Taking account of all these confidential discounts, the results showed:

- For the comparison with berotralstat for people having 2 or more attacks per month, the company's deterministic base-case ICER for garadacimab was at the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The EAG's deterministic base-case ICER for garadacimab was substantially higher than £30,000 per QALY gained. The committee's preferred assumptions (see section 3.16) also resulted in a plausible ICER for garadacimab that was substantially higher than £30,000 per QALY gained. The EAG provided a scenario in which attack disutility was calculated based on 'attacks in the past cycle' being 'attacks in the previous year' (see section 3.12). But, with the committee's preferred assumptions, assuming 'attacks in the past cycle' were either attacks in the previous 28 days or the previous year, the ICER was substantially above £30,000 per QALY gained.

- For the comparison with 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.

The committee recalled the company's preferred positioning of garadacimab as an option for people having 2 or more attacks per month. The committee agreed that it was appropriate to consider the clinical and cost effectiveness of garadacimab in this broad population and the unmet need among people ineligible for C1-INHs or lanadelumab. But, the plausible ICERs for this population were substantially higher than what is normally considered a cost-effective use of resources. So, the committee concluded that garadacimab could not be recommended for routine use for preventing recurrent attacks of hereditary angioedema in people 12 years and over.

Other factors

Equality

3.19 The committee was aware that young people have less access to long-term preventive treatments for recurrent hereditary angioedema than adults in NHS clinical practice. It noted 2 reasons for this from the access criteria (see section 3.2):

- Age: berotralstat is only available to people 12 years and over.
- Attack frequency: 2 or more attacks per month (berotralstat) or 2 or more attacks per week (C1-INHs and lanadelumab). Young people tend to have a lower attack frequency than adults, and this may be below access criteria, but they are significantly affected by the condition.

The committee noted that age is protected characteristic under the

Equality Act 2010. It added that the marketing authorisation for garadacimab is in people 12 years and over and any recommendation by NICE must be within the marketing authorisation. The committee was also aware that some religious groups may be unwilling to have blood product-derived treatments, such as C1-INHs. It noted that religion is a protected characteristic under the Equality Act 2010. It also noted that both garadacimab and lanadelumab are alternatives to C1-INHs that are not derived from human plasma. The committee agreed that any recommendation would apply equally to all people regardless of protected characteristics.

Uncaptured benefits

3.20 The committee considered whether there were any uncaptured benefits of garadacimab. It 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.

Conclusion

Recommendation

3.21 The committee acknowledged there was an unmet need for long-term preventive treatments for recurrent attacks of hereditary angioedema. It noted that this included people having fewer than 2 attacks per week who are not eligible to have C1-INHs or lanadelumab. It also noted that the most plausible ICER was considerably above the range normally considered a cost-effective use of NHS resources. So, the committee did not recommend garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical, a project manager and an associate director.

Catherine Spanswick

Technical lead

Eleanor Donegan

Technical adviser

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Project manager

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Associate director

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