National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	CSL Behring	CSL Behring believes that the evaluation of garadacimab by NICE for the routine prevention of recurrent attacks of hereditary angioedema (HAE) is appropriate due to the current unmet need for convenient and well tolerated long-term prophylaxis (LTP) options that demonstrate early and sustained efficacy in reducing the frequency and severity of attacks. Garadacimab has a novel mechanism of action which inhibits Factor XIIa, preventing the initiation of the HAE cascade and subsequently blocks the chain of events leading to an HAE attack.[1-3] CSL Behring agrees that garadacimab should be evaluated through the single technology appraisal (STA) route.	Comments noted. The committee will consider unmet need during the development of the appraisal. No action required.
	British Society for Allergy and Clinical Immunology	The evaluation and proposed evaluation route is appropriate.	Comment noted, no action required.

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	The Royal College of Pathologists	The evaluation and proposed evaluation route is appropriate.	Comment noted, no action required
Wording	CSL Behring	Considering our most current understanding of the anticipated marketing authorisation for garadacimab, CSL Behring requests that 'acute' be replaced with 'recurrent' so that the remit reads as the following: 'To appraise the clinical and cost effectiveness of garadacimab within its marketing authorisation for preventing recurrent attacks of HAE.' We believe that this revised remit is more aligned with the anticipated marketing authorisation for garadacimab and is the same as the remit of the scope used previously for technology appraisal (TA) 606 (lanadelumab for preventing recurrent attacks of hereditary angioedema). The suggested revised wording is also more aligned with the marketing authorisations and final recommendations for lanadelumab (TA606) and berotralstat (TA738).[4-7]	Comment noted. The draft remit has been amended.
	British Society for Allergy and Clinical Immunology	Yes, it does.	Comment noted, no action required.
	The Royal College of Pathologists	Yes, it does.	Comment noted, no action required.
Timing issues	CSL Behring	Given the substantial burden of HAE and limitations of current standard of care (SoC) discussed below, there is an urgent need for a convenient and well-tolerated prophylactic therapy that demonstrates early and sustained efficacy in reducing the frequency and severity of HAE attacks. This would	Comments noted. NICE aims to publish guidance as soon as possible after the

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		help more people living with HAE to achieve prolonged freedom from attacks, empowering them to feel more in control of their condition. While several treatments exist for HAE, it is presently an incurable disease and symptoms can persist throughout the affected person's lifetime.[8] LTP is a treatment strategy used for the routine prevention of recurrent HAE attacks. Historically, off-label use of attenuated androgens (e.g. danazol and oxandrolone) and antifibrinolytics (tranexamic acid) were considered standard of care (SoC) for the routine prevention of HAE attacks.[9-13] Since then, the availability of more tolerable and effective treatments has improved outcomes for people with HAE in England with the publication of the NHS England commissioning policy for plasma-derived C1-esterase inhibitors (C1-INHs) in 2016, and NICE recommendations for lanadelumab (2019) and berotralstat (2021).[5,6,14] However, there is room for further improvement in outcomes for people with HAE, including a greater reduction in attack frequency and severity, as well as prolonged freedom from attacks.[15] The safety and efficacy of garadacimab were demonstrated in a 6-month randomised, placebo-controlled, pivotal phase 3 trial (VANGUARD).2 Garadacimab has a fixed, once-monthly SC dosing schedule, which is well-tolerated and has been shown to reduce the mean overall attack rate in patients with HAE by 87% (median >99%) and the mean number of moderate or severe attacks by 90% (median >99%) compared to placebo.2 Most patients treated with garadacimab (61.5%) were attack-free from the first dose and remained attack-free throughout the treatment period.[2] In addition, currently commissioned treatments are associated with the following limitations that can be addressed by garadacimab: C1-INHs (NHS England commissioning policy for plasma-derived C1-INHs, 2016)	company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. The committee will consider unmet need during the development of the appraisal. No action required.

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		• Only a small proportion of patients experience a sufficient number of attacks (≥2 per week) to be eligible for regular C1-INH.16 In a 2019 survey across 37 UK centres by Yong et al., just 8% of patients with HAE were treated with C1-INHs.[16] • Plasma-derived C1-INHs commissioned under this policy require intravenous (IV) administration twice weekly, which is inconvenient for patients.[14] • Lanadelumab (TA606, lanadelumab for preventing recurrent attacks of hereditary angioedema, 2019) • Only a small proportion of patients (8%) experience a sufficient number of attacks (≥2 per week) to be eligible for regular lanadelumab[16] • Lanadelumab requires frequent treatment administration (every 2 weeks)[7] • Berotralstat (TA738, berotralstat for preventing recurrent attacks of hereditary angioedema, 2021) • Patients treated with berotralstat may discontinue treatment due to established tolerability concerns and/or failure to meet the continuation rule.[4,6,11] • Berotralstat must be administered daily which can lead to adherence issues.[4,10] • In the current commissioning landscape for HAE, patients who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs are left with no licensed treatment options[5,6,14] As such, garadacimab should be made available as soon as possible following its marketing authorisation to offer people with HAE a new treatment	

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		option that has the potential to achieve a rapid reduction in attack frequency and severity as well as extended periods of attack freedom.[2] Garadacimab is administered subcutaneously, offering a more convenient mode of administration than IV C1-INHs.[2,17,18] Additionally, garadacimab requires only once monthly administration, providing a less frequent treatment schedule compared with C1-INHs, lanadelumab and berotralstat.[2,4,7,17,18] Garadacimab represents an alternative treatment option to berotralstat, lanadelumab and C1-INHs. It also has the potential to address an urgent treatment gap for patients who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs.	
	British Society for Allergy and Clinical Immunology	There are approved treatments for hereditary angioedema, although there remain unmet needs for this group of patients still, so this evaluation is important for this group of patients.	Comments noted. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. The committee will consider unmet need during the development of the appraisal. No action required.

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	The Royal College of Pathologists	There are approved treatments for hereditary angioedema, although there remain unmet needs for this group of patients still, so this evaluation is important for this group of patients.	Comment noted. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. The committee will consider unmet need during the development of the appraisal. No action required.
	HAE UK	There are patients who have tried Lanadelumab or Berotralstat for whom the side effects and/or long term efficacy have proven negative, ie side effects caused the patient severe additional issues alongside their attacks and the efficacy was not long term enough to make a life change	Comment noted. The committee will consider unmet need during the development of the appraisal. No action required.
	CSL Behring	N/A	No action required

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Additional comments on the draft remit	HAE UK	An alternative treatment for attacks is required against Lanadelumab and/or Berotralstat. Garadacimab is an 'easier to use' medication than other forms of C1 and therefore could be self administered by the patient.	Comment noted. The methods of administration will be discussed during the appraisal. It will also be discussed if all benefits of garadacimab were captured in the cost-effectiveness analyses. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	CSL Behring	CSL Behring broadly agrees with the background information provided and thanks NICE for summarising the substantial symptom burden associated with HAE attacks. However, for completeness, CSL Behring would like to expand on the burden of living with HAE both during and in between experiencing attacks. Specifically, HAE attacks are associated with disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety.[19,20] In addition, as a result of the unpredictable and frequent nature of recurrent HAE attacks, people with HAE can continue to experience persistent fear, anxiety and depression between attacks.[20,21] People with HAE also often modify their lifestyles to avoid potential triggers, which may interfere with activities of daily living such as driving, exercising, working or socialising, leading to heightened emotional distress.[21]	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated to include that HAE attacks are associated with disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety. More detailed information will be

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		In addition, the burden associated with HAE extends to caregivers and families of patients with the condition.[19] This includes an emotional burden of experiencing their loved ones having an attack and needing to be prepared to take the patient for on-demand treatment or administer the injection during an attack at any time.[19] Caregivers may also need to miss work to accompany their loved ones to the hospital during severe attacks.[19] Caregivers can also experience an ongoing burden in between attacks due to the psychological impact of the unpredictability of attacks which can generate fear, anxiety, uncertainty and isolation.[22] CSL Behring also suggests the following amendments to the background section for your consideration to improve the accuracy and completeness of the disease description: • The draft scope indicates that 'most angioedema attacks are associated with trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors.' CSL Behring would like to clarify that, to the best of their knowledge, most attacks are spontaneous and are not prompted by triggers.[11] As such, CSL Behring would like to request that that wording is amended to reflect this and suggests that the following wording may be more accurate: 'Most attacks are spontaneous and not prompted by triggers,[11] although in some cases HAE attacks can be associated with a variety of conditions and events, including emotional stress, local trauma (whether accidental or associated with dental, medical or surgical procedures) and infections.[8,11,23]' • While the draft scope accurately indicates that HAE is estimated to affect between 1:50,000 to 1:100,000 people, these are based on global estimates. CSL Behring considers that the best published estimate of the epidemiology of HAE in England comes from a 2019 survey in the UK (37 centres, N=1,152 patients with HAE-1/2) by Yong	explored at the submission stage. The scope has been updated to remove the statement that suggests most angioedema attacks are associated with known triggers. The scope has been updated with the prevalence estimate from Yong et al. 2023. The scope has been updated with the additional wording form the NHS England clinical commissioning policy for the prophylactic use of C1-INHs. NICE acknowledges Ruconest and antifibrinolytics may not be used as often as other treatments, however these can still be used as prophylactic treatments so have

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		et al. 2023, which estimated the minimum prevalence of HAE-1/2 to be 1:59,000.[16] • The draft scope states that 'HAE usually presents in childhood, with the mean age of onset being between 8 and 12 years', which was based on the NHS England clinical commissioning policy for the prophylactic use of C1-INHs.[14] CSL Behring would like to note that this clinical commissioning policy further states that 'attacks rarely occur before two years of age and are less frequent before adolescence' and requests that this be included in the background section of the draft scope for completeness. This addition would also more closely align with the final scopes of TA606 (lanadelumab) and TA738 (berotralstat), which stated that 'most cases develop in childhood and some cases develop in early adulthood. HAE usually occurs during the first 10 to 20 years of life.' In addition, although CSL Behring agrees that C1-INHs are used as LTP, Ruconest is broadly used for the acute treatment of HAE attacks and is not commissioned by NHS England for use as a LTP therapy.[12,14,24] This has also been established in previous appraisals (TA606 and TA838).[5,6] As such, CSL Behring suggests removing Ruconest from the disease background section. Further, it is important to note that antifibrinolytics are no longer considered as a treatment of choice for LTP in HAE due to concerns regarding its limited efficacy, as discussed in TA606 and TA738.[5,6] For completeness, CSL Behring would request that mention of antifibrinolytics is either removed from the background section or further information is provided to contextualise its use. Please also see our comments on comparators below for more detail on reasons why CSL Behring strongly believes that Ruconest and antifibrinolytics are not appropriate for inclusion in the draft scope.	been included in the scope.

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		In the interests of full transparency, CSL Behring would like to clarify that the phase 3b open-label extension study (CSL312_3002; NCT04739059) includes two patients with HAE type III who rolled over from the phase 2 CSL312_2001 study (NCT03712228). However, CSL Behring will not present evidence on this subtype separately in this submission as HAE type III is an extremely rare subtype and was not considered by previous appraisals in HAE (TA738 and TA606), which also focus on HAE types I and II.[5,6] Recommendations received from NICE as part of TA738 and TA606 permit treatment for HAE type III patients and are not restricted to types I and II.	
	British Society for Allergy and Clinical Immunology	It should be noted that peripheral swelling can be significantly disruptive, affecting work or schooling, and resulting in days off sick or missing school. Although angioedema attacks can be triggered by various different things, it is not accurate that most of them have a known trigger. They are very often random and unpredictable, as mentioned subsequently, and the unpredictability is a significant burden for patients. Type III HAE has been re-classified in the latest guidelines, and is old nomenclature – this is now known as HAE with normal C1 inhibitor, or HAE with one of the other recognised genetic mutations. Androgens (danazol, oxandrolone) are also used unlicensed for long-term prophylaxis, although associated with androgenic side effects. Although tranexamic acid is listed as an option for prophylaxis, this has very limited evidence for efficacy.	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated to include that HAE attacks are associated with disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety. More detailed information will be explored at the submission stage. The scope has been updated to remove the statement that suggests

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			most angioedema attacks are associated with known triggers. The scope has been updated to include the updated nomenclature for Type III HAE. The scope has been updated to state that attenuated androgens can be used for long-term prophylaxis.
	The Royal College of Pathologists	It should be noted that peripheral swelling can be significantly disruptive, affecting work or schooling, and resulting in days off sick or missing school. Although angioedema attacks can be triggered by various different things, it is not accurate that most of them have a known trigger. They are very often random and unpredictable, as mentioned subsequently, and the unpredictability is a significant burden for patients. Type III HAE has been re-classified in the latest guidelines, and is old nomenclature – this is now known as HAE with normal C1 inhibitor, or HAE with one of the other recognised genetic mutations. Androgens (danazol, oxandrolone) are also used unlicensed for long-term prophylaxis, although associated with androgenic side effects. Although tranexamic acid is listed as an option for prophylaxis, this has very limited evidence for efficacy.	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated to include that HAE attacks are associated with disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety. More detailed information will be

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			explored at the submission stage. The scope has been updated to remove the statement that suggests most angioedema attacks are associated with known triggers. The scope has been updated to include the updated nomenclature for Type III HAE. The scope has been updated to state that attenuated androgens can be used for long-term prophylaxis.
	HAE UK	In general accurate	Comment noted, no action required
Population	CSL Behring	CSL Behring agrees that the population described in the draft scope is appropriate.	Comment noted, no action required
	British Society for Allergy and	The population needs to specify which types of hereditary angioedema are included.	Comment noted.

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	Clinical Immunology		The population in the scope is intended to be broad to cover the final marketing authorisation. No action required.
	The Royal College of Pathologists	The population needs to specify which types of hereditary angioedema are included	Comment noted. The population in the scope is intended to be broad to cover the final marketing authorisation. No action required.
	HAE UK	The population is generally accepted as 1 in 30,000 to 1 in 50,000	Comment noted. This estimate has been updated in the scope with a UK-based estimate.
Subgroups	CSL Behring	Garadacimab is not anticipated to be clinically more effective in any subgroup. This is aligned with previous appraisals for HAE where clinical data and expert opinion indicated that there are no treatment effect modifiers for response to LTP (namely lanadelumab and berotralstat) in people with HAE.[5,6]	Comment noted, no action required
	HAE UK	A subgroup of people exist for whom Lanadelumab and Berotralstat do not produce results or that have intolerable side effects in some patients	Comment noted. If evidence allows the company can present subgroups in their submission for the

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			committee to consider. Committee will consider the relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual.
Comparators	CSL Behring	CSL Behring agrees that long-term preventative treatments are the only appropriate comparator for garadacimab, in line with its anticipated marketing authorisation. However, we request the following amendments to ensure the comparators are an accurate representation of current commissioning policies, NICE recommendations and established clinical practice, per Sections 2.2.12–13 and Sections 6.2.2–3 of the NICE manual: • Remove Ruconest • Remove antifibrinolytics • Specify IV Berinert to avoid confusion with SC Berinert, the latter of which is not routinely commissioned in the NHS Ruconest CSL Behring requests to remove Ruconest from the comparators for this appraisal as it is predominantly used for the acute treatment of HAE attacks, in line with its marketing authorisation.[24] Ruconest is reimbursed by NHS England solely for the acute treatment of HAE attacks.[12] Although plasma derived C1-INHs are commissioned by NHS England for the routine prevention of HAE attacks, this does not apply to Ruconest, as it is a recombinant antibody.[14] In addition to not being reimbursed or recommended as an LTP option for HAE, recent market share data obtained by CSL Behring in Q4 2023 showed that of [redacted] patients on LTP, [redacted] used Ruconest for the routine prevention of HAE attacks.[25] Therefore, as per Sections 2.2.12–13 and Sections 6.2.2–3 of the NICE manual,[26] Ruconest should not be considered a relevant comparator as there is no evidence to support	Comments noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice. No action required.

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		established use in NHS practice and it is not recommended by NICE or commissioned by NHS England for the routine prevention of HAE attacks. Antifibrinolytics Antifibrinolytics are not a relevant comparator for this appraisal and should not be included in the scope.[5,6] Historically, off-label use of antifibrinolytics (mostly tranexamic acid) was considered part of the standard of care for long-term prophylaxis in HAE.[9] Since then, the availability of licensed and effective treatments in England has improved with the launch of the NHS England commissioning policy for plasma-derived C1-INHs in 2016, and NICE recommendations for lanadelumab (2019) and berotralstat (2021).[5,6,14] There are efficacy concerns associated with tranexamic acid as a preventative treatment for HAE, with a systematic review by Horiuchi et al. 2018 (N=103) concluding that while prophylactic TXA may be more beneficial than no treatment, newer and more effective therapies should be used when available.[27] This is in line with internationally recognised guidelines (The International/Canadian Hereditary Angioedema Guideline 2019 and International WAO/EAACI guideline for the management of hereditary angioedema 2021), which no longer recommend antifibrinolytics as standard of care due to limited supportive evidence and the availability of newer therapies.[9,11] Further, current market share data validates the limited use of antifibrinolytics for LTP in England, indicating that [redacted]% of HAE patients receiving LTP were treated with tranexamic acid in Q4 2023.25 In contrast, in a 2019 UK survey by Yong et al., an estimated 18% of patients with HAE on LTP were treated with tranexamic acid. This suggests that following the availability of newer LTP options such as berotralstat and lanadelumab, there has been a drastic reduction in the use of antifibrinolytics in the UK, in line with recommendations from international guidelines.[9,11,16] CSL Behring sought feedback from three clinical experts on the use of antifibrinolytics for LTP in HAE. They confirmed that antifibrinolytics are no longer commonly prescribed for the routine prevention of HAE attacks due to their ineffectiveness but may	

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		still be used in specific patient groups who have no alternative treatment options, such as children <12 years old. Therefore, as per Sections 2.2.12–13 and Sections 6.2.2–3 of the NICE manual,[26] tranexamic acid should not be considered a relevant comparator as there is no evidence to support established use in current NHS practice in the population of interest. This is also aligned with TA606 and TA738 where the committee agreed that tranexamic acid was not a relevant comparator during the appraisal process.[5,6] Berinert CSL Behring would like to point out that Berinert is available in both IV and subcutaneous (SC) administration modes. Although used off-label, the IV formulation of Berinert (IV Berinert) is routinely prescribed in UK clinical practice for the prevention of recurrent HAE attacks in patients experiencing ≥2 attacks per week.[14,28] However, SC Berinert is not routinely used in UK practice for the prevention of recurrent HAE attacks, despite being licensed for this use.[14,18] This is reflected in the market share data, which indicates very limited use of SC Berinert in clinical practice, with [redacted]% of patients on LTP in the UK using SC Berinert in Q4 2023.[25] Feedback from the three clinical experts contacted by CSL Behring was that SC Berinert would only be considered in special circumstances such as if a patient fails treatment on lanadelumab and/or has poor venous access (e.g. during pregnancy). Therefore, as per Sections 2.2.12–13 and Sections 6.2.2–3 of the NICE manual,[26] SC Berinert should not be considered a relevant comparator as its use is not established in NHS practice and it is not recommended by NICE or commissioned by NHS England for the routine prevention of HAE attacks. As such, CSL Behring wish to stress the importance of specifying 'IV Berinert' in the draft scope for clarity. In summary, CSL Behring considers the only relevant comparators for this appraisal to be lanadelumab, berotralstat and plasma-derived intravenous (IV) C1-INHs (specifically IV Berinert and Cinryze). As previously discussed in	

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		the subgroups section, these relevant comparators in the NHS are restricted to subpopulations based on the frequency of HAE attacks. C1-INHs and lanadelumab are recommended for those experiencing ≥2 HAE attacks per week,[5,14] while berotralstat is recommended for use in those experiencing ≥2 HAE attacks per month.[6]	
	British Society for Allergy and Clinical Immunology	Attenuated androgens (unlicensed, off-label) is still used as prophylaxis in some patients, although it is now less straightforward to access	Comment noted. The scope has been updated to include attenuated androgens as a potential comparator.
	The Royal College of Pathologists	Attenuated androgens (unlicensed, off-label) is still used as prophylaxis in some patients, although it is now less straightforward to access.	Comment noted. The scope has been updated to include attenuated androgens as a potential comparator.
	HAE UK	Unable to clinically comment	No action required
	Takeda	Attenuated androgens continue to be a routinely used long-term prophylactic agent in the UK and should be considered as a comparator. Yong *et al* reports on data from 2019, where 55% of patients taking long-term prophylaxis took androgens alone and 6% took androgens and tranexamic acid combined.[1] A recent interim analysis from 2024 of a Takeda UK-sponsored real world evidence study showed that 28.9% (11/38) of an adult HAE population in the UK using long-term prophylaxis were taking	Comment noted. The scope has been updated to include attenuated androgens as a potential comparator.

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		androgens, making them the most widely used long-term prophylactic agent in the UK in this dataset (n = 85).[2] 1. Yong, P.F.K. et al. (2023) 'A national survey of hereditary angioedema and acquired C1 inhibitor deficiency in the United Kingdom', The Journal of Allergy and Clinical Immunology: In Practice, 11(8), pp. 2476–2483. 2. Takeda data on file 2024.	
Outcomes	CSL Behring	CSL Behring agrees that the outcomes listed in the draft scope are appropriate and generally aligned with those assessed in the key trials. CSL Behring would like to also confirm that we will provide the following additional outcomes that we believe are important to inform decision-making: • Attack-free period • Time to first attack	Comments noted. The scope has been updated to include attack-free period and time to first attack as outcomes.
	British Society for Allergy and Clinical Immunology	Yes, outcomes are appropriate. Carer disutility should be considered as well if possible.	Comments noted. Carer health-related quality of life has been added as an outcome to the scope.
	The Royal College of Pathologists	Yes, outcomes are appropriate. Carer disutility should be considered as well if possible.	Comments noted Carer health-related quality of life has been added as an outcome to the scope.
	HAE UK	Mental health and wellbeing significantly improved over administration of difficult and painful IV alternative medications	Comment noted.

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			The methods of administration will be discussed during the appraisal. It will also be discussed if all benefits of garadacimab were captured in the cost-effectiveness analyses. No action required.
	Takeda	The outcomes listed are appropriate; additionally, frequency and duration of hospitalisation and rate of treatment failure should be considered to capture important health-related impacts of this technology. Regular monitoring of patients is important and highlighted in treatment guidelines to ensure outcomes are effectively understood.[1] **1. Maurer, M. et al. (2022) 'The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update', World Allergy Organization Journal, 15(3), p. 100627.**	Comments noted. The key outcomes relevant to the population are outlined in the scope but this is not an exhaustive list. Where relevant, the company and consultees are welcome to provide the evidence on all outcomes that are important for people with the condition during the evaluation. No action required.

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Equality	CSL Behring	CSL Behring does not believe that the draft remit or scope will exclude people protected by equality legislation. We would like to highlight that the currently available IV C1-INHs included in the scope that are used for LTP (Cinryze and Berinert) are derived from human plasma, with which some religious groups may be unwilling to be treated. As such, consideration should be given to treatment options available for people who are unwilling to receive human products, to ensure that any recommendations do not directly or indirectly discriminate based on religion. Garadacimab is a recombinant antibody, meaning it is produced using recombinant DNA technology and not directly extracted from human serum or plasma.	Comment noted. We have noted your comments on the equality impact assessment (EIA) form. No changes required to the scope.
	HAE UK	The only possible inequality that would exist is the availability within individual NHS Trusts to prescribe this medication	Comment noted. We have noted your comments on the equality impact assessment (EIA) form. No changes required to the scope.
Other considerations	CSL Behring	N/A	-
Questions for consultation	CSL Behring	**Where do you consider garadacimab will fit into the existing care pathway for the prevention of acute attacks of hereditary angioedema?** The proposed positioning of garadacimab is for patients aged 12 years and older who are eligible for routine prevention of recurrent attacks of HAE. This effectively positions garadacimab in line with the current standard of care for	Comments noted. The positioning of the technology in the treatment pathway will be considered by the

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		the routine prevention of HAE attacks (berotralstat [for those with ≥2 HAE attacks per month] and lanadelumab and C1-esterase inhibitors [for those with ≥2 attacks per week]). **Please select from the following, will garadacimab be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Garadacimab will be prescribed in secondary care with routine follow-up in secondary care. **NICE understands danazol has now been discontinued in the UK. Are attenuated androgens still used for preventing HAE attacks in NHS clinical practice?** Historically, off-label use of attenuated androgens was considered part of the standard of care for long-term prophylaxis in HAE.[9,11] Since then, the availability of licensed and effective treatments in England has improved with the launch of the NHS England commissioning policy for plasma-derived C1-INHs in 2016, and NICE recommendations for lanadelumab (TA606) and berotralstat (TA738).[5,6,14] Androgens have a well-established history of safety and tolerability concerns associated with long-term use, as described in a systematic review by Riedl et al. 2015, leading to high discontinuation rates.[29] Androgen use in the NHS is further complicated by supply issues.[5] As such, treatment with androgens is	committee during the appraisal. NICE has received feedback during consultation that attenuated androgens are still used as long-term prophylaxis in some patients. Because the list of comparators is intended to be broad, attenuated androgens have been added as a potential comparator. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice.

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		no longer recommended for patients newly starting on routine prophylaxis due to limited supporting evidence, safety concerns and difficulty in accessing treatment.[6,11] Based on market share data from [redacted] patients with HAE on LTP in the UK in Q4 2023, [redacted]% were treated with ondraxolone and [redacted]% with danazol, suggesting approximately [redacted]% of patients on LTP are treated with attenuated androgens.[25] In contrast, in a 2019 UK national survey by Yong et al., an estimated 55% of patients with HAE on LTP were treated with androgens.[16] This suggests that following the availability of newer LTP options such as berotralstat and lanadelumab, there has been a steep decline in the use of attenuated androgens for LTP in HAE in the UK, in line with current guideline recommendations, which may further reduce following the recent discontinuation of danazol.[9,11,16] CSL Behring sought feedback from three clinical experts on the use of antifibrinolytics for LTP in HAE, who confirmed that the overall use of androgens is expected to be lower than historically due to the availability of modern LTP agents. They noted that patients who continue to use androgens are typically those who have been on them historically and are satisfied with their treatment but most new patients are now offered berotralstat as a first-line treatment if they do not qualify for lanadelumab or C1-INHs. It is also important to note that in TA606 and TA738, the committee agreed that attenuated androgens were not a relevant comparator during the appraisal process.[5,6] **Are there any subgroups of people in whom garadacimab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As described above, garadacimab is not anticipated to be clinically more effective in any subgroup. However, to inform comparisons of garadacimab with current SoC that are reflective of the commissioning landscape for HAE	If evidence allows the company can present subgroups in their submission for the committee to consider. Committee will consider the relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual. During the appraisal, it will be discussed if all benefits of garadacimab were captured in the cost-effectiveness analyses. No action required.

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		in the NHS, CSL Behring will present the post-hoc subgroup analyses in patients experiencing ≥2 HAE attacks per month and ≥8 HAE attacks per month (approximating ≥2 HAE attacks per week). **Would garadacimab be a candidate for managed access?** CSL Behring does not believe that garadacimab would be suitable for managed access. While the CSL312_3002 open-label extension study is currently ongoing, CSL Behring would like to clarify that the efficacy of garadacimab has already been demonstrated in the pivotal VANGUARD trial. The ongoing open-label extension study will collect further data on the maintenance of the efficacy and safety profile and immunogenicity of garadacimab but is anticipated to provide limited additional evidence that would reduce any uncertainties in the clinical- or cost-effectiveness case. Additionally, CSL Behring would like to highlight that there is no precedence for the use of managed access agreements in comparator HAE treatments. **Do you consider that the use of garadacimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Garadacimab has the potential to offer patients a rapid reduction in the frequency of HAE attacks and prolonged freedom from attacks, thereby alleviating the burden of HAE attacks and the psychological impact associated with their unpredictability for people with HAE and their caregivers. Although QALYs will be used to quantify the estimated overall impact of HAE attacks on patient HRQoL, the true impact of HAE on daily living, absenteeism and mental health of people living with HAE and their caregivers cannot be fully captured in the QALY calculation. In particular, the health-related quality of life (HRQoL) burden of HAE on caregivers can	

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		contribute to absenteeism and impact mental wellbeing, which should be taken into consideration in addition to cost-effectiveness estimates when evaluating the holistic benefits of garadacimab.	
	British Society for Allergy and Clinical Immunology	Garadacimab should fit into the existing pathway where other NICE TA medications sit i.e. prescribed within specialised immunology services and routine follow-up by the same service. Attenuated androgens are still used for prevention of HAE attacks in NHS clinical practice, mainly in previously treated patients, although this needs to be specially imported as it is off-label and unlicensed. Garadacimab may be a candidate for managed access.	Comments noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. The scope has been updated to include attenuated androgens as a potential comparator.
	The Royal College of Pathologists	Garadacimab should fit into the existing pathway where other NICE TA medications sit i.e. prescribed within specialised immunology services and routine follow-up by the same service. Attenuated androgens are still used for prevention of HAE attacks in NHS clinical practice, mainly in previously treated patients, although this needs to be specially imported as it is off-label and unlicensed. Garadacimab may be a candidate for managed access.	The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. The scope has been updated to include attenuated androgens

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			as a potential comparator.
Additional comments on the draft scope		-	-

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Genetic Alliance UK

Neonatal and Paediatric Pharmacists Group

CSL Behring response references

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