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]

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The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Document B
Company evidence submission

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Tables and figures

Table of abbreviations

AARRCF	Average attack rate reduction carried forward
AE	Adverse event
AESI	Adverse event of special interest
AF	Attack free
AI	Auto-injector
AIC	Akaike and Bayesian Information Criterion
ATS	All treated patients
BIC	Bayesian information criterion
BIW	Twice weekly
BMI	Body mass index
BNF	British National Formulary
BSACI	British Society for Allergy and Clinical Immunology
C1-INH	C1-esterase inhibitor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
DHSC	Department of Health and Social Care
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAACI	European Academy of Allergy and Clinical Immunology
EAG	External assessment group
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQoL 5-dimension questionnaire
ERG	Evidence review group
FE	Fixed effect
FXII	Factor XII
FXIIa	Activated Factor XII
GCP	Good clinical practice
GI	Gastrointestinal
HAE	Hereditary angioedema
HMWK	High molecular weight kininogen
HR	Hazard ratio
HRQoL	Health-related quality of life
HSV	Health-utility state values
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGART	Investigator's Global Assessment of Response to Therapy
IgG4	Immunoglobulin G4

INMB	Incremental net monetary benefit
ISR	Injection site reactions
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
IU	International Units
IV	Intravenous
LOCF	Last observation carried forward
LS	Least squares
LTP	Long-term prophylaxis
LYG	Life years gained
MAIC	Matched-adjusted indirect comparisons
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
NASWSI	New Active Substance Work-Sharing Initiative
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
N/A	Not available
NR	Not reported
OD	On-demand
OLE	Open-label extension
PAS	Patient access scheme
PD	Pharmacodynamics
PFP	Pre-filled pen
PFS	Pre-filled syringe
PK	Pharmacokinetics
PP	Per protocol
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Service
PSSRU	Personal Social Services Research Unit
PT	Preferred term
Q2W	Once every two weeks
Q4W	Once every four weeks
QALY	Quality-adjusted life year
QD	Once daily
QM	Once monthly
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effect
RR	Rate ratio
SAE	Serious adverse events
SAP	Statistical Analysis Plan

SC	Subcutaneous
SD	Standard deviation
SGART	Subject's Global Assessment of Response to Therapy
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
STP	Short-term prophylaxis
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TSQM	treatment satisfaction questionnaire for medication
TTO	Time-trade off
UK	United Kingdom
US	United States
VAS	Visual Analog Scale
WAO	World Allergy Organization
WPAI:GH	Work Productivity and Activity Impairment: General Health.
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

- Hereditary angioedema (HAE) is a rare chronic genetic disorder characterised by recurrent and unpredictable attacks of swelling of the skin or submucosa.[1,2]
- HAE attacks can be frequent, debilitating, painful and potentially life-threatening. This results in a significant functional impairment to patients and a decreased health-related quality of life (HRQoL) for patients as well as caregivers.[3,4]
- The burden of HAE is also substantial between attacks since patients experience persistent fear, anxiety and depression as they frequently modify their lifestyles to avoid potential triggers.[3,5-7]
- Long-term prophylaxis (LTP) is a strategy used for the routine prevention of HAE attacks. C1-esterase inhibitors (C1-INHs) and plasma kallikrein inhibitors (berotralstat and lanadelumab) are the only licensed treatment options for LTP in the UK.[7]
- These therapies have improved outcomes for people with HAE in England who meet their respective eligibility criteria.[8-10]
- However, there is a need for further improvement in outcomes for people with HAE, including a greater reduction in attack frequency and severity, prolonged freedom from attacks and a less burdensome administration schedule.[11]
- The proposed positioning of garadacimab is as a treatment for patients aged 12 years and older who require routine prevention of recurrent attacks of HAE and experience ≥2 attacks per month.
- Garadacimab addresses an unmet need in the HAE treatment landscape as a convenient, well-tolerated and highly efficacious LTP option. Garadacimab offers patients a quick onset of action, extended periods of attack freedom and a reduction in attack severity, directly addressing the debilitating and unpredictable nature of HAE attacks.[12]

B.1.1 Decision problem

This submission focuses on part of the technology's anticipated marketing authorisation, specifically those patients aged 12 years and older who require routine prevention of recurrent attacks of hereditary angioedema (HAE) and experience ≥2 attacks per month.

This proposed position is relevant to National Health Service (NHS) clinical practice as it aligns to the commissioning landscape for long-term prophylaxis (LTP) in HAE. Innovative prophylactic treatments for HAE are currently restricted by baseline attack frequency, as outlined in the NHS clinical commissioning policy for plasma-derived C1-INHs (2016) and NICE recommendations for lanadelumab (TA606; 2021) and berotralstat (TA738; 2019).[8-10] In line with these restrictions, the eligibility criteria for innovative therapies for the prevention of recurrent HAE are as follows (Section B.1.3.2):[8-10]

- Patients experiencing ≥2 attacks per month are eligible for treatment with berotralstat but may not be eligible for lanadelumab or C1-INHs.
- Patients experiencing ≥2 attacks per week despite oral treatments are eligible for treatment with lanadelumab and C1-INHs.

By focusing on patients who experience ≥2 attacks per month, CSL Behring aims to maintain a broad positioning among the innovative LTP options available.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 12 years and over with hereditary angioedema	People 12 years and over with hereditary angioedema experiencing ≥2 attacks per month at baseline	The company has optimised its positioning to patients experiencing ≥2 attacks per month as this reflects the commissioning landscape for novel LTP therapies which restrict by baseline attack frequency.
Intervention	Garadacimab	Garadacimab	N/A
Comparator(s)	Established clinical management for preventing attacks of hereditary angioedema which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Attenuated androgens • Antifibrinolytics • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat	• Plasma-derived, intravenous C1-esterase inhibitors (Cinryze and IV Berinert) • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat	Antifibrinolytics, attenuated androgens, Ruconest and SC Berinert have not been included as comparators in the decision problem for the reasons outlined below: <u>Antifibrinolytics are not considered a relevant comparator as they are no longer a SoC option for the population in the decision problem and there is no relevant clinical trial data available to inform decision-making</u> • Historically, off-label use of antifibrinolytics (mostly tranexamic acid) was considered part of the SoC for long-term prophylaxis in HAE.[2,9] 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).[2,10] • 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 tranexamic acid may be more beneficial than no treatment, newer and more effective therapies should be used when available.[13] • Internationally recognised guidelines (The International/Canadian Hereditary Angioedema Guideline 2019 and International WAO/EAACI guideline for the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			management of hereditary angioedema 2021) no longer recommend antifibrinolytics as standard of care due to limited supportive evidence and the availability of newer therapies.[2,14] • Current UK market share data validates the limited use of antifibrinolytics for LTP in England, indicating that of [redacted] patients with HAE on LTP, [redacted]% LTP were treated with tranexamic acid in Q1 2024.[15] 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.[2,14,16] • CSL Behring sought feedback from three consultant immunologists in England 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 still be used in specific patient groups who have no alternative treatment options, such as paediatric population i.e. patients <18 years old who experience <2 HAE attacks/month and require routine prophylaxis.[17] • There is a lack of clinical trial data to show the efficacy and safety of antifibrinolytics for the routine prevention of HAE attacks, which means that it would not be feasible to perform a robust comparative analysis with garadacimab. • This is also aligned with TA606 and TA738 where the committee agreed that tranexamic acid was not a relevant comparator during the appraisal process.[9,10]

			Attenuated androgens are not considered a relevant comparator as they are no longer a SoC option for the population in the decision problem and there is no relevant clinical trial data available to inform decision-making. • Historically, off-label use of attenuated androgens was considered part of the SoC for long-term prophylaxis in HAE.[2,14] 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).[8-10] • 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.[18] Androgen use in the NHS is further complicated by supply issues.[10] As such, treatment with androgens is no longer recommended for patients newly starting on routine prophylaxis due to limited supporting evidence, safety concerns and difficulty in accessing treatment.[2,9] • Based on market share data from [redacted] patients with HAE on LTP in the UK in Q1 2024, [redacted]% were treated with ondraxolone and [redacted]% with danazol, suggesting approximately [redacted]% of patients on LTP are treated with attenuated androgens.[15] 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.[2,14,16] • CSL Behring sought feedback from three consultant immunologists in England on the use of attenuated androgens for LTP in HAE, who confirmed that the overall

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			use of androgens is expected to be lower than historical use due to the availability of modern LTP agents. They noted that patients who use androgens are typically those who have been on them historically and are satisfied with their treatment or those adults who need routine prevention of HAE attacks but are ineligible (<2 attacks/month) and/or intolerant to newly approved LTP options. Nevertheless, most new patients are now offered berotralstat as a first-line treatment if they do not qualify for lanadelumab or C1-INHs.[17] • In addition, there have been no RCTs in androgens for the prevention of HAE attacks, precluding the feasibility of a robust comparison with garadacimab.[2,10] The same conclusion was drawn in TA606 and TA738; notably, in TA606, the committee understood that there was no trial evidence for oral therapy, such as attenuated androgens, and therefore agreed it was not an appropriate comparator for the company's proposed positioning of lanadelumab.[9,10] • In TA606 and TA738, the committee agreed that attenuated androgens were not a relevant comparator during the appraisal process.[9,10] <u>Ruconest is not considered a relevant comparator as it is not routinely commissioned in clinical practice in England for the prevention of HAE attacks</u> • Ruconest is predominantly used for the acute treatment of HAE attacks, in line with its marketing authorisation.[19] It is reimbursed by NHS England solely for the acute treatment of HAE attacks.[20] 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.[8]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• In addition to not being reimbursed by NHS England or recommended as an LTP option for HAE, recent market share data obtained by CSL Behring in Q1 2024 showed that of [redacted] patients on LTP, [redacted]% used Ruconest for the routine prevention of HAE attacks.[15] This is also in line with comments by clinical experts in TA606, confirming that Ruconest was used very rarely in UK practice as a LTP option.[10] • CSL Behring sought feedback from three consultant immunologists on the use of Ruconest for LTP in HAE, who confirmed that it is rarely used as an LTP in UK clinical practice.[17] • In TA606 and TA738, Ruconest was also not considered as a relevant comparator during the appraisal process.[9,10] <u>SC Berinert is not considered a relevant comparator as it is not routinely commissioned in clinical practice in England for the prevention of HAE attacks</u> • Berinert is available in both IV and 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.[8,21] However, SC Berinert is not routinely commissioned in UK practice for the prevention of recurrent HAE attacks, despite being licensed for this use.[8,22,23] • This is reflected in the market share data, which indicates very limited use of SC Berinert in clinical practice, with [redacted]% of [redacted] patients on LTP in the UK using SC Berinert in Q1 2024.[15] • Feedback from the three consultant immunologists in England contacted by CSL Behring was that SC Berinert would only be considered in special circumstances, such as

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			when a patient fails treatment on available LTP options or is unsuitable to receive them (e.g. during pregnancy) and has poor venous access restricting them to be treated with IV C1-INHs.[17]
Outcomes	• Angioedema attacks (including frequency, severity, location and duration) • Attack-free period • Time to first attack • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Angioedema attacks (including frequency, severity, location and duration) • Attack-free period • Time to first attack • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	N/A

Abbreviations: C1-INH, C1-esterase inhibitor; EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; N/A, not applicable; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; Q1, quarter 1; RCT, randomised controlled trial; SC, subcutaneous; UK, United Kingdom; WAO/EAACI; World Allergy Organization.

B.1.2 Description of the technology being evaluated

Table 2 presents a brief description of garadacimab for the treatment of HAE. The draft Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Generic name: Garadacimab Brand name: ANDEMBRY® Alternative identifier: CSL312; ATC code: B06AC07)
Mechanism of action	Garadacimab is a novel, fully human, recombinant immunoglobulin G4 (IgG4)/lambda monoclonal antibody and specific inhibitor of activated Factor XII (FXIIa).[24] The inhibition of FXIIa blocks the cascade of events leading to an HAE attack by preventing the activation of pre-kallikrein to kallikrein and the subsequent generation of bradykinin, which is associated with the inflammation and swelling observed during HAE attacks.[24]
Marketing authorisation/CE mark status	Garadacimab is currently being reviewed through the international (collaborative procedure) Access Consortium New Active Substance Work-sharing Initiative (NASWSI) route and is anticipated to receive marketing authorisation in the United Kingdom (UK) in [redacted]. Garadacimab was granted orphan designation from the European Medicines Agency (EMA) for the treatment of hereditary angioedema (HAE) in December 2021.[25] Garadacimab is anticipated to receive a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in [redacted] and is anticipated to receive marketing authorisation from the EMA in [redacted].
Indications and any restriction(s) as described in the SmPC	Garadacimab is anticipated to [redacted]
Method of administration and dosage	The recommended dose of garadacimab is an initial loading dose of 400 mg administered as two 200 mg subcutaneous (SC) injections on the first day of treatment followed by a monthly dose of 200 mg.[24] Each garadacimab pre-filled pen (autoinjector device) is intended for single use only. Garadacimab may be self-administered or administered by a caregiver only after training on SC injection technique by a healthcare professional. The injection should be restricted to the recommended injection sites: the abdomen, the thighs and the upper outer arms. Rotation of the injection site is recommended.[24]
Additional tests or investigations	None.[24]
List price and average cost of a course of treatment	The list price of £[redacted] for one unit (autoinjector device) of garadacimab has been submitted to the Department of Health and Social Care. The cost of a course of treatment at the anticipated list price in the first year, including the initial loading dose, is £[redacted], followed by an annual cost of £[redacted] thereafter (both including 20% VAT).
Patient access scheme (if applicable)	A simple discount PAS has been submitted to NHS England with this evidence submission to NICE. This is to ensure enough time for full consideration in advance of the committee meeting. This PAS discount price for [redacted] has been included in the economic analyses in this submission. The discount cost of a course of treatment in the

	first year, including the initial loading dose, is £[redacted], followed by an annual cost of £[redacted] thereafter (both including 20% VAT).

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FXII, Factor XII; FXIIa, activated Factor XII; HAE, hereditary angioedema; IgG4; immunoglobulin G4; NASWSI, New Active Substance Work-sharing Initiative; SC, subcutaneous; SmPC, summary of product characteristics; UK, United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Overview of the disease/health condition

B.1.3.1.1 Disease overview and pathophysiology

Hereditary angioedema (HAE) is a rare, chronic genetic disorder characterised by recurrent and unpredictable inflammation and swelling of the skin (cutaneous oedema) and submucosa (submucosal oedema) resulting from inherited or spontaneous mutations in the contact system pathway.[1,2] This swelling can manifest as subcutaneous oedema of the extremities (e.g. fingers and toes), face, trunk or genitalia, or submucosal oedema of the gastrointestinal (GI) and upper respiratory tract (see Section 0).[26]

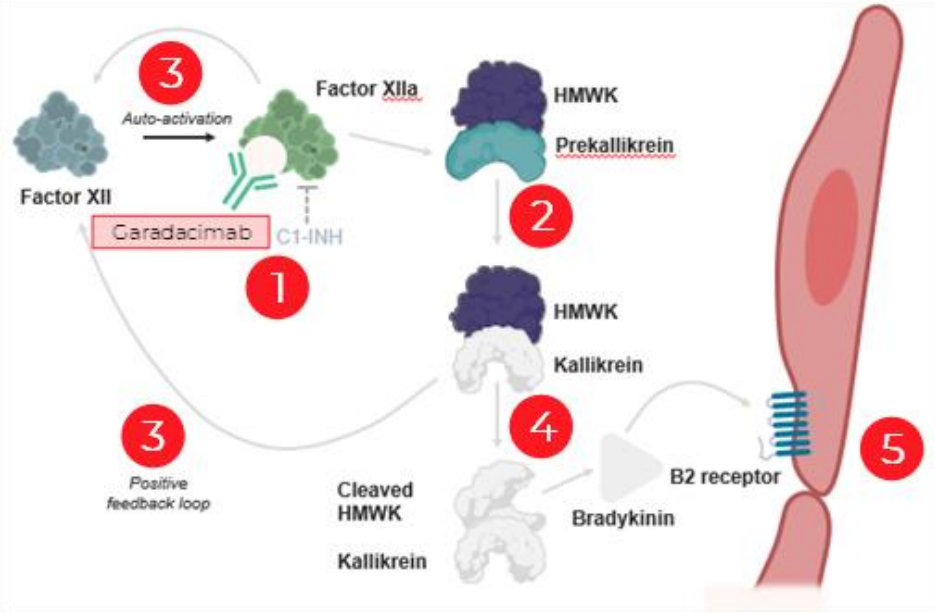
HAE usually runs in the family and, in line with the genetic nature of the disease, patients with HAE typically become symptomatic during childhood or adolescence.[2,27] If one parent has HAE, each child will have a 50% risk of inheriting the condition.[27] In a 2010 global survey, people with HAE had an average of 2 immediate and 2 extended family members who had also been diagnosed with HAE.[27]

The contact system pathway, also called the bradykinin-forming cascade, is initiated when Factor XII (FXII) is activated to FXIIa.[28,29] FXIIa converts pre-kallikrein to plasma kallikrein, which then cleaves high molecular weight kininogen (HMWK) into bradykinin.[28] Bradykinin binds to receptors on endothelial cells, resulting in smooth muscle cell relaxation, vasodilation and increased vascular permeability.[29] At normal functional physiologic levels, the endogenous C1-esterase inhibitor (C1-INH) protein regulates the production of bradykinin through this pathway by inhibiting plasma kallikrein and FXIIa.[30] However, in patients with HAE, the C1-INH protein is deficient

or defective, leading to dysregulation of the contact system, which results in inflammation and swelling (i.e. an HAE attack).[29,30]

An overview of the contact system pathway and the mechanism of action of garadacimab is illustrated in Figure 1. Garadacimab is the first novel fully human recombinant monoclonal antibody which binds to and potently inhibits FXIIa, blocking the cascade of events leading to an HAE attack earlier in the pathway compared with plasma kallikrein inhibitors (e.g. berotralstat and lanadelumab; Section B.1.3.2).[24]

Figure 1. Mechanism of action of garadacimab within the contact activation pathway



Garadacimab binds to the catalytic domain of Factor XIIa, inhibiting its catalytic activity (1), thereby blocking the activation of the kallikrein-kinin pathway (2) and blocking the activation of the positive feedback loop (3). This prevents bradykinin production (4) and the occurrence of HAE attacks (5).
Abbreviations: B2 receptor, bradykinin receptor B_2; C1-INH, C1-esterase inhibitor; HMWK, high-molecular weight kininogen.
Sources: Craig et al., 2023,[12] McKenzie et al., 2022,[31] Pawaskar et al., 2021.[32]

HAE can be categorised into clinically indistinguishable subtypes.[2] The following two subtypes account for almost all (~100%) of the cases of HAE and are both caused by mutations in the serpin family G member 1 gene (*SERPING1*) that encodes the C1-INH protein:[33,34]

- HAE type 1 (HAE-1) results from a failure to synthesise C1-INH and is characterised by low levels of normal-functioning C1-INH, accounting for ~85% of all cases of HAE.

- HAE type 2 (HAE-2) results from the synthesis of abnormal C1-INH protein and is characterised by normal levels of low-functioning C1-esterase inhibitor, accounting for ~15% of all cases of HAE.

A third type of HAE, HAE with normal C1-INH activity (HAE-nI-C1-INH, HAE type 3 [HAE-3]), accounts for a small minority of cases and is characterised by an absence of mutations in *SERPING1*.[1] Due to the extreme rarity of HAE-3 and paucity of data in patients with this subtype, the majority of the evidence presented in this submission is in patients with HAE-1 and HAE-2.

B.1.3.1.2 Diagnosis of HAE

The suspected diagnosis of HAE is based primarily on clinical presentation during an attack which is then confirmed by disease history and investigations to elucidate the possible underlying cause.[2] Several clinical practice guidelines provide recommendations for HAE diagnosis, including the UK British Society for Allergy and Clinical Immunology (BSACI) guideline (2015), the international guideline developed by the World Allergy Organization (WAO) with the European Academy of Allergy and Clinical Immunology (EAACI) (2018), and the international/Canadian Hereditary Angioedema Guideline (2019).[2,14,35]

These guidelines emphasise that a detailed clinical history is essential for an accurate diagnosis of HAE, including family history and the nature of the attacks (i.e. frequency, circumstances of onset, triggers, timing, pattern of recurrence and duration).[2,14,35] Diagnosis of HAE-1 /2 is confirmed with measurements of plasma levels of C1-INH protein, C1-INH function and C4 protein. For HAE-1, both C1-INH function and C1-INH protein levels are low (<50% of normal). For HAE-2, C1-INH function is low but C1-INH protein levels are normal or elevated. C4 levels are also usually low in HAE-1/2 patients, but the sensitivity and specificity of C4 as a sole marker for HAE is limited.[2,14,35] For cases of suspected HAE with normal C1-INH levels and function (HAE-3), the WAO/EAACI and the international/Canadian guidelines suggest for gene variants known to be associated with the condition to support diagnosis.[2,14]

Due to its clinical heterogeneity, patients with HAE may experience delayed diagnoses or misdiagnoses which can result in marked delays in access to effective treatments that can minimise the burden of attacks on patients and their caregivers (Section 0).[36,37] A UK subset (N=73) of the Icatibant Outcome Survey by Longhurst et al. (2018), which analysed data collected from HAE-1/2 patients between 2010 to 2016, reports a mean (SD) delay between first symptoms and diagnosis was 9.5 (13.9) years.[38]

Patients with HAE may also experience misdiagnoses and unnecessary diagnostic and surgical procedures due to clinicians' unfamiliarity with the condition.[36] A German questionnaire study by Hahn et al. 2018 found that people living with HAE (n=66) were 2.5 times more likely to undergo abdominal surgery than the individuals without HAE (n=122) (p=0.007).[39] The number of operations per patient with HAE was correlated with the length of delay in HAE diagnosis from symptom onset (Spearman's correlation coefficient, 0.511).[39]

B.1.3.1.3 Epidemiology

The estimated global prevalence of HAE ranges between 1:50,000[2] and 1:100,000.[40] In recognition of the rarity of the condition, garadacimab was granted orphan designation by the European Medicines Agency (EMA) in December 2021 for the treatment of HAE.[25]

The most recent published estimate of the epidemiology of HAE in the UK is based on a 2019 survey in the UK (37 centres, N=1,152 patients with HAE-1/2) by Yong et al. (2023), which estimated the minimum prevalence of HAE-1/2 and HAE-3 in the UK to be 1:59,000 and 1:3,000,000, respectively.[16] Two consultant immunologists (clinical experts) in the UK indicated that the prevalence of HAE in the UK is likely higher, with one estimating this to be around 1:50,000.[17]

Yong et al. reported a higher proportion of females (58%) compared to males (42%) among patients with HAE-1/2. The majority of patients (81%) were adults (>18 years), with 9% adolescents (12–18 years) and 10% paediatric patients (<12 years).[16] Additionally, demographic data from the UK subset (N=73) of the Icatibant

Outcome Survey provide further insights into patient characteristics.[38] The mean (SD) age of UK patients at the time of study extract was 42.9 (14.7) years and 60% were female. Patients in the UK typically experienced their first symptoms at a young age, with a mean (SD) age of 11.3 (9.5) years at symptom onset. However, as described in Section B.1.3.1.2, diagnosis often came later, with a mean (SD) age at diagnosis of 21.5 (12.7) years indicating a mean diagnostic delay of 9.5 (13.9) years.[38]

Across multiple phase 3 studies for LTP therapies, the mean number of baseline HAE attacks was 3 per month without treatment.[41-46] Where data were reported, 29–39% of patients experienced <2 attacks per month, 53–70% experienced ≥2 attacks per month and 3% experienced ≥2 attacks per week without treatment.[43-46] In the UK survey by Yong et al., it was estimated that approximately 8% of patients experienced ≥2 attacks per week.[16]

Based on the estimated prevalence of 1:50,000[17] and a mid-year 2022 England and Wales population estimate of 60 million,[47] a total of 1041 people are estimated to be living with HAE in England and Wales. Considering the proportion of people with HAE who are ≥12 years of age (86%),[47] on long-term prophylaxis (LTP) therapy ([redacted]%),[15-17] and experiencing ≥2 attacks per month at baseline (70%),[43] an estimated [redacted] people with HAE would be eligible for garadacimab in England and Wales in Year 1.

B.1.3.1.4 Clinical features and burden of disease

B.1.3.1.4.1 Clinical features

Episodes of HAE, or HAE attacks, are recurrent and can vary considerably in terms of the location, frequency and severity of attacks between patients and within an individual patient over time.[2,3] Most attacks are spontaneous and are not prompted by triggers,[2] although a variety of conditions and events are also known to trigger HAE attacks, including emotional stress, local trauma (whether accidental or associated with dental, medical or surgical procedures) and infections.[2,11,26]

A survey designed and commissioned by CSL Behring to characterise the burden of HAE was conducted from 25 September–5 October 2024 in people living with HAE and those caring for people with HAE. Voluntary participation was encouraged via HAE UK by the sharing of the link to the survey (available in reference pack of this submission)[48] to its membership. Participants were only informed of the sponsor of the survey upon completion of the questionnaire, which itself was managed by a third-party consultancy. A total of [redacted] unique respondents from the UK completed the survey.[48] In this survey, emotional stress and anxiety ([redacted]%), physical exertion ([redacted]%) and hormonal changes ([redacted]%) were most commonly noted as external triggers that may have caused attacks by people with HAE (n=[redacted]).[48]

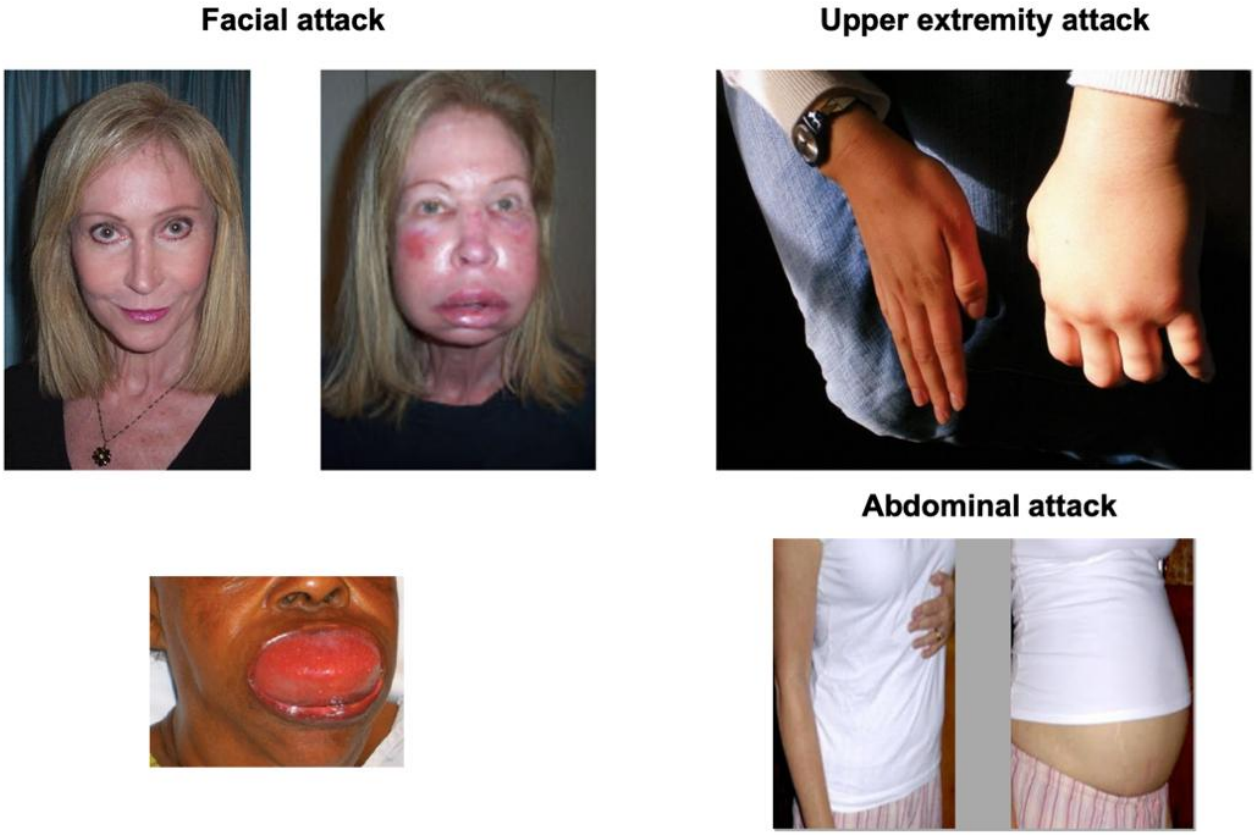
These unpredictable and varying clinical features of HAE contribute to the substantial challenge posed in managing HAE and highlights the importance of appropriate management with LTP to prevent recurrent attacks (Section B.1.3.2).[5,6]

HAE attacks can affect different areas of the body, with some attacks affecting multiple locations at the same time. A multinational patient survey by Mendivil et al. (2021) (N=242, of which N=57 [23.6%] from the UK) reported that 50% of patients had more than one location of their body affected in their most recent HAE attack.[3] According to a 2021 survey of 99 HAE patients in Germany, the body areas affected during the respondents' most recent HAE attack included the gastrointestinal tract (70%), skin involvement (e.g., extremities, genitals, eyes; 64%), airways/larynx (21%), mouth area (13%).[49] A 2021 Dutch cross-sectional survey of 69 adult HAE patients by Fijen et al. (2023) reported similar results, with the abdomen being the most common primary location of attacks (43%), followed by the extremities (28%).[50] Importantly, over a quarter of patients (26%) in the Dutch cross-sectional survey reported no dominant location of attacks, further highlighting the unpredictability and heterogeneity of the condition.[50]

Symptoms of HAE attacks are generally specific to the site(s) of the attacks. For example, HAE attacks affecting the skin generally present as non-pitting and non-pruritic skin oedema, while GI attacks present as swelling of the GI wall, resulting in abdominal pain and distension, nausea, vomiting and diarrhoea (Figure 2).[2,30,51,52]

Symptoms of a GI attack can mimic those of acute abdominal emergencies, which may result in misdiagnosis. As a result of such misdiagnosis, patients may undergo unnecessary emergency surgery (see section B.1.3.1.2).[11,37] Additionally, laryngeal attacks can lead to life threatening symptoms such as difficulty swallowing, difficulty breathing and asphyxiation (suffocation).[3,4] For mortality rates associated with these severe attacks, please see section B.1.3.1.4.3.

Figure 2. Clinical presentation of HAE attacks

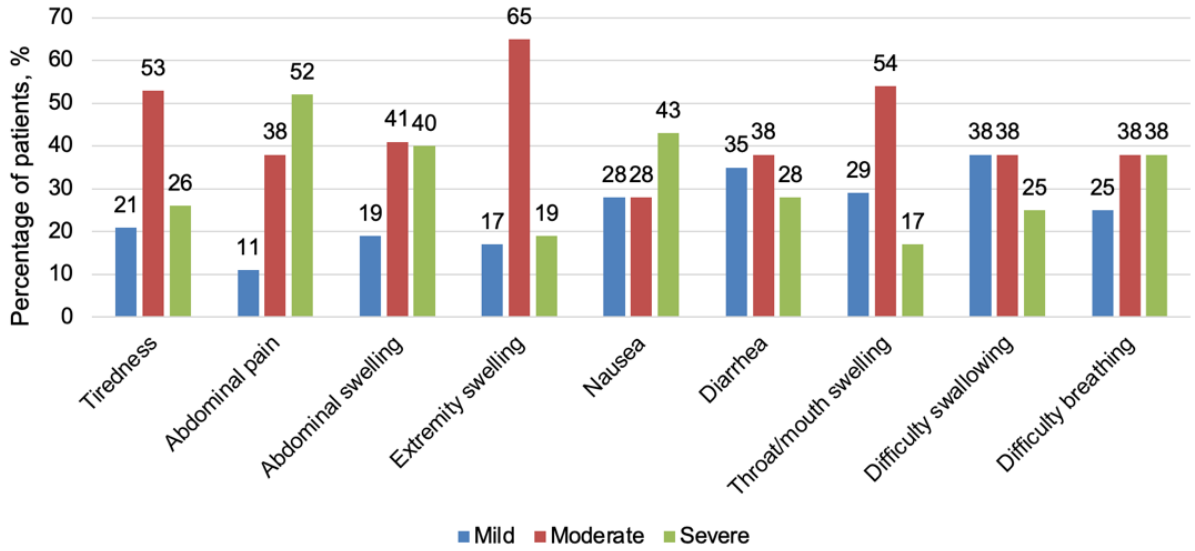


Source: www.HAEimages.com.[53] Copyright 2016. Permission for use of images obtained in March 2017.

If left untreated, HAE attacks typically progress and evolve over several hours and last for 2 to 5 days.[11] Additionally, even with prompt acute treatment initiated within 1 hour of symptom onset, the average duration of symptoms during an attack is still estimated to be 34 hours (median 24 hours).[49] In the 2024 survey of individuals with HAE and their caregivers, [redacted]% of HAE survey participants that have experienced attacks in the 3 months prior noted that it took 1–2 days to recover from a recent attack, while [redacted]% indicated that recovery has taken 3 or more days.[48]

In the survey by Mendivil et al. (2021) (N=242, of which N=57 [23.6%] from the UK), patients reported that symptoms of their most recent HAE attack were of varying severity, with most symptoms considered to be moderate to severe (Figure 3).[3] Of the symptoms experienced during an HAE attack, abdominal pain (52%), nausea (43%) and difficulty breathing (38%) were most commonly described as severe (Figure 3).[3]

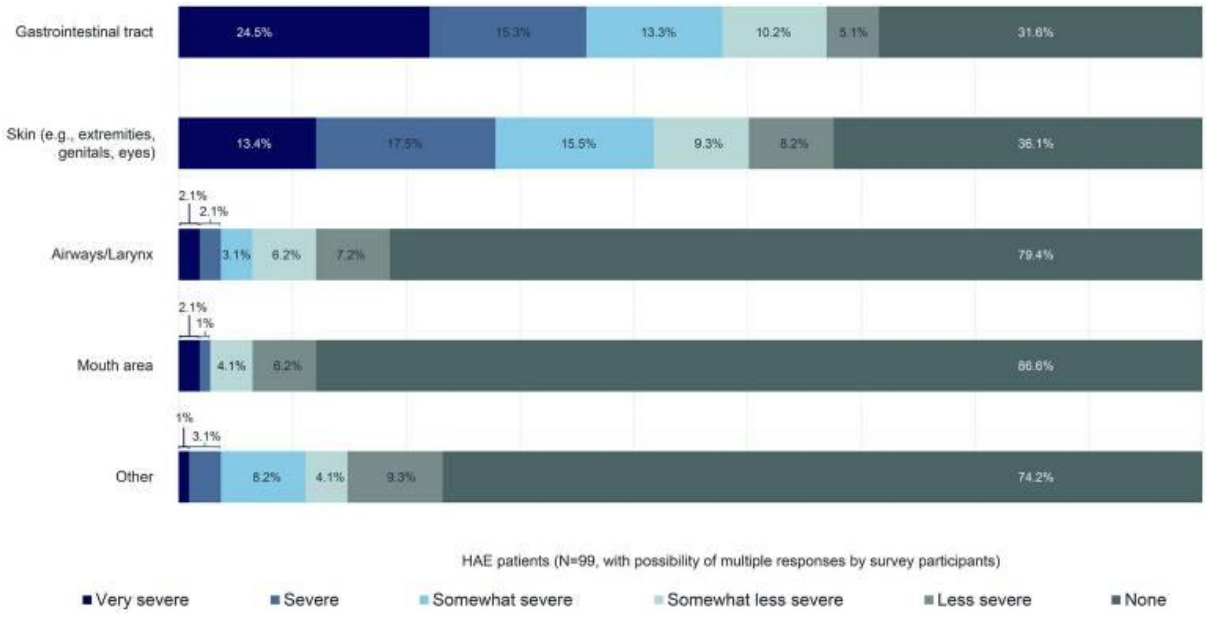
Figure 3. Symptoms and symptom severity during HAE attack



Based on a non-interventional, cross-sectional, global, web-based survey describing real-world attack characteristics and burden of illness from the perspective of patients with self-reported HAE-1/2 (N=242, of which n=57 [23.6%] from the UK). The above symptoms and associated severities were reported by patients when thinking of their most recent HAE attack at its worst.
Abbreviations: HAE, hereditary angioedema; HAE-1, hereditary angioedema type 1; HAE-2, hereditary angioedema type 2; UK, United Kingdom.
Source: adapted from Mendivil et al. 2021.[3]

Moreover, the 2021 German survey (N=99) reported on the severity of the swelling intensity of body parts during their most recent HAE attack. As shown in Figure 4, the swelling of the gastrointestinal tract and the skin were deemed the most severe, with over half of patients (53.1%) reporting the swelling intensity in their gastrointestinal tract to be between "somewhat severe" to "very severe" and just under half of patients (46.4%) reporting the same for the swelling intensity of the skin.[49]

Figure 4. Body areas affected and swelling intensity during the most recent swelling attack



Abbreviations: HAE, hereditary angioedema.
Source: adapted from Magerl et al. 2024.[49]

Attacks of HAE can recur frequently, for instance in the survey by Mendivil et al. (2021), patients with HAE reported a mean rate of 12.5 attacks in the past 6 months, with most patients having experienced their last HAE attack within the past month (79.7%) and nearly half (47.1%) within the past 7 days.[3] Moreover, approximately 22% of patients reported that their most recent attack lasted ≥3 days, despite 76.4% having used on-demand medication to treat their most recent attack.[3]

A European burden of illness study in HAE patients was conducted in 2011 and consisted of two components; a survey to quantitatively assess the humanistic and economic burden of HAE (N=186), and qualitative, open-ended interviews with 30 patients with HAE.[4,54] Results of the quantitative study, published by Aygören-Pürsün et al. (2014), indicated that 23% of participants experienced ≥1 attack per week, 41% reported ≥1 attack per month but <1 attack per week, and 36% reported <1 attack per month.[54] The mean (SD) number of attacks per year was 33.2 (39.6), despite 34% of participants reporting the use of attenuated androgens or tranexamic acid.[54]

B.1.3.1.4.2 Burden of disease

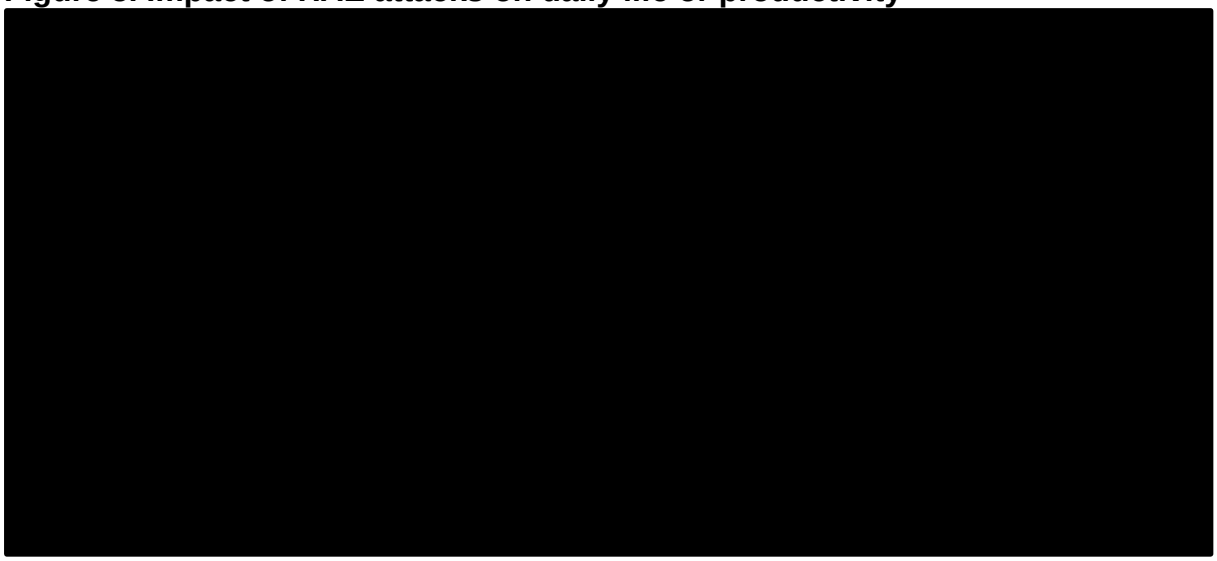
HAE attacks are unpredictable and can be frequent, debilitating, painful and potentially life-threatening, resulting in significant functional impairment and decreased health-related quality of life (HRQoL) for people living with this chronic condition.[3,4]

Patient burden during attacks

The symptom burden associated with HAE attacks is substantial, with patients potentially experiencing disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety.[3,4]

In the 2024 survey of individuals with HAE and their caregivers, the majority (n=[redacted]/[redacted], [redacted]%) of people who experienced HAE attacks in the 3 months prior indicated that their HAE attacks impacted their daily life or productivity to some extent (Figure 5).[48]

Figure 5. Impact of HAE attacks on daily life or productivity



Abbreviations: HAE, hereditary angioedema.
Note: The question posed to participants experiencing HAE attacks in the previous 3 months was: "[redacted]?"
Note: A total of [redacted] unique respondents from the UK participated in the HAE patient and caregiver survey, of which [redacted] were people with HAE who experienced at least one HAE attack in the previous three months – [redacted] participants responded to this question.
Source: CSL Behring, 2024 survey of individuals with HAE and their caregivers (2024).[48]

Additionally, the majority of participants in the 2024 survey who experienced HAE attacks in the 3 months prior indicated that their HAE attacks impacted their plans for

social events ([redacted]%) and that they felt self-conscious to some degree ([redacted]%).[48] More specifically, [redacted]%, [redacted]% and [redacted]% of these participants indicated that they have been unable to (or felt self-conscious about) socialising with others whilst experiencing/recovering from attacks and have decided to cancel their plans in some, most or all cases, respectively.[48]

In the 2021 Dutch cross-sectional survey (N=69), patients considered physical difficulties such as pain, limited mobility and fatigue (30%) and the anxiety/uncertainty related to the next attack (29%) as the most severe limitations due to HAE, with an equal degree of importance. In addition, 16% of patients described difficulties at work/school (e.g. sick leave and job loss) and 19% reported limitations on leisure activities (particularly sports and vacation) due to HAE.[50]

Moreover, results from the 2011 European HAE burden of illness study (Caballero et al., 2014) indicated that higher attack pain severity is associated with a greater impact on ability to perform daily activities and worsening anxiety following the attack.[55] Qualitative, open-ended interviews associated with the 2011 European burden of illness study further highlighted that HAE attacks have a substantial impact on the daily activities of people with HAE, including ability to perform household tasks, drive, participate in family activities, travel, or follow through on plans.[4] The duration of activity disruption varied, but in many cases lasted 1–2 days. Participants largely considered abdominal attacks to involve the most severe pain, indicating that they could last for several days, be accompanied by vomiting and may confine the participant to bed. While participants indicated that HAE attacks in extremities such as hands and feet are generally less painful, they were not necessarily less severe as they prevented participants from being able to do daily tasks, such as using a computer or driving. The inability to perform normal activities during attacks caused interruption to participants' work or schooling, including absenteeism and decreased productivity. Participants of the burden of illness study felt a great deal of emotional distress during attacks, indicating that they were anxious and fearful of the attack getting worse or potentially not being able to breathe or get to the hospital in time in the event of a laryngeal attack.[4] Patients also experienced anxiety due to activity limitations during attacks, such as not being able to participate in family activities.[4]

Patient burden in between attacks

Some of the greatest challenges in HAE are its variability and unpredictability, both between patients and within an individual patient over time.[7] There are no known prognostic markers that can predict the frequency, site or severity of HAE attacks and this unpredictability negatively impacts patient HRQoL.[5,6] As a result of the unpredictable and frequent nature of HAE attacks, there is an emotional and psychological burden associated with HAE which extends beyond the acute attacks themselves.[3,7]

The burden of HAE was discussed in a consensus meeting in 2020 with nine HAE experts from the US and Europe (including one from the UK).[7] Consensus statements were developed based on a preliminary literature review and panel discussions. HAE experts concluded that the burden of HAE continues to be substantial between attacks, as patients experience persistent fear, anxiety and depression. Additionally, patients 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.[7] In the 2024 survey of individuals with HAE and their caregivers, the majority of patients who are aware of their triggers indicated that trigger avoidance has impacted their ability to participate in activities such as sports, going on holidays or taking exams, with [redacted]%, [redacted]% or [redacted]% indicating that this occurs often, sometimes or rarely.[48] This is reflected in the comorbidities associated with HAE, as reported by Mendivil et al. (2021) (N=242, N=57 [23.6%] from the UK), which commonly include moderate or severe anxiety (38%) and depression (17%).[3] The anxiety that patients experience is apparent in results from the 2024 survey of individuals with HAE and their caregivers, in which the majority of patients ([redacted]%, n=[redacted]/[redacted]) described feeling anxious about future attacks to a certain extent, with [redacted]% indicating feeling anxious at least once a week.[48]

Importantly, it is also not possible to predict when and which patient will have a laryngeal attack, the most severe presentation that can progress to asphyxiation and death.[2] In a 2021–2022 survey of 65 people with HAE in the UK, participants have described living in a constant state of fear of a possible laryngeal attack, often

influenced by the loss of a family member with HAE who experienced such an attack. Results from the 2024 survey of individuals with HAE and their caregivers underscore this, reporting that laryngeal attacks are [redacted] among both patients and caregivers.[48] Those who have experienced laryngeal attacks describe them as extremely traumatic, often feeling like they might die.[56]

The burden of HAE and perception of disease control worsen with the frequency of attacks experienced.[3,50] Conversely, a patient's HRQoL is positively associated to their attack-free duration, as demonstrated by a global online survey by Itzler et al. (2024) of 159 patients with HAE-1/2 (n=20 [13%] from the UK).[57] The study by Itzler et al. reported that HRQoL continued to improve the longer the patients remained attack-free, with the mean Angioedema Quality of Life (AE-QoL) scores improving from 51.8 to 19.9 when comparing those who are attack-free for <1 month and ≥6 months, respectively.[57]

Further, the Dutch cross-sectional survey by Fijen et al. (N=69) found that patients with poorly controlled disease, defined as having an Angioedema Control Test score <10, had a lower EQ-5D-5L QoL value on attack-free days (mean [SD]: 0.752 [0.355]) compared to well-controlled patients (mean [SD]: 0.942 [0.089]).[50] Moreover, among 22 patients who experienced an HAE attack during the study period, the mean (SD) utility value decreased from 0.740 (0.371) on attack-free days to 0.420 (0.381) during an attack.[50] These findings suggest that HAE attacks lead to significant declines in QoL, and that better disease control contributes to higher QoL even during attack-free periods.

Caregiver burden

The QoL burden associated with HAE extends to caregivers and families of patients with the condition. In the qualitative interviews held as part of the European burden of illness study in 2011 (n=30), patients with HAE indicated that attacks have a substantial impact on their caregivers, including an emotional burden of being prepared to take the patient for on-demand treatment or administer the injection during an attack, as well as taking on additional responsibilities in the home while the patient is ill.[4] Patients also indicated that caregivers had to miss work to accompany

them to the hospital during severe attacks,[4] with a mean duration of missed time of 2.1 days for caregivers following an attack associated with severe pain.[54]

The 2024 survey of individuals with HAE and their caregivers further highlighted the caregiver burden during HAE attacks, as [redacted]% of [redacted] caregivers indicated that their caregiver responsibilities impacted their daily life or productivity (ability to carry out your work, study or look after others) to a certain extent in the prior three months, of which [redacted]% indicated severe disruptions.[48] Moreover, [redacted]% of caregivers indicated missing 1–4 days of work or education in the prior three months due to their caregiver responsibilities, with [redacted] ([redacted]%) missing more than 10 days.[48]

Caregivers can also experience an ongoing burden in between attacks due to the psychological impact of the lack of specific HAE symptoms, unpredictability of attacks and a delay in diagnosis which can generate fear, anxiety, uncertainty and isolation.[58] The worry and anxiety that caregivers experience when considering their friends or family members experiencing future HAE attacks was measured in the 2024 survey of individuals with HAE and their caregivers, which shows that [redacted]% of caregivers experience some anxiety about future attacks and that a substantial [redacted]% of caregivers state that they are always (daily) anxious (Figure 6).[48]

Figure 6. Frequency of caregivers feeling anxious about care recipients experiencing future attacks

Abbreviations: HAE, hereditary angioedema.
Note: The question posed to participants who were caregivers of people with HAE:
"[redacted]."
Note: A total of [redacted] unique respondents from the UK participated in the HAE patient and caregiver survey, of which [redacted] were caregivers to people with HAE – [redacted] participants responded to this question.
Source: CSL Behring, 2024 survey of individuals with HAE and their caregivers (2024).[48]

B.1.3.1.4.3 Mortality

Overall mortality for patients with HAE is similar to the general population, although HAE attacks which lead to laryngeal oedema present a particular risk of death due to asphyxiation (suffocation) if timely medical treatment is not administered.[59,60] As such, death due to laryngeal attacks predominantly affects patients with HAE who are undiagnosed and/or untreated.[59,61] A global literature review of real-world evidence (conducted April 2021) found that on average, 32.7% to 56.0% of deaths reported in patients with HAE were due to laryngeal oedema.[60] In a multicentre UK audit of HAE patient data from 2010 to 2013 (N=376), family history records showed there were 55 deaths in the family related directly to an HAE attack across 33 families, further highlighting the risk of death associated with the condition.[62]

B.1.3.2 Treatment pathway

There are three approaches to the management of HAE, as listed below:[7]

- Acute treatment with on-demand therapy during an HAE attack

- Short-term prophylaxis (STP) as a preventative measure before planned events that are expected to trigger an attack (e.g. surgery); not discussed further in the submission
- LTP for the routine prevention of recurrent attacks

B.1.3.2.1 On-demand therapy

Patients diagnosed with HAE receive on-demand therapy for the acute treatment of breakthrough attacks, which serves as an adjunct to long-term prophylaxis (LTP) strategies when they are used. This rescue therapy is used to address acute HAE episodes, aiming to alleviate symptoms during an attack, but does not reduce the risk of subsequent attacks. In the UK, on-demand treatment options for HAE include icatibant, a bradykinin B2 receptor antagonist, plasma-derived intravenous C1-INHs (Cinryze, IV Berinert) and recombinant intravenous C1-INH (Ruconest).[62] A total of 82% of patients with HAE identified by the 2019 UK survey by Yong et al. (2023) were provided with a home supply of on-demand treatment (either C1- INH [56%] or icatibant [45%]) and 61% could self-administer their treatment.[16]

B.1.3.2.2 Long-term prophylaxis

LTP reduces the frequency and severity of HAE attacks, and the ultimate goal of treatment is to achieve attack freedom, or extended periods of time without experiencing an HAE attack (i.e. attack-free duration).[2] As per Yong et al. (2023), an estimated 45% of patients with HAE in the UK were receiving LTP at the time of the study (2019),[16] although it should be noted that this study predates the availability of lanadelumab and berotralstat as LTP options. In a market share analysis across 25 to 30 UK centres in the first calendar quarter of 2024, of [redacted] patients with HAE, [redacted] ([redacted]%) were treated with LTP.[15]

Internationally recognised HAE guidelines by WAO/EAACI (2021) recommend plasma-derived C1-INHs, berotralstat and lanadelumab as first-line LTP options with androgens used only as a second-line option; antifibrinolytics are not recommended.[2] Three clinical experts (consultant immunologists) in England interviewed by CSL Behring agreed that, ideally, the WAO/EAACI guidelines should be followed for the management of HAE in clinical practice.[17] However, these

guidelines are challenging to adhere to in practice as they are not fully aligned with the current NHS commissioning policy for plasma-derived C1-INHs, and the NICE recommendations on berotralstat and lanadelumab, which restrict access to these treatment by attack frequency as follows:[8-10]

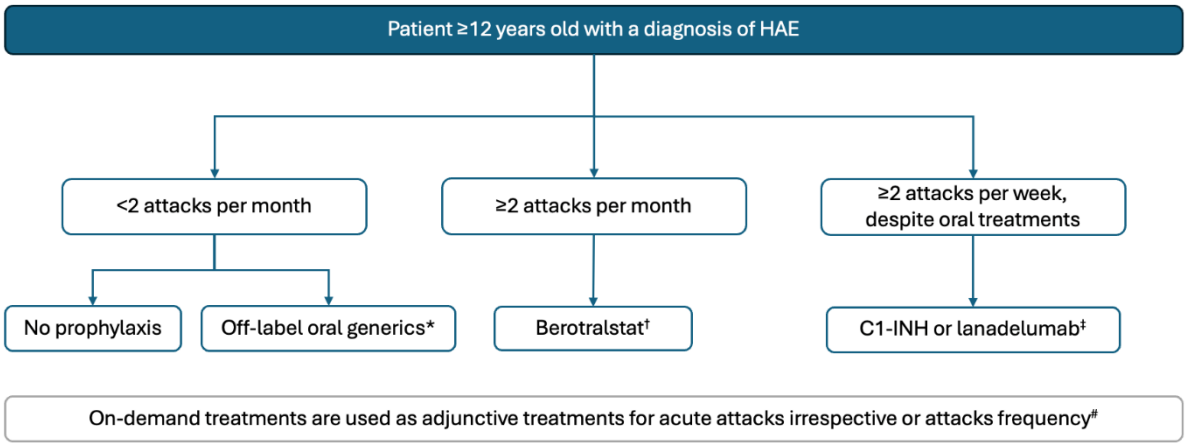
- Berotralstat is recommended by NICE (TA738) as an option for preventing recurrent attacks of HAE in people 12 years and older if they have ≥2 attacks per month and treatment is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.[9]
- Lanadelumab is recommended by NICE (TA606) for preventing recurrent attacks of HAE in people aged 12 and older, only if they are having ≥2 clinically significant attacks per week over 8 weeks despite oral preventive therapy.[10]
- Plasma derived C1-INHs (Cinryze and off-label IV Berinert) are reimbursed by NHS England for the prophylactic treatment of HAE-1/2 in patients who have failed or are intolerant to oral prophylaxis and who experience ≥2 clinically significant attacks per week.[8]

For patients experiencing <2 attacks per month, LTP options are restricted to ineffective or poorly tolerated oral generic therapies, namely attenuated androgens (e.g. danazol and oxandrolone) and antifibrinolytics (i.e. tranexamic acid).[17] Since the availability of newer and more effective LTP options, these generic therapies are not routinely initiated in the ≥2 attack per month population owing to concerns surrounding suboptimal efficacy and safety profiles, as previously identified in TA606 and TA738 and validated by three consultant immunologists in England (Section B.3.3.10).[9,10] However, in cases where patients fail to respond adequately to or are unsuitable for berotralstat, but do not meet the attack frequency threshold for lanadelumab or C1-INHs (≥2 clinically significant attacks per week), these generic therapies may still be considered due to the lack of other options.[17] In interviews conducted by CSL Behring with three consultant immunologists in England (Section B.3.3.10), 20% to 50% of patients were estimated to stop taking berotralstat due to either failure to meet its continuation rule or due to intolerance or side-effects.[17]

As such, the current treatment landscape for HAE in the UK leaves a considerable proportion of patients experiencing ≥2 attacks per month without suitable options for routine prevention of recurrent attacks. These patients must rely on suboptimal off-license oral generic LTP therapies or on-demand rescue treatment only, which is reactive and does not address the unpredictability or the HRQoL impact associated with the fear of recurring attacks (see Section B.1.3.1.4.2).

An overview of the treatment pathway for the routine prophylaxis of HAE attacks in patients ≥12 years in England is presented in Figure 7 with further detail on the comparators relevant to the decision problem summarised in Table 3.

Figure 7. Current LTP option pathway of HAE patients ≥12 years old in England



Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema.
* Off-label oral generics include tranexamic acid and attenuated androgens
† As per the TA738 NICE guidance, treatment with berotralstat is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.[9]
‡ Decision-making of treatment choice is informed by: clinical judgement of suitability, clinical effectiveness, contraindications, ability of patient/carer to use the required administration technique, regional network approval and patient choice.
# On-demand therapy (the on-demand use of C1-INHs or icatibant) is used as an adjunct therapy in all patients for the treatment of acute attacks, irrespective of attack frequency or concurrent use of LTP options.
Sources: NICE, berotralstat appraisal TA738;[9] NHS England, Clinical Commissioning Policy: C1-INH for prophylactic treatment of HAE;[8] NICE, lanadelumab appraisal TA606;[10] Maurer et al., 2021;[2] Betschel et al., 2019.[14]

Table 3. Overview of standard of care treatments in the UK for the long-term prevention of HAE attacks in patients ≥12 years of age with ≥2 attacks per month

	Berotralstat	Lanadelumab	IV Berinert	IV Cinryze
Treatment class	Plasma kallikrein inhibitor (small molecule)	Plasma kallikrein inhibitor (monoclonal antibody)	C1-INH	C1-INH
Marketing authorisation status as LTP in UK	Licensed	Licensed	Off-label	Licensed
NICE recommendations/NHS England commissioning policy	Berotralstat is recommended by NICE[9] as an option for preventing recurrent attacks of HAE in people 12 years and older, only if: • they have ≥2 attacks per month, and • it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months	Lanadelumab is recommended by NICE[10] as an option for preventing recurrent attacks of HAE in people aged 12 and older, only if they are having ≥2 clinically significant attacks (as defined in the policy) per week over 8 weeks despite oral preventative therapy, or oral therapy is contraindicated or not tolerated	Not appraised by NICE. Commissioned by NHS England for use in the following patients:[8] • Individuals who experience two or more clinically significant attacks per week, despite oral prophylaxis, over a period of at least 56 days requiring on-demand treatment • Individuals in whom oral prophylaxis is contraindicated (e.g. pregnancy)	
Administration	Oral	SC	IV	IV
Licensed dose	150 mg once-daily[63]	300 mg every 2 weeks[64] In patients who are stably attack-free on treatment, a dose reduction to 300 mg every 4 weeks may be considered, especially in patients with low weight[64]	N/A, not licensed. Assumption of dosage for health-economic model is set to 1,000 IU twice weekly (every 3–4 days), as per the licensed dosage of IV Cinryze. See Section B.3.5 for further information.	1,000 IU twice weekly (every 3–4 days)[65]

Abbreviations: C1-INH, C1-esterase inhibitors; HAE, hereditary angioedema; IU, international units; IV, intravenous; LTP, long-term prophylaxis; SC, subcutaneous; SmPC, summary of product characteristics.
Source: NICE, berotralstat appraisal TA738;[9] NHS England, Clinical Commissioning Policy: C1-INH for prophylactic treatment of HAE;[8] NICE, lanadelumab appraisal TA606;[10] berotralstat SmPC;[63] lanadelumab SmPC;[64] IV Cinryze SmPC.[65]

B.1.3.3 Limitations of current therapies and unmet need

While several treatments exist for HAE, it is presently an incurable disease and symptoms can persist throughout the patient's lifetime.[11] In a global, online survey of 159 patients with HAE, personal goals for LTP included reduced HAE attack frequency (87%), reduced attack severity (75%), reduced or eliminated troublesome attack symptoms (70%), ability to be attack-free (68%), reduced psychological problems associated with HAE (49%), and reduced utilisation of on-demand medication (39%).[57]

Androgens and antifibrinolytics are suboptimal LTP options for HAE for several key reasons. While these treatments were once considered standard care for preventing HAE attacks, their effectiveness and safety profiles are poor.[2,14,20,66,67] Tranexamic acid has shown limited efficacy, as evidenced by a systematic review by Horiuchi et al. (2018), which found that although it may be better than no treatment, newer therapies offer significantly better results.[13] Furthermore, long-term use of androgens has been associated with serious safety and tolerability issues, as highlighted in a review by Riedl et al. (2015), leading to high discontinuation rates.[18] The use of androgens is further complicated by supply shortages within the NHS.[10] Given the availability of more effective and safer treatments, androgens and antifibrinolytics are no longer recommended for patients newly starting prophylactic therapy (Section B.1.3.2). This was confirmed by clinical expert opinion in TA738 and TA606 and ratified by three clinical experts (consultant immunologists) in England interviewed by CSL Behring (Section B.3.3.10).[9,10,17]

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).[8-10] However, patients currently continue to experience frequent attacks of varying severities, as noted by the 2024 survey of individuals with HAE and their caregivers, in which [redacted]% (n=[redacted]) and [redacted]% (n=[redacted]) of patients experienced at least 2 and 5 attacks per month, respectively, in the past three months while on their current treatment regimen, which included [redacted]% (n=[redacted]) on LTP.[48] This leaves the burden

of unpredictable attacks largely unaddressed and results in patients in England perceiving their disease control as suboptimal.[3,68,69]

In a UK multicentre survey of 54 patients with HAE initiated on berotralstat, treatment was associated with a 52% reduction from baseline for months 1–3 and 65% for months 4–6, suggesting that berotralstat is effective but there is potential for further improvements in care options.[70] In a similar study of 57 patients in the UK, lanadelumab was associated with a 91% reduction in HAE attacks from baseline after 6 months and 97% reduction after 12 months of treatment.[71]

The ultimate treatment goal of prolonged freedom from attacks remains unachievable for many patients receiving currently prescribed treatment. According to the 2024 survey of individuals with HAE and their caregivers, only [redacted]% of patients (n=[redacted]) were attack-free in the last three months while on their current treatment regimen, which included [redacted]% (n=[redacted]) on LTP.[48] This included [redacted]% (n=[redacted]), [redacted]% (n=[redacted]) and [redacted]% (n=[redacted]) being attack-free after at least 3 months of treatment with berotralstat, IV C1-INHs and lanadelumab, respectively.[48]

In the phase 3 RCT for lanadelumab (HELP), less than half of patients were attack-free during the 26-week treatment period with lanadelumab (44% with 300 mg every 2 weeks [Q2W]; 31% with 300 mg every 4 weeks [Q4W]) and placebo (2.4%).[43] In the phase 3 study for berotralstat (APeX-2), the proportion of patients who were attack-free was similar between berotralstat and placebo (percentages not reported in trial publication).[45]

Standard of care LTP options are also associated with the following limitations:

Plasma-derived C1-INHs

- In a 2019 survey across 37 UK centres by Yong et al., just 8% of patients with HAE were treated with C1-INHs,[16] giving a crude indication of the small proportion of patients who experience a sufficient number of attacks (≥2 per week) to be eligible for regular C1-INHs.[16]
- Plasma-derived C1-INHs commissioned under the NHS commissioning policy require IV administration which is more invasive/uncomfortable than other

treatment options (administered orally or subcutaneously) and may eventually result in poor venous access.

- IV administration frequency may be as often as twice weekly, which some patients may view as inconvenient and lifestyle limiting.[8]

Lanadelumab

- Based on the Yong et al. estimates above for plasma-derived C1-INHs, only a small proportion of patients (~8%) are expected to experience a sufficient number of attacks (≥2 per week) to be eligible for LTP with lanadelumab.[16]
- Lanadelumab requires frequent treatment administration (every 2 weeks).[64]
- A proportion of patients do not maintain freedom from attacks with lanadelumab treatment, particularly with the less frequent dosing schedule.[43,46]

Berotralstat

- There is limited evidence to support that berotralstat is effective in maintaining attack freedom
- Berotralstat must be administered daily which can lead to adherence issues.[63,67]
- A substantial proportion of patients treated with berotralstat may discontinue treatment due to established tolerability concerns and/or failure to meet the continuation rule (20% to 50%), as estimated by clinical experts (consultant immunologists) in England.[2,9,17,63] This can leave patients with no effective, licensed treatment options if ineligible for C1-INHs or lanadelumab.[8-10]
- Further highlighting the unmet need and lack of effective treatments for patients experiencing ≥2 attacks per month, one consultant immunologist described that patients may discontinue berotralstat to achieve a higher disease activity and reach eligibility criteria for lanadelumab or C1-INHs, rather than “taking a treatment that keeps their disease activity somewhere in between with no access to any other treatments”.[17]

In summary, given the substantial burden of disease and limitations of current treatments, there is a clear unmet need for convenient and well-tolerated LTP options that demonstrate early and sustained efficacy in reducing the frequency and severity of HAE attacks. Such treatments would help individuals with HAE to achieve

freedom from recurring attacks, empowering them to feel more in control of their condition.

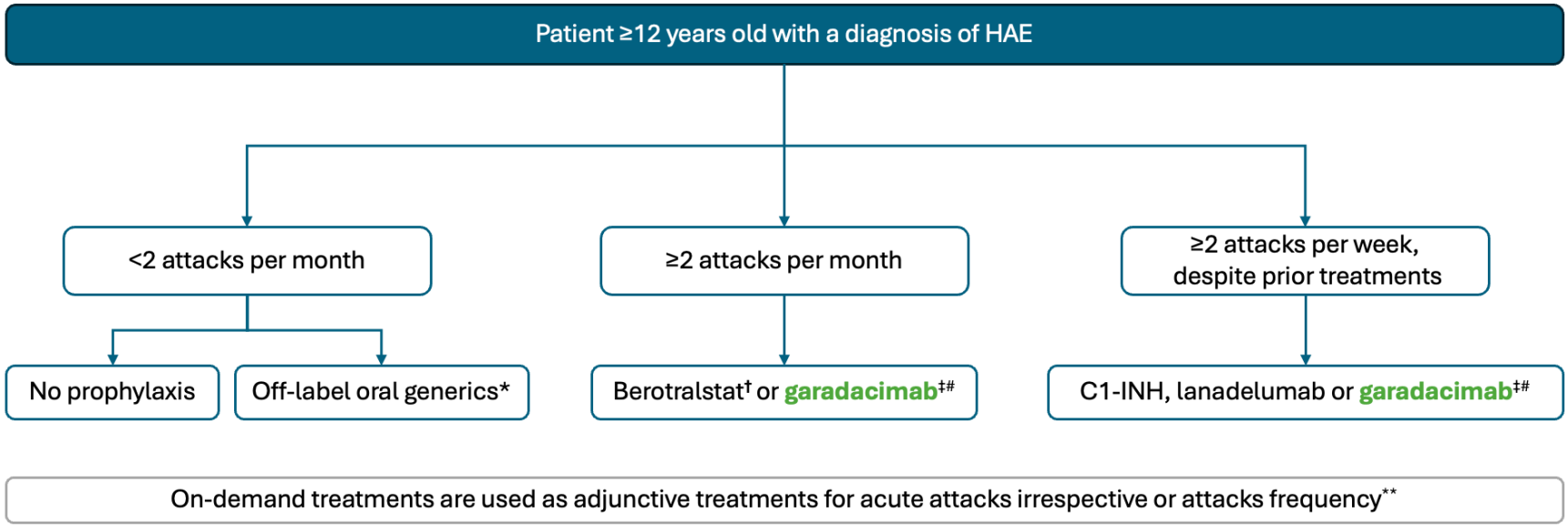
B.1.3.4 Proposed positioning

Figure 8 outlines the proposed positioning of garadacimab as a treatment for patients aged 12 years and older who require routine prevention of recurrent attacks of HAE and experience ≥2 attacks per month.[24]

Garadacimab is a first-in-class FXIIa inhibitor that addresses a clear unmet need in the HAE landscape.[24] The safety and efficacy of garadacimab were demonstrated in a 6-month randomised, placebo-controlled, pivotal phase 3 trial (VANGUARD) and ongoing open-label extension (OLE) study.[44] 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.[44] In the VANGUARD study, most patients (72%) treated with garadacimab remained attack-free for during the first three months of treatment, with 62% maintaining their attack-free status at the end of the study.[44] As such, garadacimab offers patients a rapid reduction in attacks, extended periods of attack freedom and a reduction in attack severity, directly addressing the debilitating nature of attacks and their unpredictability, ultimately alleviating the fear and anxiety associated with living with HAE. This large patient benefit has carryover effects which can improve the lives of caregivers, many of whom are related to their dependents (e.g. parents) and have the added burden of living with HAE themselves (Section B.1.3.1.1).

In addition to offering an improved option to current LTP treatments, garadacimab helps to bridge the treatment gap for patients who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs.

Figure 8. Proposed positioning of garadacimab



Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema.
The proposed positioning of garadacimab is indicated in green within the existing treatment pathway.
* Off-label oral generics include tranexamic acid and attenuated androgens
† As per the TA738 NICE guidance, treatment with berotralstat is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.[9]
‡ Patients will be eligible for garadacimab treatment regardless of prior therapy use. Garadacimab is proposed to be used ahead of the current standard-of-care treatment for the prevention of HAE attacks, as well as in patients who have previously used standard-of-care treatments.
# Decision-making of treatment choice is informed by: clinical judgement of suitability, clinical effectiveness, contraindications, ability of patient/carer to use the required administration technique, regional network approval and patient choice
** On-demand therapy (the on-demand use of C1-INHs or icatibant) is used as an adjunct therapy in all patients for the acute treatment of HAE attacks, irrespective of attack frequency or concurrent use of LTP options.
Sources: NICE, berotralstat appraisal TA738;[9] NHS England, Clinical Commissioning Policy: C1-INH for prophylactic treatment of HAE;[8] NICE, lanadelumab appraisal TA606;[10] Maurer et al., 2021;[2] Betschel et al., 2019.[14]

B.1.4 Equality considerations

CSL Behring does not believe that the draft remit or scope will exclude people protected by equality legislation. However, of note, the IV C1-INHs included in the decision problem (Cinryze and IV Berinert) are derived from human plasma which may result in their lower uptake among groups who have religious or spiritual beliefs against receiving treatments derived from human plasma. As such, consideration should be given to treatment options available for people with these beliefs 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.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

The clinical effectiveness evidence for garadacimab and its comparators presented within this submission has been retrieved through a methodologically rigorous systematic literature review (SLR) with searches conducted on 8 April 2024 and updated on 5 August 2024. Searches were conducted in MEDLINE ALL, EMBASE (via Ovid.com), The Cochrane Library databases and Centre for Reviews and Dissemination database (via York.ac.uk/crd). In accordance with NICE and the Centre for Reviews and Dissemination methods, following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract for inclusion using the eligibility criteria. Disagreements were discussed and a third reviewer involved if required.

For more extensive detail on the clinical SLR, and for further information regarding reviews for cost/resource, cost-effectiveness and utility data, please also see Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The key clinical studies supporting garadacimab for the routine prevention of recurrent HAE attacks are summarised in Table 4.

All data presented in this submission are based on the monthly subcutaneous (SC) administration of garadacimab 200 mg via a pre-filled syringe (PFS), although the therapeutic that will be launched in the UK will be a pre-filled pen (auto-injector [AI]), as noted in Section B.1.2. In the VANGUARD study, garadacimab was administered via a PFS throughout the study. In CSL312_3002, patients received garadacimab via an PFS up to the latest data cut-off (interim analysis 4 [IA4]), at which point patients were offered the opportunity to transition to administration via the AI pen (data following transition not yet available). The AI method of administration utilises both

the same dose and dose frequency of garadacimab as the PFS given to patients in the pivotal phase 3 studies.

A phase 1 study of garadacimab 200 mg in healthy participants (N=132) demonstrated that the benefit/risk ratio of garadacimab administered by AI is expected to be comparable to that observed in the phase 3 clinical studies using a PFS.[72] Following a single dose of garadacimab, comparable pharmacokinetics, safety and tolerability profiles and immunogenicity were observed for the PFS and AI. Device-related TEAEs were [redacted] with AI ([redacted]%) than NSD ([redacted]%), consistent with expectations for this type of device, although pain was infrequent for both devices ([redacted]% and [redacted]%, respectively). All injection site-related TEAEs were mild in severity. As such, the clinical evidence for garadacimab 200 mg PFS presented in this submission is generalisable to the garadacimab 200 mg AI pen. Please see Appendix M for more detail on this phase 1 study.[72]

The AI is not anticipated to be associated with any additional costs to the healthcare system compared with the PFS and has the potential to reduce healthcare costs associated with patient training as AI devices are simpler to use. Multiple studies across a range of chronic conditions have shown that patients and nurses prefer AI pens over PFS due to ease of use, convenience and reduced administration time.[58,73-75]

Table 4. Overview of clinical effectiveness evidence

Study	VANGUARD (CSL312_3001; NCT04656418)	CSL312_3002 (NCT04739059)
Study design	Phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel-arm study	Phase 3b, multinational, multicentre, open-label study
Population	Patients aged ≥12 years with HAE-1/2 who experienced ≥3 HAE attacks during the 3 months prior to screening (N=64).	Patients aged ≥12 years with HAE who experienced ≥3 HAE attacks during the 3 months prior to screening (N=161): ○ Patients who rolled over from CSL312_2001 or VANGUARD (n=92) (Section B.2.2.1) ○ Newly-recruited patients (n=79)
Intervention(s)	Garadacimab 200 mg (n=39) • Loading dose: 400 mg (administered as 2 × 200 mg SC injections) • Subsequent doses: once monthly SC injections of 200 mg at scheduled times • Patients were treated for 6 months	• Garadacimab 200 mg SC once per month (n=161) ○ Garadacimab was administered as a PFS up to the data cut-off for IA4 ([redacted]), after which garadacimab was administered via AI. ○ Since this submission includes data of the most recent data cut-off (IA4; [redacted]), all the data included in this submission is based on patients being treated with the pre-filled syringe. • For CSL312-study-naïve patients, a loading dose of 400 mg (2 × 200 mg doses) was administered SC on Visit Day 1, then 200 mg was administered SC once per month in subsequent months. • As of the latest data cut-off, the median (min, max) duration of treatment was [redacted] ([redacted]) months
Comparator(s)	Placebo (n=25) • A volume-matched loading dose of placebo administered SC as two injections. • Subsequent volume-matched placebo administered SC once monthly at scheduled times.	N/A

Study	VANGUARD (CSL312_3001; NCT04656418)	CSL312_3002 (NCT04739059)
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• HAE attack frequency and severity • Attack-free period • Time to first attack • Need for acute (on-demand) treatment • Mortality • Adverse effects of treatment • Patient and caregiver HRQoL	• HAE attack frequency and severity • Attack-free period • Time to first attack • Need for acute (on-demand) treatment • Mortality • Adverse effects of treatment
All other reported outcomes	• Response to treatment (as measured by SGART)	N/A

Abbreviations: AI, autoinjector; HAE, hereditary angioedema; HRQoL, health-related quality of life; IV, intravenous; N/A, not applicable; PFS, pre-filled syringe; SC, subcutaneous; SGART, Subjects' Global Assessment of Response to Therapy.

B.2.2.1 Phase 2 dose-finding study (CSL312_2001)

CSL312_2001 was a phase 2 dose-finding study assessing the use of garadacimab in adults with HAE. The results of this phase 2 study supported monthly 200 mg garadacimab as an optimal dose, which was then further investigated in the pivotal phase 3 VANGUARD study (CSL312_3001; see Section B.2.2.2) and phase 3b open-label extension (OLE) study (CSL312_3002; see Section B.2.2.3).[44,76] Given the availability of robust phase 3 data for garadacimab, the CSL312_2001 study is not further discussed in this submission. Of note, a total of 35 patients, including 2 patients with HAE-3, rolled over from CSL312_2001 to CSL312_3002.

B.2.2.2 Phase 3 pivotal study (VANGUARD; CSL312_3001)

The key clinical efficacy evidence for garadacimab in people aged ≥12 years with HAE is based on the VANGUARD study, a pivotal phase 3 randomised, placebo-controlled, double-blind, parallel-arm study which investigated the efficacy and safety of prophylactic treatment with garadacimab in adults and adolescents with HAE-1/2 experiencing ≥1 attack per month over a 6-month treatment period (N=65).[44] Results from this study are presented in Section B.2.6.

B.2.2.2.1 Post-hoc subgroup by baseline attack rate

A post-hoc subgroup analysis of the VANGUARD ITT population was performed in patients experiencing ≥2 attacks per month at baseline, which is reflective of the recommended use of berotralstat in the UK (see Section B.1.3.2.2). This subgroup included [redacted] patients in the garadacimab arm and [redacted] patients in the placebo arm. Only [redacted] patients from the VANGUARD study had a baseline attack rate of ≥8 attacks per month (equating to ≥2 attacks per week), precluding the feasibility of a subgroup analysis in a subpopulation that would be reflective of the commissioning policy for C1-INHs and NICE recommendations for lanadelumab (see Section B.1.3.2.2).

These post-hoc subgroup analyses have been presented in Section B.2.7.2 to provide further evidence that baseline attack rate is not a treatment effect modifier for garadacimab, in line with clinical expert opinion from consultant immunologists obtained by CSL Behring for this submission and clinical expert opinion from prior NICE appraisals in HAE (TA606 and TA738).[9,10,17]

VANGUARD was not powered to evaluate the efficacy of garadacimab in subgroups by baseline attack frequency and such analyses should be interpreted with some caution. However, CSL Behring believes that patients with ≥2 attacks per month at baseline represent a sufficiently large proportion of the overall ITT population (garadacimab arm: n=[redacted]/39, placebo arm: n=[redacted]/25) to be relevant as supplementary evidence to the ITT data to inform decision-making.

Post-hoc analyses in patients experiencing ≥2 attacks per week are not presented as this subgroup consisted of only two patients in the VANGUARD study. Therefore, conclusions may not reasonably be made or inferred from such a small evidence base.

B.2.2.3 Phase 3b open-label extension study (CSL312_3002)

The primary safety evidence and supporting efficacy evidence for garadacimab is based on the CSL312_3002 study (NCT04739059), an ongoing open-label extension (OLE) study to evaluate the long-term safety and efficacy of prophylactic treatment with garadacimab in people aged ≥12 years HAE experiencing ≥1 attack per month (N=161). This study includes patients who were previously enrolled in CSL312_2001 (n=35) and CSL312_3001 (n=57), as well as patients naïve to the garadacimab studies (CSL312 study-naïve; n=69), over a median (min, max) duration on treatment of [redacted] ([redacted]) months as of the latest data cut-off (IA4; [redacted]).[77] Results from this data cut-off are presented in Section B.2.6.

A previous data cut-off for this study (February 2023) was published in October 2024, but the safety and efficacy results from this cut-off are not presented in this submission due to the availability of more recent data.[41]

B.2.2.3.1 Post-hoc garadacimab-naïve subgroup

A total of 161 patients entered the CSL312_3002 study and received garadacimab 200 mg once monthly. Of these patients, 35 had rolled over from the CSL312_2001 study and 57 from the VANGUARD study (previously randomised to garadacimab [n=36] or placebo [n=21]). A further 69 patients were non-rollovers (newly recruited) who had not previously enrolled in any garadacimab studies (CSL312 study-naïve).

The garadacimab-naïve subgroup of CSL312_3002 (n=90) consists of 69 CSL312 study-naïve patients and 21 patients who rolled over from the VANGUARD study who were initially randomised to receive placebo. These post-hoc subgroup analyses are presented in Section B.2.6 and provide supportive efficacy evidence to demonstrate that outcomes from the CSL312_3002 study were robust against any potential bias from including patients previously treated with garadacimab in the VANGUARD or CSL312_2001 studies.

B.2.2.4 Post-hoc pooled VANGUARD and CSL312_3002 analyses

To provide evidence on the maintenance of efficacy of garadacimab beyond the 6-month randomised treatment period of the VANGUARD study, data from VANGUARD and CSL312_3002 (up to the [redacted] data cut-off) were pooled for patients who received 200 mg garadacimab in VANGUARD and rolled over to the CSL312_3002 study. The median (min, max) duration of the pooled efficacy evaluation period was [redacted] ([redacted], [redacted]) months. The pooled analyses include data from the start of the VANGUARD study through to the latest data cut-off for CSL312_3002. Results from these analyses are presented in Section B.2.2.4.

B.2.2.5 Summary of key clinical evidence from VANGUARD and CSL312_3002

An overview of the key clinical evidence presented in this submission from the VANGUARD and CSL312_3002 studies is provided in Table 5, summarising the patient populations, data cut-offs and how the data inform the clinical value of garadacimab.

Table 5. Garadacimab data sources and data cut-offs

Garadacimab study	Population	Population size	Data cut-off	Treatment duration	Evidence presented
VANGUARD (CSL312_3001)	Full randomised ITT population	64	Final data cut-off (24 June 2022)	Median (min, max) duration on treatment: [redacted] years	**Primary efficacy evidence for garadacimab**
	Safety population	64			Supportive safety evidence for garadacimab
	Post-hoc subgroup of patients experiencing ≥2 attacks per month	[redacted]			Supportive efficacy evidence for garadacimab in subpopulation of patients in pivotal study who would be eligible for berotralstat in UK clinical practice
CSL312_3002	Full ATS population that entered treatment period	161	Latest data cut-off (IA4; [redacted])	Median (min, max) duration on treatment: [redacted] months	**Primary safety evidence for garadacimab**
					Supportive efficacy evidence in the largest study population size treated with garadacimab
	Post-hoc results from the garadacimab-naïve subpopulation	90			Supportive efficacy evidence in the largest study population size who had not previously received garadacimab
Pooled VANGUARD/ CSL312_3002: Patients who rolled-over from VANGUARD and received 200 mg garadacimab throughout VANGUARD and CSL312_3002	Subgroup of patients who have been on the licensed dosage of the treatment for the longest duration	36	VANGUARD: Final (24 June 2022) CSL312_3002 Latest data cut-off (IA4; [redacted])	Median (min, max) duration on treatment: [redacted] months	Supportive efficacy evidence in patients randomised to monthly treatment with 200 mg garadacimab for the longest duration

Abbreviations: C1-INH, C1-esterase inhibitor; IA4, interim analysis 4; ITT, intention-to-treat; OLE, open-label extension; UK, United Kingdom.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study design

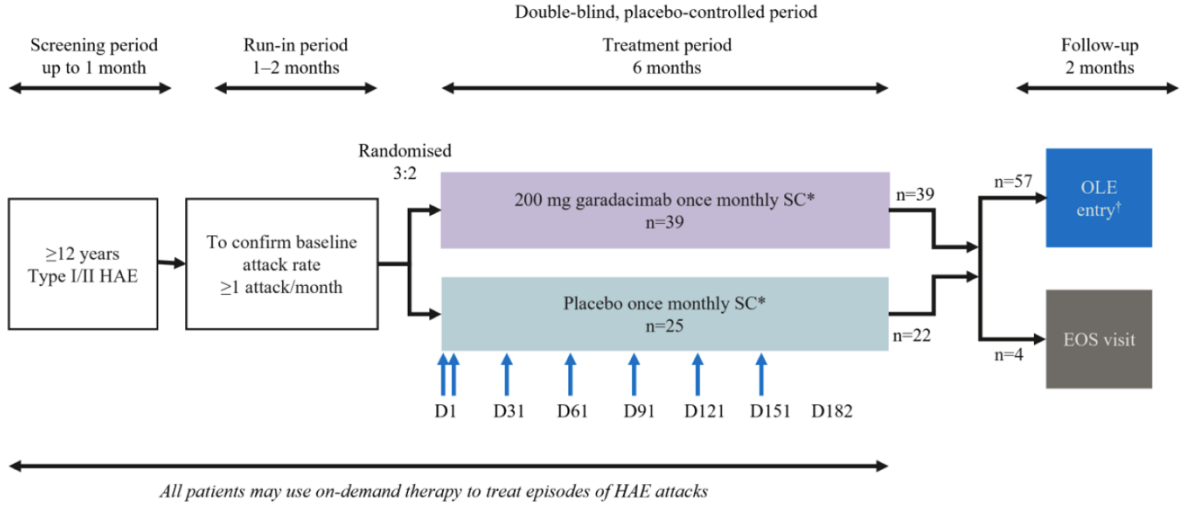
B.2.3.1.1 VANGUARD

VANGUARD was a phase 3, randomised, double-blind, placebo-controlled, multinational, multicentre study, conducted from January 2021 to June 2022.[44,78] The objective of the VANGUARD study was to evaluate the efficacy and safety of garadacimab 200 mg once monthly vs placebo for the routine prevention of HAE attacks in patients ≥12 years of age with HAE-1/2 experiencing ≥1 attack per month.[44]

The VANGUARD study design is illustrated in Figure 9. The study included a screening period (up to 1 month) to identify potentially eligible patients and a run-in period (up to 2 months) to confirm baseline HAE attack rate and eligibility. Patients discontinued routine HAE prophylaxis for ≥2 weeks before entering the run-in period. Eligible patients were randomised 3:2 to monthly garadacimab or placebo and entered the 6-month treatment period.[44]

Randomisation was stratified by patient age (≤17 years and >17 years) and, for adults, baseline attack rate observed during the run-in period (1 to <3 per month and ≥3 per month). On the first day of the treatment period (day 1), patients in the garadacimab arm were treated with a 400 mg loading dose (two 200 mg SC injections). This was followed by 5 self- or caregiver-administered monthly doses of 200 mg SC injections over the remaining treatment period.[44] Patients in the placebo group received two volume-matched doses of placebo and one monthly volume-matched dose. At the end of the treatment period, patients either entered a 2-month follow-up period or entered the CSL312_3002 OLE study (Section B.2.3.1.2).[44]

Figure 9. VANGUARD (CSL312_3001) phase 3 study design



Abbreviations: D, study day; EOS, end-of-study; HAE, hereditary angioedema; OLE, open-label extension; SC, subcutaneous.
Note: The 2-month follow-up period started 3 months post-last treatment dose.
*Patients received a 400-mg loading dose of garadacimab (2x 200 mg) or volume-matched placebo as first dose.
†Entry into phase 3b CSL312_3002 OLE study, ClinicalTrials.gov identifier: NCT04739059.
Source: Craig et al., 2023.[44]

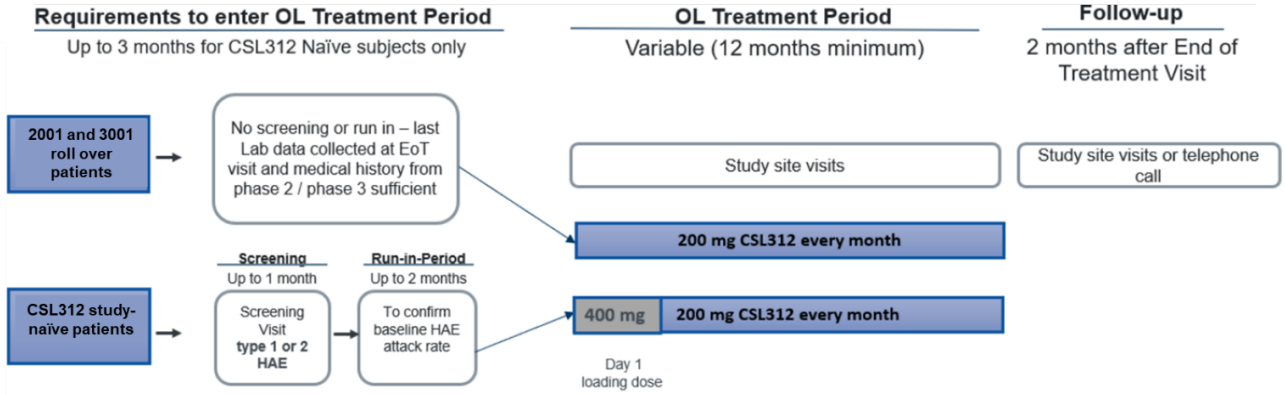
B.2.3.1.2 CSL312_3002

The CSL312_3002 study is an ongoing phase 3b, multinational, multicentre, open-label study in patients aged ≥12 years with HAE experiencing ≥1 attack per month (N=161). This study includes patients previously enrolled in the phase 3 VANGUARD study and the phase 2 CSL312_2001 study, as well as eligible patients who were not previously enrolled in the garadacimab studies (CSL312 study-naïve). The objective of the CSL312_3002 study is to evaluate the long-term safety and efficacy of garadacimab 200 mg once monthly for prophylaxis to prevent HAE attacks in patients ≥12 years of age.[79]

The CSL312_3002 study design is illustrated in Figure 10. Prior to entering the open-label treatment period, eligible CSL312 study-naïve patients were required to initiate CSL312_3002 with a screening period (up to 1 month) to identify potentially eligible patients and a run-in period (up to 2 months) to confirm baseline HAE attack rate and eligibility. During the treatment period, patients are treated with garadacimab once-monthly; for CSL312-study-naïve patients, an initial loading dose of 400 mg was administered at the start of the treatment period (day 1). The

treatment period was variable in duration (criteria not reported), but all patients were to receive garadacimab for ≥12 months; at the end of the treatment period, patients entered a 2-month follow-up period.[79]

Figure 10. CSL312_3002 study design



Abbreviations: CLS312, garadacimab; EoT, end of treatment; HAE, hereditary angioedema; OL, open-label.
Source: CSL Behring Data on File, CSL312_3002 CSR (2023).[79]

B.2.3.2 Study methods

The study methods for the VANGUARD and CSL312_3002 studies are summarised in Table 6.

Table 6. Comparative summary of study methodology

Study number (acronym)	CSL312_3001 (VANGUARD; NCT04656418)[44,78]	CSL312_3002 (NCT04739059)[79]
Study design	Phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel-arm study	Phase 3b, multinational, multicentre, open-label study
Settings and locations where the data were collected	28 sites in 7 countries (Canada, Germany, Hungary, Israel, Japan, the Netherlands, and the US)	47 sites in 14 countries (Australia, Canada, Czech Republic, Germany, Hong Kong, Hungary, Israel, Japan, the Netherlands, New Zealand, Russia, Spain, Taiwan, and the US)

Eligibility criteria for participants (Key Inclusion)	• Male or female aged ≥12 years
	• Diagnosis of HAE-1/2, confirmed by the following criteria:
	  ○ Documented clinical history consistent with HAE,
	  ○ C1-INH functional activity <50% of normal, and
	  ○ C4 antigen concentration below the lower limit of the reference range (0.16–0.38 mg/mL)
	• Experienced ≥3 HAE attacks during the 3 months before screening
	• Participated in the run-in period for ≥1 month and experienced ≥1 attack per month in the study run-in period	

Eligibility criteria for participants (Key Exclusion)	• Concomitant diagnosis of other forms of angioedema (e.g. idiopathic or acquired HAE)* • Use of monoclonal antibodies ≤3 months before the run-in period • Use of oestrogen-containing medications with systemic absorption ≤4 weeks before the run-in period • Use of C1-INH products, androgens, antifibrinolytics, or other small molecule medication for routine prophylaxis against HAE ≤2 weeks prior to the run-in period	

Study number (acronym)	CSL312_3001 (VANGUARD; NCT04656418)[44,78]	CSL312_3002 (NCT04739059)[79]
Study drugs **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	**Intervention: garadacimab 200 mg once monthly (n=39)** • Loading dose: 400 mg (administered as 2 × 200 mg SC injections) • Subsequent doses: once monthly SC injections of 200 mg at scheduled times **Comparator: Placebo (n=25)** • A volume-matched loading dose of placebo administered SC as 2 injections. • Subsequent volume-matched placebo administered SC once monthly at scheduled times.	**Intervention: garadacimab 200 mg once monthly (n=161)** • Loading dose: of 400 mg (2 × 200 mg doses) was administered SC on Visit Day 1 (for CSL312 study-naïve patients only) • Once monthly 200 mg was administered SC once per month in subsequent months **Comparator: N/A**
Permitted and disallowed concomitant medication	**Prohibited medications:** • Routine (long-term) prophylaxis to prevent HAE attacks with the use of C1-INH products, androgens, antifibrinolytics, lanadelumab, or future approved medications • Angiotensin-converting enzyme inhibitors • Use of oestrogen-containing contraceptive regimens or replacement therapy with systemic absorption (e.g. oral contraceptive or hormonal replacement therapy) On-demand therapies were permitted as per patient treatment plans.	**Prohibited medications:** • Routine (long-term) prophylaxis to prevent HAE attacks with the use of C1-INH products, androgens, antifibrinolytics, lanadelumab, or future approved medications • Use of oestrogen-containing contraceptive regimens or replacement therapy with systemic absorption (e.g. oral contraceptive or hormonal replacement therapy) On-demand therapies were permitted as per patient treatment plans.

Study number (acronym)	CSL312_3001 (VANGUARD; NCT04656418)[44,78]	CSL312_3002 (NCT04739059)[79]
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the investigator-assessed time-normalised number of HAE attacks during the 6-month treatment period (Days 1 to 182). Symptoms of an HAE attack were recorded in a patient's electronic diary and then assessed by the investigator at each monthly visit to confirm whether the symptoms represented an HAE attack.	The primary endpoint was TEAEs
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints** Three secondary efficacy endpoints comparing garadacimab 200 mg with placebo were tested in the following hierarchical order: • Percentage reduction in the monthly number of HAE attacks from baseline to the end of the treatment period • Number of patients who were attack-free at the end of the treatment period • Percentage of patients rating therapy as "good" or better with the SGART at the end of the treatment period Additional secondary efficacy endpoints were: • Attack rate reductions compared with the run-in period (defined as ≥50%, ≥70%, ≥90%, or 100% reduction) • Attack rates over prespecified timepoints (Month 1 to 3, Month 4 to 6, Month 1 to 6)	**Secondary efficacy endpoints** • Time-normalised number of HAE attacks • Percentage reduction in the number of HAE attacks per month compared with the run-in period (defined as ≥50%, ≥70%, ≥90%, or 100% reduction) ○ For patients previously treated with garadacimab, the run-in period considered for this outcome was from their initial study (VANGUARD or CSL312_2001) • Time-normalised number of HAE attacks requiring on-demand treatment • Time-normalised number of moderate or severe HAE attacks **Exploratory endpoints** • Time to first HAE attack (in garadacimab-naïve patients)

Study number (acronym)	CSL312_3001 (VANGUARD; NCT04656418)[44,78]	CSL312_3002 (NCT04739059)[79]
	• Number of attacks per month requiring rescue medication, and number of moderate or severe attacks per month **Exploratory efficacy endpoints** • Time to first HAE attack • AE-QoL and EQ-5D-5L **Safety endpoints** • TEAEs • Deaths	
Further secondary and exploratory outcomes	PK and PD exploratory analyses consisted of garadacimab concentrations at scheduled timepoints during the treatment period, and FXII concentration and FXIIa-mediated kallikrein activity at scheduled timepoints.	An analysis of garadacimab plasma concentrations was performed in garadacimab-naïve patients, and factor XIIa-mediated kallikrein activity was reported for all patients as a percentage of baseline
Pre-planned subgroups	• Japanese vs non-Japanese • Adolescent (12 to ≤17 years) vs adult [>17 years] patients (PK and PD analyses only)	Several subgroups are defined for the efficacy, safety, PK and PD analyses: • Treatment-naïve vs non-treatment-naïve • Japanese vs non-Japanese • Asian vs non-Asian • Adolescent (12 to ≤17 years old) vs adult (>17 years old) • Pharmacokinetic subgroup of adult, garadacimab-naïve patients

Study number (acronym)	CSL312_3001 (VANGUARD; NCT04656418)[44,78]	CSL312_3002 (NCT04739059)[79]
Duration of follow-up / loss to follow-up / cross over	The treatment period of the study was 6 months (182 days). Patients who successfully completed VANGUARD had the option to roll-over into the CSL312_3002 study (as outlined in next column). • Patients who chose not to participate in CSL312_3002 were required to complete the Follow-up Visit for VANGUARD (Day 242, which was approximately 3 months after the last dose of the investigational product). • For the patients who chose to participate in CSL312_3002, assessments were collected on Day 182 of VANGUARD to fulfil applicable assessments for Day 1 of Study CSL312_3002. • If discontinuation occurred before Day 182, patients were encouraged to remain in the study until Day 182 in order to complete the End of Treatment Period Visit and collect relevant study and safety assessments. • If the patient withdrew from the study and withdrew consent for disclosure of future information, any data collected before withdrawal of consent may have been retained and analysed by CSL Behring. If a patient discontinued the study early after being continuously the first 30 days in the treatment period, the observation is terminated by the Early Termination Visit. It is assumed that the attack rate for subjects, who discontinued the study after the 30th study day and before the end of the 6th month, is	The treatment period has a variable duration for individual patients but will last for a minimum of 12 months. Patients are contacted approximately 2 months after the End of Treatment Visit to complete final study assessments. If a patient repeatedly failed to return for scheduled visits, the site attempted to contact the patient and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wished to and/or should have continued in the study. All attempts to contact the patient were documented in the patient's medical record. A patient was considered lost to follow-up if they repeatedly failed to return for scheduled visits and were unable to be contacted by the study site. Patients lost to follow-up were considered to have withdrawn from the study.

Study number (acronym)	CSL312_3001 (VANGUARD; NCT04656418)[44,78]	CSL312_3002 (NCT04739059)[79]
	comparable to the attack rate from patients who have the entire 6 months treatment period observed • The time-normalised number of HAE attacks was not calculated if the patient's observation time for the Treatment Period was less <30 days, i.e. patient discontinued within 30 days after first study drug administration.	

*Study CSL312_3002 included two patients with HAE-3 who rolled over from the phase 2 CSL312_2001 study
Abbreviations: AE, adverse event; AESI, adverse event of special interest; AE-QoL, Angioedema QoL questionnaire; C1-INH, C1-esterase inhibitor; EQ-5D-5L, EuroQoL 5-dimension 5-level questionnaire; HAE, hereditary angioedema; IGART, Investigator Global Assessment of Response to Therapy; LTP, long-term prophylaxis; PD, pharmacodynamics; PK, pharmacokinetics; PRO, patient-reported outcome; TEAE, treatment-emergent adverse events; TSQM, treatment satisfaction questionnaire for medication; WPAI:GH, Work Productivity and Activity Impairment: General Health.
Source: Craig et al., 2023;[12] CSL Behring Data on File, CSL312_3001 CSR (2022);[78] CSL Behring Data on File, CSL312_3002 CSR (2023).[79]

B.2.3.3 Patient disposition and baseline characteristics

B.2.3.3.1 VANGUARD

Of the 80 patients screened, a total of 65 were randomised 3:2 to garadacimab 200 mg or placebo. One patient was randomly assigned in error and did not enter the treatment period. As a result, the intention-to-treat (ITT) population comprised of 64 patients treated with garadacimab (n=39) or placebo (n=25). The study analysis sets from the VANGUARD study are detailed in Section B.2.4 and the CONSORT diagram is supplied in Appendix M.

Overall, 39 patients in the garadacimab arm and 22 patients in the placebo arm completed the 6-month treatment period, thereby achieving an adequate sample size for powering.[12,78]

Key baseline patient characteristics were similar across both treatment groups (Table 7). For example, the majority of patients in the garadacimab and placebo arms were female (62% and 56%, respectively) and White (85% and 88%, respectively), and had a similar mean (95% CI) age at screening (43.3 [redacted] and 37.8 [redacted] years, respectively).[12]

The VANGUARD study population was representative of the HAE patient population in the UK, as characterised by the Yong et al. audit and Icatibant Outcome Survey (Section B.1.3.1.3), and ratified by three consultant immunologists in England interviewed by CSL Behring (Section B.3.3.10). Across these surveys, UK patients with HAE were mostly female (~60%) with a mean age of 43 years, in line with the VANGUARD population.[12,16,38] In the Yong et al. study, 19% of patients were <18 years of age, which was higher than the 9% in the VANGUARD study but in line with the HELP study for lanadelumab.[12,16,43]

Table 7. VANGUARD baseline patient characteristics – ITT population

Characteristic	Garadacimab (n=39)	Placebo (n=25)	Total (N=64)
Demographic characteristics			
Age at screening (years) Mean (SD)	43.3 (17.5)	37.8 (12.8)	41.2 (15.9)

Characteristic	Garadacimab (n=39)	Placebo (n=25)	Total (N=64)
Median (min, max)	[redacted]	[redacted]	[redacted]
Age group at diagnosis, n (%), years			
<18	[redacted]	[redacted]	[redacted]
18 to <40	[redacted]	[redacted]	[redacted]
40 to <65	[redacted]	[redacted]	[redacted]
≥65	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	24 (61.5)	14 (56.0)	38 (59.4)
Male	15 (38.5)	11 (44.0)	26 (40.6)
BMI at screening, kg/m^2			
Mean (SD)	27.9 (6.0)	28.4 (7.6)	28.1 (6.6)
Median (min, max)	[redacted]	[redacted]	[redacted]
Baseline weight group (kg), n (%)			
<50	[redacted]	[redacted]	[redacted]
50 to <75	[redacted]	[redacted]	[redacted]
75 to <100	[redacted]	[redacted]	[redacted]
≥100	[redacted]	[redacted]	[redacted]
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Japanese	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other PI	[redacted]	[redacted]	[redacted]
White	33 (84.6%)	22 (88.0%)	55 (85.9%)
Other	[redacted]	[redacted]	[redacted]
HAE history			
HAE type, n (%)			
1	34 (87%)	22 (88%)	56 (88%)
2	5 (13%)	3 (12%)	8 (13%)
Baseline number of HAE attacks per month during run-in, n (%)			
<2	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]
≥8	[redacted]	[redacted]	[redacted]
Patients on prophylactic therapy ≤3 months before screening,[a] n (%)	14 (36%)	7 (28%)	21 (33%)
Number of HAE attacks ≤3 months before screening or at the start of prophylaxis, mean (95% CI)	8.6 (6.3, 10.9)	9.3 (6.4, 12.2)	8.9 (7.1, 10.6)
Number of HAE attacks during run-in period, mean (95% CI)	3.1 (2.4, 3.7)	2.5 (2.1, 2.9)	NR
History of laryngeal attacks, n (%)	21 (54%)	17 (68%)	38 (59%)

Characteristic	Garadacimab (n=39)	Placebo (n=25)	Total (N=64)
Location of HAE ≤3 months before screening, n (%)			
Cutaneous (extremities)	30 (77%)	20 (80%)	50 (78%)
Abdominal	30 (77%)	18 (72%)	48 (75%)
Cutaneous (head, face, lip, neck)	13 (33%)	8 (32%)	21 (33%)
Throat, larynx, or tongue	3 (8%)	2 (8%)	5 (8%)
Peripheral[b]	1 (3%)	0	1 (2%)

Abbreviations: BMI, body mass index; C1-INH, C1-esterase inhibitor; CI, confidence interval; HAE, hereditary angioedema; ITT, intention-to-treat; IV, intravenous; NR: not reported;SC, subcutaneous; SD, standard deviation.
[a] During the 3 months before entering the run-in period, all 21 (33%) patients receiving HAE prophylaxis discontinued their prophylactic treatments, including C1-INH (SC or IV), berotralstat, lanadelumab, tranexamic acid, and danazol.
[b] As described by the investigator using the free text option in the patient's eDiary.
Abbreviations: BMI, body mass index; C1-INH, C1-esterase inhibitor; CI, confidence interval; HAE, hereditary angioedema; ITT, intention-to-treat; IV, intravenous; PI, Pacific Islander; SC, subcutaneous; SD, standard deviation.
Source: Craig et al., 2023;[12] CSL Behring Data on File, CSL312_3001 TFLs (2024).[80]

B.2.3.3.2 CSL312_3002

A total of 161 patients entered the CSL312_3002 study and received garadacimab once monthly. Of these patients, 35 had rolled over from the CSL312_2001 study and 57 from the VANGUARD study (previously randomised to garadacimab [n=36] or placebo [n=21]). A further 79 patients who were not previously enrolled in the CSL312 studies (CSL312-study-naïve) were screened for inclusion, of whom 69 entered the treatment period. All patients who entered the treatment period (n=161) were included in the all treated patients (ATS) population.[79]

As of the latest data cut-off (IA4), a total of 14 patients had prematurely discontinued treatment and six had completed the study. A total of 147 (91.3%) patients have been treated with garadacimab for ≥12 months.[81]

The study analysis sets from the CSL312_3002 study are detailed in Section B.2.4 and the CONSORT diagram is supplied in Appendix M.

The baseline demographics and HAE history characteristics were similar in patients who were previously garadacimab-naïve and those who rolled over from garadacimab treatment in VANGUARD, showing that the characteristics are

well-balanced between these subpopulations (see Appendix O for baseline characteristics in these subpopulations).[82,83]

Key baseline demographics and disease characteristics of the ATS population of CSL312_3002 are shown in

Table 8. Most patients were female (62.7%) and the mean age at screening was 42.3 years, in line with baseline characteristics of VANGUARD and the general population of patients with HAE in the UK as described in Section B.2.3.3.1.[41]

Table 8. CSL312_3002 baseline patient characteristics – ATS population

Characteristic	Garadacimab (n=161)
Demographic characteristics	
Age at screening (years)	
Mean (SD)	42.3 (15.3)
Median (min, max)	[redacted] (13, 73)
Age group at diagnosis, n (%), years	[redacted]
<18	
18 to <40	
40 to <65	
≥65	
Sex, n (%)	
Female	101 (62.7)
Male	60 (37.3)
BMI at screening, kg/m^2	[redacted]
Mean (SD)	
Median (min, max)	
Baseline weight group (kg), n (%)	
<50	[redacted]
50 to <75	
75 to <100	
≥100	
Number missing	
Race, n (%)	
Asian	22 (13.7)
Japanese	[redacted]
Black or African American	2 (1.2)
White	135 (83.9)
Other	1 (0.6)
Multiple	1 (0.6)
HAE history	

Characteristic	Garadacimab (n=161)
HAE type, n (%)*	
HAE-1	145 (90.1)
HAE-2	14 (8.7)
HAE-3	2 (1.2)
Patients on prophylactic therapy ≤3 months before screening, n (%)*	59 (36.6)
Number of HAE attacks ≤3 months before screening or at the start of prophylaxis, mean (95% CI)†	[redacted]
Number of HAE attacks during run-in period, mean (95% CI)	4.7 (4.2, 5.1)
History of laryngeal attacks, n (%)*	103 (64.0)
Primary locations of HAE ≤3 months before screening, n (%)*#	
Cutaneous - Extremities	124 (77.0)
Abdomen	123 (76.4)
Cutaneous - Head/Face/Lip/Neck	51 (31.7)
Cutaneous - Trunk	16 (9.9)
Throat	15 (9.3)
Cutaneous – Genito-urinary	[redacted]

Abbreviations: ATS, all treated patients; BMI, body mass index; SD, standard deviation.
* Percentages are based on the ATS analysis set.
† Patients without HAE prophylaxis: number of HAE attacks during the 3 months before screening; patients with HAE prophylaxis: number of HAE attacks during the 3 months before starting the HAE prophylaxis.
# Up to three locations could be selected per patient.
Sources: Reshef et al. 2024;[41] CSL Behring Data on File, CSL312_3002 CSR (2023);[79] CSL Behring Data on File, CSL312_3002 IA4 TFLs (2024).[81]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses and definition of study groups for the VANGUARD and CSL312_3002 studies are presented in Table 9. The full details of all studies included in this submission are presented in Appendix D.

Table 9. Summary of statistical analyses

Trial number (acronym)	VANGUARD (CSL312_3001)	CSL312_3002
Study objectives and structure	**Primary objective**: to evaluate the safety and efficacy of garadacimab in the prophylactic treatment of patients with HAE. The study consisted of a screening period (up to 1 month), a run-in period (up to 2 months), a treatment period (6 months), and either a 2-month follow-up period (i.e. 3 months after last investigational product administration) or entry into the open-label phase 3b CSL312_3002 study.[84]	**Primary objective**: to evaluate the long-term safety of garadacimab in the prophylactic treatment of patients with HAE. The study consisted of four periods: screening, run-in (for garadacimab-naïve patients), open label treatment period (≥12 months), and a follow-up period.[79]
Endpoints	**Primary endpoint**:[84] • Time-normalised number of HAE attacks during treatment from Day 1 through Day 182 **Secondary endpoints**:[84] • Reduction in attack rate during the treatment period compared to the run-in period, as well as for the first 3-months and second 3 months of treatment • The time-normalised number of HAE attacks during the treatment period, as well as for the first 3-months and second 3 months of treatment • The time-normalised number of moderate and/or severe HAE attacks during the treatment period, as well as for the first 3-months and second 3 months of treatment	**Primary endpoint**:[79] • TEAEs **Secondary efficacy endpoints**:[79] • Time-normalised number of HAE attacks for the run-in and treatment period • The reduction in attack rate during the treatment period compared to the run-in period • The time-normalised number of HAE attacks requiring on-demand treatment in patients on treatment • The time-normalised number of moderate and/or severe HAE attacks in patients on treatment • SGART

Trial number (acronym)	VANGUARD (CSL312_3001)	CSL312_3002
	• Time-normalised number of HAE attacks and reduction in attack rate during the treatment period compared to the run-in period for the first 3-months and second 3 months of treatment • SGART distribution of responses compared between the garadacimab and placebo groups at the end of the treatment period at Day 182 • Safety endpoints including TEAEs, SAEs, AESIs and garadacimab-induced anti-drug antibodies during the entire treatment period until follow-up or final visit **Key exploratory endpoints**:[84] • Time to first HAE attack after Day 1 and Day 14 • HRQoL, as measured by EQ-5D-5L and AE-QoL	• Safety endpoints including SAEs, deaths, related TEAEs, TEAEs leading to study discontinuation, AESIs, and anti-drug antibodies **Key exploratory endpoints:[79]** • Time to first HAE attack in garadacimab-naïve patients • HRQoL as measured by AE-QoL
Study hypotheses	Four tests were planned in a hierarchical order with a 2-sided alpha of 5% each. The four null hypotheses were defined as follows:[84] • **First hierarchical test (H01)**: the time-normalised number of HAE attacks in the 6-month treatment period of the garadacimab arm and placebo arm are equal. • **Second hierarchical test (H02)**: the percentage reduction in the means of the time-normalised number of HAE attacks in the 6-month treatment period of the garadacimab arm and placebo arm are equal to zero. • **Third hierarchical test (H03)**: the number of patients who do not experience an HAE attack in the first 3 months of treatment in the garadacimab arm and placebo arm are equal. • **Fourth hierarchical test (H04)**: the percent of patients with good or excellent responses to the SGART at the end of the	There are no formal hypotheses for this study. Instead, this study is designed for the assessment of long-term safety and efficacy of 200 mg garadacimab in HAE patients.[85]

Trial number (acronym)	VANGUARD (CSL312_3001)	CSL312_3002
	treatment period (Day 182) are equal for patients treated with garadacimab and placebo.	
Analysis sets	**Intention-to-treat (ITT) Analysis Set (N=64):** All randomised patients. **Safety Analysis Set (N=64):** All patients in the ITT Analysis Set who received at least 1 dose of study treatment and was analysed using the actual treatment received.	**All Treated Patients (ATS) Analysis Set (N=161):** All patients who were assigned to treatment. **Safety Analysis Set (N=161):** All patients in the ATS Analysis Set who received at least 1 dose of investigational product and was analysed using the actual treatment received.
Sample size, power calculation	A sample size of 60 patients, including five adolescents, would be required to ensure 6-month study completion by at least 40 patients to detect a treatment difference in the time-normalised number of investigator-confirmed attacks between garadacimab and placebo with approximately 90% power using a two-sided Wilcoxon test (α-level 0.05), assuming an attack rate per month of 0.3125 with garadacimab and 1.3 with placebo.[78]	Approximately 150 patients are planned to be enrolled into the study and a minimum of 100 patients are planned to receive treatment for a minimum of 12 months.[85] The sample size for this single arm, open-label study is based on the guideline E1A issued by the ICH, March 1995.[86] The sample size of 100 patients allows observation of ≥1 AE with a probability of 3% at 95% confidence.[85]
Sensitivity analysis on primary analysis	The primary endpoint (time-normalised number of HAE attacks over the 6 month treatment period) was adjusted for baseline attack rate in a sensitivity analysis using a generalised linear model for count data assuming a Poisson distribution. The time-normalised number of HAE attacks of the run-in period as a covariate and the logarithm of the length of patient treatment as an offset variable were included.[78]	The COVID-19 pandemic was ongoing throughout the conduct of the study. To evaluate the impact of COVID-19 on the primary endpoint, the overview summary of TEAEs and the summary table by SOC and PT were repeated excluding all of the COVID-19 related TEAEs (per the corresponding SMQ).[85]
Subgroup analysis	The pre-defined subgroup analyses were previously outlined in Table 6 of Section B.2.3.2. Since the pre-defined subgroup included ≥5 patients, the analysis was conducted as planned.[78]	The pre-defined subgroup analyses were previously outlined in Table 6 of Section B.2.3.2. Since each of the pre-defined subgroups included ≥5 patients, subgroup analyses were conducted as planned.[85]

Trial number (acronym)	VANGUARD (CSL312_3001)	CSL312_3002
Interim analyses	N/A	This submission presents data from IA4. Another interim analysis is planned to be conducted when approximately 100 patients have 12 months exposure of garadacimab in the CSL312_3002 study alone or across all studies, i.e. the phase 2 CSL312_2001 study, VANGUARD and CSL312_3002, dependent on patients' enrolment in the CSL312_3002.[85] In addition, further interim analyses may be conducted on an as-needed basis in order to support regulatory activities.[85]
Data management, patient withdrawals	• Patients could discontinue study treatment with garadacimab or withdraw from the study at any time at their own request, or at the discretion of the investigator or CSL Behring for safety, behavioural, or administrative reasons (e.g. due to an AE, protocol deviation, loss to follow-up, patient noncompliance, study terminated by CSL Behring).[78,84] • Patients who discontinued treatment were encouraged to remain in the study until Day 182 in order to complete the End of Treatment Period Visit and collect relevant study and safety assessments.[78,84] • If the patient withdrew from the study and also withdrew consent for disclosure of future information, any data collected before withdrawal of consent may have been retained and analysed by CSL Behring.[78,84]	• Patients could withdraw from the study at any time at their own request or at the discretion of the investigator or CSL Behring for safety, behavioural, or administrative reasons (e.g. because of an AE, protocol deviation, loss to follow-up, patient noncompliance, or study termination).[79,85] • If a patient was withdrawn from the study, attempts were made to complete and document the End of Treatment Visit assessments. If the patient was withdrawn from the study after receiving garadacimab, every effort was made to ensure that the relevant safety assessments were completed. The patient may also have been asked by the investigator to complete other study assessments.[79,85] • If the patient withdrew from the study and also withdrew consent for disclosure of future information, CSL Behring could retain and continue to use any data collected before such withdrawal of consent.[79,85]

Abbreviations: AE, adverse event; AESI, adverse event or special interest; AE-QoL, Angioedema quality of life questionnaire; ATS, All Treated Patients; C1-INH, C1-esterase inhibitor; COVID-19; Coronavirus disease 2019; eCRF, electronic case report form; GCP, Good Clinical Practice; HAE, hereditary angioedema; ICH; International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IA4, interim analysis 4; IGART, Investigator's Global Assessment of Response to Therapy; ITT, intention-to-treat; PD, pharmacodynamic, PK, pharmacokinetic; PP, per-protocol, PT, preferred term; QoL, quality of life; SAE, serious adverse event; SAP, Statistical Analysis Plan; SGART, Subject's Global Assessment of Response to Therapy; SMQ, Standardised MedDRA Query; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Sources: CSL Behring Data on File, CSL312_3001 CSR (2022);[78] CSL Behring Data on File, CSL312_3001 SAP (2021),[84] CSL Behring Data on File, CSL312_3002 CSR (2023);[79] CSL Behring Data on File, CSL312_3002 SAP (2021).[85]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for the pivotal phase 3 study VANGUARD and the phase 3b open-label extension study VANGUARD OLE are presented in Appendix D.

B.2.6 Clinical effectiveness results of the relevant studies

The main efficacy results are presented herein from the final data cut-off of the 6-month pivotal VANGUARD study (N=65).[12] Supporting efficacy evidence is also provided from the latest data cut-off of the CSL312_3002 OLE study (IA4; [redacted]), which included 161 patients with a median (min, max) duration of treatment of [redacted] ([redacted]) months, which is >[redacted] longer than the treatment period of the VANGUARD study.[81]

A tabulated summary of key efficacy results is provided in Section B.2.9. which covers these studies and the post-hoc analyses listed previously in Section B.2.3.

B.2.6.1 Time-normalised number of HAE attacks

The VANGUARD study met its primary endpoint by demonstrating that during the treatment period, the mean number of investigator-confirmed HAE attacks per month was 7.4 times lower in the garadacimab group (0.27; 95% CI: 0.05, 0.49) than in the placebo group (2.01; 95% CI: 1.44, 2.57; p<0.0001).[12] This equated to a relative difference in the mean time-normalised number of HAE attacks of −86.5% (p<0.001) between garadacimab and placebo.

Consistent results for garadacimab were observed in the CSL312_3002 study, in which the mean number of investigator-confirmed HAE attacks per month was also low with garadacimab treatment ([redacted]; 95% CI: [redacted]).[81] This was independent of outcomes from rollover patients who had previously received garadacimab treatment over a longer duration, as shown in a post-hoc subgroup analysis of garadacimab-naïve patients (n=90), who experienced a mean number of HAE attacks per month of [redacted] (95% CI: [redacted]).[82]

In the pre-specified sensitivity analysis for the VANGUARD study, after adjusting for baseline number of attacks, the clinical benefit of garadacimab remained consistent and the difference in the least squares (LS) mean monthly number of attacks between garadacimab and placebo was −89.2%. This provides further evidence that the efficacy of garadacimab is independent of any differences in baseline attack frequency between treatment arms.

B.2.6.2 Reduction from baseline in the time-normalised number of HAE attacks

In the VANGUARD study, the baseline mean number of HAE attacks per month established during the run-in period was similar for the garadacimab and placebo arms.[12] At the end of the treatment period, patients treated with garadacimab experienced a 90.7% (95% CI: 83, 98) mean reduction in attacks from baseline, which was significantly greater compared to a reduction of 20.2% (95% CI: 2, 38) with placebo (p<0.0001). This statistically significant difference between garadacimab and placebo was observed during both the first 3 months (nominal p<0.001) and second 3 months of treatment (nominal p<0.001).[78] Most patients treated with garadacimab experienced a ≥50% and ≥90% reduction in the number of monthly attacks from baseline at the end of the treatment period (92% and 74%, respectively), compared to 17% and 8% in the placebo group, respectively.[12]

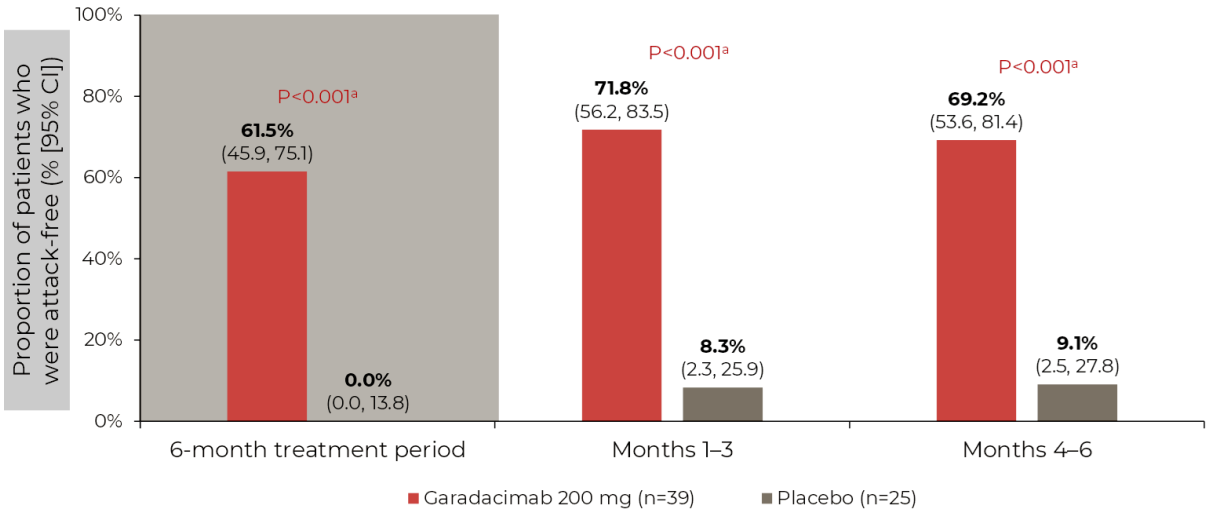
In the CSL312_3002 study, treatment with garadacimab was still associated with a substantial reduction in mean time-normalised number of attacks from baseline ([redacted]% reduction; 95% CI: [redacted]%).[81] Similar results were maintained in a post-hoc subpopulation of patients who were naïve to garadacimab at the start of the CSL312_3002 study (n=90), with a mean reduction in HAE attack rate from baseline of [redacted]% (95% CI: [redacted]).[82]

B.2.6.3 Proportion of patients achieving attack freedom

Achieving attack freedom is a key goal of HAE management (Section B.1.3.3). A significantly higher proportion of patients treated with garadacimab in the VANGUARD study were attack-free (i.e. had 100% reduction in HAE attacks from

baseline) vs. placebo (61.5% vs 0%, nominal p<0.001) over the 6-month treatment period. The difference between garadacimab and placebo in the proportion of patients achieving attack freedom was seen during the first 3 months of treatment (71.8% vs 8.3%, p<0.001 [H03]), potentially indicative of the rapid onset of action of garadacimab.(Figure 11).[12] Additionally, in the CSL312_3002 study, most patients ([redacted]%; 95% CI: [redacted]) remained attack free at the time of the latest data cut-off.[81] Similar results were maintained in a post-hoc subpopulation of patients who were naïve to garadacimab at the start of the CSL312_3002 study (n=90), with a [redacted]% of patients attack-free at the latest data cut-off.[82]

Figure 11. Proportion of patients who were attack-free (VANGUARD, ITT population)



Abbreviations: CI, confidence interval, ITT, intention-to-treat
[a] Nominal p-value
Note: In VANGUARD, one patient in the placebo group stayed less than 30 days in the treatment period and was excluded from the analysis, as per the clinical study protocol. In the placebo group, 24 patients were included in the analysis for the first half of the treatment period (months 1–3) and 22 in the second half of the treatment period (months 4–6).
Source: CSL Behring Data on File, CSL312_3001 CSR (2022).[78]

An overview of all patients enrolled in VANGUARD and the occurrence of HAE attacks during the run-in period and the treatment period is shown in Appendix N, further demonstrating the early onset of protection with garadacimab for most patients from treatment initiation through to the end of the treatment period.[12]

B.2.6.4 Time-normalised number of HAE attacks requiring on-demand treatment

Garadacimab has the potential to reduce resource use associated with on-demand treatment for HAE attacks. In the VANGUARD study, [redacted]% of HAE attacks in patients treated with garadacimab required on-demand treatment compared with [redacted]% with placebo.[78] Patients in the garadacimab group had a significantly lower mean number of time-normalised attacks per month that required on-demand treatment compared with patients in the placebo group (0.23 [95% CI: 0.02, 0.45] vs 1.86 [95% CI: 1.26, 2.46]), corresponding to a mean difference of 88% (p<0.0001)[12]

Garadacimab also demonstrated similar efficacy in the CSL312_3002 study, with a mean time-normalised number of HAE attacks requiring on-demand treatment per month of [redacted] (95% CI: [redacted]) in the ATS population and [redacted] (95% CI: [redacted]) in the post-hoc subpopulation of patients who were naïve to garadacimab at the start of CSL312_3002 (n=[redacted]).[81,82]

B.2.6.5 Time-normalised number of moderate and/or severe HAE attacks

The mean time-normalised number of moderate and/or severe HAE attacks per month in patients treated with garadacimab during the VANGUARD study was 90% less than with placebo (0.13 [95% CI: [redacted]] vs 1.35 [95% CI: [redacted]]; p<0.0001).[78]

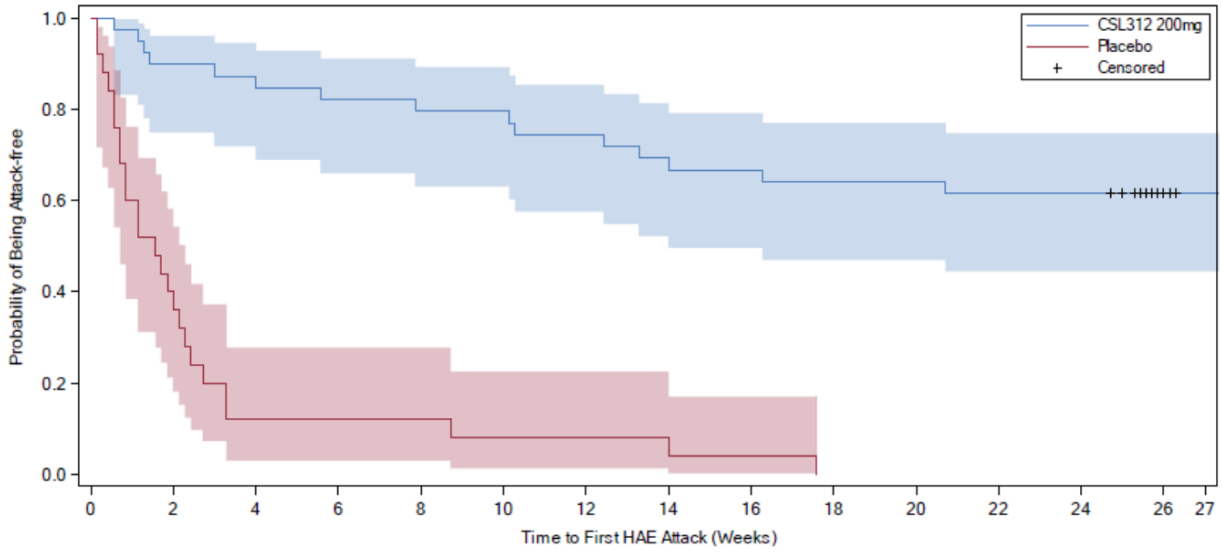
Similarly, in the CSL312_3002 study, the mean time-normalised number of moderate and/or severe HAE attacks per month was [redacted] (95% CI: [redacted] in the ATS population and [redacted] (95% CI: [redacted] in the post-hoc subgroup of patients who were naïve to garadacimab at the start of CSL312_3002.[81,82]

B.2.6.6 Time to first HAE attack

From the first dose of treatment in the VANGUARD study, time to first HAE attack for 75% of patients was ≥72 days for garadacimab compared with ≥5 days for placebo (Figure 12).[12] The median time to first attack was not estimable for garadacimab (more than 50% of patients were attack-free during the 6-month treatment period) and was 11

days for placebo.[12] In patients who were previously naïve to garadacimab in the CSL312_3002 study, the median time to first attack was ~[redacted] years ([redacted] days).[82]

Figure 12. Kaplan-Meier curve for time to first HAE attack (VANGUARD, Safety Analysis Set)



Shaded areas represent 95% CIs. Patients with no hereditary angioedema attacks were censored at study visit day 182 or at the end of study visit (whichever occurred first).
Sources: CSL Behring Data on File, CSL312_3001 CSR (2022);[78] Craig et al., 2023.[12]

B.2.6.7 Maintenance of treatment effect

A post-hoc pooled analysis of the VANGUARD and CSL312_3002 studies was conducted in patients who were randomised to garadacimab once monthly in VANGUARD and rolled over to the CSL312_3002 study (n=36; see Section B.2.2.4 for further information). This analysis supports the maintenance of the long-term treatment effect of garadacimab and includes data from the start of the VANGUARD study through to the latest data cut-off for the CSL312_3002 study, resulting in a median (min, max) treatment duration of [redacted] ([redacted]) months. The baseline demographics and HAE history characteristics for these patients are presented in Appendix E and were similar to the VANGUARD ITT population and CSL312_3002 ATS population.[83] A tabulated summary of key efficacy results can be found in Section B.2.9.

Results from these post-hoc analyses indicate that the efficacy of garadacimab in reducing the time-normalised number of attacks from baseline is maintained beyond the

randomised 6-month treatment period of VANGUARD with no evidence of waning of treatment effect even after >2 years of treatment, thus mitigating the uncertainty associated with the relatively short duration of the VANGUARD study (Figure 13). The mean time-normalised number of HAE attacks remained consistently low throughout the time period of the analysis and as of the latest data cut-off for CSL312_3002, the mean time-normalised number of attacks per month in the pooled subpopulation was [redacted] (95% CI: [redacted]), showing continued improvement compared with the garadacimab group at the end of the VANGUARD treatment period (0.27; 95% CI: 0.05, 0.49) and a treatment benefit consistent with the CSL312_3002 ATS population ([redacted]; 95% CI: [redacted]).[83]

Figure 13. Percentage reduction in time-normalised number of HAE attacks per month, monthly time windows (VANGUARD/CSL312_3002 pooled population)

Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema; no., number; q4wk, once every 4 weeks; SC, subcutaneous; time-norm., time-normalised;
Note: The percentage reduction in the time-normalised number of HAE attacks is calculated within a patient as: 100*[1–(time-normalised number of HAE attacks per month during treatment period/time-normalised number of HAE attacks per month during run-in period)]. 1 week is equal to 7 days, 1 month is equal to 28 days.
Note: pooled population includes patients who were on active treatment in VANGUARD and rolled over into CSL312_3002.
Note: Data are from completed study VANGUARD (CSL312_3001) and the latest ([redacted], IA4) data cut-off from study CSL312_3002, with a median (min, max) duration of exposure of [redacted] months.
Source: CSL Behring Data on File, pooled CSL312_3001/CSL312_3002 IA4 TFLs (2024).[83]

Similarly, the time-normalised attacks that required on-demand treatment continued to reduce on garadacimab with a mean monthly rate of [redacted] (95% CI: [redacted] at the data cut-off for CSL312_3002 compared with 0.23 (95% CI: 0.02, 0.45) at the end of the VANGUARD study.[83] The time-normalised rate of moderate and/or severe attacks also

continued to improve on garadacimab, with a mean monthly rate [redacted] (95% CI: [redacted]) at the data cut-off for CSL312_3002 vs. 0.13 (95% CI: 0.03, 0.22) after 6 months of treatment in the VANGUARD study.[83]

Additionally, the efficacy of garadacimab in prolonging the time to first attack was maintained through to the latest data cut-off of CSL312_3002, with median time to first attack not reached as most patients remained attack-free ([redacted] [redacted]%]; Figure 14).[83] Notably, nearly [redacted]% of patients in the pooled subpopulation remained attack-free after two years of treatment.

Figure 14. Kaplan-Meier curve for time to first HAE attack after Day 1 (VANGUARD/CSL312_3002, pooled population)

Abbreviation: CSL312, garadacimab; HAE, hereditary angioedema
Note: Shaded areas represent 95% CIs.
Note: Data are from completed study VANGUARD (CSL312_3001) and the latest ([redacted], IA4) data cut-off from study CSL312_3002, with a median (min, max) duration of exposure of [redacted] months.
Note: pooled population includes patients who were on active treatment in VANGUARD and rolled over into CSL312_3002.
Source: CSL Behring Data on File, pooled CSL312_3001/CSL312_3002 IA4 TFLs (2024).[83]

B.2.6.8 PROs

In the VANGUARD study, HRQoL was measured via the EuroQoL-Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire as an exploratory outcome. This outcome was mapped to EQ-5D-3L using the DSU Hernadez Alva et al. (2020) algorithm, which

informs the utility values used to input a scenario analysis in the cost-effectiveness model (Section B.3.4.5).[78,87] Patient-reported outcome (PRO) data were also obtained using the Subject's Global Assessment of Response to Therapy (SGART), AE-QoL questionnaire, Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire and Investigator's Global Assessment of Response to Therapy (IGART). The age considerations for these assessments were as follows: EQ-5D-5L, SGART, and IGART used for all ages; WPAI:GH used for ≥16 years; AE-QoL used for ≥18 years.[78] Here, results from EQ-5D-5L, AE-QoL (key disease-specific PRO) and SGART (secondary endpoint) are presented, while results from the IGART and WPAI are presented in Appendix Q.

B.2.6.8.1 EQ-5D-5L

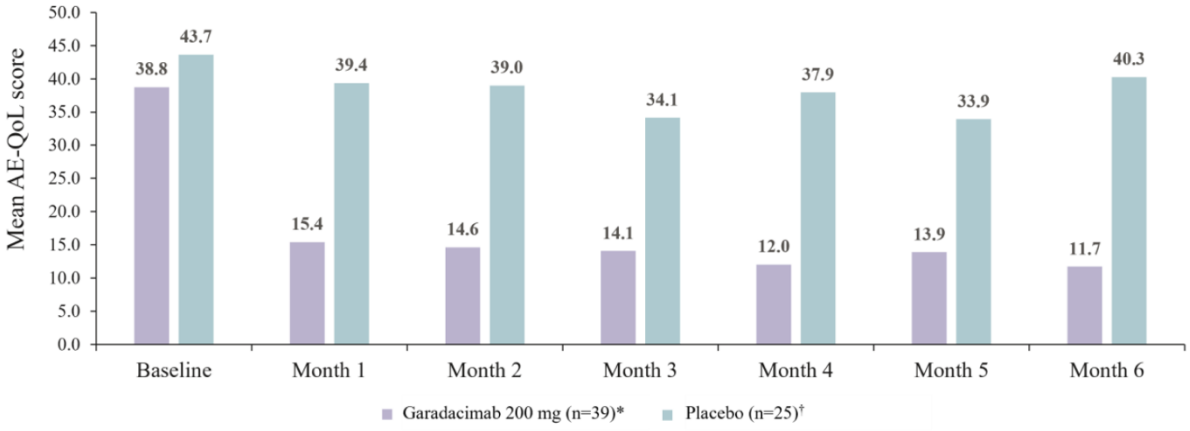
At baseline, mean EQ-5D-5L domain scores, VAS and overall health-utility state values (HSVs) were comparable between garadacimab (200 mg; n=39) and placebo (n=25) in the ITT population. The mean VAS score improved from [redacted] at baseline to [redacted] at end of the treatment period in the garadacimab arm, while it worsened in the placebo arm from [redacted] to [redacted]. Mean HSV score in the garadacimab arm improved from [redacted] at baseline to [redacted] at the end of the treatment period and worsened in the placebo arm from [redacted] to [redacted]. The difference in HSV scores over the course of the treatment period was primarily due to improvement in pain and discomfort in the garadacimab arm, while in the placebo arm patients reported worse pain and discomfort at Month 6 than they did at baseline (Appendix Q).[78]

B.2.6.8.2 AE-QoL

The Angioedema QoL (AE-QoL) questionnaire is a disease-specific instrument to assess QoL impairment in patients with recurrent angioedema attacks.[88] For patients in the garadacimab group, a clinically meaningful improvement (≥6-point reduction) of the mean AE-QoL questionnaire total score was observed at Day 31, with a 23.7-point reduction from the run-in period. Further improvements were observed at Day 182, with a 26.5-point reduction, exceeding 4 times the minimal clinically important difference (MCID). In contrast, for patients in the placebo group, no clinically meaningful

improvement in mean AE-QoL score was observed.[12] A higher proportion of patients treated with garadacimab achieved a clinically meaningful improvement from baseline in AE-QoL compared with placebo ([redacted]% vs [redacted]%).[78]

Figure 15. Mean AE-QoL questionnaire total scores observed at Month 1–6 in patients treated with garadacimab and placebo



Abbreviation: AE-QoL, Angioedema quality of life questionnaire.
*Data reflect different numbers of evaluable patients; (n=35) during month 1 and month 2 visits; (n=34) during baseline, month 3, month 5 and month 6 visits; (n=33) during month 4 visit.
†Data reflect different numbers of evaluable patients; (n=22) at baseline and month 1 visits; (n=21) at month 2 and month 6 visits; (n=20) at month 4 visit; (n=19) at month 3 visit; (n=18) at month 5 visit.
Source: Craig et al., 2023.[12]

Based on mean (SD) AE-QoL total scores, patients on garadacimab who were attack-free throughout the treatment period of the VANGUARD study experienced a lower QoL burden ([redacted] [redacted]) compared with patients treated with garadacimab who were not attack-free ([redacted] [redacted]) and a substantially lower burden compared with patients on placebo, all of whom were not attack-free ([redacted] [redacted]).[78]

B.2.6.8.3 SGART

The overall response to treatment with the investigational product was self-assessed by the patient using the SGART, which measures the patient's overall treatment response to the investigational product.[78] At the end of treatment (Day 182), the most frequently rated response to therapy in patients treated with garadacimab was "excellent" (65.8%) or "good" (15.8%), and in the placebo arm was "none" (41.7%).[12] A significantly greater

proportion of patients in the garadacimab group rated their response to therapy as "good or better" (81.6%) compared to 33.3% in the placebo arm (p<0.0001 [H04]).[12]

B.2.7 Subgroup analysis

B.2.7.1 Pre-specified subgroups

In the VANGUARD study, the pre-specified subgroup analyses assessed several outcomes for Japanese and all patients. These analyses were not performed based on an assumption that garadacimab may have a different efficacy profile, but rather to support with the regulatory approval process in Japan. Results of the primary and secondary efficacy analyses in the Japanese subgroup were consistent with results observed in the ITT population.[78]

In the CSL312_3002 study, the pre-specified subgroups analyses assessed several efficacy outcomes for adolescent patients and Japanese patients. Results of the analyses in these subgroups were consistent with results observed in the overall ATS population with, most notably, the subgroup of adolescent patients (10/161) showing a similar rate of HAE attacks and a comparable safety profile to the overall ATS population.[79]

B.2.7.2 Post-hoc analysis: patients with ≥2 attacks per month

As discussed in more detail in Section B.2.2.2.1, post-hoc subgroup analyses of the VANGUARD study were performed in patients experiencing ≥2 attacks per month at baseline (garadacimab arm: n=[redacted], placebo arm: n=[redacted]). The main aim of these subpopulation analyses was to provide further evidence that there are no treatment effect modifiers for consideration in this appraisal, including baseline attack rate, further reinforcing the ITT population as the most appropriate source of clinical evidence for garadacimab. These analyses will also help to inform the value of garadacimab within the current commissioning landscape for berotralstat.

B.2.7.2.1 Baseline characteristics

Baseline characteristics of the ≥2 attacks/month subgroup are summarised in Appendix E, which were largely aligned with the VANGUARD ITT population, with the ratio of female:male and patients' age and BMI at screening being very similar across both populations. The baseline number of HAE attacks, the percentage of patients using prophylactic therapy and the number of patients with a history of laryngeal attacks were slightly higher in the ≥2 subgroups compared to the VANGUARD ITT population, which is expected as this subpopulation is reflective of patients experiencing more frequent attacks than the full ITT population that includes patients with ≥1 HAE attack per month at baseline.

B.2.7.2.2 Key efficacy outcomes

Key efficacy outcomes of the subgroups of patients experiencing ≥2 HAE attacks per month are summarised below, with further detail available in Section B.2.9.

While the proportion of patients treated with garadacimab who were attack-free (experiencing a 100% reduction in HAE attack rates) was [redacted] in patients receiving garadacimab in the ≥2 attacks/month subgroup ([redacted]%) compared with the ITT population (61.5%), the reduction in attack rate from baseline with garadacimab was [redacted] in the ≥2 attacks/month subgroup ([redacted]%) and the full VANGUARD ITT population (90.7%).[78,89]

Additionally, in patients receiving garadacimab treatment:[79,89]

- The mean number of attacks per month was [redacted] in the ≥2 attacks/month subgroup and 0.27 in ITT population.
- The relative difference in mean time-normalised number of HAE attacks for garadacimab vs. placebo was −[redacted]% in the ≥2 attacks/month subgroup and −86.5% in ITT population.
- The mean number of attacks that required on-demand treatment per month was [redacted] in the ≥2 attacks/month subgroup and 0.23 in the ITT population.

- The mean number of moderate and/or severe attacks per month was [redacted] in the ≥2 attacks/month subgroup and 0.13 in the ITT population.
- The median time to first attack after Day 1 could not be calculated for the ≥2 attacks/month subgroup or the ITT population, as for both populations >50% of patients were attack-free during the 6-month treatment period.

Together, these results show that the key efficacy outcomes for garadacimab that were reported for the VANGUARD ITT population were consistent in the subgroup experiencing ≥2 attacks per month at baseline, supporting that baseline attack rate is not a treatment effect modifier for garadacimab.

B.2.8 Meta-analysis

It was not necessary to conduct a meta-analysis as the key efficacy and safety data for garadacimab informing this submission are provided from one pivotal study (VANGUARD).

B.2.9 Summary of efficacy results for garadacimab across studies and subpopulations

Table 10 summarises the key efficacy results from Sections B.2.6.1 to B.2.6.7 for ease of comparison between the presented studies and post-hoc analyses across multiple endpoints. As shown, the efficacy of garadacimab is robust and consistent across different time on treatment, prior exposure to treatment and baseline attack frequency.

Table 10. Garadacimab efficacy results across phase 3 studies and subpopulations

	VANGUARD				**CSL312_3002**		**Pooled VANGUARD/CSL312_3002**
	ITT population		**≥2 attacks per month**		**ATS population**	**Gara-naïve subpopulation**	**Patients who received gara throughout both studies**
	Gara (n=39)	**Placebo (n=24)**	**Gara (n=[redacted])**	**Placebo (n=[redacted])**	**Gara (n=161)**	**Gara (n=90)**	**Gara (n=36)**
Number of evaluable patients, n (%)	39 (100.0)	24 (96.0)[a]	[redacted]	[redacted][a]	161 (100.0)	90 (100.0)	36 (100.0)
Mean (95% CI) number of HAE attacks per month at baseline	3.07 (2.41, 3.73)	2.52 (2.13, 2.91)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of HAE attacks							
Mean (95% CI) number of attacks per month	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (95% CI) number of attacks per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	p<0.001 [H01]		[redacted]		N/A	N/A	N/A
Relative difference in means (95% CI); p-value	−86.5% (−95.7, −57.8); p<0.001 [H02]		[redacted]		N/A	N/A	N/A
Reduction from baseline in monthly HAE attacks							
Mean reduction in monthly HAE attacks in the treatment period vs. the run-in period[d], % (95% CI)	90.7% (83.4, 97.9)	20.2% (2.2, 38.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	<0.001		[redacted]		N/A	N/A	N/A
Proportion of patients achieving attack freedom (i.e. 100% reduction in HAE attacks from baseline)							
Proportion of patients, % (95% CI)	61.5% (45.9, 75.1)	0.0% (0.0, 13.8)	[redacted] (NR)	[redacted] (NR)	[redacted]	[redacted] (NR)	[redacted] (NR)

	VANGUARD				CSL312_3002		Pooled VANGUARD/CSL312_3002
	ITT population		≥2 attacks per month		ATS population	Gara-naïve subpopulation	Patients who received gara throughout both studies
	Gara (n=39)	Placebo (n=24)	Gara (n=[redacted])	Placebo (n=[redacted])	Gara (n=161)	Gara (n=90)	Gara (n=36)
p-value	p<0.001		[redacted]		N/A	N/A	N/A
Number of HAE attacks requiring on-demand therapy							
Mean (95% CI) number of attacks per month	0.23 (0.02, 0.45)	1.86 (1.26, 2.46)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (95% CI) number of attacks per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	<0.001		[redacted]		N/A	N/A	N/A
Relative difference in means	−87.5%		[redacted]		N/A	N/A	N/A
Number of moderate or severe HAE attacks							
Mean (95% CI) number of attacks per month	0.13 (0.03, 0.22)	1.35 (0.86, 1.84)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (95% CI) number of attacks per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	<0.001		[redacted]		N/A	N/A	N/A
Relative difference in means	−90.4%		[redacted]		N/A	N/A	N/A
Time to first HAE attack							
Median (min, max) time to first attack after Day 1 of treatment, days	NE [redacted]	11 [redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]

Abbreviations: ATS, all treated patients; CI, cfonfidence interval; gara, garadacimab; H01, first hierarchical test; H02, second hierarchical test; HAE, hereditary angioedema; ITT, intent-to-treat; max, maximum; min, minimum; N/A, not applicable, NE, not evaluable; NR, not reported.

Results are presented for the entire treatment period, defined as Days 1–182 for the VANGUARD study (6 months), and up to the latest data cut-off ([redacted]) for the CSL312_3002 study (with a median [min, max] treatment duration of 17.6 months [3.0, 25.2]). For the pooled analyses, the median (min, max) treatment duration was [redacted] months.

[a] One patient in the placebo group stayed in the treatment period <30 days and was excluded from the analysis, as per the clinical study protocol.

[b] For roll-over patients, the Run-in Period of the previous study was used to determine the baseline attack rate.

Sources: Craig et al., 2023,[12] CSL Behring Data on File, CSL312_3001 CSR (2022),[78] CSL Behring Data on File, CSL312_3001 ≥2 attacks/month subgroup TFLs (2024),[89] CSL Behring Data on File, CSL312_3002 IA4 TFLs (2024)[81], CSL Behring Data on File, CSL312_3002 IA4 garadacimab-naïve subgroup TFLs (2024),[82] , CSL Behring Data on File, pooled CSL312_3001/CSL312_3002 IA4 TFLs (2024).[83].

B.2.10 Indirect and mixed treatment comparisons

In the absence of head-to-head studies, a network meta-analysis (NMA) has been conducted to determine the comparative efficacy and safety of garadacimab against berotralstat, lanadelumab and plasma-derived IV C1-INHs in people aged ≥12 years with HAE-1/2. The technical report with full details of the methodology for the NMA is provided in the reference pack accompanying this submission.

B.2.10.1 Methodology

B.2.10.1.1.1 Study selection

An SLR of RCTs investigating LTP treatments in men or women (at least 12 years old) with HAE-1/2 was conducted on 8 April 2024 and updated on 5 August 2024 (see Appendix D for more detail). As outlined in Section B.1.1, the comparators of interest for this submission are berotralstat, lanadelumab and plasma-derived IV C1-INHs (Cinryze and IV Berinert [off-label treatment]). The only plasma-derived IV C1-INH with RCT data available was Cinryze, which is also used as a proxy for IV Berinert in the cost-effectiveness analysis (Section B.3.3.1). SC Berinert was included in the NMA report as the document is intended to be adapted for use globally and SC Berinert is a comparator of interest in other countries. However, since it is not considered a relevant comparator in this submission (Section B.1.1), comparative results for garadacimab against SC Berinert are not discussed here.

Of the intervention and comparators of interest for this submission, the SLR identified seven unique phase 2 and phase 3 RCTs investigating five LTP options:

- Garadacimab: CSL312_2001[76] and VANGUARD[44]
- Berotralstat: APeX-2[45] and APeX-J[90]
- Lanadelumab: HELP-03[43]
- Cinryze: CHANGE[91]

A rigorous NMA feasibility assessment was undertaken to ascertain the extent of clinical heterogeneity across these studies and determine the risks and benefits of indirectly comparing treatment effects. Study design characteristics, patient eligibility criteria,

baseline patient characteristics and outcome characteristics were all explored as potential sources of heterogeneity.[92]

NMAs were deemed feasible for eight outcomes, including six efficacy outcomes, one safety outcome and one patient-reported outcome (

Table 11).92 The generic EQ-5D scale was not selected as an outcome of interest. In line with prior NICE appraisals for HAE LTP therapies (TA606 and TA738), literature-based EQ-5D evidence was favoured over trial-based utilities as the primary evidence source for this submission's cost-effectiveness analysis (Section B.3.4.1). As such, the disease-specific AE-QoL questionnaire was prioritised. The AE-QoL scale is more representative of quality of life in patients with HAE and was frequently administered and reported across comparator trials.

Table 11: Outcomes deemed feasible for the NMA

Efficacy outcomes
Time-normalised number of HAE attacks (or relative to placebo)
Time-normalised number of HAE attacks requiring on-demand treatment
Time-normalised number of moderate and/or severe HAE attacks
Proportion of attack-free patients over trial period
Patients with ≥90% attack rate reduction
Attack-free days
Safety outcomes
Any TEAEs/AEs
Patient-reported outcomes
Change from baseline in AE-QoL total score

Abbreviations: AE, adverse event; AE-QoL, Angioedema Quality of Life; HAE, hereditary angioedema; TEAEs, treatment-emergent adverse events
Source: CSL Behring Data on File, NMA report (2024).[92]

Following the feasibility assessment, of the intervention and comparators of interest for this submission, six RCTs investigating three LTP options (garadacimab, lanadelumab, berotralstat) were included in the **base case** analyses. Cinryze was investigated in a randomised, double-blind, placebo-controlled crossover study (CHANGE), which was infeasible to include in the NMA base case as it included patients from 9 years of age. In addition, publicly available data were not available for the pre-crossover period only

and no other studies in the network included post-crossover data. Despite the heterogeneity with the other studies in the network, in the absence of alternative RCT data for Cinryze or any other plasma-derived IV C1-INH, ITCs were still considered for **scenario analyses** using the published pooled pre- and post-crossover data from the CHANGE study.[91] The only outcome deemed feasible for inclusion in the NMA scenario analyses with Cinryze was the time-normalised number of HAE attacks, due to the lack of reporting of other outcomes.[92]

Additionally, during the feasibility analysis, a slight difference in garadacimab administration was noted between the VANGUARD and CSL312_2001 studies. In the VANGUARD study, 200 mg garadacimab was administered subcutaneously (SC) once a month, whereas the same dosage was administered once every four weeks in the CSL312_2001 trial. However, these dosing regimens were assumed equivalent for the purposes of the analysis, with sensitivity analyses conducted where necessary to account for potential heterogeneity.

A summary of studies included in the NMA is presented in Table 12.

Table 12: Summary of RCTs included in the NMA

Intervention	Trial name	Trial phase	Treatment regimen
Garadacimab	VANGUARD[44]	3	Garadacimab 200 mg, SC, once monthly
	CSL312_2001[76]	2	Garadacimab 200 mg, SC, once monthly
SC Berinert	COMPACT[93†]	3	SC Berinert 60 IU/kg, SC, twice weekly
Lanadelumab	HELP-03[43]	3	Lanadelumab 300 mg, SC, once every 2 weeks
			Lanadelumab 300 mg, SC, once every 4 weeks
Berotralstat	APeX-2[45]	3	Berotralstat 150 mg, oral, once daily
	APeX-J[90]	3	Berotralstat 150 mg, oral, once daily
Cinryze[‡]	CHANGE[91]	3	IV Cinryze, once every 3 days
			IV Cinryze, once every 4 days

Abbreviations: IU, international units; IV, intravenous; SC, subcutaneous.
† The COMPACT study had a crossover design; only pre-crossover data collected at 16 weeks was used in the NMA to maintain consistency with the other included studies in the network, nearly all of which were not of a crossover design (with the exception of the CHANGE study). Pre-crossover data from COMPACT were provided directly by CSL Behring.
‡The only outcome assessed with Cinryze was the time-normalised number of HAE attacks, due to the lack of reporting of other outcomes in the CHANGE study
Source: CSL Behring Data on File, NMA report (2024).[92]

B.2.10.1.1.2 NMA

NMAs were conducted using a Bayesian framework as described in the National Institute of Health and Care Excellence (NICE) Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) series.[94] Base-case analyses considered only licensed dosages for the interventions of interest and were conducted using both fixed effect (FE) and random effect (RE) models. All sensitivity analyses employed fixed effects (FE) models. Notably, NMAs using FE models produced results with narrower credible intervals (CrIs), indicating less variability, and a higher number of statistically significant effect estimates compared to NMAs using RE models. The RE model was used to account for potential variability across studies, accommodating differences in treatment effects that the FE model may not fully capture.

For dichotomous outcomes where further follow-up is likely to result in more events (e.g., proportion of attack-free patients and any TEAEs), a binomial model with complementary log-log (cloglog) link function and maximum follow-up offset was used to account for the variable treatment duration between trials

Various sensitivity analyses were conducted to assess the robustness of results, including analyses incorporating all identified dosages (licensed and unlicensed, to increase patient data) and excluding phase 2 trials (to increase homogeneity across the network). All sensitivity analyses were conducted using fixed-effect models.[92]

Results were summarised using rate ratios (RRs) for rate outcomes, mean differences for continuous outcomes and hazard ratios for dichotomous outcomes, with associated 95% CrIs.[92]

B.2.10.2 Results

A summary of results from the FE and RE NMAs are provided in Section B.2.10.2.1.8.

B.2.10.2.1.1 Time-normalised number of HAE attacks

The scenario analysis including Cinryze comprised of a network consisting of five treatment nodes (garadacimab, berotralstat, lanadelumab Q2W, lanadelumab Q4W and

Cinryze) informed by six placebo-controlled RCTs (not counting SC Berinert).[43-45,76,90,91] Timepoint of measurement for this outcome ranged from 12 weeks (CSL312_2001 and CHANGE) to 26 weeks (VANGUARD and HELP).

Based on results of this FE NMA, [redacted] (Figure 16).[92] In the base case analysis excluding Cinryze, [redacted]. In comparison to the fixed effect NMA, results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16).[92]

In a sensitivity analysis of the base case with the phase 2 CSL312_2001 study removed to reduce cross-trial heterogeneity [redacted]. No other changes to the order occurred compared to the base case.[92]

B.2.10.2.1.2 Time-normalised Number of HAE Attacks requiring on-demand treatment

The base case network consisted of four treatment nodes (garadacimab, berotralstat, lanadelumab Q2W, lanadelumab Q4W) informed by five placebo-controlled RCTs (not counting SC Berinert).[43-45,76,90] Timepoint of measurement for this outcome ranged from 12 weeks (CSL312_2001) to 26 weeks (VANGUARD and HELP).

Based on results of the FE NMA [redacted] (Figure 16). Results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16).

In a sensitivity analysis with the phase 2 CSL312_2001 study removed to reduce cross-trial heterogeneity, no changes to the order occurred between garadacimab and the comparators of interest.[92]

B.2.10.2.1.3 Time-normalised number of moderate and/or severe HAE attacks

The base case network consisted of four treatment nodes (garadacimab, berotralstat, lanadelumab Q2W, lanadelumab Q4W) informed by five placebo-controlled RCTs (not counting SC Berinert).[43-45,76,90] Timepoint of measurement for this outcome ranged from 12 weeks (CSL312_2001) to 26 weeks (VANGUARD and HELP).[92]

In the FE NMA, all treatments were [redacted]. In comparison to the FE NMA, results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16). Of note, [redacted] in the RE NMA (Figure 16).[92]

In a sensitivity analysis of the base case with the phase 2 CSL312_2001 study removed to reduce cross-trial heterogeneity, no changes to the order occurred between garadacimab and the comparators of interest, [redacted].[92]

B.2.10.2.1.4 Proportion of attack-free patients

The base case network consisted of four treatment nodes (garadacimab, berotralstat, lanadelumab Q2W, lanadelumab Q4W) informed by four placebo-controlled RCTs (not counting SC Berinert).[43-45,76] Timepoint of measurement for this outcome ranged from 12 weeks (CSL312_2001) to 26 weeks (VANGUARD and HELP).

Based on results of the FE NMA, [redacted] (Figure 16). Results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16).

In a sensitivity analysis of the base case with the phase 2 CSL312_2001 study removed to reduce cross-trial heterogeneity, no changes to the order occurred between garadacimab and the comparators of interest.[92]

Using the same network as the base case, in a sensitivity analysis without Cloglog function, there were no changes to the order of treatments compared to the base case analysis.

B.2.10.2.1.5 Attack-free days per month

The base case network consisted of three treatment nodes (garadacimab, lanadelumab Q2W and lanadelumab Q4W) informed by three placebo-controlled RCTs (not counting SC Berinert).[43,44,76] Timepoint of measurement for this outcome ranged from 12 weeks (CSL312_2001) to 26 weeks (VANGUARD and HELP).[92]

Based on results of the FE NMA, [redacted] (Figure 16). Results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16).[92]

In a sensitivity analysis of the base case with the phase 2 CSL312_2001 study removed to reduce cross-trial heterogeneity, [redacted]. No other changes to the order occurred between garadacimab and the comparators of interest.[92]

B.2.10.2.1.6 TEAEs

The base case network consisted of four treatment nodes (garadacimab, berotralstat, lanadelumab Q2W, lanadelumab Q4W) informed by four placebo-controlled RCTs (not counting SC Berinert).[43-45,76] Timepoint of measurement for this outcome ranged from 12 weeks (CSL312_2001) to 26 weeks (VANGUARD and HELP).[92]

In the FE NMA, all treatments were [redacted]. Garadacimab [redacted] (Figure 16). Results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16).[92]

In a sensitivity analysis of the base case with phase 2 trials removed to reduce cross-trial heterogeneity, no changes to the order occurred between garadacimab and the comparators of interest.[92]

Using the same network as the base case, in a sensitivity analysis without Cloglog function, [redacted]. There were no other changes compared to the base case analysis.[92]

B.2.10.2.1.7 AE-QoL

The base case network consisted of four treatment nodes (garadacimab, berotralstat, lanadelumab Q2W, lanadelumab Q4W) informed by four placebo-controlled RCTs (not counting SC Berinert).[43-45,90] Timepoint of measurement for this outcome ranged from 24 weeks (APeX-2 and APeX-J) to 26 weeks (VANGUARD and HELP).[92]

In the FE NMA, [redacted], garadacimab was [redacted] (Figure 16). In comparison to the FE NMA, results of the RE NMA were similar apart from much wider credible intervals, as expected (Figure 16). Of note, [redacted] in the RE NMA.[92]

B.2.10.2.1.8 Summary of results

A summary of the fixed effect and random effect pairwise comparisons between garadacimab 200 mg once monthly and comparators of interest for all outcomes is provided in Figure 16.

Figure 16. Summary of results from fixed effect and random effect NMAs

Abbreviations: BIW, twice weekly; CrI, credible interval; HR, hazard ratio; IV, intravenous; NR, not reported; QM, once monthly; QD, once daily; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RR = rate ratio; SC, subcutaneous.
Dark blue fill indicates garadacimab 200 mg QM is significantly superior vs the comparator; light blue fill indicates garadacimab 200 mg QM is numerically superior vs the comparator; light orange fill indicates garadacimab 200 mg QM is numerically inferior vs the comparator; grey fill indicates data were not available for the comparator to perform a pairwise comparison.
* RR <1 implies that garadacimab performs better than comparator. † Fixed effect results for this outcome are aligned with the outcomes from the scenario analysis including Cinryze. ‡ HR >1 implies that garadacimab performs better than comparator. # Mean difference >0 implies that garadacimab performs better than comparator. § HR <1 implies that garadacimab performs better than comparator. ** Mean difference <0 implies that garadacimab performs better than comparator.
Source: CSL Behring Data on File, NMA report (2024).[92]

B.2.10.3 Strengths and limitations

The NMAs represent a novel undertaking in health outcomes research for HAE. Few ITCs have been published in this disease area to date and, to the best of our knowledge, this is the first NMA to investigate safety, efficacy, and quality of life in HAE using contemporary treatments for LTP.[92]

A notable strength of the NMAs is the careful development of the analyses using well-established principles; the NMA methodology followed best practices for conducting and reporting NMAs as described by NICE, ensuring transparency and reproducibility. The analyses were informed by a comprehensive, peer-reviewed SLR to ensure all relevant comparator data was captured.[92]

All included studies underwent a risk of bias assessment to determine the strength of the body of evidence, which found all studies to be of high quality. Moreover, a thorough feasibility assessment was conducted to highlight sources of inter-study heterogeneity and ensure the validity of results. Any decisions to exclude studies based on heterogeneity were informed by clinical experts.[92] Cinryze introduced additional heterogeneity due to differences in study design, population and outcome definitions. Reasons for this increased heterogeneity included the cross-over design, the inclusion of paediatric patients from 9 years of age and the reporting of mean number of HAE attacks rather than time-normalised attacks in the Cinryze study. However, it should be noted that CSL Behring provided the most robust analysis possible based on the available data.[92]

Despite efforts to minimise bias by excluding insufficiently similar study data, residual heterogeneity between studies may have reduced the validity of some analyses. The potential threats to analysis validity caused by differences in outcome definitions could not always be fully understood, particularly where HAE attacks were either uniquely defined or not clearly defined.[92]

The evidence networks were sparse, with connections between treatment nodes typically informed by single trials. All trials were placebo-controlled rather than head-

to-head, further simplifying network structures and increasing the potential for biased treatment effect estimates.

Please refer to the full NMA report (provided in the reference pack of this submission) for the full discussion of strengths and limitations of the analysis.[92]

B.2.10.4 Conclusions

The NMAs indicate that garadacimab is a highly competitive LTP option in HAE. Across multiple efficacy endpoints, garadacimab consistently ranked first among berotralstat, lanadelumab, and Cinryze. Safety profiles were comparable, with garadacimab showing an advantage over biweekly lanadelumab in TEAEs. Quality of life improvements were [redacted] (data not available for Cinryze).[92]

B.2.11 Adverse reactions

The safety and tolerability of garadacimab was assessed in the full safety analysis population of the phase 3 open-label CSL312_3002 extension study (N=161). These results are presented herein and form the basis of the safety assessment of garadacimab. Please see Appendix F for the tabular safety data of CSL312_3002, as well as a summary of safety outcomes from the randomised placebo-controlled VANGUARD study (N=64).

B.2.11.1 Extent of exposure

As of the most recent data cut-off ([redacted]), [redacted]% and [redacted]% of patients had ≥12 and ≥18 months of exposure to garadacimab, respectively, with a median (min, max) duration of exposure of [redacted] ([redacted]) months. The total garadacimab exposure was [redacted] patient-years and there were no dose adjustments up to the latest data cut-off.

B.2.11.2 Overview of adverse events

As of the most recent data cut-off for the CSL312_3002 study, [redacted]% of patients experienced ≥1 treatment-emergent adverse event (TEAEs). Most TEAEs were mild ([redacted]%) or moderate ([redacted]%) in severity. Severe TEAEs were reported in [redacted]% of patients, of which [redacted] was deemed related to study treatment. Most TEAEs had resolved or been recovered from ([redacted]% of events and [redacted]% of patients).[81]

The majority of TEAEs were not considered related to study treatment ([redacted]% of events and [redacted]% of patients). A total of [redacted] ([redacted]%) patients experienced [redacted] injection site reactions (ISRs), of which [redacted] events were considered related to the study treatment.[81]

A total of [redacted] serious adverse events (SAEs) were reported, which included [redacted] cases of COVID-19, [redacted] HAE attack and [redacted] drug reaction/eruption.[81] [redacted] SAEs were resolved by the time of the data cut-off and [redacted] were considered to be related to study treatment or led to study discontinuation.[81]

There were [redacted] deaths due to TEAEs and [redacted] patients were assessed by the investigator as experiencing an adverse event of special interest (AESI) as per the protocol. Treatment with garadacimab was discontinued in [redacted]% of patients.[81] A total of [redacted] patients ([redacted]%) experienced a TEAE which led to discontinuation, including [redacted] cases of ISRs (injection site irritation, n=[redacted] and injection site urticaria n=[redacted]) and [redacted] of experiencing mood swings ([redacted]%). Additionally, [redacted] withdrew from the study and study treatment due to pregnancy.

B.2.11.3 Common treatment-emergent adverse events

A summary of the most common TEAEs is presented in Appendix F by the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC) and preferred term (incidence of ≥10% and ≥5%, respectively). The SOCs with the highest incidence of reported TEAEs were infections and infestations ([redacted]% patients, [redacted]% events), general disorders and administration site conditions ([redacted]% patients, [redacted]% events), gastrointestinal disorders ([redacted]% patients, [redacted]% events) and musculoskeletal and connective tissue disorders ([redacted]% patients, [redacted]% events). The most frequently reported TEAEs were COVID-19 ([redacted]% patients, [redacted]% events), nasopharyngitis ([redacted]% patients, [redacted]% events) and injection site erythema ([redacted]% patients, [redacted]% events).[81]

B.2.11.3.1 Treatment-related TEAEs

Overall, the number of patients experiencing treatment-related TEAEs was low, with [redacted]% of patients experiencing an TEAE that was assessed to be related to garadacimab treatment.[81] Most treatment-related TEAEs were noted in the SOCs of general disorders and administration site conditions ([redacted]% of patients; [redacted] events). No other treatment-related TEAEs were reported in ≥2% of patients.[81]

B.2.11.3.2 Deaths, serious adverse events and adverse events of special interest

As of the most recent data cut-off, there have been [redacted] deaths during the CSL312_3002 study.

A total of [redacted] SAEs were reported in [redacted] ([redacted]%) patients, which included:[81]

- COVID-19 in [redacted] patients ([redacted] unrelated to study treatment)
  - In [redacted] cases, the patients' dose of garadacimab was not changed, and the reporter considered the events of COVID-19 infection as serious because of the initial or prolonged hospitalisation
- [redacted] HAE attack ([redacted])
  - [redacted] dose of garadacimab was [redacted], and the reporter considered the [redacted] of abdominal HAE attack as serious because of [redacted]
- [redacted] drug reaction/eruption ([redacted])

[redacted] SAEs were resolved by the time of the data cut-off and [redacted] were considered to be related to study treatment or led to study discontinuation.[81]

Overall, there were [redacted] patients that were assessed by the investigator as experiencing an AESI during the study as per the protocol.[81]

B.2.11.3.3 Clinical laboratory evaluation and immunogenicity

The clinical laboratory evaluation found that there were [redacted] clinically relevant trends over time or from baseline in haematology, biochemistry, coagulation, or urinalysis parameters.[81]

There were few, very low-level anti-garadacimab antibody responses recorded up to the latest CSL312_3002 data cut-off. [redacted]) enrolled from the VANGUARD phase 3 study tested positive at baseline (titre value: [redacted]), at 6 months (titre value: [redacted]), and at 12 months (titre: [redacted]). Additionally, [redacted] tested positive at the end of treatment at 5 months (titre value: [redacted]), and [redacted] ([redacted]%) tested positive at 12 months (titre value: [redacted] for all [redacted] patients).[79,81]

There was no impact observed of the presence on anti-garadacimab antibodies on the pharmacokinetics, pharmacodynamics, safety or efficacy of garadacimab.[81]

B.2.11.4 Conclusion

The safety results from the phase 3 OLE study (CSL312_3002) were consistent with the pivotal VANGUARD study with no new safety signals and demonstrated that monthly SC administration of 200 mg garadacimab had an acceptable safety profile that is well-tolerated in patients with HAE when used as prophylaxis to prevent HAE attacks.

B.2.12 Ongoing studies

The open-label extension study CSL312_3002 is ongoing, with the next interim assessment of CSL312_3002 (IA5) anticipated to be [redacted] in [redacted] and submitted for publication in [redacted].

A publication on an [redacted] including the overall population enrolled in phase 2 and phase 3 clinical studies is anticipated in [redacted], utilising the 13 February 2023 data cut-off of CSL312_3002 which is an earlier data cut-off than that presented in this submission ([redacted]). The CSL312_3002 study is planned to complete by [redacted], assessing up to [redacted] months of treatment with garadacimab. A publication on the [redacted] will follow, estimated for [redacted].

In addition, publications on the following aspects are anticipated to be submitted in [redacted]:

- [redacted] in VANGUARD and CSL312_3002 (using the IA2 data cut-off for CSL312_3002)
- [redacted] across all garadacimab clinical studies (using the IA2 data cut-off for CSL312_3002)
- [redacted] presented in this submission
- [redacted]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Summary of clinical evidence

Garadacimab is a first-in-class Factor XIIa inhibitor, studied in a 6-month randomised placebo-controlled phase 3 pivotal trial (VANGUARD; N=65) and ongoing OLE (CSL312_3002; N=161) in adults and adolescents with HAE experiencing ≥1 attack per month.

Garadacimab is highly effective for the routine prevention of recurrent HAE attacks

The goals of LTP in HAE are to minimise the number and severity of attacks and achieve total control of the disease in the form of attack freedom (Section B.1.3.3).[12] Garadacimab is a highly effective LTP option for patients with HAE, meeting its primary endpoint in the VANGUARD study and demonstrating a 91% reduction from baseline in patients treated with garadacimab and a significant 7.4-fold lower mean number of investigator-confirmed HAE attacks per month versus placebo ($p<0.0001$). Moreover, compared to placebo, garadacimab achieved a significantly lower mean number of time-normalised attacks per month that required on-demand treatment (mean difference −88%; $p<0.0001$) and time-normalised moderate or severe HAE attacks per month (mean difference −90%; $p<0.001$).

Garadacimab can offer prolonged freedom from attacks

The unpredictability of attacks is a key contributor to the humanistic burden of HAE (Section B.1.3.1.4.2). Achieving and maintaining prolonged periods of attack-free status can help reduce this burden and empower people with HAE to feel more in control of their condition. In the VANGUARD study, most patients on garadacimab were attack-free during the first three months of treatment (71.8%) compared with only 8.3% in the placebo group ($p<0.0001$). This was maintained throughout the entire 6-month treatment period, with most patients (62%) remaining attack-free, compared to none who were on placebo. Together, these results indicate that garadacimab treatment is associated with early and sustained protection from HAE

attacks. This is in contrast to the phase 3 lanadelumab study, in which less than half of all treated patients (44%, 31% in well-controlled patients) were attack-free during the treatment period (26 weeks),[64] and the phase 3 study for berotralstat, in which the proportion of patients who were attack-free during the treatment period (24 weeks) was similar between berotralstat and placebo (percentages not reported in trial publication).[45]

Garadacimab efficacy is sustained beyond two years with no evidence of waning of treatment effect observed

The efficacy of garadacimab in the CSL312_3002 OLE study was consistently aligned with the VANGUARD study, demonstrating that the efficacy of garadacimab is sustained in larger population size and extends beyond 6 months of treatment.[81] Analyses of a post-hoc subpopulation of patients who were naïve to garadacimab at the start of CSL312_3002, indicated that the efficacy shown throughout the CSL312_3002 treatment period across all key endpoints was robust and independent of prior treatment with garadacimab before the study.[82]

The maintenance of treatment effect with garadacimab was further demonstrated in a post-hoc analysis of patients who rolled over from VANGUARD to CSL312_3002 and received 200 mg garadacimab throughout. These patients had a median duration of treatment of [redacted] months and experienced a mean reduction in HAE attacks from baseline of [redacted]%, with [redacted]% of patients remaining attack-free as of the latest data cut-off in the CSL312_3002 study.[83] This demonstrates that the efficacy observed in the 6-month treatment period of the VANGUARD study was maintained through to the latest data-cut off in the CSL312_3002 study, with no waning of treatment effect observed. Notably, nearly [redacted]% of patients in the pooled subpopulation remained attack-free after two years of treatment, empowering a substantial proportion of patients to feel in control of their condition through attack freedom over a prolonged period.[83]

Garadacimab efficacy is independent of baseline attack rate

To demonstrate that the ITT population from VANGUARD is the most appropriate and robust source of efficacy evidence for garadacimab across all comparisons, post-hoc analyses were conducted in patients with a baseline attack frequency ≥2 attacks per month, reflective of the current commissioning landscape for modern LTP options in the NHS (Section B.1.3.2.2). In the VANGUARD study, the efficacy of garadacimab in patients experiencing ≥2 attacks per month were (n=[redacted]) consistent with the full garadacimab-treated populations of the VANGAURD study (n=39) and CSL312_3002 (N=161) studies, providing further supportive evidence that baseline attack frequency is not a treatment effect modifier for garadacimab.[89]

Garadacimab treatment is associated with improvements in HRQoL

In the VANGUARD study, patients treated with garadacimab reported substantial and clinically meaningful improvements in AE-QoL mean scores within approximately one month (23.7-point reduction) that were maintained over the 6-month treatment period (26.5-point reduction). In contrast, patients in the placebo group experienced a mean reduction in AE-QoL score of 5 points at Day 31 and 2.2 points at the end of the treatment period, demonstrating no clinically meaningful improvement from baseline. Similarly, mean EQ-5D-5L HSV scores in the garadacimab arm improved from [redacted] at baseline to [redacted] at the end of the treatment period and worsened in the placebo arm from [redacted] to [redacted].[78]

Most patients treated with garadacimab (82%) rated their response to treatment as “good” or better (according to SGART) compared with 33% with placebo.[12]

Garadacimab has a favourable safety profile

The incidence of TEAEs in the VANGUARD study was similar between the garadacimab and placebo arms. In the CSL312_3002 study, the safety profile of garadacimab remained acceptable long-term, with no new safety signals and the majority of TEAEs being mild or moderate in severity. Most TEAEs had resolved or been recovered from ([redacted]% of events and [redacted]% of patients) and the majority of

TEAEs were not considered related to study treatment ([redacted]% of events and [redacted]% of patients).[81]

Garadacimab is a highly competitive LTP option in HAE

The current SoC for LTP in HAE includes lanadelumab, berotralstat and IV C1-INHs (Section B.1.3.2). NMAs indicate that garadacimab is a highly competitive LTP option for HAE, demonstrating [redacted] for time-normalised number of HAE attacks and [redacted]. Where data were available, garadacimab demonstrated [redacted] across all other efficacy endpoints of interest (no additional endpoints were reported for Cinryze).[92]

B.2.13.2 Method of administration

Garadacimab has an innovative method of administration

Garadacimab is administered subcutaneously via an autoinjector pen, offering a more convenient mode of administration than IV C1-INHs and a more straightforward method of self-administration compared to existing subcutaneous (pre-filled syringe) options such as lanadelumab (Section B.1.3.3).[12,65,95] Additionally, garadacimab requires only once monthly administration, providing a less frequent treatment schedule compared to C1-INHs, lanadelumab and berotralstat.[96] This dosing frequency is anticipated to reduce the burden of treatment on patients who otherwise would be treated up to twice weekly intravenously or twice monthly subcutaneously and was noted as an extrinsic strength of the VANGUARD study in a comment on Craig et al. (2023)[96]

While the phase 3 data for garadacimab were collected using a pre-filled syringe (PFS) device, it is anticipated that an auto-injector (AI) would be the only commercially available formulation in the UK. Both devices administer garadacimab 200 mg via subcutaneous injection, and a phase 1 study demonstrated comparable pharmacokinetics and tolerability between the two. Therefore, no significant safety concerns are expected regarding the long-term use of the AI, and its benefit/risk ratio

is anticipated to be similar to that observed in the phase 3 clinical studies using the PFS.

It is understood that patients generally favour home administration due to cost and time savings, improved flexibility and fewer hospital visits, although some patients have difficulty achieving consistent and successful self-injection due to poor manual dexterity, or experience anxiety at the prospect of self-injection.[97] These factors can reduce patients' medication adherence and overall experience. The garadacimab AI is a single-use disposable device that administers 200 mg of garadacimab into subcutaneous tissue and requires no skin pinching.[24] This well-designed AI may help improve patients' self-injection confidence and medication adherence compared with SC administration with a PFS.[97]

B.2.13.3 Strengths and limitations of the evidence base

Key strengths

The main safety and efficacy evidence for garadacimab was derived from the pivotal phase 3 VANGUARD study, which had several strengths. The VANGUARD study employed a randomised, double-blind, placebo-controlled trial design. The inclusion of patients aged 12 and older also broadened the applicability of the results to a wide demographic. In addition, the frequency and severity of HAE attacks were assessed by investigators, ensuring a more objective and reliable measurement compared to patient self-reporting for key efficacy outcomes. This is in contrast to the evidence presented in the berotralstat NICE submission (TA738), where the measurement of attack severity was deemed subjective. To overcome this, the more objective outcome of attack location was used as a proxy for attack severity in TA738, the impact of which the committee remained unknown and was deemed an uncertainty.[9] As such, the investigator assessment of the frequency and severity of HAE attacks ensures objectivity and makes it a key strength of the evidence base.

As described in Sections B.2.3.3.1 and 0, The VANGUARD and CSL312_3002 study populations were representative of the HAE patient population in the UK, as characterised by the Yong et al. audit and Icatibant Outcome Survey (Section

B.1.3.1.3), and ratified by three consultant immunologists in England interviewed by CSL Behring (Section B.3.3.10).

Results from the pivotal trial have been bolstered by data from a large phase 3b open-label extension study (CSL312_3002; N=161), which provides further validation of the safety and efficacy of garadacimab in a large sample size and over a longer duration of treatment. Post-hoc subgroup analyses in garadacimab-naïve patients in the open-label study support the robustness of its findings, independent of the effects of roll-over patients from other garadacimab studies.

Notably the durability of efficacy beyond two years of treatment has been demonstrated with a post-hoc pooled analysis of the VANGUARD and the CSL312_3002 study (n=36). This extensive body of evidence, drawn from two well-conducted phase 3 studies, underscores the robustness of the data supporting the clinical benefits of garadacimab with consistent findings across multiple studies, subpopulations and timeframes.

Key limitations

Owing to the rarity of HAE, the VANGUARD study comprised of 39 patients randomised to garadacimab and 25 to placebo, which is a relatively small sample sizes for informing decision -making.[78] This is aligned with other landmark phase 3 studies for novel LTP options in HAE such as the HELP (NCT02586805; lanadelumab 150 mg every 4 weeks, n=28; lanadelumab 300 mg every 2 weeks, n=27; placebo, n=41) and APeX-2 (NCT03485911; berotralstat 150 mg, n=40; placebo, n=40).[9,43,45]

While patient demographics and baseline disease characteristics were overall generalisable to people ≥12 years old with HAE in England (Sections B.2.3.3.1, 0 and Key Strengths above), there is an underrepresentation of ethnic and racial minorities in VANGUARD. It is established that, while HAE affects all races and sexes equally, minority patients are underrepresented in clinical trials and may be at risk of additional disease burden,[98] as is evident from similar limitations having been

reported in other phase 3 studies in HAE.[43,45] It should be noted that the disparity between the general population and the VANGUARD study is relatively small (86% of the VANGUARD trial identified as White, compared to 82% of the general population in England).[98]

Another limitation is the relatively short treatment period of 6 months of the pivotal study VANGUARD, which was addressed by the ongoing phase 3b CSL312_3002 OLE study which assesses the long-term safety and efficacy of garadacimab in 161 people living with HAE. As of the latest data cut-off, the median duration of treatment was 17.6 months.

Finally, the lack of UK study sites for the garadacimab studies is a key limitation. However, besides the ethnic and racial underrepresentation described above, the baseline characteristics of both clinical studies are overall generalisable to people ≥12 years old living with HAE within England, minimising this limitation.

B.2.13.4 Conclusion

The outcomes from the randomised-controlled clinical trial demonstrate that prophylactic monthly SC 200 mg garadacimab is highly effective in reducing the frequency and severity of HAE attacks compared with placebo. The pre-specified and ad-hoc data provided from the OLE study and pooled analyses provides supportive evidence that the treatment efficacy is maintained over longer durations and that garadacimab is safe and well-tolerated. The indirect treatment comparison (the NMA) demonstrates that garadacimab has a superior efficacy in the routine prevention of HAE attacks compared to existing standard of care LTP options.

Together, this evidence suggests that garadacimab represents a step-change towards the main treatment objective of HAE, which is achieving attack freedom that is maintained in the long-term. The presented sum of data suggests that garadacimab provides a great potential to achieve and maintain attack freedom independent of baseline attack frequency and other potential treatment effect modifying characteristics.

B.3 Cost effectiveness

Summary of cost-effectiveness analysis

- A *de novo* Markov model was developed to evaluate the cost-effectiveness of garadacimab compared with current clinical management in England for HAE patients in accordance with the NICE reference case.[99]
- The model is comprised of the following health states: attack; no attack (month 1, 2, 3, 4, 5 and 6 without attack) and death. A partial memory has been added to the model structure to account for periods without HAE attacks to record any improvements associated with attack freedom during that time.
- The analysis was conducted from an NHS/Personal Social Service (PSS) perspective with a lifetime horizon and with costs and outcomes discounted at 3.5% per annum.
- Efficacy data for garadacimab were derived from VANGUARD pivotal trial and efficacy for the comparator were derived from the NMA.[78] [92]
- HAE baseline utility was estimated/derived from Nordenfelt et al., 2014.[100]
- Garadacimab is estimated to have large health benefits for HAE patients versus all comparators, comprising of berotralstat, lanadelumab, IV Berinert and IV Cinryze. generating an incremental QALY of [redacted] and a [redacted] in costs, garadacimab [redacted].
- DSA showed similar trends in all four comparator analyses, with relative efficacy of LTPs and baseline number of attacks being some of the most sensitive parameters to variation.

- Garadacimab is expected to be a cost-effective alternative treatment option for patients who are currently being treated with berotralstat, lanadelumab and C1-INHs within NHS clinical practice.

B.3.1 Published cost-effectiveness studies

An SLR of economic evaluations, costs and healthcare resource use and health-related quality of life (HRQoL) in HAE were conducted in April 2024. Full details of methodology and results of the SLR are detailed in Appendix G, Appendix H and Appendix I.

The economic evaluations SLR identified twelve studies exploring the cost-effectiveness of prophylactic treatments in HAE. However, these studies explored different payer perspectives and alternative comparators not relevant to the decision problem. See Appendix I for full details.

B.3.2 Economic analysis

The objective of this economic analysis was to assess the cost-effectiveness of garadacimab compared with current clinical management in England for patients aged ≥12 years who require routine prevention of recurrent attacks of HAE and experience ≥2 attacks per month.

The cost-effectiveness analysis for garadacimab adopted a three-health state Markov model, with the addition of six tunnelling states, to reflect the natural history of patients with HAE. A similar modelling approach was taken in NICE TA606 (lanadelumab) and TA738 (berotralstat).[9,10] Aligning with NICE committee preferences, a *de novo* model was deemed appropriate for decision making in HAE. The analysis was conducted from the perspective of the NHS and PSS and included direct medical costs only over a lifetime horizon.

B.3.2.1 Patient population

The patient population in the economic model is the ≥2 HAE attacks per month at baseline population from the phase 3 pivotal trial for garadacimab, VANGUARD.

This narrower population has been chosen in the base-case cost-effectiveness analysis to reflect the current clinical commissioning of LTPs.

As discussed in Section B.2.7.2, subgroup analyses presented from VANGUARD demonstrated that the key efficacy outcomes for garadacimab that were reported for the ITT population were consistent in the subgroup experiencing ≥2 attacks per month at baseline, supporting that baseline attack rate is not a treatment effect modifier for garadacimab and the ITT population is the most appropriate source of clinical evidence for garadacimab. The baseline characteristics of the patients in VANGUARD have been described in Section B.2.3.3.1 and these were considered generalisable to the population of HAE in the NHS, as confirmed by UK clinical experts.[17]

Hence, the ≥2 attacks per month subgroup is in line with the population defined in the NICE final scope and the anticipated marketing authorisation of garadacimab, that is, [redacted].[24]

B.3.2.2 Model structure

A *de novo* cohort-based Markov model was developed in Microsoft Excel® to accurately reflect the natural progression and clinical pathway of HAE in the UK.

B.3.2.2.1 Justification of model structure

Conducting an economic evaluation for HAE presents significant challenges due to rarity of the disease, leading to scarcity of available data and small patient numbers in existing clinical studies. The following factors were considered when selecting the most appropriate model structure:

- Precedence from published cost-effectiveness models in HAE including the NICE technology appraisals for lanadelumab (TA606) and berotralstat (TA738).[9,10]
- Key efficacy endpoints from VANGUARD including time to first HAE attack.[8,9]
- Availability of evidence from the VANGUARD study and existing literature for HRQoL and resource use.

- Improvements in HRQoL and impact on resource use associated with attack freedom.

Considering these factors and data available for garadacimab and its comparators, a *de novo* cohort-level Markov model was deemed the best approach to characterise the patients experience in HAE, as a health states network would capture the key consideration mentioned above.

B.3.2.2.2 Model description

The model consists of three primary health states, with the addition of tunnelling states which track the amount of time since the previous HAE attack for patients Figure 17 and Figure 18):

- Alive, experiencing a HAE attack (mild, moderate, severe non-laryngeal and severe laryngeal)
    - The model distinguishes between severe laryngeal and severe non-laryngeal attacks to account for potential disparities in resource utilisation, with laryngeal attacks often requiring more extensive NHS resources.
- Alive, without an attack (month 1, 2, 3, 4, 5 and 6 without attack) and;
- Death

This structure is an extension of the previously appraised NICE TA606 and TA738 models, which considered an 'alive, alive-attack, death' health state system, with the key differentiator in this model being the inclusion of tunnelling states within the alive (without attack) health state to capture the improvements in HRQoL for patients based on the amount of time they spend attack-free since their last attack.[9,10]

Figure 17. Overall model structure

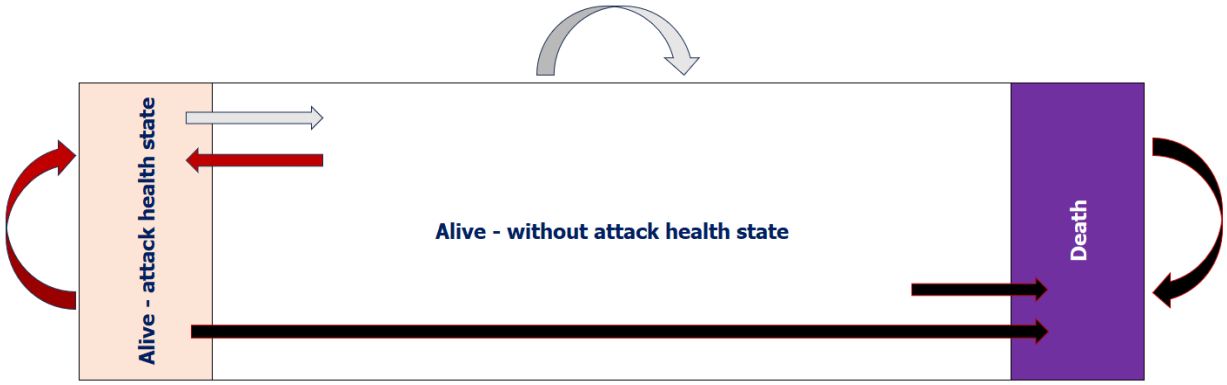
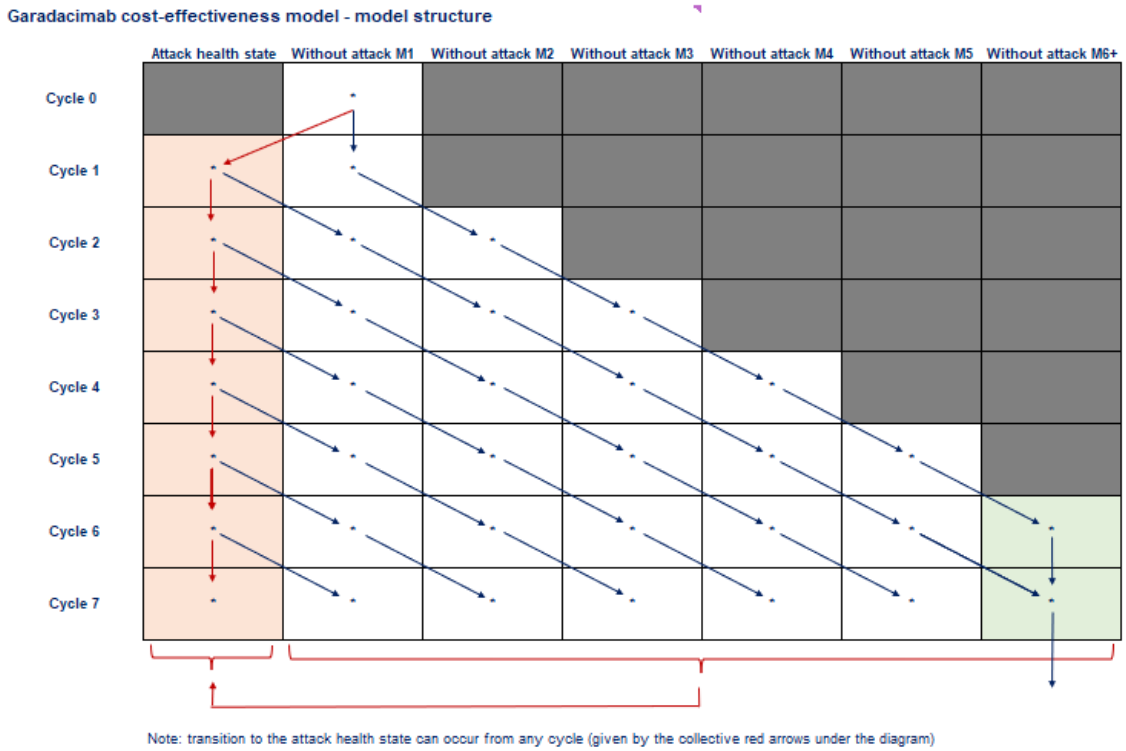


Figure 18. Granular model structure



Colour coding: orange, attack health state; white, without attack health state; green, ultimate without attack health state, consistent with the upper utility estimate

Recent discussions with clinical experts based in England and literature[17,57] indicated six tunnelling states was a reasonable estimate to define patients who are “attack-free” i.e. experienced prolonged periods without attacks. Therefore, for model simplicity in the base case the cost-effectiveness analysis utilising six tunnelling states aligned with clinical expert opinion.[17,57] This new model structure adds partial memory to the Markov states, where patients are tracked for the number of months they have gone without an attack based on the probability of experiencing an attack, calculated from clinically informed attack rates from the NMA. A patient who suffers an attack transitions to the attack health state and then rejoins the tunnel as and when they experience consecutive months without an attack. This model extension accounts for the resource use and quality-of-life considerations for patients who have been alive without having an attack for consecutive months. The model extension is important to incorporate since patients experiencing prolonged periods of attack freedom require less clinical management than patients suffering an attack and are expected to experience a significant reduction in the burden of fear/shame and

anxiety/depression experienced because of attacks forgone.[57] This modelling method has been chosen to endogenously capture the improvements in quality of life associated with experiencing freedom from HAE attacks. The prime diagonal of the tunnel health states, constituting x months without an attack x cycles into the modelling horizon, provides key insights into the time to first HAE attack outcome as further elaborated in Appendix J.

B.3.2.3 Features of the economic analysis

The economic analysis was conducted in accordance with the NICE reference case, which indicates that the time horizon in an economic evaluation should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.[99] In line with previous NICE appraisals TA606 and TA738,[9,10] and given the typical age at diagnosis (the mean age at baseline was [redacted] years in VANGUARD, ≥2 attacks per month patients),[78] a lifetime horizon (60 years) was deemed appropriate for decision making. In line with garadicamab's anticipated marketing authorisation, a scenario with a starting age of 12 years (88 years) old has been explored in the model. A cycle length of 28 days was considered appropriate in line with previous submissions.

Both costs and outcomes were discounted at 3.5% annually, as per the NICE reference case.[99] The economic analysis adopts the perspective of the NHS and PSS perspective in England and Wales for costs and outcomes, aligned with NICE guidance.[99]

The results of the cost-effectiveness analysis are reported in terms of discounted costs per QALY gained. The key features of the economic analysis are described in Table 13 alongside those used in the NICE technology appraisals in the same disease area (HAE), namely lanadelumab (TA606) and berotralstat (TA738).[9,10]

Table 13. Features of the economic analysis

Factor	Previous evaluations		Current evaluation	
	TA606	**TA738**	**Chosen values**	**Justification**
Time horizon	Lifetime (60 years)	Lifetime (56 years)	Lifetime (60 years)	In line with NICE reference case and previously appraised NICE TAs.[99] A lifetime time horizon was deemed appropriate and captures differential outcomes over the lifetime of the individual. Additionally, it is sufficiently long enough to capture all meaningful differences in technologies being compared.
Cycle length	28 days	28 days	28 days	In line with VANGUARD study and previous NICE appraisals.
Discount for utilities and costs	3.5%	3.5%	3.5%	In line with NICE reference case[99] and previous appraisals
Perspective	NHS and personal social services (PSS)	NHS and personal social services (PSS)	NHS and personal social services (PSS)	In line with NICE reference case[99] and previous appraisals
Treatment waning effect	Lifetime	Lifetime	Lifetime	See section B.3.3.5 and previous appraisals

Source of utilities	Attack utility values based on EQ-5D-5L data from Nordenfelt et al. (2014)[100] Treatment administration utilities were based on data from Jorgensen (2017) Caregiver disutilities were not considered.	'Attack' and 'attack free' utilities were based on EQ-5D-5L data from Nordenfelt et al. (2014)[100] Caregiver disutilities were informed by a TTO study commissioned by BioCryst Pharmaceuticals. Scenario analyses: 'Attack' and 'attack free' utilities informed by a TTO study commissioned by BioCryst Treatment administration utilities based on data from Holko (2018)	'Attack' and 'attack free' utilities were based on EQ-5D-5L data from Nordenfelt et al. (2014)[100] A temporary 'attack-free' health state has been assumed when a patient is without a HAE attack for 6 months. As patients continue to remain in this temporary, their utility gradually approaches the general population utility of near full health (age-gender appropriate. This will be calculated and informed by general population utility derived from Ara and Brazier (2010).[101] Caregiver disutilities are considered and were informed by a study conducted by Lo et al (2022)[102]	EQ-5D-5L data was collected during VANGUARD. However, due to the unpredictability of HAE attacks, the data were not a reliable measure of the HRQoL for patients with HAE. This is the same conclusion as in past appraisals looking at other HAE trials. In response to this lack of validity, the HAE baseline utility is informed by Nordenfelt et al (2014) as in previous appraisals.[100] See Section B.3.4 for more information. Clinical expert opinion has indicated that patients without attacks progress towards a utility level in-line with the general population utility.[17] Similarly, expert opinion, Evidence Assessment Groups in TA606 and TA738,[9,10] the 2024 survey of individuals with HAE and their caregivers and literature strongly and consistently conclude that caregiver outcomes are an important aspect of HAE (Section B.3.4.5)[103]
Source of costs	NHS reference costs, literature and expert opinion	NHS reference costs, British National Formulary (BNF) costs, Personal Social Services Research Unit (PSSRU) costs and expert opinion.	NHS reference costs, British National Formulary (BNF) costs,[104] Personal Social Services Research Unit (PSSRU) costs and expert opinion.[105].[17]	In line with the NICE reference case.[99] Unit costs are obtained from UK national resources where possible to reflect the NHS perspective. Clinical opinion was sought to inform resource use.

Abbreviations: BNF, British National Formulary; EQ-5D-5L, EuroQol 5-dimensional 5-level descriptive system; HAE, hereditary angioedema; HRQoL, health-related quality of life; NHS, National Health Service; PSSRU, personal social services research unit; SLR, systematic literature review; TTO, time-trade off.

B.3.2.4 Intervention technology and comparators

Treatments in the model include garadacimab compared with current LTP options used to prevent recurrent HAE attacks in UK clinical practice. These comparators include lanadeulmab, berostralstat and plasma-derived intravenous C1-INHs (including IV Cinryze and off-label IV Berinert).

B.3.2.4.1.1 Intervention

As outlined in Section B.2.5, the intervention of interest in the economic analysis is garadacimab, a novel, fully human, recombinant immunoglobulin G4 (IgG4)/lamba monoclonal antibody and specific inhibitor of activated Factor XII (FXIIa), with an anticipated indication for the routine prevention of recurrent attacks of HAE in patients aged 12 years and older.[3,9,10,24] The treatment is administered subcutaneously with patients able to self-administer at home.

The dosing schedule covered by the anticipated UK license for garadacimab is a 200mg monthly dose, with an initial loading dose of 400 mg, administered as two 200 mg SC injections on the first day of treatment. This is aligned with the regimen used in the key clinical trial supporting the submission (VANGUARD)[24] and reflects the expected UK dosing regimen. In line with garadacimab's anticipated marketing authorisation, a continuation rule for garadacimab has not been considered in this economic analysis.

B.3.2.4.1.2 Comparators

In line with Section B.1.3.2

Table 14 summarises the comparators that are explored in the economic analysis. A comprehensive summary of the treatment pathway adopted for HAE in the UK is illustrated in Figure 7. For details on why other treatments mentioned in NICE scope were not considered as relevant comparators, please refer to Table 1.

Table 14. Comparators included in the economic analysis

Comparators included in economic analysis	Berotralstat	Lanadelumab*	IV Berinert	IV Cinryze
Administration	Oral	SC	IV	IV
Dosing regimen used in economic analysis	150mg once daily[63]	300 mg every 2 weeks[64] In patients who are stably attack-free on treatment, a dose reduction to 300 mg every 4 weeks may be considered, especially in patients with low weight[64]	1,000 IU twice weekly (every 3–4 days) 6 [Assumed same as Cinryze in lack of trial data on this]	1,000 IU twice weekly (every 3–4 days)[65]
Continuation rule	Treatment is discontinued after 3 in patients who do not experience a ≥50% reduction in attack frequency. As per NICE TA606 and feedback from UK immunologists.[10,17]	N/A		
Additional notes	Treatment switching is treated separately to discontinuation, see Section B.3.5.1			
Justification	See section B.1.1	See section B.1.1	See section B.1.1	See section B.1.1

Notes: *The SmPC for lanadelumab states that the 150 mg/Q2W dose may be considered in patients under the weight of 40 kg. However, there are no cycles in the model for which there are patients under the 40 kg threshold as according to the growth charts[106] (Section B.3.3). As a simplifying assumption, the 150 mg dose is not considered in the cost-effectiveness analysis. Abbreviations: SC, subcutaneous; IV, intravenous; N/A, not applicable; IU, international units

B.3.3 Clinical parameters and variables

The clinical parameters and variables included in the cost-effectiveness analysis are described in Section B.2.6 and Section B.2.10.1.1.2 detailing the trial outcomes and indirect treatment comparisons (ITCs) used in the cost-effectiveness analysis, respectively.

The baseline characteristics for the modelled cohort in terms of age, gender distribution and weight were derived from VANGUARD. Table 15 presents the patient population demographics used in the cost-effectiveness analysis and have been validated as being reflective of those patients being treated in the UK by three immunologists.[17] The ≥2 attack subgroup is used in the base case.

Table 15. Demographics of the cost-effectiveness analysis population of VANGUARD

Category: mean (standard deviation)	**≥2 attack per cycle subgroup**			**Value used**
	garadacimab 200mg (n=[redacted])	**Placebo (n=[redacted])**	**Total (n=[redacted])**	
Gender, Male (%)	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Weight at screening (kg)	[redacted]	[redacted]	[redacted]	General pop. weight
Baseline number of HAE attacks	[redacted]			[redacted]

Abbreviations: kg, kilogram; mg, milligram; pop., population Note: The sources of RCPCH growth charts and NHS Digital (2022)[106-108] have been used across the model to predict weight at each age. The growth (or decline) between two sets of ages happens in a linear fashion. Source: Table UK 14.1.3.1.1 of CSL312_3001.

B.3.3.1 Attack rates in the cost-effectiveness model

In the absence of head-to-head trials, rate ratios were derived from the NMA to inform clinical efficacy parameters, as discussed in section B.2.10. The technology-specific NMA based rate ratio for the outcome of time-normalised number of HAE attacks is applied to the baseline number of attacks experienced by placebo patients of VANGUARD to arrive at the number of HAE attacks per cycle by technology.[92] Similarly, the rate ratios for the outcome of time-normalised number of HAE attacks

requiring adjunct on-demand treatments are applied to the baseline number of attacks requiring adjunct treatments, as informed by the VANGUARD study[78]. These values can be seen in Table 16 and Table 17. Due to the absence of RCT data for IV Berinert, the assumption of equal efficacy to IV Cinryze is applied as they are both intravenous, human C1-INH treatments and essentially the same protein. However, due to data limitations with respect to the relationship between the dose of Berinert and its efficacy, Appendix R offers a threshold analysis on IV Berinert's rate ratio to examine the uncertainty around its effectiveness as an intervention.

Table 16. HAE attack rate ratios and per cycle HAE attack rates

Technology	Placebo arm HAE time-normalised attack rate for the ≥2 attack per month population of VANGUARD: [redacted]	
	HAE attack rate, rate ratio	Resulting HAE attack rate per cycle
Garadacimab	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	[redacted]
Lanadelumab Q4W	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]
Berinert	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; HAE, hereditary angioedema; Q2W, every two-week dose; Q4W, every four-week dose Note: outcome not available for Berinert, so assumed the same rate ratio Cinryze. Source: NMA multiplied by baseline attack rate.

Table 17. HAE attacks that require on-demand treatment rate ratios and per cycle HAE attack rates that require on-demand treatment

Technology	Placebo arm HAE time-normalised attack rate requiring on-demand for the ≥2 attack subgroup population of VANGUARD: [redacted]	
	HAE attack rate requiring on-demand, rate ratio	Resulting HAE attack rate requiring on-demand per cycle
Garadacimab	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	[redacted]
Lanadelumab Q4W	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]
Berinert	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema; Q2W, every two-week dose; Q4W, every four-week dose. Note: outcome not available for Berinert, so assumed the same rate ratio Cinryze

B.3.3.2 Transitional probabilities in the cost-effectiveness model

In each cycle, there are two transitions possible for alive patients, either; they transition to the attack health state or progress along the 'without attack' tunnel states. The number of attacks that a patient is subject to in a particular cycle by technology is the prime factor determining a patient's transition. Therefore, the standard formula of converting (attack) rates into probabilities is used to characterise patient movement across the alive health states including the tunnel states. The standard formula follows Equation 1 of:

Equation 1. Standard formula for converting rates into probabilities

$$p = 1 - e^{-rt}$$

- Where p is the probability of attack,
- e is Euler's number,
- r is the HAE attack rate,
- t is the time scalar (which is always equal to one since all quoted HAE attack rates are time-normalised to the cycle length)

Table 18 summarises the HAE attack probabilities per technology by cycle.

Table 18. Probability of HAE attack based on standard formula attack rates for the ≥2 attack per month subgroup per cycle

Technology	Probability of attack
Garadacimab	[redacted]
Lanadelumab Q2W	[redacted]
Lanadelumab Q4W	[redacted]
Berotralstat	[redacted]
Berinert	[redacted]
Cinryze	[redacted]
Placebo	[redacted]

Abbreviations: Q2W, every two-week dose; Q4W, every four-week dose

B.3.3.3 Survival analysis and time to first HAE attack

The standard formula of Equation 1 underestimates the time to first HAE attack of garadacimab patients in model as compared to the trial data (see Figure 12). Understanding this, survival analysis on this endpoint like that requested at the clarification stage during TA606 was conducted. Full detail of the analysis can be

found in Appendix J. No cost-effectiveness analysis was conducted based on the survival analysis due to the plateau towards the tail end of the observation period, suggesting a decreasing number of attacks over time which is an inconsistent conclusion. Nevertheless, alternative methods have been used to characterise the trends of HAE attacks used in the model.

B.3.3.4 Poisson regressions for predicting time-normalised number of HAE attacks

Poisson regressions have been used widely in the TA606 submission, serving as the basis for predicting the attack rates considered in the cost-effectiveness analysis.[10] Poisson regressions are a good choice to establish quantitative relationships among count outcomes and potential explanatory variables. Garadacimab and placebo patients of the main analysis of the VANGUARD study have been considered in the following Poisson regression analysis, and their characteristics have been described in Section B.2.3.3.1.[78] However, a total of four patients have been dropped from the analysis due to censoring, as those patients did not have event data for all cycles six of the analysis.

Table 19 provides the summary characteristics of the patients included in the Poisson regression analysis by treatment arm. The variables are formatted as dichotomous with the specified threshold provided in the table.

Table 19. Baseline characteristics of the patients in the Poisson regression analysis

Variable	Garadacimab (n=39)	Placebo (n=21)
Age (=1 if above 40, =0 if below 40)	[redacted]	[redacted]
Gender (=1 if female, 0= if male)	[redacted]	[redacted]
Weight (=1 if over 75kg, 0=if under 75kg)	[redacted]	[redacted]
Baseline number of attacks	[redacted]	[redacted]

Abbreviations; kg, kilogram. The percentage reflects the proportion of the patients that satisfy the criteria being true.

Although the lack of treatment effect modifiers was confirmed in the model specification stage of the analysis, baseline patient characteristics, baseline number

of attacks and number of attacks in the previous cycle were considered as explanatory variables in this analysis. A series of models were run for every cycle and generally the simple singular number of attacks in the previous cycle model was parsimonious over the cycles considered. Table 20 provides the AIC values for each family (column) of the tested models.

Table 20. Poisson regression statistical goodness of fit measures and significance for the garadacimab arm

Cycle	Baseline no. of attacks	Previous cycle no. of attacks family	All previous cycles no. of attacks family	Age	Gender	Weight
Cycle 1	50.310[#]	**50.310[#]**	50.310[#]	49.665	47.636	48.433
Cycle 2	61.236	**38.325[#]*** **	38.325[#]***	60.599	52.471	61.634
Cycle 3	48.401	**26.335*** **	28.305	41.606	46.407	47.407
Cycle 4	76.596	**64.358*** **	64.960	77.037	74.310	75.157
Cycle 5	40.903	31.570*** **	**29.879***	35.408	39.875	41.166
Cycle 6	52.753	38.565*** **	**32.613***	54.648	51.350	53.676

Abbreviations: AIC, Akaike information criterion; no. number.
Bolded values indicate the lowest AIC value.
highlights which models are equivalent based on description.
Asterisks refer to the level of significance of the variables considered: *** p=0.001, ** p=0.01, * p=0.05.

Although the ‘All previous cycles’ family of regression models had the lowest AIC values for cycles 5 and 6 of the analysis, the individual variables themselves were not significant in isolation for cycles 5 and 6 of the ‘All previous cycles’ model, as only one variable reached the 5% level of significance. Therefore, these regressions were considered less relevant than the ‘Previous cycles’ of family regressions. Furthermore, the ‘Previous cycle’ family of regression models had consistently better results on the residual deviation and dispersion tests of fit. Non-linearity and heteroskedasticity have not been flagged as issues during the visual inspection of residuals of both the ‘Previous cycle’ and ‘All previous cycles’ families. As such, the ‘Previous cycle’ is deemed as the best regression model. This fact is compounded by the possibility of overfitting the placebo regression with the ‘All previous cycles’

series of regressions due to the large number of explanatory variables for the latter cycle regressions.

Equation 2 presents the chosen Poisson regression family to be used in the cost-effectiveness analysis and Table 21 provides the models summary statistics. In this equation, $events_t$ is the number of HAE attacks a patient experienced at time t. It is the fitted coefficients of the ultimate Cycle 6 model that are responsible for extrapolating attack rates beyond the trial horizon as it is the most mature cycle of data.

Equation 2. The Poisson regression specification

$$\log(events_t) = \hat{b}_0 + \hat{b}_1 * events_{t-1}$$

Table 21. Summary of the parsimonious Poisson regression specification by treatment arm at cycle 6

Model and coefficient	Mean and significance level	Standard error	Lower 95% confidence interval	Upper 95% confidence interval
Garadacimab – AIC: 38.565; residual deviance: 22.345; dispersion test value; 1.44543				
$\hat{b}_0$ - fitted intercept	[redacted]	[redacted]	[redacted]	[redacted]
$\hat{b}_1$ – fitted previous cycle number of attacks	[redacted]	[redacted]	[redacted]	[redacted]
Placebo - AIC: 56.995; residual deviance: 16.381; dispersion test value; 0.7001218				
$\hat{b}_0$ - fitted intercept	[redacted]	[redacted]	[redacted]	[redacted]
$\hat{b}_1$ – fitted previous cycle number of attacks	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion

Overall, the Poisson regression coefficients perform well when predicting the number of attacks within the observation period, as despite the challenges of limited degrees of freedom and zero-value observations, there is only a small difference between the observed and predicted number of HAE attacks per cycle as displayed in Figure 19. Scenario number 25 examines the impact of the Poisson predicted attack rates in the cost-effectiveness analysis.

Figure 19. Observed and Poisson predicted mean number of HAE attacks over the trial horizon

The number of HAE attacks is predicted by the 'Previous cycle' family of Poisson regression described in Equation 2

B.3.3.5 Long-term effectiveness in the cost-effectiveness model

Section B.2.6.7 describes the maintenance of treatment effect for garadacimab by examining 36 patients who have been on the licensed dosage of garadacimab for the longest duration. The patients show limited to no signs of waning of treatment effect. Moreover, Section B.2.11.3.3 describes the lack of impact of anti-garadacimab antibodies on the pharmacokinetics, pharmacodynamics, safety or efficacy of garadacimab. Thereby, clinical evidence strongly suggests that garadacimab's treatment effect would be durable over a considerable amount of time, given the lack of evidence of waning of treatment effect.

Clinical experts based in England also agreed that the assumption of a lifelong treatment effect with garadacimab is appropriate.[17] Furthermore, a review of NICE TAs related to monoclonal antibodies (published between 2019-2024) demonstrated

precedence that in the absence of the development of neutralising antibodies, the assumption of extended treatment effect has been widely accepted by committees.

The following subsections appraise two possible methods to quantify the lifelong treatment effect of garadacimab.

B.3.3.5.1 Average attack rate reduction carried forward (AARRCF)

To characterise the potential developments of attack rates beyond the trial period, the average attack rate reduction carried forward (AARRCF) methodology was modelled in the cost-effectiveness analysis. Appendix R contains is the tabulation of Figure 20, with the average attack rate reduction across all months being carried forward for all cycles beyond the trial horizon. In the TA738 submission, the EAG argued there was an extent of placebo effect over the first 3 months, and as such, only average attack rates over months 4–12 were carried forward for berotralstat.[9] However, in case of garadacimab, given the absence of placebo effect present visually, stratification of average attack rate over a specific time period could not be justified and as such the average over the whole period is carried forward.

Figure 20. Percentage reduction in time-normalised number of HAE attacks per month, monthly time windows (VANGUARD/CSL312_3002 pooled population 2)

Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema; no., number; q4wk, once every 4 weeks; SC, subcutaneous; time-norm., time-normalised;
Note: The percentage reduction in the time-normalised number of HAE attacks is calculated within a patient as: 100*[1–(time-normalised number of HAE attacks per month during treatment period/time-normalised number of HAE attacks per month during run-in period)]. 1 week is equal to 7 days, 1 month is equal to 28 days.
Note: pooled population 2 includes patients who were on active treatment in VANGUARD and rolled over into CSL312_3002

Consequently, the average percent reduction in time-normalised number of HAE attacks for all patients over the time horizon amounted to [redacted]%, producing a garadacimab HAE attack rate of [redacted] attacks per cycle for patients with the ≥2 attack per month baseline.

B.3.3.5.2 Poisson regressions over time

Another tool used in a previous NICE submission (TA606) in HAE for estimating HAE attacks rates beyond the trial period is the Poisson regression,[10] which aims to directly predict the HAE attack rate (number of events) at any cycle on an individual patient level.

The Poisson regression specified in Equation 2 can be used to predict the number of HAE attacks at any cycle. As in the Poisson regression conducted in TA606,[10] the number of HAE attacks over time stabilises, predicting a constant attack rate of [redacted] attacks per cycle over the long run.

B.3.3.5.3 Base case attack rates over the long run

The AARRCF and Poisson regression methods considered to evaluate the development of HAE attack rates over the long run produced similar and stable results. However, based on the simple and intuitive attributes of carrying the average attack rate reduction from the trial period, and precedence in previous HAE appraisals (TA606 and TA738), the AARRCF method has been chosen as the basis for HAE attack rates past cycle 24 for garadacimab.

B.3.3.6 Attack severity in the cost-effectiveness model

The severity of HAE attacks is a key clinical feature and impact the burden of disease, as described in Section B.2.6.5. Table 10 highlights that garadacimab proportionally reduces the number of moderate and severe attacks compared to placebo, in turn reducing the burden of disease. Table 22 reports the severity of attacks for all comparator technologies analysed in the cost-effectiveness model, along with the resulting number of HAE attacks by severity per technology for the ≥2 attacks per month subgroup.

Table 22. Attack severity distribution and number of HAE attacks split per distribution by technology for the ≥2 attack per month subgroup

Technology	Mild		Moderate		Severe (non-laryngeal)		Severe (laryngeal)		Source
	Attack distribution	Number of HAE attacks	Attack distribution	Number of HAE attacks	Attack distribution	Number of HAE attacks	Attack distribution	Number of HAE attacks	
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	VANGUARD[78]
Lanadelumab (Q2W)	20%	[redacted]	67%	[redacted]	12%	[redacted]	2%	[redacted]	HELP[43]
Lanadelumab (Q4W)	30%	[redacted]	50%	[redacted]	18%	[redacted]	2%	[redacted]	HELP[43]
Berotralstat	37%	[redacted]	46%	[redacted]	15%	[redacted]	2%	[redacted]	Riedl (2016)[18]
Berinert	32%	[redacted]	52%	[redacted]	14%	[redacted]	2%	[redacted]	COMPACT
Cinryze	59%	[redacted]	28%	[redacted]	12%	[redacted]	2%	[redacted]	Zuraw et al. (2010)[91]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	VANGUARD[78]

Abbreviations: Q2W, every two weeks; Q4W, every four weeks; .Asterisks highlights a small, but non-zero value.

B.3.3.7 Attack duration in the cost-effectiveness model

The disutility of an event like an HAE attack is often scaled to its direct clinical duration, but clinical expert opinion has suggested that the detrimental effects of a HAE attack last considerably longer than the clinical duration of the event, from one to two weeks per an attack.[17] This may be due to a variety of factors including fear/shame from the previous attack, or resurgent anxiety/depression in anticipation of a subsequent HAE attack. To account for the varied nature of HAE attacks, the model utilises insights from clinical expert opinion to determine the overall duration of patient impact, including both immediate and long-term consequences. (see Section B.3.4.5).

B.3.3.8 Mortality

As discussed in section B.2.11.3.2, there were no deaths reported in the pivotal VANGUARD trial.[78] This aligns with the previous NICE submissions in HAE which concluded that there is insufficient evidence to quantify an excess risk of death for HAE patients above that of the general population. This is true despite the presence of some literature evidence assessing mortality due to laryngeal attacks such as Zanichelli (2015)[110], but overall, this evidence too is insufficient to quantify the mortality risk associated with laryngeal attacks. Therefore, no disease specific mortality has been considered in the cost-effectiveness model.

Background mortality for HAE patients within the economic model was informed by life tables sourced from the Office of National Statistics (ONS, 2024) for the years 2018–2020, which were matched for the age and gender of the patient population in the economic model.[47]

B.3.3.9 Adverse events

The safety profile of garadacimab has been presented in Section B.2.11.4, which shows its acceptable safety profile. While results in B.2.11.4 are presented for the full safety population of the open-label extension study, the outcomes are consistent with those shown in the randomised-controlled trial.

Nevertheless, a broad perspective on quantifying adverse events has been utilised in the cost-effectiveness to ensure the broadest safety data are presented ahead of decision-making process using the most relevant clinical data sources where possible, particularly in relation to quality of life. Section B.3.4.4 presents the quality of life data associated with the adverse events, and, in line with Section B.2.11.4, costs associated with adverse events have been assumed to be zero because they are assumed to not be severe enough to trigger resource use of any kind. Appendix R presents all adverse event probabilities by technology.

B.3.3.10 Clinical expert selection and interview process

Three consultant immunologists with significant experience in the treatment of HAE in England were identified for participation. An outreach e-mail was sent out to them describing the objective and process of engagement. The stated objective was to gain insights into the treatment landscape and clinical pathway for HAE in England. To this end, a discussion guide and pre-read materials were then sent to all three clinical experts in time for review and interview preparation. Thereafter, between 2–8 August 2024, 1:1 video interviews were conducted by MAP on behalf of CSL Behring via Microsoft Teams with all three consultant immunologists.

A structured interview approach was used to collect information from all three clinical experts which included discussions that explored the place in therapy for garadacimab in the clinical pathway and validate several key model assumptions applied in the economic evaluation. Due to the nature of qualitative structured interview, a quantitative calculation of the number of responses to each specific question is not provided. Instead, aggregate responses from all three clinical experts were summarised into one concise report.

All clinical experts were named and marked in confidence for reporting and no answers were attributed to any specific interviewees. The summary report can be found in the reference pack accompanying this submission.

B.3.4 Measurement and valuation of health effects

The quality of life of patients with HAE is significantly affected across their entire lifespan as described in Section B.1.3.1.4.2. Section B.2.6.8 outlines the patient-reported outcome measures that have been used to measure and value health effects from the pivotal and supporting clinical studies.

B.3.4.1 Health-related quality of life data from clinical trials

The VANGUARD study collected EQ-5D-5L domain scores, VAS and HSV scored for Visit Days 1, 91 and 182 (Section B.2.6.8). [78] While EQ-5D-5L is an appropriate tool for measuring general HRQoL in clinical trials, the tool is limited in its value when considering the HRQoL outcomes in people living with HAE. In a similar manner as seen in TA606 when discussing HELP-03, very few of the EQ-5D questionnaires coincided with an ongoing or recent attack.[10] HAE attacks are spontaneous and unpredictable as per Section B.1.3.1.4.2 and as such, EQ-5D is understood to be an unreliable measure of HRQoL in this disease setting when paired up with the patient numbers observed. This has resulted in a small number of relevant observations collected in VANGUARD, where only [redacted] ([redacted] of the EQ-5D-5L responses occurring across any one of the Visit Days 'during' an ongoing HAE attack, where 'during' is defined as the completion of the EQ-5D-5L response within seven days of an HAE attack. [78]

Moreover, the EQ-5D-5L responses also have limitations in providing estimates of the baseline utility values used in modelling, i.e. utility values that are representative of an average HAE patient. Firstly, both the garadacimab and placebo patients expressed mapped utility values higher than that of the general population, indicating limited face validity given the high burden of disease. Secondly, there is limited scope to conduct ad-hoc regression analyses to increase the usefulness of the data in economic modelling due to the scarcity of responses and respondent sample sizes.

Other HRQoL tools such as AE-QoL were utilised more frequently during the VANGUARD trial. However, due to the lack of a mapping algorithm between AE-QoL

and EQ-5D (as per the database of mapping studies), the disease specific AE-QoL could not be used to generate preference-based utilities suitable to be used in the cost-effectiveness analysis. An attempt was made to discover a conceptual overlap between the two questionnaires to try and overcome the abovementioned limitations. However, as shown in Appendix S, there is limited scope to perform a mapping exercise between AE-QoL and EQ-5D due to the limited domain correlation.

As such, the economic analysis primarily relies on HRQoL studies identified in Section B.3.4.3. For completeness, garadacimab and placebo trial responses as upper and lower baseline utility estimates have been explored as scenario number 14 in Section B.3.11.3, while Section B.3.4.2 describes the (mapped) utility using the EQ-5D-5L responses from the VANGUARD study for all Visit Days.

B.3.4.2 Mapping

In line with NICE methods guidance, mapping of EQ-5D-5L responses to the EQ-5D-3L value set was conducted using the DSU Hernadez Alva et al. (2020) algorithm.[87] Table 23 presents the mapped utilities for the EQ-5D-5L responses from the VANGUARD study, showing garadacimab patients to report higher utilities across the Visit Days.

Table 23. EQ-5D-3L utility values per Visit Day by treatment arm for the ≥2 attack subgroup

Visit Day	garadacimab (n=25) mean EQ-5D-3L utility value (N, SD)	Placebo (n=14) mean EQ-5D-3L utility value (N, SD)
Visit Day 1	[redacted] (25, [redacted])	[redacted] (14, [redacted])
Visit Day 91	[redacted] (24, [redacted])	[redacted] (12, [redacted])
Visit Day 182	[redacted] (25, [redacted])	[redacted] (12, [redacted])

N; number of responses complete; SD, standard deviation. Source: CSL312_3001 – Hernandez mapped values.[87]

B.3.4.3 Health-related quality-of-life studies

Appendix H provides the full details of the identification, selection and extraction of the HRQoL studies identified by the SLR. To support the cost-utility analysis, the following studies have been chosen from the SLR and described below:

- Nordenfelt et al. (2014) – A retrospective study of HAE patients (n=103) from a Swedish registry captured by the Sweha-Reg census. The study captured patient EQ-5D-5L responses for both the attack-free state and the last HAE attack.[100]

- Aygören-Pürsün et al. (2016) – A cross-sectional study of HAE patients (n=111) from Spain, Germany and Denmark captured by the HAE European Burden of Illness survey. The study captured EQ-5D-3L responses for all respondents for the period of acute attacks and between attacks.[111]

- Itzler et al. (2024) – A panel study of HAE patients on long-term prophylaxis (n=159) from the United States, Australia, Canada, the United Kingdom, Germany and Japan conducted by MarketCast International. The study reported AE-QoL and Angioedema Control Tests results per attack-free durations of <1 month, 1-6< months and ≥6 months (n=67, 43 and 45, respectively). [57]

- Lo et al. (2022) – A vignette study of HAE patients and carers and clinical expert (n=15, 5 and 1, respectively) from England. The study reports the vignette development and time-trade off (TTO) results for attack-free, attack and care provision for HAE attack states. [102]

B.3.4.4 Adverse reactions

Appendix R reports the probability of various adverse events by technology as a naïve comparison utilising data straight from the original sources was used in the base case, such as the relevant pivotal trials. Naïve comparisons have been used, as although the NMA does report relative safety outcome comparisons, 1) the number of treatment-emergent adverse events (TEAEs) from any data source in HAE is limited and 2) the NMA reports insignificant differences in TEAEs across technologies.[92] These conclusions are consistent with conclusions that are consistent with those drawn in previous NICE appraisals in this disease area, that adverse events have a limited impact in cost-effectiveness outcomes but for completeness, adverse events have been included in the economic analysis.

Table 27 lists the adverse events that are considered in the cost-effectiveness analysis.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.5.1 Baseline utility value

Baseline utility is widely used in the cost-effectiveness model as it serves as the foundation for all other utility values. The Nordenfelt et al. (2014) study has been used to derive baseline utility values in the base-case cost-effectiveness analysis.[100] Nordenfelt et al. provides robust estimates of baseline utility data (sourced from responses of patients not experiencing an HAE attack) and provides consistency in decision making due to its use in the previous HAE appraisals.

For example, the utility value in the attack health state is derived from the baseline utility value net of the HAE attack(s) disutility (and other technology-specific disutilities). Furthermore, the value of the individual tunnel state is a function of linear progression from the baseline utility value to the upper utility estimate value.

The baseline utility value is derived from the equation featured in Equation 3. It states that the baseline utility value for a given age is a function of age and the number of HAE attacks experienced in the previous cycle.

Equation 3. Nordenfelt et al. (2014) baseline utility equation

$$Baseline\ utility\ value = 0.825 - 0.02205 * age - 0.0043 * no.of\ attacks\ in\ previous\ cycle$$

B.3.4.5.2 Tunnel state utility values

As described in Section B.3.2.2, there are a total of six tunnel states in the base-case cost-effectiveness analysis. These tunnel states house patients who have not had an attack in successive cycles. As confirmed with clinical expert opinion, these patients experience increasing utility the more successive cycles they spend without an attack. The experts also considered six tunnel states as appropriate.

Furthermore, Itzler et al. (2024) report that longer attack-free durations are strongly associated with a lower fear/anxiety of having an attack, fewer psychological problems, fewer days missed from school or work and fewer limitations on social and/or physical activity.[57] The study supports the notion of using six months as the time over which improvements in quality of life from attack-free periods is accumulated, since it identifies six months as a significant pivot in categorising the outcomes mentioned.

To capture these significant improvements in quality-of-life in patients with periods without HAE attacks, the cost-effectiveness model employs a linear increase towards the general population utility across the tunnel states. The general population utility chosen as the upper estimate of utility (the utility experienced in the sixth and final month without an attack) is based on the widely used Ara and Brazier (2010) study.[101] Equation 4 states the formula for the general population utility value as a function of age and gender:

Equation 4. Ara and Brazier (2010) general population utility equation101

$$General\ population\ utility = 0.951 - 0.0002587 * age - 0.000032 * age^2 + 0.0212126 * gender$$

The alternative Hernandez et al. (2022) general population utility is explored as a scenario to test the impact on the cost-effectiveness conclusions.[112]

Clinical experts based in England have said that some patients may never reach the general population utility value in the ultimate without attack health state due to lingering fear/anxiety of the next attack. The auxiliary coefficient of the ‘not in perfect health state’ from the UK EQ-5D-3L value set has been explored in marginally decreasing the upper utility estimate value to characterise lingering fear/anxiety.[113] However the magnitudes of variables that describe the decrements from perfect health are relatively high when applied to general population values meaning it is difficult to accurately portray such quality of life outcomes in the cost-effectiveness analysis. Decrements of 0.01, 0.02 and 0.03 from the general population utility have explored as scenarios in Section B.3.11.3.

B.3.4.5.3 HAE attack disutility values

Building on Section B.3.3.5, the base-case of the cost-effectiveness analysis employs Nordenfelt et al. (2014) to inform the disutility of HAE attacks by severity. The study already accounts for the difference in the baseline (EQ-5D today) and HAE attack (EQ-5D attack) values and therefore the disutility associated with the severity of an attack can be directly applied as a decrement like in TA606.[10,100]

Additionally, the Aygören-Pürsün et al. (2016) HAE attack disutility values are used in a scenario analysis.[111] The HAE attack disutility value is derived as the difference among 'Between HAE attack' and 'By pain severity of last attack' utility values. .[111]

Clinical expert opinion indicated that the quality of life consequences of HAE attacks last longer than the clinical duration.[17] To accurately represent this fact for HAE patients in the cost-effectiveness analysis, the consequence of all HAE attacks has been extended beyond the clinically observed duration up to a length of seven days as opposed to the observed average length of [redacted].

Overall, Table 24 consolidates the information presented in this section regarding the disutility and duration of HAE attacks they are considered in the cost-effectiveness analysis. The table presents disutility values and the scaled disutility values in brackets, adjusted to reflect the indirect duration of the HAE attack.

Table 24. Raw and scaled HAE attack disutility values

Source	Mild attack disutility value	Moderate attack disutility value	Severe (non-laryngeal) attack disutility value	Severe (laryngeal) attack disutility value
Nordenfelt et al. (2014)[100]	0.070 (0.0175)	0.369 (0.0923)	0.486 (0.1215)	0.486 (0.1215)
Aygören-Pürsün et al. (2016)[111]	0.109 (0.0273)	0.255 (0.0638)	0.642 (0.1605)	0.642 (0.1605)

B.3.4.5.4 Caregiver disutility

The literature, patient group feedback and clinical expert opinion are consistent that the burden to caregivers of HAE patients is substantial.[54,58] Furthermore, owing to the hereditary nature of the condition, in many cases the caregivers/parents

themselves have HAE (Section B.1.3.1.1). In that sense, with stress, anxiety and trauma all known as excitatory triggers for HAE attacks, the caregiving responsibility in this case may involve perverse spillover effects that worsen the management of the condition of another individual. The reference case states that the perspective on outcomes should include all health effects, including carers where relevant.[99] Hence, this section outlines the rationale for including caregiver outcomes in the base case of the cost-effectiveness analysis and the associated quality-of-life data.

The ERG (now EAG) proposed and supported the narrative for the inclusion of caregiver outcomes in the TA606 submission.[10] However, lack of utility data on the topic prevented the company from modelling caregiver outcomes. This has been addressed by the recently published Lo et al. (2022) study described below.[102]

In addition, the ERG found it reasonable to consider the impact of HAE attacks on caregivers in TA738 and in principle agreed that the QoL burden experienced by caregivers should be incorporated into the QALY calculation.[9] However, due to committee disagreeing over the magnitude of the carer impact and its broad application, caregiver outcomes were not accepted in the base case. This conclusion was based on an acceptable range of 0.01–0.173 per year for caregiver disutility, as reported in a NICE DSU report.[9]

Another factor preventing inclusion of caregiver outcomes in the base case of TA738 was the extent to which berotralstat was able to provide improvements above and beyond the standard of care.[9] However, the efficacy of garadacimab in the following areas provide convincing arguments showing improvements in caregiver outcomes above and beyond the standard of care:

- Significant reductions in time-normalised number of attacks (Section B.3.3.1) – [redacted] number of HAE attacks avoided over a lifetime compared to C1-INHs
- Significant improvements in the time to first HAE (Appendix J) – [redacted]% of patients attack free over 12-months

- Significant improvements in the life years spent in the without attack health states (Section B.3.10) – [redacted] life years in without attack health states for garadacimab compared to [redacted] life years for berotralstat

To better characterise the lived experience of carers of individuals with HAE, CSL Behring proposes a more limited application of carer HRQoL in the base case. As recognised in TA738, the age of the treated population impacts the level of carer support dependents are likely to require. For example, TA958.[114] considered a treatment for severe hair loss in those aged >12 where a carer utility impact was accepted for all individuals aged 12–18. The rationale for this acceptance was that both carer and dependent share the condition (as is seen in HAE).[114]

Hence, our base case considered some of the abovementioned developments in modelling caregiver outcomes. Namely, that the resources associated with caregiver support are only required in 52.4% of attacks as per the burden of illness study by Aygören-Pürsün et al. (2014) and as such, this value has been conservatively applied to adolescents aged 12–18 years old.[111]

In most circumstances, for individuals who are over the age of 18, the natural and legal obligation for guardianship and caregiver support is removed which implies that the opportunity to access carer support is much lower. Likewise, patients pursuing further study and employment, may not seek the same level of caregiver support and necessary recovery from attacks as would be recommended. This is supported by evidence from the 2024 survey of individuals with HAE and their caregivers.[48] To that extent, it is assumed that patients over the age of 18 would nevertheless require carer support for severe attacks, due to their debilitating and inhibiting nature.

Furthermore, it has been confirmed with clinical experts that the quality-of-life impacts from an HAE attack lasts longer than the clinical duration for the patients, and so this has also been applied to caregiver disutility due to the likely second hand trauma and the lasting impact of social isolation and physical drain arising from caregiving during the clinical duration of the HAE attack.[17]

Therefore, as a conservative approach the base case analysis includes caregiver disutility in 52.4% of adolescents aged 12–18 years old and adult patients who experience a severe (whether laryngeal or not) attack over a period of seven days.

Table 25 presents the main variables considered with respect to modelling caregiver outcomes. The analysis focuses on the Lo et al. (2022) TTO, which reports a health utility value of 0.762 for carers of patients experiencing HAE attacks[102] which was subtracted from the general population utility value of 0.907, the reported value for the median UK population age of 40.4.[115] For simplicity, it is assumed that the disutility impact on carers remains constant throughout the analysis period.

Table 25. Summary of variables used to quantify caregiver outcomes in the cost-effectiveness analysis

Variable	Value
Caregiver state while caring for someone having an HAE attack	0.762
General population utility value for the median age carer	0.907
Unscaled caregiver disutility per HAE attack	0.145
Average number of carers per household	1.46
Percentage of HAE attacks requiring caregiver assistance (aged 12–18 years old)	52.4%
Percentage of HAE attacks requiring caregiver assistance (ages ≥18 years old)	All severe non-laryngeal and laryngeal attacks

Abbreviations: HAE, hereditary angioedema,

B.3.4.5.5 Administration disutility

The route of administration varies for LTP options in HAE. The SLR did not pick up any HRQoL studies relating to disutility associated with administration of these technologies specifically. Previous HAE appraisals accounted for administration disutility, however quality of life implications from dosing frequencies from the literature did not align with the administration frequencies.

The Matza et al. (2013) study has been chosen to quantify the administrative disutility associated with LTP options in HAE, because it reports the disutility per administration, allowing these values to be scaled to the appropriate number of administrations for all technologies.[116] The values used from the study are a disutility

of 0.004 for a subcutaneous injection and a 0.02 disutility for a 30-minute infusion, whereas oral technologies have been assumed to have a zero disutility. Given, garadacimab is administered with a pre-filled autoinjector pen, applying the subcutaneous injection disutility value to it can be considered conservative. Table 26 reports the administration related variables explored in the scenario analysis section.

Table 26. Administration disutility variables by technology

Technology	Administration route	Disutility per admin	Disutility per cycle
Garadacimab	Autoinjector pen	0.004	0.037*
Lanadelumab (Q2W)	Subcutaneous	0.004	0.008
Lanadelumab (Q4W)	Subcutaneous	0.004	0.004
Berotralstat	Oral	0	0
Berinert	Intravenous	0.02	0.16
Cinryze	Intravenous	0.02	0.16

Abbreviations: Q2W; Once every two weeks; Q4W, Once every four weeks. *Asterisks refers to the fact that garadacimab follows a once monthly (QM) pattern.

B.3.4.5.6 Adverse event disutility

Table 27 shows the disutility associated with adverse events analysed in the cost-effectiveness model. Table 27 reports the duration for which the adverse events last.

B.3.4.6 Summary of health-related quality-of-life data used in the cost-effectiveness analysis

Table 27 is a summary of all non-technology specific utility and disutility values. Since these values vary with age and number of attacks and are therefore gradually changing across the modelling horizon, Table 27 is fixed representation of quality-of-life outcomes for a 40 year old male HAE patient, with the number of HAE attacks experienced in the attack health state being three, with the number of attacks in the previous cycle being four. These have been validated with clinical experts.[17]

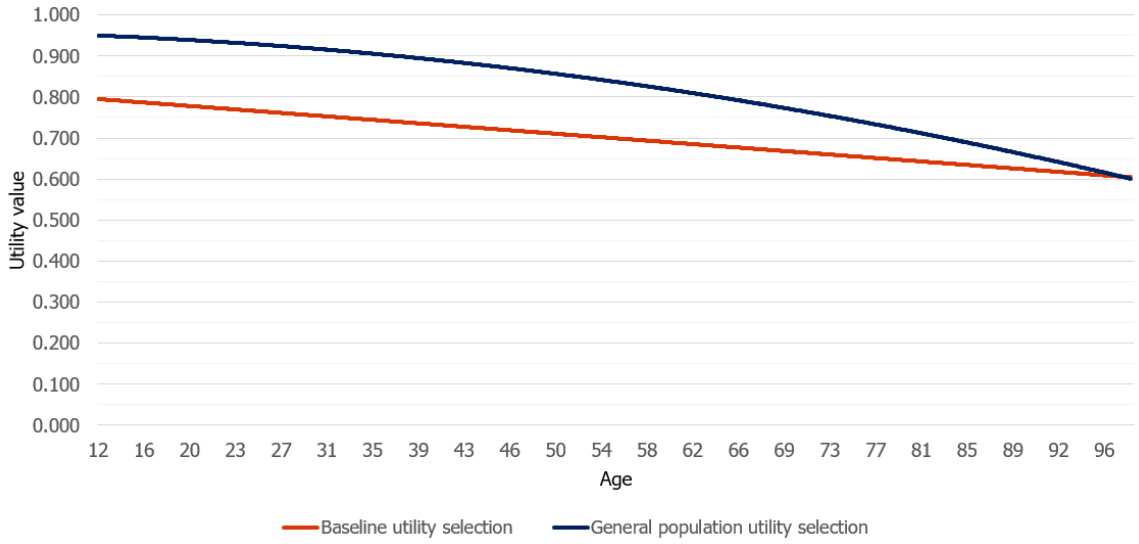
Figure 21 is an illustration of the development of the baseline utility values and general population utility values over the modelling horizon. The figure demonstrates that the opportunity cost associated with losing the accumulated utility because of being without attack for a prolonged period is highest in the younger population, highlighting the importance of a technology that is able to provide immediate and long-lasting protection.

Table 27. Summary of utility values for cost-effectiveness analysis

Health state/ adverse event	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Attack health state (three mild attacks)	0.667 (*)	-*	Section B.3.4.5.3	Baseline utility combined with HAE attack disutility sources.
Attack health state (three moderate attacks)	0.443 (*)	-*		
Attack health state (three severe attacks)	0.355 (*)	-*		
Attack health state (three laryngeal attacks)	0.355 (*)	-*		
Month 1 without an attack	0.755 (*)	-*	Section B.3.4.5.2	Clinical expert opinion on quality-of-life outcomes. The outcomes are made up of - baseline utility value, Nordenfelt et al. (2014); upper utility estimate value, Ara and Brazier (2010).[17,100,101]
Month 2 without an attack	0.785 (*)	-*		
Month 3 without an attack	0.816 (*)	-*		
Month 4 without an attack	0.847 (*)	-*		
Month 5 without an attack	0.878 (*)	-*		
Month 6 without an attack	0.909 (*)	-*		
Nausea	-0.050; 1 d	-0.05125, -0.04875	Section B.3.4.5.6	Beusterein et al. (2010)[117]
Vomiting	-0.035; 1 d	-0.035075, -0.034125		Sullivan et al. (2006)[118]
Diarrhoea	-0.035; 1 d	-0.035075, -0.034125		
Abdominal pain	-0.035; 1 d	-0.035075, -0.034125		
Headache	-0.200; 1 d	-0.195, -0.205		Stafford et al. (2012)[119]
Nasopharyngitis	-0.012; 4 d	-0.117, -0.123		Matza et al. (2019)[120]
Back pain	-0.045; 1 d	-0.43875, -0.46125		
Injection Site Erythema	-0.009; 0.5 d	-351/40000, -369/40000		
Injection site Pain	-0.009; 0.5 d	-351/40000, -369/40000		
Upper respiratory tract infection	-0.012; 4 d	-0.117, -0.123		
Viral upper respiratory tract infection	-0.012; 4 d	-0.117, -0.123		
Myalgia	-0.045; 1 d	-0.43875, -0.46125		
Fatigue	-0.060; 1 d	-0.057, -0.063		
Rash	-0.007; 0.5 d	-273/40000, -287/40000		

*Since the quoted values are a result of a composite formulas, the exact mathematical representations of their uncertainty statistics are not available. The composite outcomes are made up of - baseline utility value, Nordenfelt et al. (2014); upper utility estimate value, Ara and Brazier (2010); HAE attack disutility values, Nordenfelt et al. (2014).

Figure 21. Baseline utility and general population utility by age



Baseline utility selection: Nordenfelt et al. (2014); General population utility selection, Ara and Brazier et al. (2010). Tunnel state utility values occupy the area between the curves

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was conducted to identify published studies relevant for inclusion within the cost-effectiveness model. The majority of studies highlighted the high drug acquisition costs and resource use associated in European countries. The findings of the SLR are reported in Appendix I. To support the cost-utility analysis, the following studies have been chosen from the SLR and listed below:

- Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z et al. (2014) Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis 9 99.[54]

- Helbert M, Holbrook T, MacCulloch A and Mannan A. Understanding the cost of hereditary angioedema in England. The European Conference on Rare Diseases and Orphan Products. Berlin: Germany, 2013.[121]

B.3.5.1 Intervention and comparators' costs and resource use

Costs included in the economic analyses were drug acquisition costs, resource use for acute attacks and disease monitoring costs.

B.3.5.1.1 Drug acquisition costs of intervention and comparators

The recommended dose of garadacimab is an initial loading dose of 400 mg administered as two 200 mg SC injections on the first day of treatment followed by a monthly dose of 200 mg.[24] Garadacimab is available in a 200mg unit pre-filled pen which has a list price of [redacted]. A simple PAS fixed price of [redacted] which equates to a [redacted] discount off the list price has been submitted to NHS England. This confidential net price has been modelled in the cost-effectiveness analysis.

Drug posology and pack costs for garadacimab and its comparators are summarised in Table 28. List prices for lanadelumab, berotralstat, IV Cinryze and IV Berinert were taken from the BNF.[104] The list price for 200mg garadacimab dose has been submitted to the Department of Health and Social Care (DHSC) and is pending approval.

In calculating drug costs per cycle for C1-INHs, a dose of 1,000 IU every 3-4 days was assumed for IV Cinryze, consistent with its license.[65] It was anticipated that patients would use two 500 IU vials per administration and receive eight doses per cycle. Due to lack of licensed sources on the matter, the same dose has been applied to IV Berinert as they are in effect the same protein.

B.3.5.1.2 Administration costs

For all patients on non-oral treatment regimens, a one-time, one hour of nurse time-cost has been allocated in the model. This mimics the time-cost required for training the patients to self-administer at home for the course of the treatment. NHS Schedule of Reference cost reference - District nurse, adult, face to face (code N02AF).

B.3.5.1.3 Lanadelumab dose switching

For lanadelumab the SmPC states patients should receive a dose of 300mg every two weeks and in patients who are stable attack-free on treatment, a dose reduction to 300mg every 4 weeks may be considered, especially in patients with low weight.[64] Dose switching for lanadelumab has been explored in the model; one of the possible

dosing schedule switch stems from TA606, where 76.9% of patients will be on the 300mg/Q4W dosing schedule by the end of the first year as per trial estimates.[10]

Real world evidence from Dorr et al. (2022) study examines pre and post data on n=60 lanadelumab patients from across 16 centers in the UK.[71] The study claims that the commissioning criteria require greater baseline attack rates for initiation of lanadelumab than that explored in clinical trials, and as such this submission considers this data to be most appropriate for inclusion in the base case of the cost-effectiveness analysis. The study reports that 45.0% of patients are on the Q4W dosing frequency for lanadelumab, and the cost-effectiveness model will assume that this percentage is gradually reached over one-year, since that is the longest reported data availability in the study.

Table 28. Drug posology, form, administration, unit size, pack size and costs

Treatment	Posology			Unit strength	Pack size	Cost per pack	Cost per 28-day cycle	Loading dose
	Dose	Administration	Frequency					
Garadacimab	200mg	SC - Pen	Monthly	200mg	1	[redacted]	[redacted]	[redacted]
Lanadelumab	300mg	SC	Every 2 weeks or Every 4 weeks	300mg	1	£12,420	£24,840 or £12,420	N/A
Berotralstat	150mg	Oral	Once daily	150mg	28	£10,205	£10,205	N/A
IV Cinryze	1,000IU	IV	Every 3-4 days	500IU	1	£670	£10,688	N/A
IV Berinert	1,000IU	IV	Every 3-4 days	500IU	1	£670	£10,720	N/A

Abbreviations: IV, intravenous; SC, subcutaneous; IU, international units; N/A. not applicable.

B.3.5.1.4 Continuation of long-term prophylaxis technologies

Conclusions from TA738 indicate that the prophylactic use of berotralstat should be discontinued if the stopping criteria has been met. The stopping criteria is defined as less than 50% reduction in the HAE attack rate after three months of treatment initiation with berotralstat.[9]

Clinical expert input suggested that this stopping criterion is well adhered to in clinical practice.[17] Based on this feedback and clinical information from the APeX trial, the proportion of patients that discontinue berotralstat treatment due to lack of efficacy and/or tolerability was estimated. The cost-effectiveness analysis takes this into consideration and assumes that [redacted] of patients on berotralstat discontinue treatment after three months.[17,45]

Other technologies do not have formal continuation rules. Literature estimates were available for lanadelumab and C1-INH's for long term continuation patterns. A total of 32/34 patients continued lanadelumab over a 4-year real world observation period, and only 1/47 C1-INH patients discontinued treatment due to ineffectiveness over 15 months as reported by a multi-centre review of LTP. In the CSL312_3002 study of garadacimab, [redacted] patients remained enrolled in the latest data cut. The continuation patterns have been normalised to a common 40-year period over which discontinuation may occur, after which a steady state is reached where no further discontinuation takes place.

The impact of no discontinuation of any long-term prophylaxis treatment on the cost-effectiveness results is accounted for in scenario number 11 in Section B.3.11.3.

B.3.5.1.5 Adjuvant acute therapies

It is assumed that patients receiving LTPs require acute treatment at the onset of HAE attacks to alleviate symptoms and shorten their attack duration. Table 29 shows the acute therapies licensed in UK to alleviate HAE attack symptoms.

Table 29. Adjuvant acute therapies costs

Treatment	Indication	Posology		Pack size	Cost per pack	Total cost per attack	Market shares (normalised)
		Dose	Units per admin				
IV Berinert	Treatment of acute angioedema attacks[21]	20IU/kg	0.04	500	£670	£26.80#	[redacted]
IV Cinryze	Treatment of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE) [65]	1000IU	2	500	£688	£668	[redacted]
IV Ruconest	Treatment of acute angioedema attacks in adults, adolescents and children (aged 2 years and above) with HAE due to C1-INHs[19]	50IU/kg	0.02	2100	£750	£17.86#	[redacted]
SC Firazyr	Symptomatic treatment of acute attacks of HAE in adults, adolescents and children aged 2 years and older, with C1-INHs[122]	30mg	1	30	£1,395	£1,395	[redacted]
SC Icatibant	Treatment of acute angioedema attacks in adults, adolescents and children (aged 2 years and above) with HAE due to C1-INHs[123]	30mg	1	30	£837	£837	[redacted]
Basket		-			[redacted] flat price per attack, plus [redacted] extra per kg		

Abbreviations: IU, international unit; SC, subcutaneous; IV, intravenous; kg, kilogram; mg, milligram. #Refers to the cost per kilogram per attack as these are weight-based treatments.
Source: BNF, Adivo Report Q1 2024

B.3.5.2 Health-state unit costs and resource use

In addition to drug acquisition costs, patients with HAE may require additional medical resources to manage their attacks. However, due to the heterogeneity of HAE, resource use varies substantially and is subjective i.e. dependent on attack severity, its location and patient preference. Therefore, similar to the approach used in NICE TA738,[9] it was essential to estimate resource use for HAE attacks based on severity rather than simply calculating an average and applying it to all attacks. Hence, resource use for attacks was estimated as per attack severity.

The previously identified study conducted by Aygören-Pürsün et al. (2014) took a European perspective, with potentially limited generalisability to the HAE patient management in the NHS.[54] Hence, in the absence of UK specific data it was necessary to gain further UK clinical experts insights. [54]

Three clinical experts in England were consulted to estimate the frequency and nature of resource utilisation in patients experiencing HAE with differing levels of attack severity. In general, all three of them found it challenging to estimate resource use and noted that their responses were contingent on a case-by-case basis.[17] Thus, based on the variability in responses received, a mean value was assumed in case of conflicting estimates. Clinical feedback was used in the base case.

Similar to the approach used in NICE TA606, the average length of each hospital stay was estimated using data from previously identified Helbert et al. (2013)[10,121] which showed that HAE patients had a significantly higher mean number of hospital visits (1.85 vs 0.33) and bed days (3.02 vs 0.95) per year compared to non-HAE patients in the UK. Additionally, to estimate the average length of each hospital stay, the difference in bed days per patient per year between the two groups (2.07) was divided by the difference in hospital visits (1.52), resulting in an estimated average stay of 1.36 day.

Unit costs were derived from NHS reference costs 2021/22 and latest PSSRU published costs.[105,124] Table 30 presents the resource values used in the cost-effectiveness analysis.

Table 30. Health care resource use consumption and costs for acute attacks

Variable	Prob. per mild	Prob. per moderate	Prob. per severe	Prob. per laryngeal	Cost	NHS Code
Family physician	[redacted]	[redacted]	[redacted]	[redacted]	£76.08	Follow-up, adult, Face to Face (code AS08)
Home nurse	[redacted]	[redacted]	[redacted]	[redacted]	£54.00	District nurse, adult, face to face (code N02AF)
Accident and emergency visit	[redacted]	[redacted]	[redacted]	[redacted]	£5.93	Emergency Medicine, No Investigation with No Significant Treatment (code VB11Z)
Inpatient hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	£19.08	Non-Elective Inpatient Short Stay for Abdominal Pain without Interventions (code FD05B)
Radiography	[redacted]	[redacted]	[redacted]	[redacted]	£90.11	Computerised Tomography Scan of One Area, without Contrast, 19 years and over (code RD20A)
Blood tests	[redacted]	[redacted]	[redacted]	[redacted]	£2.96	Haematology test (code DAPS05)
Electro cardiography	[redacted]	[redacted]	[redacted]	[redacted]	£159.36	Electrocardiogram Monitoring or Stress Testing (EY517Z)
Ear, Nose and Throat consultation	[redacted]	[redacted]	[redacted]	[redacted]	£247.30	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0 (CB02F)
Total resource use for treatment of acute attacks	£5.73	£108.76	£226.49	£1,192.78	-	-

Abbreviations: Prob, probability

B.3.5.2.1 Monitoring costs

Monitoring costs have also been included in the economic analysis. This addressed an oversight in previous TAs that led to an underestimated the cost of HAE. The SLR did not identify costs or resources associated with monitoring HAE patients and so information obtained from the three clinical experts was used in the model.[17]

Monitoring costs are divided into attack free (AF) i.e. stable patients (defined as living six months without an attack) and patients experiencing a HAE attack. Table 31 summarises the monitoring costs used in the base-case analysis.

Table 31. Monitoring costs

Resource	Rate per cycle	Rate per cycle (AF)	Cost	NHS code
Family physician	[redacted]	[redacted]	£76.08	Follow-up, adult, Face to Face (code AS08)
Specialist nurse	[redacted]	[redacted]	£54.00	District nurse, adult, face to face (code N02AF)
Radiography	[redacted]	[redacted]	£90.11	Computerised Tomography Scan of One Area, without Contrast, 19 years and over (code RD20A)
Blood test	[redacted]	[redacted]	£2.96	Haematology test (code DAPS05)
Immunologist	[redacted]	[redacted]	£175.12	Consultant led, clinical immunology and allergic service (313)
Electrocardiogram	[redacted]	[redacted]	£159.36	Electrocardiogram Monitoring or Stress Testing (EY517Z)
Total resource use for monitoring HAE patients per cycle	**£75.67**	**£35.58**		

Abbreviations: AF, attack-free; HAE, hereditary angioedema

B.3.5.3 Adverse reaction unit costs and resource use

As discussed in section B.3.4.4 adverse events are not considered as part of the economic analysis from the cost perspective as generally they are not severe enough to trigger resource use of any kind.

B.3.5.4 Miscellaneous unit costs and resource use

There are no miscellaneous costs in the economic analysis.

B.3.6 Severity

CSL Behring does not anticipate garadacimab will meet the criteria for the severity weighting.

B.3.7 Uncertainty

Hereditary angioedema is a rare chronic genetic disorder that has historically limited the availability of robust clinical and economic evidence. Nevertheless, garadacimab benefits from a large body of evidence regarding its efficacy, especially for parameters relating to the time-normalised number of HAE attacks. A number of analyses including the Poisson regression (Section B.3.3.4) ensures that the highest level of validity has been established for the cost-effectiveness analysis. The OLE study for garadacimab contextualises the efficacy evidence over a prolonged period of time, in turn, addressing potential long-term variations of HAE attack rates. Expectations of long-term efficacy have been confirmed by clinical expert opinion and the alternative sources used to inform this parameter have been examined in the scenario analysis (Section B.3.11.3).

In absence of head-to-head trials, uncertainty arises in directly comparing the effectiveness of garadacimab to the other established long-term prophylaxis technologies used in the NHS. To address this challenge, an NMA comparing the clinical trials of VANGURD, HELP, APeX and CHANGE has been conducted using a range of statistical analyses and scenarios to inform relative efficacy.

The unpredictable nature of HAE hinders the collection of consistent quality of life data due to varying attack frequency and severity. To address this, a wide range of sources has been utilised to ensure the robustness of quality of life variables in cost-effectiveness analyses. Additionally, clinical expert opinions have been incorporated to accurately reflect patient experiences with HAE.

Patient preferences are diverse, making it challenging to quantify them in cost-effectiveness analyses. These preferences can include attitudes towards continuing long-term prophylaxis (LTP) regimes or preferred administration methods. These

variables have been examined in scenario analyses to better understand patient preferences (Section B.3.11.3).

The overarching variable and parameter uncertainties within the cost-effectiveness analysis have been actively characterised within the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) A frameworks. The associated outcomes can be found in Sections B.3.11.1 and B.3.11.2.

B.3.8 Managed access proposal

A manged access proposal has not been made for garadacimab as CSL Behring do not believe it is a suitable candidate.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Appendix R contains a wholistic summary of base-case analysis inputs along with the probabilistic parametrisations. Generally, attack rate variables have been assigned the lognormal distribution; attack severities the Dirichlet distribution; costs the gamma distribution; and utilities the beta distribution.

B.3.9.2 Assumptions

Table 32 details the key assumptions used in the cost-effectiveness analysis along with the associated justification and reference to the relevant section of the submission.

Table 32. Assumptions used in the cost-effectiveness analysis

Assumption	Justification	Reference
All HAE attacks cause progression to the attack-health state	Clinical experts indicated that patients respond to attack differently. On average you would expect any attack even if untreated with adjunct therapies, to cause patients to return to the attack health state.[17]	Section B.3.3.1
Tunnel length of six cycles	Itzler et al. (2024) and clinical experts show that this is an appropriate amount of time to model attack free outcomes over[57]	Section B.3.2.2.1

Assumption	Justification	Reference
Efficacy measures (RR, HR) remain constant over time	Standard modelling simplification in absence of long-term head-to-head comparisons	-
IV Berinert assumed same efficacy outcomes as Cinryze	Both technologies are C1-INH prophylaxis technologies and essentially the same protein.	Section B.3.3.1
Distribution of attack severity profiles by technology remain constant over time	No data to indicate why or how attack severity profiles would change over time	Section B.3.3.6
Linear growth of weight according to Growth Charts and NHS sources	Best sources used to accurately quantify patient weight over time; an important consideration for weight-based dosed technologies	-
Resource use of 'attack free' patients is only applicable in the ultimate tunnel state	Assumed that monitoring patterns of HAE are consistent and only patients with prolonged periods without an attack would be less frequently seen.	Section B.3.5.2
Resource and monitoring use assumed constant over the modelling horizon	Apart from the above consideration of 'attack free patients', standard modelling simplification. No data to suggest older patients require greater care following an attack.	-
No administration disutility considered	Lack of HAE specific sources on administration burdens. Considered in the scenarios	Section B.3.4.5.5
Adverse event probabilities, disutility and duration all constant over the modelling horizon	Standard modelling simplification in absence of long-term head-to-head comparisons	Section B.3.4.5.6
Gender split in the model assumed to remain constant over the modelling horizon	Standard modelling simplification	Section B.3.2.1
Linear increase of utility across tunnel health states	A method to account that the feeling of being 'attack-free' progressively achieved.	Section B.3.4.5
Patients who remain attack free for more than six cycles have the same quality-of-life outcomes as patients who remain attack free for six cycles	A standard cap so patients do not experience utility greater than that of the general population even though they may experience attack freedom for more than the number of tunnel states.	Section B.3.2.2
Attack disutility and caregiver disutility remain constant over time	Standard modelling assumption.	Section B.3.4.5.4

Abbreviations: HR, Hazard Ratio; NHS, National Health Service; RR, Rate ratio.

B.3.10 Base-case results

As detailed in Section B.3.5.1.1, a confidential PAS discount has been submitted and is expected to be approved prior to the first appraisal committee meeting. All results are generated using garadacimab's confidential net price per pack of [redacted] Due to the confidentiality of the PAS discounts that are in effect for the comparator technologies in the decision-problem, the base-case results are presented using the list price for the comparators.

Garadacimab presents itself as a long-term prophylaxis option that provides the highest number of QALYs, but it is also a cost-saving treatment. These results stem from garadacimab's effect in reducing the number of HAE attacks, which lead to reduce costs for acute treatment of HAE attacks, reduced disutility from HAE attacks, and quality of life benefits derived from more time spent between attacks. Overall, garadacimab is a cost-effective solution for preventing recurrent attacks of hereditary angioedema in people 12 years and over.

The base case includes LTP options that are typically restricted to the ≥2 attacks per week subgroup in order to have a complete fully incremental analysis from the health economic perspective and to maintain brevity. The impact of the ≥2 attacks per week clinical characteristics on the economic analysis is explored in the scenario analyses Section B.3.11.3 and subgroup Section B.3.11.3.1.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Table 33 presents the fully incremental cost-effectiveness analysis for the base case which covers HAE patients that experience ≥2 attacks per month. At the confidential net price, garadacimab is cost effective at willingness-to-pay threshold (WTP) of £20,000/QALY. Table 34 presents the disaggregated cost breakdown by category for the technologies considered in the base case analysis. Table 35 presents the cost breakdown by health state for the technologies considered in the base case. Table 36 presents the (quality adjusted) life years breakdown by health state for the technologies considered in the base case Table 37 presents the breakdown of attacks by severity per technology over the patient's lifetime.

Table 33. Fully incremental deterministic results for the ≥2 attack per month subgroup

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Garadacimab	[redacted]	21.38	[redacted]	-	-	-	-	-
Berotralstat	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	Dominated
Cinryze	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	Dominated
Berinert	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	Dominated
Lanadelumab	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	Dominated

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio

Table 34. Disaggregated costs breakdown by category for the base case analysis

Technology	Loading costs (£)	Prophylactic costs (£)	Acute HAE attack treatment costs (£)	Acute HAE attack management costs (£)	Monitoring costs (£)	Total costs (£)
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema

Table 35. Disaggregated cost breakdown by health state for the base case analysis

Technology	Without attack – Month 1 (£)	Without attack – Month 2 (£)	Without attack – Month 3 (£)	Without attack – Month 4 (£)	Without attack – Month 5 (£)	Without attack – Month 6 (£)	Attack health state (£)
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 36. Disaggregated life years and quality-adjusted life years by health in the base case analysis

Technology	Without attack – Month 1 (QALY/LY)	Without attack – Month 2 (QALY/LY)	Without attack – Month 3 (QALY/LY)	Without attack – Month 4 (QALY/LY)	Without attack – Month 5 (QALY/LY)	Without attack – Month 6 (QALY/LY)	Attack health state (QALY/LY)
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QA(LY), quality-adjusted (life year)

Table 37. Disaggregated number of HAE attack per severity by technology for the base case analysis

Technology	Number of attacks - mild	Number of attacks - moderate	Number of attacks – severe (non-laryngeal)	Number of attacks – severe (laryngeal)	Number of attacks - Total
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Table 38 presents the fully incremental probabilistic cost-effectiveness analysis for the base case which covers HAE patients that experience ≥2 attacks per month. The analysis was conducted over 10,000 iterations, resulting in the probabilistic outcomes closely converging on the deterministic outcomes. The convergence test of Hatswell et al. (2018)[125] showed that the confidence intervals of the incremental net monetary benefit (INMB) values do not contain the zero value at the standard cost-effectiveness thresholds meaning further iterations of the PSA would not change the conclusions of the analysis.

Figure 22 presents the incremental cost-effectiveness plane for the first 200 iterations of the PSA. Note that garadacimab is situated at the origin, meaning iterations in the south-east quadrant are dominated by garadacimab.

Figure 23 presents the cost-effectiveness acceptability curve for the PSA analysis conducted. In effect, the figure also presents the cost-effectiveness acceptability frontier, as the garadacimab curve constitutes the outer envelope of the frontier.

Based on the above findings, garadacimab has a [redacted] chance of being cost-effective at the £20,000 WTP cost-effectiveness threshold.

Table 38. Fully incremental probabilistic results for the ≥2 attack subgroup

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Probability of cost effectiveness at £20,000/QALY WTP threshold
Garadacimab	[redacted]	21.38	[redacted]	-	-	-	-	100%
Berotralstat	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	
Cinryze	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	
Berinert	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	
Lanadelumab	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio

Figure 22. Incremental cost-effectiveness plane

Figure 23. Cost-effectiveness acceptability curve/frontier

B.3.11.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted to identify which model parameters had the greatest influence on results, by varying one parameter at a time between the 95% CI and assessing the impact on model outputs. Where the 95% CI were not available, the standard error was assumed to be equal to 20% of the point estimate.

The deterministic sensitivity analysis (DSA) is made up of four paired comparisons of garadacimab against each of the relevant comparators. The top 10 most influential univariate variations are presented for each pair. The findings suggest that the variables with the largest impacts are consistently those that relate to the number or treatment of HAE attacks such as rate ratios and the baseline attack rate, followed by variables that define the baseline utility values. However, overall, even the extreme values considered in the analysis do not alter the cost-effectiveness conclusions.

Table 39, Table 40, Table 41, and Table 42 provide the univariate DSA outcomes against lanadelumab, berotralstat, Berinert, and Cinryze respectively.

Table 39. Deterministic sensitivity analysis results against lanadelumab

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
2	Rate ratio for the requirement of on-demand treatment - Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
3	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
4	Attack rate requiring on-demand treatment - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio for the requirement of on-demand treatment - Lanadelumab (Q4W)	[redacted]	[redacted]	[redacted]	[redacted]
6	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
7	Rate ratio - Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
8	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
9	Proportion of males	[redacted]	[redacted]	[redacted]	[redacted]
10	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 40. Deterministic sensitivity analysis results against berotralstat

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Attack rate requiring on-demand treatment - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
2	Rate ratio for the requirement of on-demand treatment - Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
3	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
4	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
6	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
7	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
8	Attack rate - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
9	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
10	Duration over the impact of an attack is felt (days)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 41. Deterministic sensitivity analysis results against Berinert

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Rate ratio for the requirement of on-demand treatment - Berinert	[redacted]	[redacted]	[redacted]	[redacted]
2	Attack rate requiring on-demand treatment - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
3	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
4	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
6	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
7	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
8	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
9	Attack rate - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
10	Duration over the impact of an attack is felt (days)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 42. Deterministic sensitivity analysis results against Cinryze

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Rate ratio for the requirement of on-demand treatment - Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
2	Attack rate requiring on-demand treatment - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
3	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
4	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
6	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
7	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
8	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
9	Attack rate - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
10	Rate ratio - Cinryze	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

B.3.11.3 Scenario analysis

Scenario analyses examine the impact of variables whose uncertainty is not adequately characterised by the PSA or DSA, such as alternative sources of data for a set of variables.

A total of 25 scenarios have been conducted to ensure that all structural uncertainties and all alternative data sources have been examined for their impact on the cost-effectiveness conclusions. While the conclusions are robust with respect to many scenarios, the most significant impact on the cost-effectiveness results from scenarios that vary discounting and continuation rates to treatment.

Continuation rates for all treatments set to 100% as opposed to a gradual decline over time in the base case are impactful because this variable affects both the clinical outcomes and significantly contributes to the cost of prophylaxis over time. Garadacimab proves to be an even more efficient use of NHS resources with scenario, however, Section B.3.5.1.4 described why the base case values are more appropriate for decision making.

Other scenarios such as number of months in a tunnel or utility data choices have limited impact on the cost-effectiveness highlighting that the base case assumptions are robust and appropriate and that garadacimab is a cost-effective use of NHS resources.

Table 43 presents the incremental costs and QALYs for all 25 scenarios for garadacimab compared with lanadelumab and berotralstat, whereas Table 44 provides the scenario analysis for garadacimab compared with IV Berinert and Cinryze.

Table 43. Scenario analyses against berotralstat and lanadelumab

Scenario name	Incremental costs against lanadelumab (£)	Incremental QALYs against lanadelumab	INMB against lanadelumab (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
Undiscounted QALYs and costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Males only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ages 12-100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ages 18-100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against lanadelumab (£)	Incremental QALYs against lanadelumab	INMB against lanadelumab (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
9 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack rate: ≥ 8 attacks per month subgroup*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternate HAE management source - A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against lanadelumab (£)	Incremental QALYs against lanadelumab	INMB against lanadelumab (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
Alternate upper utility - B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VANGUARD phase III utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternate HAE disutility - C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of administration disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAE attack disutility duration informed by VANGUARD ([redacted] days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against lanadelumab (£)	Incremental QALYs against lanadelumab	INMB against lanadelumab (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
Three day HAE attack disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.01 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.02 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against lanadelumab (£)	Incremental QALYs against lanadelumab	INMB against lanadelumab (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
0.03 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adults (>18 years) requiring caregiver support for 52.40% of attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against lanadelumab (£)	Incremental QALYs against lanadelumab	INMB against lanadelumab (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
Last observation carried forward (all cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poisson regression (all cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema, INMB, incremental net monetary benefit; QALY, quality-adjusted life year, Source: A Aygören-Pürsün et al (2014)[54] ;B, Hernandez Alva et al. (2022)[87]; C, Aygören-Pürsün et al. (2016)[111]. Note: *Rate ratio from intention-to-treat population applied from NMA

Table 44. Scenario analyses against IV Berinert and Cinryze

Scenario name	Incremental costs against IV Berinert (£)	Incremental QALYs against Berinert	INMB against IV Berinert (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against Cinryze	Incremental QALYs against Cinryze	INMB against Cinryze (£) at £30,000 threshold	Relative change of INMB from base case
Undiscounted QALYs and costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Males only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ages 12-100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ages 18-100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against IV Berinert (£)	Incremental QALYs against Berinert	INMB against IV Berinert (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against Cinryze	Incremental QALYs against Cinryze	INMB against Cinryze (£) at £30,000 threshold	Relative change of INMB from base case
9 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack rate: ≥ 8 attacks per month subgroup*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternate HAE management source - A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against IV Berinert (£)	Incremental QALYs against Berinert	INMB against IV Berinert (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against Cinryze	Incremental QALYs against Cinryze	INMB against Cinryze (£) at £30,000 threshold	Relative change of INMB from base case
Alternate upper utility - B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VANGUARD phase III utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternate HAE disutility - C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of administration disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAE attack disutility duration informed by	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against IV Berinert (£)	Incremental QALYs against Berinert	INMB against IV Berinert (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against Cinryze	Incremental QALYs against Cinryze	INMB against Cinryze (£) at £30,000 threshold	Relative change of INMB from base case
VANGUARD ([redacted] days)								
Three day HAE attack disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.01 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.02 decrement from general population utility to approximate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against IV Berinert (£)	Incremental QALYs against Berinert	INMB against IV Berinert (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against Cinryze	Incremental QALYs against Cinryze	INMB against Cinryze (£) at £30,000 threshold	Relative change of INMB from base case
patient's fear of attack								
0.03 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adults (>18 years) requiring caregiver support for 52.40% of attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against IV Berinert (£)	Incremental QALYs against Berinert	INMB against IV Berinert (£) at £30,000 threshold	Relative change of INMB from base case	Incremental costs against Cinryze	Incremental QALYs against Cinryze	INMB against Cinryze (£) at £30,000 threshold	Relative change of INMB from base case
No caregiver disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last observation carried forward (all cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poisson regression (all cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema, INMB, incremental net monetary benefit; QALY, quality-adjusted life year, Source: A Aygören-Pürsün et al (2014)[54] ;B, Hernandez Alva et al. (2022)[87]; C, Aygören-Pürsün et al. (2016)[111] Note: *Rate ratio from intention-to-treat population applied from NMA

B.3.11.3.1 IV Berinert threshold analysis

Given the lack of clinical data regarding Berinert's (unlicensed dose) and its prophylactic efficacy, a threshold analysis has been conducted to illustrate the impact of a range of values for Berinert's rate ratios (for both time normalised number of HAE attacks and time normalised number of HAE attacks requiring on-demand) on the cost-effectiveness conclusions. This analysis has been conducted in the ≥8 attack subgroup since that is where IV Berinert is available in the NHS and is found in Appendix R.

B.3.12 Subgroup analysis

B.3.12.1 ≥2 attacks per week subgroup analysis

The majority of LTP options available in the NHS are restricted to the ≥2 attacks per week (equates to ≥8 attacks per month) subgroup. This subgroup analysis explores the cost-effectiveness landscape for this group. Due to the variety of treatments and prescribing options, the analysis includes strategies involving treatment sequencing. The sequences are as follows:

- Garadacimab -> C1-INH (Berinert)
- Garadacimab -> Lanadelumab (with progression to Q4W)
- Lanadelumab (with progression to Q4W) -> C1-INH (Berinert)
- C1-INH (Berinert) -> Lanadelumab (with progression to Q4W)

Patients progress towards the next treatment sequence according to their discontinuation rates mentioned in Section B.3.5.1.4. Note that lanadelumab Q2W patients may directly discontinue to the next treatment in the sequence rather than progressing first to the less frequent dosing schedule of Q4W. IV Berinert is used as a representative C1-INH to simplify the sequencing choices.

As presented in Table 45, both strategies that initiate with garadacimab make up the top two cost-effective solutions in the analysis, largely due to garadacimab's efficacy.

Table 45. Fully incremental cost-effectiveness analysis with treatment sequencing, for the ≥2 attacks per week subgroup

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Garadacimab (C1-INH)	[redacted]	21.38	[redacted]	-	-	-	-	-
Garadacimab (lanadelumab)	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	£357,445	£357,445
C1-INH (lanadelumab)	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	Dominated
Lanadelumab (C1-INH)	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	Dominated

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio

B.3.13 Benefits not captured in the QALY calculation

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. Therefore, to fully assess the holistic benefits of garadacimab, it is essential to consider not only the direct impact on patients but also the indirect impact on caregivers. While QALYs will be used to measure patient HRQoL, the significant burden on caregivers, including absenteeism and mental impact, cannot be ignored, as highlighted by UK clinical experts.[17] Therefore, the cost-effectiveness analysis includes the impact on caregivers in the base case, however, not all aspects of carer outcomes could have been considered.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The model was aligned with NICE's preferred methods. The model was built to align with the NICE reference case and adopted an NHS PSS perspective. The model used a lifetime horizon to capture all costs and QALY gains associated with the intervention.

Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. These procedures included verification of all input data with original sources, programme validation included checks of the model results, calculations, data references, model interface and visual basic for application code.

B.3.15 Interpretation and conclusions of economic evidence

HAE is a rare chronic genetic disorder. While several treatments exist for HAE, it is presently an incurable disease, and symptoms in the form of unpredictable attacks can persist throughout the patient's lifetime.[11] The current treatments in the NHS for the prevention of recurrent HAE attacks include technologies such as lanadelumab, berotralstat and C1-INH.

Garadacimab has shown to significantly improvement quality of life outcomes to berotralstat and numerically superior to lanadelumab (Section B.2.10). In addition to offering an improved option to the current LTP treatments, garadacimab helps to bridge the treatment gap for patients who do not benefit or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs.

Garadacimab has been positioned as a treatment option for people aged 12 years and older who require routine prevention of recurrent attacks of HAE and experience ≥2 attacks per month. With this positioning, garadacimab has the potential to offer an improved option to current modern LTP treatments as well as help to bridge the treatment gap for patients who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs.

The economic analysis is based on a *de novo* economic model with the structure designed to reflect the natural history of patients with HAE, as it builds on the NICE committee preferences from TA606 and TA738. Base case results demonstrated that garadacimab is cost-effective at the NICE willingness to pay threshold of £20,000-£30,000, dominating all comparators by generating substantially improved QALYs and cost-savings (see Section B.3.10 and B.3.11).

In line with the guidance from NICE, both structural and parameter uncertainty have been explored. The robustness of the base case results was assessed via comprehensive probabilistic, deterministic and scenario analyses, with results demonstrating the stability of the base case with a high degree of certainty.

Strengths

- The economic analysis is underpinned by a well-designed pivotal phase 3 randomised, placebo-controlled, double-blind, parallel-arm study (VANGUARD), that is broadly representative of the expected patient population in England and Wales.

- The model structure and assumptions were based on NICE committee preferences in TA606 and TA738 for HAE and input from three immunologists

specialising in treating HAE in the UK. Namely, the tunnel states captured an important aspect of life with HAE, of time to first attack.

- Uncertainty has been explored through various types of sensitivity analysis and results have demonstrated robustness of model and assumptions.

Limitations

- A limitation of the economic analysis includes the absence of head-to-head trial between garadacimab and LTPs, which meant that an NMA was used to inform comparator efficacy estimates and by default associated with uncertainty.

- Owing to low patient numbers, evidence gaps are inherent in rare diseases such as HAE. To address these, various methods were used (see Section B.3.7) and to ensure credibility, it was essential to obtain validation from immunologists in England.

Conclusions

Garadacimab is expected to be a cost-effective alternative treatment option for patients who are currently being treated with berotralstat, lanadelumab and C1-INHs within NHS clinical practice, where it shows greater health benefits and lower costs. As a first-in-class FXIIa inhibitor, garadacimab has demonstrated significant efficacy and safety in reducing attack frequency and severity vs. placebo and superiority over other LTP options across several efficacy outcomes (Sections B.2.6 and B.2.10).

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B.5 Appendices

See separate document [add details/file names]

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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]

Appendix T - Additional evidence addendum

15 November 2024

File name	Version	Contains confidential information	Date
ID6394 Garadacimab Company Evidence Submission – Addendum – Appendix T [noCON]	vFINAL	No	15 November 2024

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Table of abbreviations

AE-QoL	Angioedema quality of life (questionnaire)
AgD	Aggregated patient data
BIW	Twice weekly
BMI	Bosy mass index
C1-INH	C1 esterase inhibitor
CrI	Credible interval
DIC	Deviation information criterion
DSU	Decision support unit
ESS	Effective sample size
HAE	Hereditary angioedema
IPD	Individual patient level data
IU	International units
IV	Intravenous
kg	kilogram
LTP	Long-term prophylaxis
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
MAIC	Matching-adjusted indirect comparisons
mg	milligram
ML-NMR	Multi-level network meta regression
PBO	Placebo
pD	Effective number of fitted parameters
Q2W	Once every two weeks
Q4W	Once every four weeks
QD	Once daily
QoL	Quality of life
QM	Once monthly
RCT	Randomised controlled trial
SC	Subcutaneous
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TSD	Technical support document

1. Executive summary

CSL Behring delivered a full evidence submission to NICE of garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over on 07 November 2024. Since the submission, the results of a multi-level network meta regression (ML-NMR) have become available and are included in this additional evidence addendum to supplement the existing network meta-analysis (NMA) used in the company evidence submission.

This addendum provides a ML-NMR analysis of efficacy data comparing garadacimab to berotralstat[1], lanadelumab[2] and HAEGARDA (a subcutaneous C1-esterase inhibitor named Berinert SC in the NHS)[3]. This analysis is to supplement the existing NMA used in the company's cost-effectiveness model by further exploring the base case assumption that there is no evidence of treatment effect modification that would necessitate adjustment, be it for garadacimab or the comparator technologies. Such an assumption has been made for previous NICE TA606 and TA738[4,5]

Berinert SC has not been identified as a relevant comparator in the scope of the decision problem as it would only be considered in special circumstances, such as when a patient fails treatment on available long-term prophylaxis (LTP) options or is unsuitable to receive them (e.g. during pregnancy) and has poor venous access restricting them to be treated with IV C1-INHs.[6 7] This analysis has been aligned to the NMA, which also includes Berinert SC, to cater to the evidence requirements of other CSL Behring affiliates.

The ML-NMR explores the following endpoints:

- Time-normalised number of hereditary angioedema HAE attacks
- Time-normalised number of moderate and or/severe HAE attacks
- Time-normalised number of HAE attacks requiring on-demand treatment
- Change from baseline in Angioedema quality of life (AE-QoL) total score
- Any treatment emergent adverse event (TEAE)
- Change from baseline in number of attack-free days per month

The ML-NMR considered the feasibility of adjusting the above endpoints, across the covariates of baseline number of HAE attacks, BMI, age and sex. The use of these covariates has been described in Section 3.2.

Table 1 provides a comparative summary of the analysis performed from the ML-NMR and the resulting impact against the NMA. Overall, the results from the ML-NMR methodology are consistent with the conclusions from the NMA, that garadacimab is statistically superior to placebo for all efficacy outcomes considered, and not significantly different to placebo in terms of safety outcomes.

Table 1. Summary of outcomes derived from ML-NMR vs NMA

Endpoint	Final analysis	Impact on NMA conclusions
Time-normalised number of HAE attacks	Fixed effects ML-NMR performed adjusting for baseline HAE attack rate	Impact – moderate* (see Section 5)
Time-normalised number of moderate and/or severe HAE attacks	Fixed effects ML-NMR performed adjusting for baseline HAE attack rate	Impact – moderate*. (see Section 5)
Time-normalised number of HAE attacks requiring on-demand treatment	Fixed effects ML-NMR performed adjusting for baseline HAE attack rate	Impact – moderate* (see Section 5)
Proportion of attack-free patients	None – continuity correction did not produce a feasible analysis. See Section 3.1	N/A
Change from baseline in AE-QoL total score	Fixed effects and random effects ML-NMR performed adjusting for baseline HAE attack rate, BMI, age and sex.	Impact – minimal (see Section 5)
Any treatment emergent adverse event	Fixed effects and random effects ML-NMR performed adjusting for baseline HAE attack rate	Impact – minimal (see Section 5)
Change from baseline in number of attack-free days per month	Fixed effects and random effects ML-NMR performed adjusting for baseline HAE attack rate, BMI, age and sex.	Impact – minimal (see Section 5)

Abbreviations: HAE, hereditary angioedema; ML-NMR, multilevel network meta regression; NMA, network meta-analysis; BMI; Body mass index; AE-QoL, Angioedema quality of life. Asterisk indicates that the time-normalised number of HAE attacks endpoints have been estimated using the negative binomial distribution, causing some deviation from Poisson based aggregate NMA outcomes

2. Introduction

In the absence of head-to-head studies, a network meta-analysis (NMA) was conducted to determine the comparative efficacy and safety of garadacimab against berotralstat, lanadelumab and plasma-derived IV C1-INHs in people aged ≥12 years with HAE 1/2. The results indicated that across multiple endpoints, garadacimab fared consistently better when compared to berotralstat, lanadelumab, and Cinryze which makes it a highly competitive LTP option in HAE.

However, despite best efforts made to minimise bias by excluding insufficiently similar study data residual heterogeneity between studies included in the NMA may have reduced the validity of some analyses. Hence to further support the conclusions derived from the NMA, a ML-NMR was undertaken as it offers distinct methodological benefits in capturing and adjusting for heterogeneity and contextual factors that a standard NMA may overlook. The decision to conduct ML-NMR aligns with the NICE Decision Support Unit (DSU) Technical Support Documents (TSDs)[8], particularly those addressing complex methods in NMA, model-based evidence synthesis, and the need for robust handling of heterogeneity and inconsistency across studies.

As per NICE DSU TSD18[8] population-adjusted indirect treatment comparison (PA-ITC) method like MAIC, STC and NMR offers advantages over simpler indirect comparison (ITC) methods that rely solely on aggregated data. Aggregated data ITCs do not account for differences in patient characteristics (treatment effect-modifying variables) between trials, which can lead to biased estimates, especially when comparing only two trials.[9] Please see Table 2 which compares the characteristics of ITC methods considered for this submission.

Table 2. Overview and comparison of possible ITC methods

Feature	ML-NMR	NMA	MAIC
Data usage	Uses both IPD and AgD	Primarily uses AgD	Uses both IPD and AgD
Population adjustment	Adjusts for differences in covariates between populations	Assumes patient characteristics are homogenous across trials	Adjusts for differences in covariates between populations
Comparison type	Direct and indirect comparison within a network of treatments	Direct and indirect comparison within a network of treatments	Indirect comparisons between pairs of treatments
Modelling approach	Embeds a probabilistic approach to population adjustment	Relies on the assumption of no difference in the distribution of trial-level effect modifiers	Estimates relative treatment effects between pairs of trials
Complexity	High – involves Bayesian statistical inference	Moderate, uses standard statistical methods	Moderate, involves weighting and regression models
Flexibility	High, can include IPD and covariate information from all trials	Moderate, limited by the assumption of similar covariate characteristics	Limited, can only compare pairs of treatments with available IPD

Abbreviations: AgD, aggregated patient level data; IPD, individual patient level data; MAIC, matching-adjusted indirect treatment comparisons; NMA, network meta-analysis.

In summary, while conducting the NMA was justified as a default to inform the cost-effectiveness analyses, considering a MAIC or ML-NMR further gives credence to the NMA results. As such, between the two PA-ITC methods we chose ML-NMR since a MAIC would not have been the most appropriate given it conforms well with conducting pairwise treatment comparisons which in our case was not feasible given the number of comparators in the network. Furthermore, the results from a MAIC would have been difficult to interpret since each treatment effect estimate (for a

given endpoint) would be for a different study population i.e. the populations of the individual target studies. Hence, conducting a ML-NMR offered a more comprehensive and less biased approach when dealing with a complex network by not only reducing the number of pairwise comparisons but also maintaining the network approach of the NMA. These reasons justified ML-NMR's role in improving decision robustness, in line with NICE's methodological standards and with the potentially diverse clinical landscape of HAE in NHS England.

2.1 Addressing treatment and population heterogeneity

TSD 18 ("Methods for Population-Adjusted Indirect Comparisons in Health Technology Assessment")[8] advises that standard NMA assumptions of consistency and homogeneity are often insufficient when substantial heterogeneity exists across patient populations, study designs, and treatment delivery contexts. ML-NMR offers a structured approach to account for variability across study-level covariates, allowing adjustment for treatment-by-covariate interactions that may otherwise bias pooled estimates. This flexibility is particularly valuable when assessing interventions within diverse patient subgroups which may be the case for garadacimab's submission, a need highlighted in TSDs 3 and 10, which stress the importance of maintaining model generalisability and relevance to NICE's broad patient focus.[10,11]

2.2 Incorporating contextual & structural differences via multilevel modelling

The TSDs emphasise the importance of capturing hierarchical data structures that may arise from different study designs and varying treatment contexts. Using a multilevel structure within an ML-NMR model aligns with TSD 5 on handling heterogeneity, enabling a layered approach that treats studies as clusters, thus addressing correlation within these clusters[12]. By doing so, ML-NMR provides an improved nuanced understanding of treatment effectiveness across different healthcare settings, improving external validity. This is particularly relevant for interventions where effectiveness may vary significantly by geographic or healthcare system context. For example, in the NHS, the clinical commissioning structurally separates the prescribing patterns of long-term prophylaxis treatments according to the patients baseline number of HAE attacks per month.[4,5,13]

2.3 Improving decision robustness through adjusted, relevant estimates

ML-NMR enhances robustness in decision-making by reducing unexplained between-study heterogeneity, aligning with the guidance provided in TSD 4 and 5 on appropriately handling variability and inconsistency[12,14]. By including study-level covariates that are both clinically and economically relevant, ML-NMR models allow the NICE committee to interpret treatment effects within specific subpopulations or healthcare contexts that align with real-world application. This relevance supports the NICE dossier requirement for clarity and precision in reporting cost-effectiveness, as per NICE guidelines. Furthermore, the ML-NMR can draw on the pooled population increasing effective sample size compared to the pairwise comparisons of the MAIC approach. Thereby, the ML-NMR provides valuable context to the treatment effect modification discussions present in previous NICE submissions in HAE.

2.4 Facilitating model transparency and reproducibility

ML-NMR is conducive to transparent modelling, as it involves explicit modelling of covariates and structural parameters that NICE TSDs advocate. By following TSD recommendations, particularly TSD 2, for clearly stating assumptions, covariates, and model structure, the application of ML-NMR in the company's evidence submission ensures that underlying assumptions are visible and challengeable, enhancing model reproducibility and credibility[15]. Furthermore, transparency in handling subgroup effects provides the NICE committee with a clear basis for understanding how these analyses relate to cost-effectiveness estimates and decision uncertainty.

2.5 Aligning with best practices in HTA and NICE Decision-Making

The use of ML-NMR aligns with NICE's drive towards methodological innovation that maintains rigor while incorporating new insights from health technology assessment (HTA) practices globally.[8] By adhering to DSU guidance, this approach enables the company's evidence submission to leverage best-practice methodologies that meet

NICE’s evidentiary standards, demonstrating a commitment to methodological rigor and the practical value of results for policy decisions.

In summary, applying ML-NMR in the company’s evidence submission to NICE is justified by its advantages in managing heterogeneity, adjusting for critical contextual factors, and providing robust, transparent estimates, all of which support more accurate and relevant assessments in line with NICE’s DSU Technical Support Documents. Most importantly, the ML-NMR provides further evidence on the relative efficacy of long-term prophylaxis options in NHS, which has been identified as a key contributor to cost-effectiveness outcomes in the company evidence submission of garadacimab. The ML-NMR serves as a sensitivity analysis to the NMA, providing further valuable context to the decision-making process.

3. Methodology

3.1 Models

Bayesian ML-NMR models were fitted for each endpoint, using a fixed effects model as the base case, modelled in R version 4.2.1, with Bayesian models ran in an R language Stan; version 2.32.2. The fixed effects model assumes that all studies are estimating a single true underlying treatment effect per comparison. Random effects models were also explored, where possible though due to small numbers of studies these were unstable/infeasible in some cases. The random effects model assumes that the studies are not estimating a single true underlying effect per pairwise comparison, but rather that they come from a distribution with a common mean.

Table 3 lists the likelihoods and link functions that were assumed for each endpoint, based on the type of outcome considered. Notably, the individual level likelihood for the time-normalised family of outcomes have been assumed to follow a negative binomial, due to improvements in convergence. This is because the for the time-normalised number of HAE attacks endpoints, overdispersion was observed for which the negative binomial is more suited to account this at the individual patient level compared to the Poisson likelihood function. Whilst overdispersion was thereby accounted for in CSL312 trials (2001 phase II and 3001 pivotal phase III) when

pooled together, any potential overdispersion in the comparator trials could not have been addressed due to the unavailability of individual patient level data.

The correction towards the negative binomial approach for the time-normalised endpoints necessitated changes to the ML-NMR R-code developed by the DSU. These changes aligned with suggestions informally provided by David Phillippo, the author of the R-code within the DSU who led the development and implementation of the ML-NMR methodology for NICE HTA submissions.

The proportion of attack-free patients was an endpoint conducted in the NMA as the continuity correction method was applied to overcome the zero-observation issue in the Placebo arm of the garadacimab studies, i.e., no patients in this arm experienced a 100% decline in the HAE attack rate at month 6 relative to the observed baseline number of HAE attacks. Continuity correction entails adding a small constant to overcome the zero observation to the aggregate level data to avoid the rate ratios approaching infinity (as the Placebo arm is the denominator in the rate ratio calculation). This method was explored in the ML-NMR however, adding constants to zero-observation values on the individual level has a major issue that outcomes are highly specific to which patients the correction is applied to, resulting in the omission of this endpoint from the ML-NMR. This was deemed the best approach given that the possibility of estimating proportion of attack-free patients through the time-normalised number of HAE attacks endpoint to establish a comparative metric as alternative insight.

Table 3. Likelihood and link function assumptions for endpoint analyses

Endpoint	Individual level likelihood	Aggregate level likelihood	Link function
Time-normalised number of HAE attacks	Negative binomial	Poisson	Log
Time-normalised number of moderate and/or sever HAE attacks	Negative binomial	Poisson	Log
Time-normalised number of HAE attacks requiring on-demand treatment	Negative binomial	Poisson	Log

Proportion of attack-free patients	No analysis conducted. - Continuity correction did not produce a feasible analysis. See Section 3.1		
AE-QoL Total Score	Gaussian	Gaussian	Identity
Any TEAE	Binomial	Binomial (two-parameter approximation)	complimentary log-log (cloglog)
Attack-free days per month	Gaussian	Gaussian	Identity

Abbreviations: HAE, hereditary angioedema; AE-QoL, Angioedema quality of life.

Non-informative (vague) priors were assumed for all model parameters. Four independent Monte Carlo Markov chains (MCMC) were initialised. Model convergence was assessed using the R-hat statistic, and graphical examination of the posterior samples (density, trace plots). The models were considered to converge if the R-hat statistic was close to 1 for each parameter in the model. The efficiency of the posterior was assessed using the (bulk and tail) effective sample size (ESS) for each parameter. Results were presented using the posterior median and 95% credible interval (CrI) in each case. The ESS and R-hat values for the time-normalised number of HAE attacks family of outcomes is presented in section 3.3.

3.2 Covariates

The following covariates (in order of expected priority below) were adjusted for in the ML-NMR model.

- Baseline HAE attack rate (during run-in)
- Body Mass Index (BMI)
- Age
- Sex

Main effects and their interactions with treatment were fitted for each of these covariates within the models. In case of poor convergence and/or low ESS, covariates were removed one-by-one as per the above priority order. The following marginal distributions were assumed for each of the covariate

- baseline HAE attack rate = Poisson
- BMI = Gamma
- Age = Gamma
- Sex = Bernoulli

The suitability of these distributions was assessed by graphically comparing the fitted parametric density to the empirical distributions observed within the individual patient level data (IPD) across both studies jointly (CSL312_2001, CSL312_3001)[16,17]. Given that correlations between covariates in the aggregate-data studies were unavailable, it was assumed that these were the same as the observed correlations in the available IPD.

3.3 Model comparison

For continuous and binary outcomes, model fit was assessed using the Deviance Information Criterion (DIC), where possible. A smaller DIC indicates better fit (e.g. for fixed vs. random effects). These model comparison outcomes are presented in Table 4, and these values are indicative of the fixed effects model being an appropriate measure relative to the random effects models.

Table 4. Model diagnostic Deviance Information Criterion results for the continuous outcomes

Outcome	Fixed effects	Random effects
AE-QoL Total Score	Residual deviance: [redacted] pD: [redacted] DIC: [redacted]	Residual deviance: [redacted] pD: [redacted] DIC: [redacted]

Any TEAE	Residual deviance: [redacted] pD: [redacted] DIC: [redacted]	Residual deviance: [redacted] pD: [redacted] DIC: [redacted]
Attack-free days per month	Residual deviance: [redacted] pD: [redacted] DIC: [redacted]	Residual deviance: [redacted] pD: [redacted] DIC: [redacted]

Abbreviations: AE-QoL, Angioedema quality of life; DIC, Deviance Information Criterion; pD, effective number of fitted parameters.

Table 5, Table 6 and Table 7 present log-mean, log standard deviation and goodness of fit metrics of the posterior samples for the rates ratio estimated values for the time-normalised family of outcomes with the overall pooled study population across all relevant intervention and comparator trials. The baseline number of HAE attacks equals [redacted] and [redacted], respectively for the three time-normalised number of HAE attacks endpoint pooled populations considered in analysis. These values can be compared to the other individual treatment study populations as found in the *Appendix – Multi-level comparisons* at the end of the document. Generally, the overall pooled study population ESS values are much greater than 100, strongly satisfying a common rule of thumb and the R-hat values are near the value of one also strongly satisfying a common rule of thumb.[18]

Table 5. Time-normalised number of HAE attacks overall pooled mean covariate values with ESS and R-Hat for the overall pooled study population (includes all relevant intervention and comparator trials)

Treatment and dose	Log mean	Log S.D	Bulk ESS	Tail ESS	R-hat
Garadacimab 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAEGARDA 60IU/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Berotralstat 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300m Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; IU, international units; kg, kilograms; mg, milligrams; Q2W, once every two weeks; Q4W, once every four weeks.

Table 6. Time-normalised number of moderate and/or severe HAE attacks overall pooled mean covariate values with ESS and R-Hat for the pooled study population (includes all relevant intervention and comparator trials)

Treatment and dose	Log mean	Log S.D	Bulk ESS	Tail ESS	R-hat
Garadacimab 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAEGARDA 60IU/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300m Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; IU, international units; kg, kilograms; mg, milligrams; Q2W, once every two weeks; Q4W, once every four weeks.

Table 7. Time-normalised number of HAE attacks requiring on-demand treatment overall pooled mean covariate values with ESS and R-Hat for the pooled study population (includes all relevant intervention and comparator trials)

Treatment and dose	Log mean	Log S.D	Bulk ESS	Tail ESS	R-hat
Garadacimab 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAEGARDA 60IU/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Lanadelumab 300mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab 300m Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; IU, international units; kg, kilograms; mg, milligrams; Q2W, once every two weeks; Q4W, once every four weeks.

4. Results

The results section reports for each of the outcomes assessed, the relevant forest plots and league tables, providing the magnitude, direction and uncertainty of estimates. Table 8 maps the results for each endpoint. Each league table is complemented by the relevant NMA alternative, to ease the readers ability to compare outcomes across the two study methods used.

Table 8. Results outline per endpoint

Endpoint	Forest plot – fixed effects	League table	Forest plot – individual treatment study populations	Network diagram
Time-normalised number of HAE attacks	Figure 1	Figure 2	Figure 4	Figure 5
Time-normalised number of moderate and/or sever HAE attacks	Figure 6	Figure 7	Figure 9	Figure 10
Time-normalised number of HAE attacks requiring on-demand treatment	Figure 11	Figure 12	Figure 14	Figure 15
AE-QoL Total Score	Figure 16	Figure 17	Figure 19	Figure 20
Any TEAE	Figure 21	Figure 22	Figure 24	Figure 25
Attack-free days per month	Figure 26	Figure 27	Figure 29	Figure 30

4.1 Time-normalised number of HAE attacks

Figure 1. Forest plot (active treatments vs placebo) for fixed effects ML-NMR for time-normalised number of HAE attacks (pooled population – includes all relevant intervention and comparator trials)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Notes: Based on Bayesian ML-NMR model adjusting baseline HAE attack rate, assuming the overall covariate means across trials. Posterior medians presented with 95% CrIs. Rate ratios are in reference to placebo.

For reference the unadjusted rate ratios (95% CrI) are estimated to be

respectively for the treatments found in the column of Figure 1. Therefore, adjusting for baseline HAE attack rate has very limited impact on the results.

Figure 2. League table for fixed effects ML-NMR for time-normalised number of HAE attacks (pooled population – includes all relevant intervention and comparator trials)

Figure 3. League table for fixed effect NMA of time-normalised number of HAE attacks

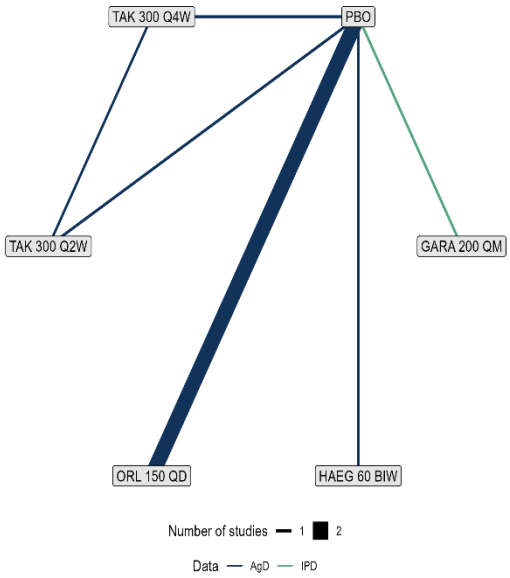
Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Note: Posterior medians for the rate ratios presented with 95% CrIs. Rate ratio < 1 implies that column is better than row. Based on

Bayesian ML-NMR model adjusting for baseline HAE attack rate, assuming the overall covariate means across trials. For the NMA, pink squares are statistically different.

Figure 4. Forest plot (active treatments vs placebo) for fixed effects ML-NMR for time-normalised number of HAE attacks (indivdual treatment study populations)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Note: Posterior medians presented with 95% CrIs. The relative effect is the rate ratio in reference to placebo. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate.

Figure 5. Study network for ML-NMR of time-normalised number of HAE attacks



Abbreviations: PBO, placebo; HAE, hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert).; IPD, individual patient level data; AgD, aggregate patient level data.

4.2 Time-normalised HAE attacks (moderate severe)

Figure 6. Forest plot (active treatments vs placebo) for fixed effects ML-NMR for time-normalised number of moderate and/or severe HAE attacks (pooled population – includes all relevant intervention and comparator trials)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Notes: Based on Bayesian ML-NMR model adjusting baseline HAE attack rate, assuming the overall covariate means across trials. Posterior medians presented with 95% CrIs. Rate ratios are in reference to placebo.

For reference the unadjusted rate ratios (95% CrI) are estimated to be

[redacted] respectively for the treatments found in the column of Figure 6. Therefore, adjusting for baseline HAE attack rate has very limited impact on the results.

Figure 7. League table for fixed effects ML-NMR for time-normalised number of moderate and/or severe HAE attacks (pooled population – includes all relevant intervention and comparator trials)

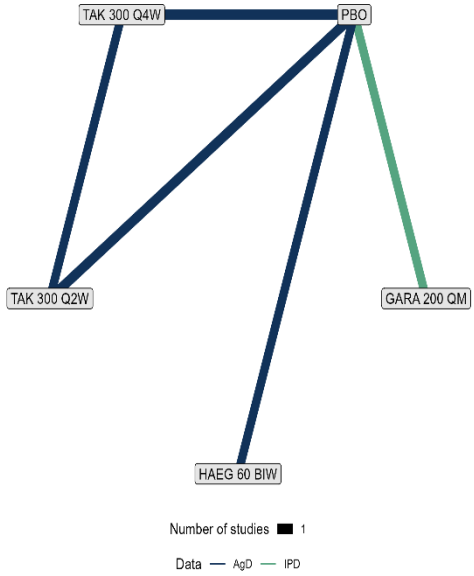
Figure 8. League table for fixed effect NMA of time-normalised number of moderate and/or severe HAE attacks

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Note: Posterior medians for the rate ratios presented with 95% CrIs. Rate ratio < 1 implies that column is better than row. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, assuming the overall covariate means across trials.

Figure 9. Forest plot (active treatments vs placebo) for fixed effects ML-NMR for time-normalised number of moderate and/or severe HAE attacks (individual treatment study population)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab;; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Note: Posterior medians presented with 95% CrIs. The relative effect is the rate ratio in reference to placebo. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate.

Figure 10. Study network diagram ML-NMR of time-normalised number of moderate and/or severe HAE attacks



Abbreviations: PBO, placebo; HAE, hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); IPD, individual patient level data; AgD, aggregate patient level data. Note: CSL312-2001 and CSL312-3001 studies pooled to increase sample size

4.3 Time-normalised attacks requiring on-demand treatment

Figure 11. Forest plot (active treatments vs placebo) for fixed effects ML-NMR for time-normalised attacks required on-demand treatment (pooled population – includes all relevant intervention and comparator trials)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Notes: Based on Bayesian ML-NMR model adjusting baseline HAE attack rate, assuming the overall covariate means across trials. Posterior medians presented with 95% CrIs. Rate ratios are in reference to placebo.

For reference the unadjusted rate ratios (95% Crl) are estimated to be [redacted] respectively for the treatments found in the column of Figure 11. Therefore, adjusting for baseline HAE attack rate has very limited impact on the results.

Figure 12. League table for fixed effects ML-NMR for time-normalised number of HAE attacks requiring on-demand treatment (pooled population – includes all relevant intervention and comparator trials)

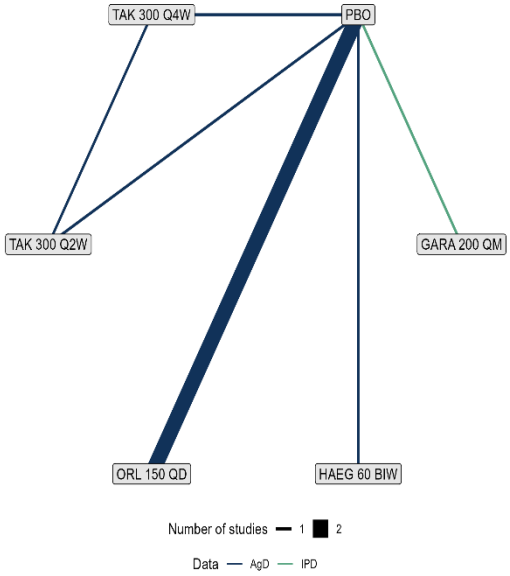
Figure 13. League table for fixed effect NMA of time-normalised number of HAE attack requiring on-demand treatment

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Note: Posterior medians for the rate ratios presented with 95% CrIs. Rate ratio < 1 implies that column is better than row. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, assuming the overall covariate means across trials.

Figure 14. Forest plot (active treatments vs placebo) for fixed effects ML-NMR for time-normalised number of HAE attacks requiring on-demand treatment (individual treatment study populations)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Note: Posterior medians presented with 95% CrIs. The relative effect is the rate ratio in reference to placebo. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate.

Figure 15. Study network diagram ML-NMR of time-normalised number of HAE attacks requiring on-demand treatment



Abbreviations: PBO, placebo; HAE, hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); IPD, individual patient level data; AgD, aggregate patient level data

4.4 Change from baseline in AE-QoL total score

Figure 16. Forest plot (active treatments vs PBO) for fixed effects multi-level network meta regression (ML-NMR) of change from baseline in Ae-QoL total score (pooled population – includes all relevant intervention and comparator trials)

Abbreviations: BMI, Body mass index; CrI, Credible interval; HAE, Hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, BMI, age and sex, assuming the overall covariate means across trials. Posterior medians presented with 95% CrIs. Mean differences are in reference to Placebo.

Figure 17. League table for fixed effects multi-level network meta regression (ML-NMR) for change from baseline in AE-QoL total score (pooled population – includes all relevant intervention and comparator trials)

Figure 18. League table for fixed effect NMA of change from baseline in AE-QoL total score

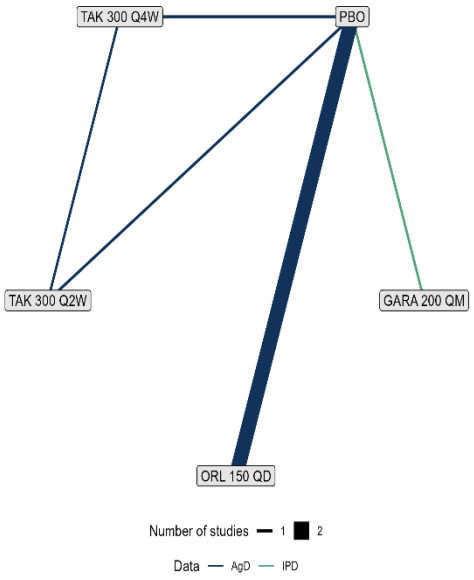
Abbreviations: BMI, Body mass index; CrI, Credible interval; HAE, Hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab. Posterior medians for the mean difference in treatment effects presented with 95% CrIs. Mean difference < 0 implies that column is better than row. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate,

BMI, age and sex, assuming the overall covariate means across trials. For the NMA pink squares are statistically significant.

Figure 19. Forest plot (active treatments vs PBO) for fixed effects multi-level network meta regression (ML-NMR) of change from baseline in AE-QoL total score (individual treatment study populations)

Abbreviations: BMI, Body mass index; CrI, Credible interval; HAE, Hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab. Posterior medians presented with 95% CrIs. The relative effect is the mean difference in reference to Placebo. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, BMI, age and sex.

Figure 20. Study network diagram for ML-NMR of AE-QoL total score



Abbreviations: ML-NMR, multi-level network meta regression. PBO, placebo; HAE, hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; IPD, individual patient level data; AgD, aggregate patient level data

4.5 Any treatment emergent adverse event

Figure 21. Forest plot (active treatments vs PBO) for fixed effects multi-level network meta regression (ML-NMR) of any TEAE (pooled population – includes all relevant intervention and comparator trials)

Abbreviations: BMI, Body mass index; CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, BMI, age and sex, assuming the overall covariate means across trials. Posterior medians presented with 95% CrIs. Mean differences are in reference to Placebo.

Figure 22. League table for fixed effects multi-level network meta regression (ML-NMR) for any TEAE (pooled population – includes all relevant intervention and comparator trials)

Figure 23. League table for fixed effect NMA of TEAEs

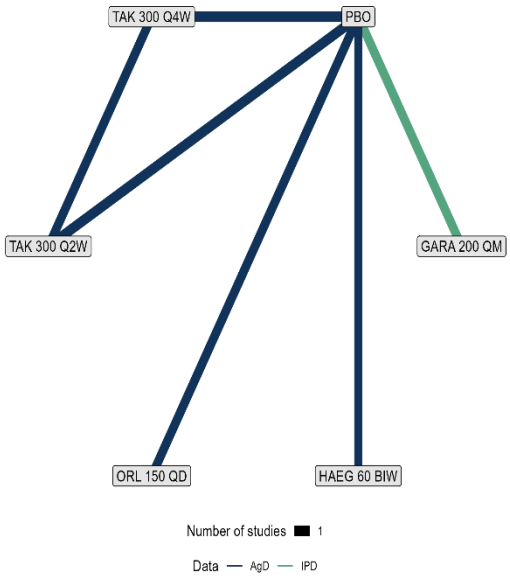
Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Posterior medians for the mean difference in treatment effects presented with 95% CrIs. Hazard ratio < 1 implies that column is better than

row. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, assuming the overall covariate means across trials. For the NMA pinks squares are statistically significant.

Figure 24. Forest plot (active treatments vs PBO) for fixed effects multi-level network meta regression for any TEAE (individual treatment study populations)

Abbreviations: CrI, Credible interval; HAE, hereditary angioedema; ML-NMR, multi-level network meta regression; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert). Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate. Posterior medians presented with 95% CrIs. Mean differences are in reference to Placebo

Figure 25. Study network diagram for multi-level network meta regression (ML-NMR) of any TEAE



Abbreviations: ML-NMR, multi-level network meta regression; PBO, placebo; HAE, hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); IPD, individual patient level data; AgD, aggregate patient level data. CSL312-2001 and CSL312-3001 studies pooled to increase sample size

4.6 Change from baseline in number of attack-free days per month

Figure 26. Forest plot (active treatments vs PBO) for fixed effects multi-level network meta regression (ML-NMR) of change from baseline in attack-free days per month (pooled population – includes all relevant intervention and comparator trials)

BMI: Body mass index. Crl, Credible interval; HAE, Hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, BMI, age, and sex, assuming the overall covariate means across trials. Posterior medians presented with 95% Crls. Mean differences are in reference to Placebo.

Figure 27. League table for fixed effects multi-level network meta regression (ML-NMR) for attack-free days per month (pooled population – includes all relevant intervention and comparator trials)

Figure 28. League table for fixed effect NMA of attack-free days per month

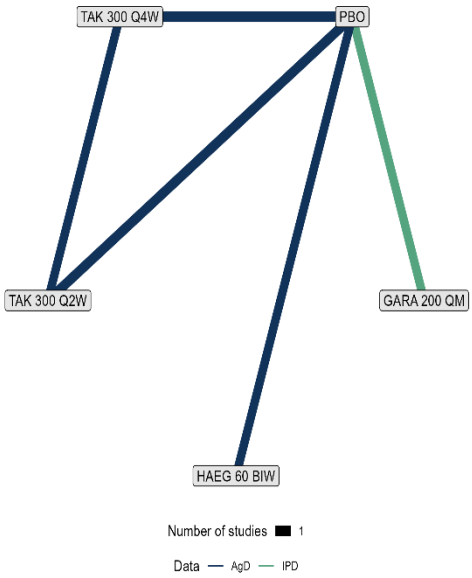
Abbreviations; BMI, Body mass index; CrI, Credible interval; HAE, Hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab. Posterior medians for the mean difference in treatment effects presented with 95% CrIs. Mean difference > 0 implies that column is better than row. Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, BMI, age, and sex, assuming the overall covariate means across trials. For the NMA pink squares are statistically

significant.

Figure 29. Forest plot (active treatments vs PBO) for fixed effects multi-level network meta regression (ML-NMR) of change from baseline in attack-free days per month (individual treatment study populations)

Abbreviations; BMI: Body mass index; CrI, Credible interval; HAE, Hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab. Posterior medians presented with 95% CrIs. The relative effect is the mean difference in reference to Placebo.Based on Bayesian ML-NMR model adjusting for baseline HAE attack rate, BMI, age, and sex.

Figure 30. Study network diagram for ML-NMR of attack-free days per month



Abbreviations: ML-NMR, multi-level network meta regression; PBO, placebo; HAE, hereditary angioedema; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); IPD, individual patient level data; AgD, aggregate patient level data. CSL312-2001 and CSL312-3001 studies pooled to increase sample size

5. Discussion

A comprehensive statistical analysis has been conducted, adjusting for potential heterogeneity that an NMA may have been unable to account for in establishing relative efficacy and safety estimates of the long-term prophylaxis options for the prevention of recurrent attacks in hereditary angioedema. The statistical analysis provided greater flexibility with regards to the potential number of covariates considered and benefited from the aggregation of the overall pooled study population from across all the HAE trials within the given networks relative to a potential MAIC.

The ML-NMR consistently indicates garadacimab to be statistically superior to placebo in all efficacy outcomes considered, and insignificantly different in safety to placebo. The credible intervals among the two methods are often closely matched in terms of the range of overlap. In turn, multi-level network meta regression estimates complement the network meta-analysis conclusions of garadacimab's efficacy relative to established long-term prophylaxis treatment options in the NHS, doing so in a transparent and replicable manner. Similar conclusions have been reached considering different structural assumptions on heterogeneity, and different likelihood functions for the time-normalised endpoints as described in Section 3.1.

Notably, the ML-NMR statistical analysis provided further evidence of limited to no impact of treatment effect modifiers on key clinical outcomes in HAE, through the comparison of adjusted and unadjusted outcomes, as has been a discussion point in previous HAE NICE submissions.[4,5]

5.1 Strengths

- Models account for differences in pre-identified treatment effect modifiers, unlike the original NMA
- In general, ML-NMR results were more precise than the original NMA for the continuous and binary outcomes (i.e. narrower 95% credible intervals).

5.2 Limitations

- Due to the small number of patients in the CSL312_2001 and CSL312_3001 studies, it was not possible to include a study effect for these in the models. Therefore, these studies were considered as a single

(pooled) randomised controlled trial (RCT) and, hence, the model(s) assumed that the baseline risk was equivalent across the two.

- Due to convergence issues, not all covariates could be included for some endpoints.
- Due to small number of studies, it was not possible to fit random effects models.
- Due to zero observed events in the Placebo arm of both CSL312 studies, it was not possible to fit an ML-NMR model for the endpoint proportion of attack-free patients on the individual patient level with the continuity correction.
- Due to the need for using negative binomial models for the time normalised family of outcomes and lack of convergence due to overdispersion, the rate ratios may not be comparable to those reported in the NMA but are closely matched in terms of the lower credible interval range estimates.

6. References

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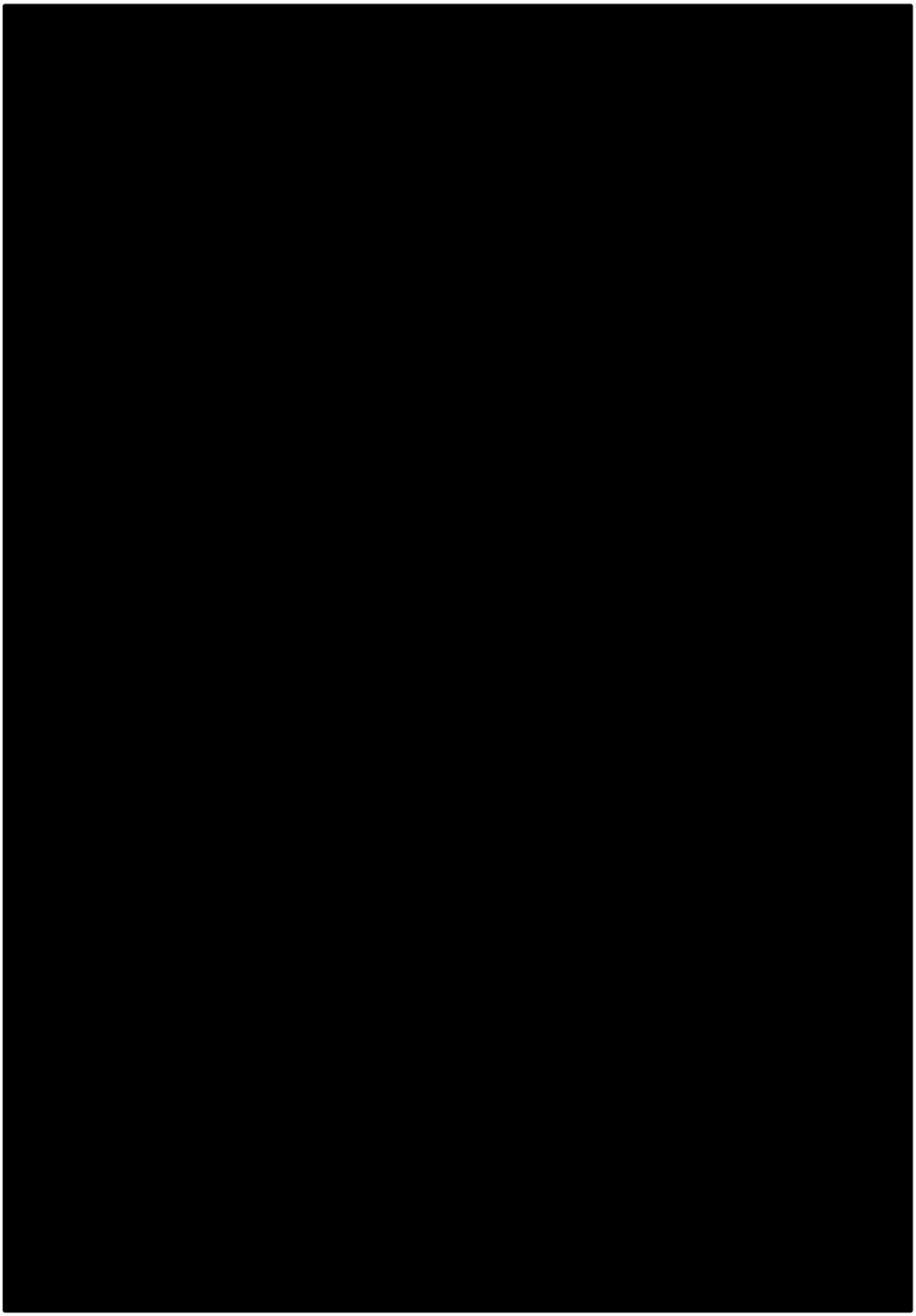
Appendix – Multi-level comparisons

Figure 31. Time-normalised number of HAE attacks fixed effects multi-level comparison of individual treatment study populations results

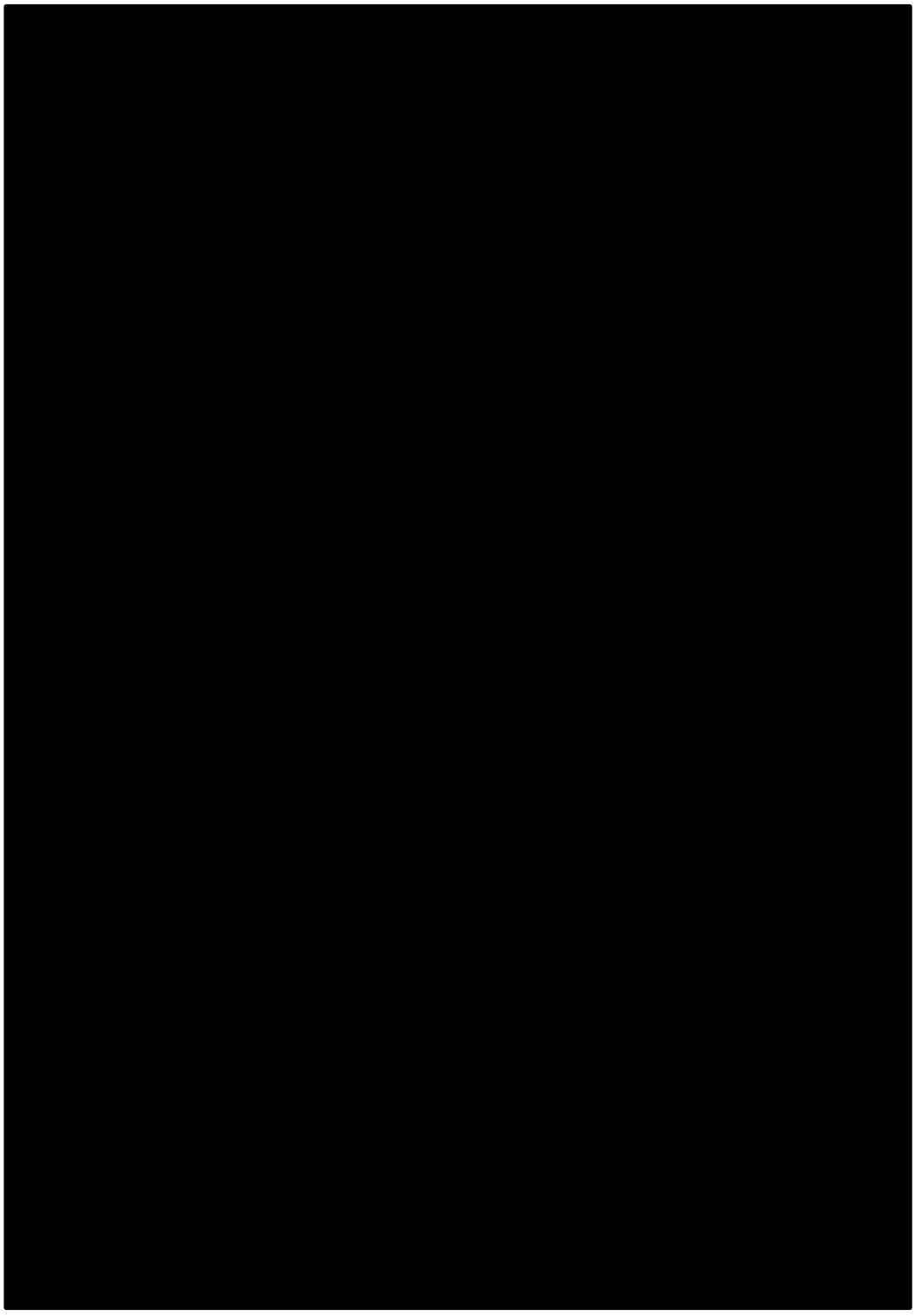


Abbreviations: BLHAE, baseline number of HAE attacks; ESS, effective sample size; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); sd, standard deviation.

Figure 32. Time-normalised number of HAE attacks (moderate/severe) fixed effects multi-level comparison of individual treatment study populations results

Abbreviations: BLHAE, baseline number of HAE attacks; ESS, effective sample size; QM, once monthly; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); sd, standard deviation.

Figure 33. Time-normalised number of HAE attacks requiring on-demand fixed effects multi-level comparison of individual treatment study populations results



Abbreviations: BLHAE, baseline number of HAE attacks; ESS, effective sample size; QM, once monthly; QD, once daily; Q2W, every two weeks; Q4W, every four weeks; BIW, twice weekly; GARA, garadacimab; ORL; berotralstat; TAK, landadelumab; HAEG, subcutaneous C1-INH (SC Berinert); sd, standard deviation.

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]

Summary of Information for Patients (SIP)

November 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6394_Garadacimab_Company_Evidence_Submission_SIP_22Nov2024_[noCON]	**Final (updated)**	**No**	**22 November 2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Garadacimab 200 mg solution for injection in pre-filled pen (autoinjector) Brand name: ANDEMRBY®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Garadacimab is anticipated to be used for the routine prevention of recurrent attacks in people with HAE aged 12 years and over with hereditary angioedema (HAE) experiencing two or more attacks per month. HAE is a rare genetic disorder characterised by unpredictable and recurrent episodes of severe swelling in various parts of the body, known as 'HAE attacks' (see section 2a for more detail).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for garadacimab is pending. Garadacimab is currently being assessed through the international (collaborative procedure) Access Consortium New Active Substance Work-sharing Initiative (NASWSI) route. The expected approval date is included in Document B, Section B.1.2, Table 2.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

CSL Behring collaborates with several patient organisations in the rare disease area to ensure patient voice is represented. These collaborations are always in line with the strict principles and

guidance of the Association of the British Pharmaceutical Industry (ABPI) code (see glossary). Below, we have included all payments made to the relevant patient groups (HAE UK and the Genetic Alliance UK) in calendar years 2022 and 2023.

2022

- Genetic Alliance UK: £12,800. Support for Rare Disease UK Campaign run by Genetic Alliance.
- HAE UK: £36,500. Grant for the purpose of developing a website, 24/7 Emergency Advice Line and A&E Awareness Campaign. Contracted Service to support CSL Behring in the process of recruitment of people with HAE for filming and photoshoot.

2023

- HAE UK: £35,000. Grant for the purpose of covering activities including but not limited to developing A&E Awareness Campaign, developing a self-advocacy campaign and disease awareness, 24/7 Emergency Advice Line and website update.

As part of CSL Behring's due diligence, the company always ensures they are not the sole or majority funder to any organisation. All of the above is in line with standard industry practices with appropriate disclosure, meaning that these does not represent a true conflict of interest.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Disease background information

HAE (hereditary angioedema) is a rare genetic condition that causes recurrent episodes of swelling in different parts of the body, known as 'HAE attacks' (1-3). These attacks can occur in places like the skin, throat, stomach, or intestines (4). Attacks that affect your throat or larynx (voice box) can be dangerous or even life threatening (1, 3). HAE is a condition that can run in families, but some people may not have a family history (3).

People with HAE are typically born with a deficiency or dysfunction in a protein called C1-INH (C1-esterase inhibitor), which regulates several processes in the body, including the production of bradykinin through a process known as the kallikrein-kinin pathway. Bradykinin affects the blood vessel walls, making them expand and become more porous. When C1-INH is deficient or not working properly, the body produces too much bradykinin, causing fluid to leak from blood vessels into surrounding tissues, leading to the swelling typical of HAE attacks (5, 6).

The following three types of HAE are known, all of which have the same clinical symptoms (3):

- **Type 1**: C1-INH is absent or produced in very low quantities (approximately 85% of cases)
- **Type 2:** C1-INH is produced at normal or high levels but does not function properly (approximately 15% of cases)
- **Type 3:** HAE attacks are linked to a genetic alteration but C1-INH is functional and produced at normal levels (extremely rare)

It is estimated that a total of 1,041 people live with HAE in England and Wales (Section B.1.3.1.3 in Document B) (7). Garadacimab is being appraised for the treatment of a proportion of these people who are aged ≥12 years and experience two or more attacks per month.

Clinical features and impact of HAE

HAE attacks are recurrent (occurring repeatedly) and can vary by location, frequency and severity between people and within an individual over time (1, 8). Most HAE attacks are spontaneous (1), although some can be triggered by emotional stress, injury (whether accidental or associated with dental, medical or surgical procedures) and infections (1, 4, 9).

HAE significantly impacts quality of life, both during and between attacks. The symptom burden associated with HAE attacks is substantial, as they can be frequent, debilitating, painful and potentially life-threatening (8, 10). There are also no reliable ways to predict how often HAE attacks will occur, where they will happen, or how severe they will be. This unpredictability has a significant negative impact on the quality of life of people with HAE and contributes to an emotional and psychological burden that extends beyond the attacks themselves, leaving individuals struggling to carry out daily activities and experiencing persistent fear and anxiety about the next attack (7, 10-12).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The suspected diagnosis of HAE is based primarily on clinical presentation during an attack which is then confirmed by medical history and blood tests (1).

A detailed clinical history is essential for an accurate diagnosis of HAE, including family history and the nature of the attacks (i.e. frequency, circumstances of onset, triggers, timing, pattern of recurrence and duration) (1, 11, 12). The diagnosis of HAE is then confirmed through blood test(s) to examine the levels and functioning of proteins such as C1-INH (1, 11, 12).

There are no additional diagnostic tests required for the use of garadacimab.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are three approaches to the management of HAE, as listed below (13):

- **On-demand therapy:** treatment during an HAE attack to relieve symptoms
- **Short-term prophylaxis:** preventative therapy to take short-term before planned events that are expected to trigger an attack (e.g. surgery)
- **Long-term prophylaxis:** preventative therapy taken routinely to prevent recurrent attacks

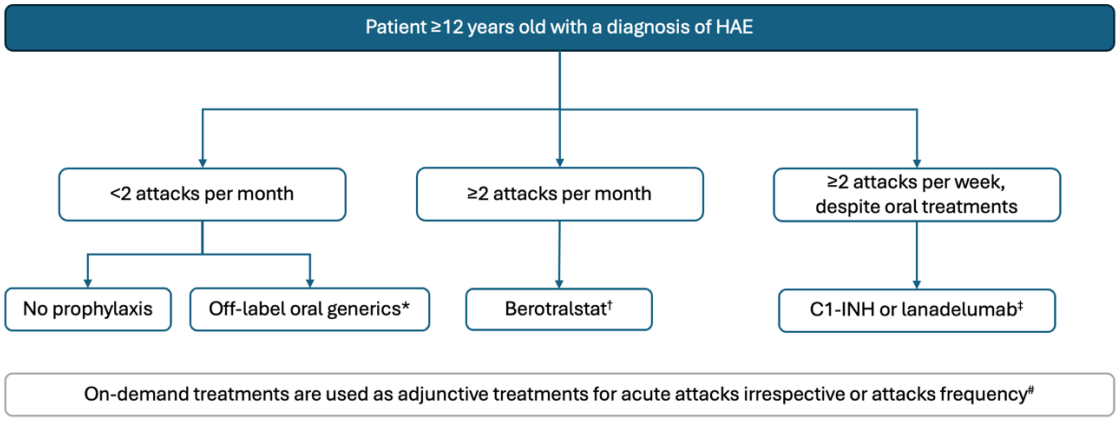
Garadacimab is being appraised as a long-term prophylaxis treatment for people experiencing two or more attacks per month. Long-term prophylaxis is used to reduce the frequency and severity of attacks, with the ultimate goal of achieving attack freedom, or extended periods of time without experiencing an attack (i.e. attack-free duration) (1).

In the NHS, the eligibility for long-term prophylaxis treatments is based on the individual's frequency of attacks, as shown in Figure 1 below. As such, depending on the frequency of attacks, the long-term prophylaxis options for people with HAE include the following:

- Berotralstat for those experiencing two or more HAE attacks per month (14)
- Lanadelumab (15) and different variants of a therapeutic called C1-INH (including Cinryze and off-label Berinert) for those experiencing two or more HAE attacks per week (16)
- For people with HAE who are experiencing less than two attacks per month, long-term prophylaxis options are restricted to off-label, suboptimal therapies such as attenuated androgens (e.g. danazol and oxandrolone) and antifibrinolytics (i.e. tranexamic acid) (17).

Additionally, all people with HAE who experience an attack can be treated with on-demand treatment options (including icatibant or C1-INHs) as an adjunct to alleviate symptoms (Figure 1)(18).

Figure 1. Current treatment options in people with HAE aged 12 years or older in England



Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema.
* Off-label oral generics include tranexamic acid and attenuated androgens
† As per the TA738 NICE guidance, treatment with berotralstat is stopped if the number of attacks per month does not reduce by at least 50% after 3 months(14).
‡ Decision-making of treatment choice is informed by: clinical judgement of suitability, clinical effectiveness, contraindications, ability of individual with HAE or carer to use the required administration technique, regional network approval and patient choice
# On-demand therapy (the on-demand use of C1-INHs or icatibant) is used as an adjunct therapy in all people with HAE for the treatment of acute attacks, irrespective of attack frequency or concurrent use of LTP options.
Sources: NICE, berotralstat appraisal TA738 (14); NHS England, Clinical Commissioning Policy: C1-INH for prophylactic treatment of HAE (16); NICE, lanadelumab appraisal TA606 (15); Maurer et al., 2021 (1); Betschel et al., 2019 (12).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what

matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Several PBE sources explore and report on the needs and disease experiences of people with HAE, of which the key sources and results are described below.

A survey designed and commissioned by CSL Behring to characterise the burden of HAE in the UK was conducted from 25 September–5 October 2024 in people in the UK living with HAE and those caring for people with HAE.(19, 20) Results from this HAE survey indicate that:(19)

- The majority of participants with HAE were not attack-free in the prior three months, despite most receiving some form of long-term prophylaxis therapy.
- Emotional stress and anxiety, physical exertion and hormonal changes were most commonly noted as external triggers that may have caused HAE attacks and the majority of individuals who are aware of their triggers indicated that trigger avoidance has impacted their ability to participate in activities such as sports, going on holidays or taking exams
- The majority of people who experienced HAE attacks in the 3 months prior indicated that their HAE attacks impacted, to some extent, their daily life or productivity (ability to carry out work, study or look after others), their plans for social events and their self-consciousness.
- The majority of participants with HAE described feeling anxious about future attacks to a certain extent, and for caregivers, their anxiety was even more substantial.
- Similarly, the majority of caregivers indicated that their caregiver responsibilities impacted their daily life or productivity to a certain extent.

A European burden of illness study in people with HAE was conducted in 2011 which included qualitative, open-ended interviews with 30 individuals with HAE (10). In these interviews, participants indicated that attacks have a substantial impact on their daily activities, including ability to perform household tasks, drive, participate in family activities, travel, or follow through on plans (10). The duration of activity disruption varied, but in many cases lasted 1–2 days. Participants largely considered abdominal attacks to involve the most severe pain, indicating that they could last for several days, be accompanied by vomiting and may confine the participant to bed. While participants indicated that attacks in extremities such as hands and feet are generally less painful, they were not necessarily less severe as they prevented participants from being able to do daily tasks, such as using a computer or driving. The inability to perform normal activities during attacks caused interruption to participants' work or schooling, including absenteeism and decreased productivity. Participants felt a great deal of emotional distress during attacks, indicating that they were anxious and fearful of the attack getting worse or potentially not being able to breathe or get to the hospital in time in the event of a laryngeal attack. People with HAE also experienced anxiety due to activity limitations during attacks, such as not being able to participate in family activities (10).

In a 2021 Dutch cross-sectional survey in 69 people with HAE (21), individuals considered physical difficulties such as pain, limited mobility and fatigue (30%) and the anxiety/uncertainty related to the next attack (29%) as the most severe limitations due to HAE, with an equal degree of importance. In addition, 16% of people with HAE described difficulties at work/school (e.g. sick leave and job loss) and 19% reported limitations on leisure activities (particularly sports and vacation) due to HAE (21). Further, this study found that individuals with poorly controlled disease had a lower quality of life scores on attack-free days compared to those with well-controlled

disease, which suggests that attacks lead to significant declines in quality of life and that better disease control contributes to higher quality of life even during attack-free periods (21).

An online global survey in 159 people with HAE (of which 20 individuals [13%] from the UK) also investigated the association between an individual's health-related quality of life and their attack-free duration and found that that health-related quality of life continued to improve the longer they remained attack-free (22).

A 2021–2022 survey of 65 people with HAE in the UK assessed the experiences of individuals with regards to emergency care and medication use (23). In this survey, participants have described living in a constant state of fear of a possible laryngeal attack (swelling of the upper airway), which is the most severe presentation of HAE that can lead to asphyxiation (not getting enough oxygen, suffocation) and be life-threatening (1). Participants stated that their fear is often influenced by the loss of a family member with HAE who experienced such an attack, and those who have experienced laryngeal attacks describe them as extremely traumatic, often feeling like they might die (23).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

As discussed in Section 2a, HAE attacks are typically caused by excessive levels of bradykinin, which the body produces through a process known as the kallikrein-kinin pathway. This pathway starts with the activation of a protein called Factor XII (FXII). Blood levels of activated FXII have been shown to increase in individuals during HAE attacks. Activated FXII can trigger a series of biochemical steps leading to bradykinin overproduction. This causes blood vessels to leak fluids into the surrounding tissue resulting in the swelling seen during HAE attacks.

Garadacimab prevents HAE attacks by inhibiting activated FXII from starting the events that leads to bradykinin overproduction (3). This new way of treating HAE differs from other available long-term prophylaxis options such as berotralstat and lanadelumab, which work later in the bradykinin production process. As such, garadacimab may potentially offer a broader control of HAE attacks compared to therapies that target later events in the pathway, which may lead to better prevention and fewer breakthrough attacks, potentially improving quality of life for people with HAE.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
No, garadacimab is intended to be used alone as a long-term prophylaxis therapy. In the event of an acute attack during treatment with garadacimab, on-demand therapies such as icatibant and C1-INHs can be used to alleviate symptoms, but these would used as an adjunct to long-term prophylaxis, not as a combination therapy.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Garadacimab is administered via once-monthly injections in the fatty tissue just below the skin (subcutaneous injections) (24). The recommended dose of garadacimab is an initial loading dose of 400 mg, administered as two 200 mg subcutaneous injections on the first day of treatment, followed by a monthly dose of 200 mg (24). Garadacimab may be self-administered or administered by a caregiver only after training on the injection technique by a healthcare professional and the injection should be restricted to the fatty tissue in the tummy (abdomen), thigh or upper arm, ideally changing (rotating) the location of the injection site with each injection (24). Since garadacimab is administered subcutaneously once a month, it offers a more convenient mode of administration than intravenous (IV) C1-INHs (25-27) and provides a less frequent treatment schedule compared to C1-INHs, lanadelumab and berotralstat(25, 26, 28-30). Additionally, garadacimab will be available as a pre-filled pen, which is more convenient than a pre-filled syringe (which are used for the subcutaneous injection of lanadelumab) because it's easier to use, especially for people without medical training. The pen is designed to deliver the exact dose simply by pinching the skin and pushing down the pen onto the skin and, since the needle is hidden, it makes the injection process less scary or painful for the user compared to a pre-filled syringe. Multiple studies across a range of chronic conditions have shown that patients and nurses prefer pre-filled pens over pre-filled syringes due to their ease of use, convenience and reduced administration time.(31-34)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
The safety and efficacy of garadacimab has been investigated in the following studies: • Study CSL312_3001 (VANGUARD): a carefully controlled clinical study where neither the patients nor the researchers knew who was receiving the treatment (randomised-controlled study, see glossary) which was conducted at multiple sites. A total of 65 patients with HAE who were aged 12 years and older and experienced more than 1 HAE attack per month were included in the study, which provides the main evidence for how effective garadacimab is in preventing recurrent HAE attacks (efficacy) (27)

- Study CSL312_3002: an ongoing study in 161 patients with HAE which includes both patients who have previously received garadacimab or placebo in other clinical studies and those who have never received garadacimab, allowing researchers to gather longer-term data on its safety and effectiveness (open-label extension study, see glossary).

No sites in the UK were included in the studies mentioned above, although baseline characteristics across both studies were generalisable to people aged 12 years or older living with HAE within the NHS (Document B, Sections B.1.3.1.3 and B.2.7.2.1).

The main efficacy results are presented in this submission are from the final data cut-off of the 6-month pivotal VANGUARD study (27, 35). Supporting efficacy evidence is also provided from the latest data measurement (16 June 2023) of the CSL312_3002 study, which included 161 patients with a median duration of treatment that is approximately >11 months longer than the treatment period of the VANGUARD study (36). While results from VANGUARD are published by Craig et al. (2023) (27) (see link in Section 4a), results from CSL312_3002 are not yet published.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy of garadacimab as a long-term prophylaxis option for recurrent HAE attacks in people with HAE aged 12 years or older was assessed in the pivotal phase 3 randomised-controlled study VANGUARD and the open-label extension study CSL312_3002.

Results of the key study (VANGUARD, CSL312_3001)

Garadacimab is a highly effective long-term prophylaxis option for patients with HAE, achieving its main goal in the VANGUARD study by demonstrating a 91% reduction from baseline (without long-term prophylaxis) in patients treated with garadacimab and a significant 7.4-fold lower mean number of attacks per month compared to placebo ($p<0.0001$) (27). Moreover, compared to placebo, garadacimab achieved a significantly lower mean number of HAE attacks per month that required on-demand treatment (mean difference −88%; $p<0.0001$) and moderate or severe HAE attacks per month (mean difference −90%; $p<0.001$) (27).

Outcomes of particular importance for people with HAE

Since the unpredictability of attacks is a key contributor to the humanistic burden of HAE, the main goals of long-term prophylaxis in HAE are to minimise the number and severity of attacks and achieve total control of the disease in the form of attack freedom (27).

Achieving and maintaining prolonged periods of attack-free status can help reduce this burden and empower people with HAE to feel more in control of their condition. In the VANGUARD study, most patients on garadacimab were attack-free during the first three months of treatment (71.8%) compared with only 8.3% in the placebo group ($p<0.0001$). This was maintained throughout the entire 6-month treatment period, with most patients (62%) remaining attack-free, compared to none who were on placebo. Together, these results indicate that garadacimab treatment is associated with early and sustained protection from attacks. This is in contrast to the phase 3 study assessing lanadelumab, in which less than half (31% to 44%) of all treated patients were attack-free during the treatment period (26 weeks) (30), and the phase 3 study for berotralstat, in which the proportion of patients who were attack-free during the treatment

period (24 weeks) was similar between berotralstat and placebo (percentages not reported in trial publication) (37).

Longer-term treatment effect: results of the open-label extension study (CSL312_3002)
Importantly, the efficacy of garadacimab in the CSL312_3002 open-label extension study was consistent with the VANGUARD study across all outcomes, demonstrating that the efficacy of garadacimab is also seen in a larger population size and extends beyond 6 months of treatment (36).

Similar results were found when assessing the patients who had been on the licensed dosage of garadacimab for the longest studied period of time, with the majority of these patients remaining attack-free after two years of treatment (see Company Submission Document B, Section B.2.6.7) (38). This demonstrates that the efficacy observed in the 6-month treatment period of the VANGUARD study was maintained through to the latest available data from the CSL312_3002 study, with no reduction in treatment effect observed.

Comparative evidence with current standard of care: indirect treatment comparison
Since there were no direct studies comparing garadacimab to the current standard treatments for long-term prevention in the UK, an indirect comparison was made with the existing options for long-term prevention in the UK: lanadelumab, berotralstat and Cinryze (an intravenous C1-INH) (39). Indirect treatment comparisons are a standard approach when there are no direct comparisons in clinical studies available. These indirect treatment comparisons indicate that garadacimab is a highly effective long-term prophylaxis option for HAE, demonstrating benefits over lanadelumab, berotralstat and Cinryze for number of HAE attacks per month. Where data were available, garadacimab also showed benefit over lanadelumab and berotralstat across all other efficacy outcomes of interest (published data were not reported for Cinryze) (39).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the VANGUARD study, several quality of life assessments were used, including the following questionnaires (35):

- **EuroQoL-Group 5-Dimension 5-Level (EQ-5D-5L)**, a standardised questionnaire used to measure a person's overall health-related quality of life. It covers five key dimensions of health: mobility, self-care, usual activities (work, study, housework etc), pain/discomfort and anxiety/depression.
- **Angioedema Quality of Life (AE-QoL)**, a disease-specific patient-reported outcome tool. It was specifically designed to measure the impact of recurrent angioedema on a person's health-related quality of life. It assesses different aspects of an individual's well-being, including physical, emotional, and social functioning, as they experience episodes of angioedema.
- **Subject's Global Assessment of Response to Therapy (SGART)**, a self-reported measure where individuals evaluate their overall response to a given treatment. It typically asks individuals to rate or describe how well they feel the therapy has worked in managing

their symptoms, considering factors like symptom relief, improvement in quality of life, or side effects.

In the VANGUARD study, treatment with garadacimab showed improvements across all key patient-reported outcomes (35):

- Patients treated with garadacimab reported substantial and clinically meaningful improvements in AE-QoL mean scores within approximately one month that were maintained over the 6-month treatment period. In contrast, patients in the placebo group did not demonstrate any clinically meaningful improvement over the treatment period. This demonstrates that garadacimab improves the burden associated with recurrent HAE attacks
- Mean EQ-5D-5L scores in the garadacimab arm improved during the treatment period and worsened in the placebo arm, again demonstrating that treatment with garadacimab improves overall health-related quality of life
- According to SGART responses, most patients treated with garadacimab (82%) rated their response to treatment as "good" or "better" compared with 33% with placebo (27), demonstrating that patients are generally satisfied with the treatment effect of garadacimab

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common side effects with garadacimab are injection site reactions (redness, bruising or itchiness of the injection site) which may affect up to 1 in 10 people (3). These injection site reactions are generally mild or moderate in severity and resolve within 13 days of onset (35).

The overall safety database is based on the CSL312_3002 study which includes 161 patients with HAE. Analyses of the safety population indicate that monthly subcutaneous administration of 200 mg garadacimab had an acceptable safety profile that is well-tolerated in patients with HAE when used as long-term prophylaxis to prevent attacks.

Comparison to side effects of current standard of care

Garadacimab has a favourable safety profile compared to the currently available LTP options, which commonly include:

- Berotralstat: the most common side effects include abdominal pain, diarrhoea and headache, which were all categorised as very common (affecting 1 in 10 people or more) and vomiting, acid reflux, flatulence (farting) and rash (affecting up to 1 in 10 people)(28)
- Lanadelumab: the most common side effects include injection site reactions (very common, affecting 1 in 10 people or more) and hypersensitivity, dizziness, muscle pain and rash (common, affecting up to 1 in 10 people)(30)
- IV Cinryze: the most common side effects include headache and nausea (very common, affecting 1 in 10 people or more) and hypersensitivity, dizziness, vomiting, rash and injection site reactions (common, affecting up to 1 in 10 people) (25).

For individuals with HAE who are not eligible for these licensed LTP options, the off-label use of attenuated androgens or anti-fibrinolytics may be the only option. There is a lack of clinical trial data for antifibrinolytics and attenuated androgens, but particularly 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 (40).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The burden of living with HAE is substantial and there is an unmet need for convenient and well -tolerated therapies that work quickly to reduce the frequency and severity of HAE attacks, with the effects of treatment lasting over time. Such treatments would help individuals with HAE to achieve freedom from recurring attacks, empowering them to feel more in control of their condition. Garadacimab is a new type of treatment that works in a completely different way than any other available therapies for the prevention of recurrent HAE attacks.

Data from the VANGUARD study indicate that garadacimab is a highly effective treatment for the prevention of recurrent HAE attacks

- Patients treated with garadacimab had an average 91% reduction in HAE attacks compared with before treatment
- The HAE attack rate per month was over seven times lower with garadacimab treatment compared with placebo (no prophylaxis)
- Garadacimab had a fast onset of action, with the majority of patients (72%) remaining attack-free in the first three months of treatment. This was maintained throughout the entire 6-month treatment period, with most patients (62%) remaining attack-free, compared to none who were on placebo
- Treatment with garadacimab was associated with substantial improvements in HRQoL
- Garadacimab's efficacy in reducing HAE attack and increasing the duration of attack freedom is anticipated to lower the burden on caregivers as well as people living with HAE

Indirect treatment comparisons suggest that garadacimab can improve outcomes compared with other long-term prophylaxis options

- When indirectly comparing the efficacy of garadacimab to that of currently available therapies for HAE (lanadelumab, berotralstat and intravenous Cinryze), the results indicate that patients receiving garadacimab experienced fewer attacks
- Garadacimab has the potential to offer more people with HAE the chance to achieve attack freedom over a prolonged period compared with current treatment options, including lanadelumab and berotralstat

Garadacimab can treat patients who may otherwise be left without tolerable and effective options

- In addition to offering an improved option to current LTP treatments, garadacimab helps to bridge the treatment gap for individuals with HAE who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs. Currently, these individuals are left with no treatment options other than suboptimal therapy with androgens and antifibrinolytics.

Garadacimab is convenient to administer

- Garadacimab is administered subcutaneously, offering a more convenient mode of administration than IV C1-INHs (25-27) (Section 3c).
- Garadacimab is given once monthly, which is a more convenient treatment schedule compared with C1-INHs, lanadelumab and berotralstat (25, 26, 28, 30) (Section 3c).
- Since garadacimab will be available as a pre-filled pen, administration of garadacimab will be more convenient, easier to use and less scary or painful than a pre-filled syringe (which are used for the subcutaneous injection of lanadelumab) because it's easier to use, especially for people without medical training (Section 3c).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Garadacimab is administered as a subcutaneous injection, which is more invasive than the oral administration of berotralstat. Subcutaneous injections can be associated with injection site reactions, which are listed as a possible side effect of garadacimab (Section 3g). Although this may increase the treatment burden of garadacimab compared with berotralstat, the impact is not anticipated to be substantial given its once monthly administration schedule (compared with once daily for berotralstat) and trial data demonstrating that side effects associated with injecting garadacimab are expected to be mild or moderate in severity.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

Health economic models are important for the NICE appraisal process. They compare the overall cost and health benefits of the new treatment with current care in the NHS over a patient's lifetime. A health economic model was built to compare the cost and health benefits of garadacimab with long-term prophylaxis treatment in England. As discussed in section 2c, long-term prophylaxis treatment in the UK include lanadelumab (15), berotralstat (14) and different variants of a therapeutic called C1-INH (16). Therefore, to reflect current care within the NHS and following NICE recommendations, the following treatments are included in the economic analysis:

- Garadacimab
- Berotralstat
- Lanadelumab
- IV Berinert (C1-INH)
- IV Cinryze (C1-INH)

The health economic model includes patients with an average age of 41+ who have been diagnosed with HAE. The model includes the following health states: attack, no-attack (month 1, 2, 3, 4, 5 and 6 without attack) and death. Health states are a description of a person's health status and different health stages they can encounter at one moment in time within a disease. An individual can move to different health states over time but can only be in one health state at any moment. The model evaluates patients monthly and assess patients whether they've experienced a HAE attack or "no-attack".

Modelling how much treatment extends life

- Evidence on the impact of laryngeal attacks on mortality is scarce. Therefore, the possibility of a patient living longer with HAE has not been linked to any extra risk of death.
- To predict the number of HAE attacks a patient might have in a model cycle (in this case it would be 28-days), a treatment-based rate was applied to the baseline number of HAE attacks experienced by placebo patients in VANGUARD.
- In line with NICE methodology, a survival analysis using Kaplan-Meier curves from VANGUARD was used to predict how long it takes for a patient to have their first HAE attack. The base case dataset used came from a group of patients in the CSL312_3002 study who had not taken 200mg garadacimab before. These patients were followed up for 110 weeks, and the analysis considered any HAE attack after Day 1 as an "event" for the purpose of measuring the time until first attack.
- Based on discussions with clinical experts and precedence from previous NICE TAs in HAE and monoclonal antibodies suggests that the life-long treatment effectiveness of garadacimab lasts for life (17). Therefore, the model assumes patients on garadacimab will not see a reduction in its benefit over time. Different methods were used to explore this idea, including carrying forward the average reduction in attack rates, using the last observation carried forward and Poisson regression. Last observation carried forward was used in the base case.

Modelling how different treatments impact attacks of different severity

- The VANGUARD study showed that garadacimab reduces the number of moderate and severe attacks compared to patients receiving placebo, in turn reducing the burden of disease (33).
- To highlight how various treatments influence the severity of HAE attacks, the baseline distribution of attack severity for each treatment is taken from literature and CSL312_3001 study (33).
- The model assumes that the attack severity distributions remain constant over time.

Modelling how much a treatment improves quality of life

- Utility refers to a measure of the QoL or well-being a person experiences, on a scale from 0 to 1. A utility value of 1 means the person is in perfect health, while 0 represents death. In health economic models, its often used to show how a condition (i.e. HAE) affects someone's overall quality of life, with higher utility values meaning better and lower values meaning worse health.
- A partial memory has been added to the model that tracks the time since a patient's last HAE attack. This helps accounts for any improvements or benefits a patient may experience during periods without attacks, starting from any point in the model.
- As discussed in section 3f, several QoL instruments were used, including EQ-5D -5L however due to inconsistent reporting and small patient numbers, the data were not a reliable measure of the HRQoL for patients with HAE. In response to this lack of validity, the baseline measure for HAE impact on quality of life is informed by Nordenfelt (2014).
- Clinical expert opinion has indicated that patients without a HAE attack progress towards a quality of life (i.e. utility) like that of the general population (17).
- Garadacimab is expected to improve quality of life in patients with HAE, by decreasing the number of HAE attacks, allowing patients to feel the freedom of an attack for longer.

Modelling how carers are impacted by the attacks of their dependents

- It is crucial to emphasise the value and importance of including caregiver outcomes, as confirmed by UK clinical experts and patient groups. For instance, clinicians highlighted the substantial burden HAE places on caregivers and families, especially for younger patients, often leading to anxiety and stress (17).
- Garadacimab has the potential to offer patients a rapid reduction in the frequency of attacks and prolonged freedom from attacks, thereby alleviating the burden of attacks and the psychological impact associated with their unpredictability for people with HAE and their caregivers.
- To quantify the true impact of HAE on daily living for patients with HAE and their caregivers, the economic model indirectly captures the health-related quality of life burden of HAE on caregivers, which can contribute to absenteeism and negative mental well-being.

What additional costs will garadacimab bring according to the model?

- Garadacimab is not anticipated to incur any additional costs to health care resource use.
- Garadacimab is expected to significantly reduce HAE attacks rates and therefore limit the additional costs that are typically required to manage these acute attacks.

Uncertainty

- Uncertainty within the model has been explored by sensitivity analysis, this is whereby key input parameters and structural assumptions have been varied to assess the level of confidence associated with any economic evaluation.
- Sensitivity analyses highlighted the relative efficacy of LTPs and baseline number of attacks had the largest impact on the economic analysis. To mitigate these uncertainties the economic analysis takes the average of these potential variations over a large number of simulations resulting in unbiased estimates.
- The duration of treatment benefit for garadacimab is based on last observation carried forward methodology from VANGUARD, as long-term data is not yet available. However, CSL Behring have used multiple methodologies to model to durability of garadacimab effect. Supplementary data from the open-label extension study is used to best support garadacimab's long-term effectiveness.

Results

- Results show garadacimab reduces the number of HAE attacks compared to berotralstat, lanadelumab and C1-INHs, improving the quality of life of individuals with HAE and their caregivers, as well as being a cost-saving treatment (at the comparators list price and do not take account of confidential discounts that may be available to the NHS for some comparators).
- In addition to offering an improved option to current LTP treatments, garadacimab helps to bridge the treatment gap for patients who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation

Garadacimab is a first-in-class, efficacious and well-tolerated long-term prophylaxis option for people with HAE experiencing two or more attacks per month. As described in Section 3a, garadacimab works by inhibiting a cascade that results in swelling. Notably, garadacimab interrupts this cascade at its origin, while the other available long-term prophylaxis options lanadelumab and berotralstat target proteins further into the cascade. By preventing the cascade from even starting, garadacimab could potentially offer a more comprehensive control of HAE attacks compared to therapies that target downstream mediator (Section 3a).

Notably, indirect treatment comparisons using clinical trial data show that garadacimab offers longer attack freedom compared to currently available options, which can help reduce the burden of HAE by achieving control of the disease in the form of attack freedom (Sections 3e and 3h) (27).

QALY benefits that have not been captured in the economic model

Not applicable.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

CSL Behring does not believe that there are any aspects of this submission that would exclude people who are particularly disadvantaged.

However, it should be noted that the intravenous C1-INHs included as comparators in the submission (Cinryze and Berinert) are derived from human plasma, with which some religious groups may be unwilling to be treated. It is important that treatment options are 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 not directly extracted from human serum or plasma and, as such, could provide such an option.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on HAE:

- HAE UK: https://www.haeuk.org
- HAE international: https://haei.org
    - UK-specific information: https://haei.org/hae-member-countries/united-kingdom/

Scientific publications on the efficacy and safety and avapritinib:

- Results of the pivotal phase 3 study, VANGUARD: Craig et al., 2023. https://pubmed.ncbi.nlm.nih.gov/36868261/
- Results of the randomised-controlled period of the dose-finding phase 2 study, CSL312_2001: https://pubmed.ncbi.nlm.nih.gov/35219377/
- Results of the open-label extension phase of the dose-finding phase 2 study, CSL312_2001: Craig et al. 2022. https://pubmed.ncbi.nlm.nih.gov/38710185/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- Association of the British Pharmaceutical Industry (ABPI) code: a set of ethical guidelines that pharmaceutical companies in the UK must follow to ensure their marketing and interactions with healthcare professionals are responsible, honest and prioritise patient welfare.

- Indirect treatment comparison: statistical comparison of data from different clinical trials with treatments of interest used to demonstrate which options can offer more benefit. This approach is used when direct evidence (such as a single trial including all relevant treatments) does not exist.
- Intravenous injection: an injection directly into the vein, often called an infusion or abbreviated as IV.
- On-demand treatment: the administration of therapy at the time of an attack.
- Open-label extension study: a study that allows participants to keep receiving a treatment after the original trial ends and with both the participants and researchers knowing what treatment is given, so that the long-term safety and efficacy of the treatment can be studied.
- Prophylaxis treatment: the regular administration of therapy with the aim to prevent attacks.
- Randomised-controlled study: a research method where participants are randomly assigned to different groups (such as treatment or control/placebo groups) to compare the effects of an intervention, ensuring results are less biased.
- Subcutaneous injection: an injection in the fatty tissue just below the skin.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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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]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
ID6394 garadacimab Clarification template TA_HST [noCON]	1	No	17 December 2024

Section A: Clarification on effectiveness data

NHS care

A1. The company noted in Section B.2.13.2 of the report that it is anticipated that an auto-injector (AI) would be the only commercially available formulation in the UK. Please could you elaborate on why this has occurred and who made the decision on which formulation will be commercially available in the UK.

The single anticipated commercially available presentation of garadacimab worldwide, including the UK, is the pre-filled autoinjector pen (AI). The pre-filled syringe with a needle safety device (PFS) is not intended for commercialisation. The decision to focus commercialisation to the AI was made after considering the below factors:

1) The AI drug delivery system will ease subcutaneous administration in a chronic condition (HAE), as it can be safely and consistenly self-administered at home with minimal health care support

2) Clinical evidence demonstrates the AI to be a safe and effective alternative delivery system to of garadacimab to the PFS

With reference to point 1, it is well documented that convenience of the route of administration is a major clinical decision-maker in HAE. Published literature indicates that AIs developed for SC self-injection medications can provide greater convenience, home use, a lower risk of error and better acceptance of treatment compared with a pre-filled syringe (PFS).[1-6] Moreover, AIs can also provide patients more autonomy, allowing them to take better control of their treatment schedule, save time and rely less on caregivers and healthcare providers, which may help to reduce the psychological burden of living with a chronic condition and improve overall quality of life.[6-10] Therefore, administering garadacimab via a user-friendly AI may be of benefit to people with HAE, as it not only reduces the impact of injection anxiety and the risk of needle-stick injury, but it can also consistently deliver accurate doses. These advantages can significantly improve treatment adherence and overall quality of life for patients requiring lifelong management of HAE.[11]

To address point 2, we provide below both safety and efficacy considerations from the clinical development program for garadacimab. For further information on this subject, see also the response made to A7b.

Since a PFS was being used to administer garadacimab in the ongoing clinical trials, CSL Behring conducted a study (CSL312_1004) to compare the safety and pharmacokinetic (PK) properties of garadacimab when using AI or PFS. As described on page 45 of the Company Submission, the PK and safety profiles were comparable between administration methods, and as such, it was decided that all patients in the phase 3 OLE study CSL312_3002 would transition from PFS to AI following the IA4 interim data cut-off ([redacted], the data cut-off used for all CSL312_3002 and pooled VANGUARD/CSL312_3002 data in the Company Submission).

Since then, preliminary data from the latest interim data cut-off ([redacted]) of CSL312_3002 has become available, in which all [redacted] ongoing patients in CSL312_3002 have transitioned to using the AI device for self-administration at home, with a median (min, max) duration of AI use of [redacted] ([redacted], [redacted]) months. At the latest data cut-off of CSL312_3002 and when considering only the treatment period in which AI was used, the mean (95% CI) time-normalised number of HAE attacks per month remained low at [redacted] [[redacted], [redacted]], compared to [redacted] ([redacted], [redacted]) at baseline. This corresponds to a mean percent reduction of [redacted]% from baseline. The mean (95% CI) number of investigator-confirmed HAE attacks per month results are consistently low and even improved compared to the VANGUARD ITT population (0.27 [0.05, 0.49] for the garadacimab group)[12] and the IA4 data cut-off from CSL312_3002 ([redacted] [[redacted]] in the ATS population), at which point patients still received garadacimab via PFS.[13]

Similarly, the mean (95% CI) time-normalised number of HAE attacks per month that required on-demand treatment was [redacted] ([redacted], [redacted]), which is consistent and even improved compared to the VANGUARD ITT population (0.23 [0.02, 0.45] for the garadacimab group)[12] and the IA4 data cut-off from CSL312_3002 ([redacted]] in the ATS population), at which point patients still received garadacimab via PFS.[13] Moreover, the mean (95% CI) time-normalised number of moderate and/or severe HAE attacks per month also remained low at [redacted] ([redacted], [redacted]), consistent and even

improved compared to the VANGUARD ITT population (0.13 [redacted][14] and the IA4 data cut-off from CSL312_3002 ([redacted] [redacted] in the ATS population).[13]

Therefore, there is no evidence to suggest that transitioning from PFS to AI would be associated with a reduction in efficacy of garadacimab.

At the latest data cut-off of CSL312_3002 and when considering only the treatment period in which AI was used, the median (min, max) duration of AI use of [redacted] ([redacted], [redacted]) months, with a total of [redacted] patient-years of AI use. During this time, [redacted] ([redacted]%) patients experienced [redacted] TEAEs, of which the majority were mild ([redacted] TEAEs) or moderate ([redacted] TEAEs) in severity. A total of [redacted] events were severe, [redacted] of which were classed as being related to the study treatment. There were [redacted] deaths and [redacted] TEAEs leading to study discontinuation. A total of [redacted] patients ([redacted]%) experienced [redacted] TEAEs that were related to the study treatment. [redacted] of the treatment-related TEAEs were injection site reactions (ISRs) that were classed as mild, as identified by the investigator. There was [redacted] adverse event of special interest (AESI), as identified by the investigator, and [redacted] serious adverse events (SAEs), [redacted] of which were deemed to be related to the study treatment. In combination with the safety data for CSL312_1004 (summarised on page 45 of the Company Submission) no safety concerns are anticipated that would impact the suitability for long-term use of the AI.

As such, with the AI formulation, CSL Behring delivers a patient-centric and convenient product that is safe and effective and can be self-administered at home.

Pivotal trial

A2. Priority: What types of LTP had the ITT population received prior to enrolment on the VANGUARD/CSL312_3002 studies?

The types of long-term prophylaxis (LTP) that were used prior to enrolment of the VANGUARD and CSL312_3002 are summarised in Table 1. Please note that, while the table indicates 'prior and concomitant medications', routine use of LTPs were prohibited during the VANGUARD study, and as such, Table 1 outlines the prior use of LTPs only.

Furthermore, patients eligible for the VANGUARD and CSL312_3002 studies were prohibited from using routine prophylaxis to prevent HAE attacks during the run-in period for at least 1 month. Therefore, the use of prior LTPs is not anticipated to have any meaningful impact outcomes observed in the studies.

Table 1. Long-term prophylaxis treatments used prior to study enrolment (VANGUARD ITT and CSL312_3002 ATS populations)

Preferred Term* Reported Term	VANGUARD (CSL312_3001)			CSL312_3002
	Garadacimab 200mg (N=39) n (%)†§	Placebo (N=25) n (%)†§	Total (N=64) n (%)†§	Garadacimab 200mg (N=161) n (%)‡#
Any prior or concomitant medication	[redacted]	[redacted]	[redacted]	[redacted]
Complement C1-esterase inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
Haegarda	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
Type not clarified	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat**	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab††	[redacted]	[redacted]	[redacted]	[redacted]
Tranexamic acid	[redacted]	[redacted]	[redacted]	[redacted]
Danazol	[redacted]	[redacted]	[redacted]	[redacted]
Stanozolol	[redacted]	[redacted]	[redacted]	[redacted]
Desloratadine	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]	[redacted]

* Medications are coded using WHO Drug Dictionary B3/C3 Version March 2022 for VANGUARD and Version September 2023 for CSL312_3002.
† Percentages are based using Intention-to-Treat Analysis Set including subjects with less than 30 days Treatment Period.
‡Percentages are based on the All Treated Subjects Analysis Set.
#Last Prior Long-Term Prophylaxis Medication is selected from medications with a start date prior to first study treatment start date.
§ Included are medications with a start date prior to first study treatment start date.
** This includes WHO preferred terms 'Berotralstat' and 'Berotralstat dihydrochloride'
†† This includes WHO preferred terms 'Lanadelumab' and 'Lanadelumab flyo'

A3. Priority: What types of LTP had the ≥2 HAE attacks per month subgroup previously received prior to enrolment on the VANGUARD/CSL312_3002 studies?

The types of long-term prophylaxis (LTP) that were used prior to enrolment of VANGUARD and CSL312_3002 in patients who experienced ≥2 attacks at baseline are summarised in Table 2. Please note that, while the table indicates 'prior and concomitant medications, routine use of LTPs were prohibited during the VANGUARD study, and as such, Table 2 outlines the prior use of LTPs only.

Furthermore, patients eligible for the VANGUARD and CSL312_3002 studies were prohibited from using routine prophylaxis to prevent HAE attacks during the run-in period for at least 1 month. Therefore, the use of prior LTPs is not anticipated to have any meaningful impact outcomes observed in the studies.

Table 2. Long-term prophylaxis treatments used prior to study enrolment in patients experiencing ≥2 attacks per month at baseline (VANGUARD and CSL312_3002)

Preferred Term* Reported Term	VANGUARD (CSL312_3001), ≥2 attacks per month subpopulation			CSL312_3002, ≥2 attacks per month subpopulation
	Garadacimab 200mg (N=[redacted]) n (%)†§	Placebo (N=[redacted]) n (%)†§	Total (N=[redacted]) n (%)†§	Garadacimab 200mg (N=[redacted]) n (%)‡#
Any prior or concomitant medication	[redacted]	[redacted]	[redacted]	[redacted]
Complement C1-esterase inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
Haegarda	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
Type not clarified	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat**	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab††	[redacted]	[redacted]	[redacted]	[redacted]
Tranexamic acid	[redacted]	[redacted]	[redacted]	[redacted]

Danazol	[redacted]	[redacted]	[redacted]	[redacted]
Stanozolol	[redacted]	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]	[redacted]

* Medications are coded using WHO Drug Dictionary B3/C3 Version March 2022 for VANGUARD and Version September 2023 for CSL312_3002.
† Percentages are based using Intention-to-Treat Analysis Set including subjects with less than 30 days Treatment Period.
‡Percentages are based on the All Treated Subjects Analysis Set.
#Last Prior Long-Term Prophylaxis Medication is selected from medications with a start date prior to first study treatment start date.
§ Included are medications with a start date prior to first study treatment start date.
** This includes WHO preferred terms 'Berotralstat' and 'Berotralstat dihydrochloride'
†† This includes WHO preferred terms 'Lanadelumab' and 'Lanadelumab flyo'

A4. Priority: Please present the subsequent LTP treatments received by people who discontinued garadacimab in the VANGUARD/CSL312_3002 trials.

CSL Behring is unable to fulfil this request, since these data were not collected as a part of the VANGUARD or CSL312_3002 studies.

A5. How was missing data in the VANGUARD trial addressed in the analysis?

Patients could discontinue study treatment with garadacimab or withdraw from the study at any time at their own request, or at the discretion of the investigator or CSL Behring for safety, behavioural, or administrative reasons (e.g., due to an adverse event [AE]), protocol deviation, loss to follow-up, subject noncompliance, study terminated by CSL Behring).[14,15]

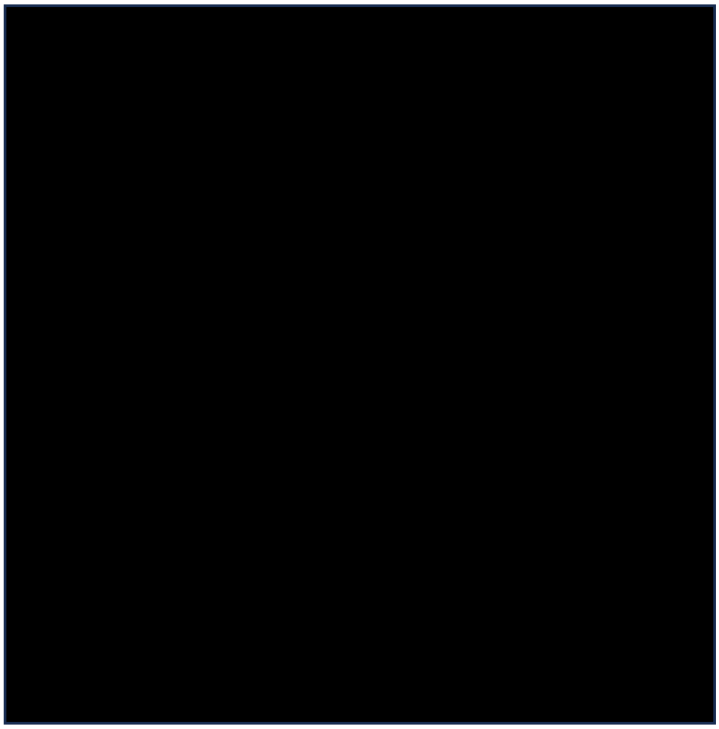
In addition to the below repsonse, see also section B.2.3.2 (Table 6) of the Company Submission where detail is also provided regarding the handling of loss of follow-up in the VANGUARD trial.

If a patient discontinued the study early after being continuously treated for the first 30 days of the treatment period, the observation was terminated by the Early Termination Visit. While early discontinuation may introduce potential differences, the use of time-normalised data minimises bias by calculating the primary endpoint based on HAE attacks reported up to the Early Termination Visit. As such, it is assumed that the attack rate for patients who discontinued the study after 30 days of the treatment period but before the end of the study is comparable to the attack rate observed in patients who completed the full 6-month treatment period.[15] This

assumption is supported by data from the CSL312_2001 trial, which demonstrated that the treatment effect of garadacimab was consistent over time.[16] However, it is important to note that in the VANGUARD study, discontinuation rates were low with all patients (100%) in the garadacimab arm and 22/25 patients in the placebo arm (88%) completing the full six months of treatment.[12]

Missing values would occur only if the observation time for the treatment period was less than 30 days, i.e., a patient discontinued within 30 days after first study drug administration.[15] During the VANGUARD study, only one patient in the placebo group discontinued within 30 days and as such had a missing primary endpoint.[12] To assess the impact of missing data from one patient in the placebo group on the primary efficacy estimand, a systematic approach was applied. For each treatment arm, a range of values for the number of time-normalised HAE attacks per month from 0 to 6 subdivided was generated. All possible combinations from the subdivided ranges were imputed to replace the missing values. For the comparison of active treatment versus placebo, observed and imputed data was analysed using the Wilcoxon Test and results were classified into negative (i.e., placebo significantly better), neutral (i.e., no significant difference) and positive (i.e., active treatment significantly better).[15] In this analysis, garadacimab consistently remained significantly better than placebo, demonstrating no potential impact of the missing data on the primary endpoint observed in VANGUARD (Figure 1).[14]

Figure 1. Sensitivity analysis for time-normalised number of HAE attacks per month at 6 months – tipping point analysis (ITT population; 6-months)



Abbreviations: HAE, hereditary angioedema; ITT, intention-to-treat.
[1] Wilcoxon Test and results were classified into negative (i.e., placebo significantly better, coloured red), neutral (i.e., no significant difference, no colour) and positive (i.e., active treatment significantly better, coloured green).
[2] Number of imputed patients treated with placebo = 1.
[3] Number of imputed patients treated with garadacimab (CSL312) = 0.
Source: VANGUARD CSR.[14]

A6. Priority: Please present the on-demand treatment, and treatment dose, received in each treatment arm during the VANGUARD/CSL312_3002 studies.

The on-demand treatments and dosages as used during the VANGUARD and CSL312_3002 studies are shown in Table 3.

As shown, while mean total dose per attack were broadly comparable between treatment groups in VANGUARD, more attacks occurred and were treated in the placebo arm compared to the garadacimab arm of the VANGUARD study. Moreover, the percentage of patients receiving certain treatments and their respective dosages are roughly comparable between the garadacimab arm of VANGUARD and the full ATS population of CSL312_3002 (who all received 200 mg garadacimab).

Table 3. On-demand treatment dose during study treatment periods (VANGUARD ITT and CSL312_3002 ATS populations)

Preferred Term*	VANGUARD (CSL312_3001)		CSL312_3002
	Garadacimab 200mg (N=39)	Placebo (N=25)	Garadacimab 200mg (N=161)
Total number of HAE attacks	[redacted]	[redacted]	[redacted]
Total number of HAE attacks requiring on-demand treatment	[redacted]	[redacted]	[redacted]
Complement C1 esterase inhibitor in IU			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, IU†	[redacted]	[redacted]	[redacted]
Complement C1 esterase inhibitor in units			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, units†	[redacted]	[redacted]	[redacted]
Icatibant acetate in mg			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, mg†	[redacted]	[redacted]	[redacted]
Conestat alfa in units			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, units†	[redacted]	[redacted]	[redacted]
Conestat alfa in IU			
Patients, n (%)	[redacted]	[redacted]	[redacted]

Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, units†	[redacted]	[redacted]	[redacted]
Blood plasma in bags			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, bags†	[redacted]	[redacted]	[redacted]
C1-esterase inhibitor in mg			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, mg†	[redacted]	[redacted]	[redacted]
Icatibant acetate in µg			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, µg†	[redacted]	[redacted]	[redacted]
Investigational drug in mg			
Patients, n (%)	[redacted]	[redacted]	[redacted]
Attacks treated, n	[redacted]	[redacted]	[redacted]
Total number of treatments, n	[redacted]	[redacted]	[redacted]
Average number of treatments per attack, n	[redacted]	[redacted]	[redacted]
Mean (95% CI) total dose per attack, mg†	[redacted]	[redacted]	[redacted]

CI, confidence interval; HAE, hereditary angioedema; IU, international units
Note: HAE on-demand medication as reported via the 'On-demand Treatment' CRF form are included only.
Note: patients in the Intention-to-Treat Analysis Set including those with less than 30 days Treatment Period are shown.
* On-demand medications are coded using WHO Drug Dictionary B3/C3 Version March 2022 for VANGUARD and Version September 2023 for CSL312_3002.
† For each attack reported the total dose is derived and summarised.

A7. In section B.2.2 the company stated that following a single dose of garadacimab, comparable pharmacokinetics, safety and tolerability profiles and immunogenicity

were observed for the PFS and AI. Device-related TEAEs were [redacted] with AI ([redacted]%) than NSD ([redacted]%), consistent with expectations for this type of device.

a) What is an NSD?

In the submission, we have drawn distinction between two mechanisms of the delivery of 200 mg garadacimab:

1) A pre-filled pen (also called autoinjector [AI], the subject of this submission for which CSL Behring is seeking recommendation and commercialisation)

2) A pre-filled syringe (PFS, the mechanism of delivery utilised in the main supportive clinical evidence from VANGUARD and CSL 3002, presented in this submission)

The PFS is assembled with a needle safety device (NSD). The source of the data supporting the quotation in question is the CSL312_1004 clinical study report, in which “NSD” is used as the acronym for the PFS. As such, please consider “NSD”, within the context as this quote, as referring to the PFS mechanism of delivery of 200 mg garadcimab. For further information regarding the nature of the needle safety device of the PFS, please see the draft patient information leaflet for the PFS as provided in the reference pack of these responses.[17]

b) Given an NSD is safer and has comparable pharmacokinetics, safety and tolerability profiles and immunogenicity, why change to an AI?

The considerations that factored into the decision-making of launching the AI are described in the response to A1. In short, using a user-friendly and convenient AI reduces injection anxiety compared to PFS, while consistently delivering accurate doses. These advantages can significantly improve treatment adherence and overall quality of life for patients requiring lifelong management of HAE.[11]

It is not accurate to state that the PFS is safer than the AI and the benefit/risk assessment for garadacimab has not changed due to the numerical higher TEAEs observed with the AI in CSL312_1004. As described in Appendix M of the company submission, safety profiles were comparable between both devices in the CSL312_1004 study, with a slightly higher incidence of injection site reactions (ISRs)

in the AI group ([redacted]%) compared with the PFS group ([redacted]%), which were mild and transient. The incidence of all other TEAEs was similar across groups. Most TEAEs were mild in severity, with no severe TEAEs reported. There were no serious TEAEs, deaths, or TEAEs leading to study withdrawal in either group.[18] The reported ISRs preferred terms induration, erythema, and pain are well understood with the administration of biologicals.

The expected higher incidence of a transient (not beyond 8 hours) induration can be explained by the inability of the study participant to control the injection speed and a limited flexibility of the injection angle with the AI. The incidence of injection site reactions are expected to decrease over time with patient experience and likewise a patient may experience improved local tolerability by switching to a better accessible injection site.

Further, in a preliminary analysis of the latest data cut-off of CSL312_3002, over a median of [redacted] months of the use of the AI, device-related TEAEs were overall low in number (n=[redacted] events, [redacted]%) and pertained only to injection site reactions that were mild in severity (see response to A1).

Considering these data from CSL312_1004 and CSL312_3002, there are no safety concerns anticipated that would impact the suitability for long-term use of the AI. Moreover, considering that garadacimab is intended to treat the chronic condition of HAE, the benefits of the convenience of the AI over the PFS listed below greatly outweighs the potential inconvenience due to slight increase in mild and transient injection site reactions:

- The AI allows for uniform delivery of medication with every single use. PFS may have a uniform amount enclosed, but human error may impact the precise dose self-administered.

- The AI device is overall considered safer (despite increased occurrence of mild transient injection site reactions) as there is no time-point at which the needle remains outside of the casing except for the actual instant of delivery, thereby eliminating the potential for exposure to injury by the patient or caregiver.

- The AI device is compact and convenient for travel across locations, including international travel and can be easily carried in baggage.

- Torque studies have been performed proving ease of use of AI device for subjects of advanced age or who suffer with disabilities affecting dexterity or strength. The results of these examinations have revealed the AI is suitable for all patients.

- The AI device is rapid and requires no consistency of strength, pressure or speed of administration on the part of the subject.

A8. Please present a breakdown of the number of people in the VANGUARD/CSL312_3002 studies recruited from each country.

A tabulated breakdown of the number of people per county in the VANGAURD and CSL312_3002 studies is provided in Table 4 below.

Table 4. Overview of country of residence of patients enrolled in VANGUARD and CSL312_3002

Country	VANGUARD		CSL312_3002
	Garadacimab 200 mg (N=39)	Placebo (N=25)	Garadacimab 200 mg (N=161)
USA	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Israel	[redacted]	[redacted]	[redacted]
Canada	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Hong Kong	[redacted]	[redacted]	[redacted]
Czech Republic	[redacted]	[redacted]	[redacted]
Hungary	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
New Zealand	[redacted]	[redacted]	[redacted]
Russia	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Taiwan			[redacted]

A9. Priority: Why was baseline attack rate chosen as a stratification factor for VANGUARD if it is not believed to be a treatment effect modifier (B.2.2.2.1)?

In VANGUARD, randomisation was stratified by the variables age (≤17 years, >17 years) and, for adults, the patient's baseline attack rate (1 to <3 attacks/month, and ≥3 attacks/month) during the run-in period.[15] This stratification factor was included for trial recruitment after identifying that a similar approach was also followed in HELP-03 and APEX-2. Both studies stratified randomisation by baseline monthly attack rate and measured treatment efficacy by the number of HAE attacks observed during the treatment period.[19,20] In all cases, for all studies, it could not be conclusively stated that baseline attack rate is, or is not, a treatment effect modifier before the trial takes place.

VANGUARD included this stratification factor to facilitate comparisons between studies and to explore the potential impact that it may have had on results. As noted in the statistical analysis plan for VANGUARD, age and baseline attack rate were **not** regarded as a confounder or an effect modifier.[15] Further evidence has been provided in Section 2.7.2 of the Company Submission to demonstrate that there has been no clinically meaningful difference observed in treatment response based on baseline attack rate.

The stratification by baseline attack rate ensured equal distribution to the garadacimab and placebo arms for subgroups with 1 to <3 attacks/month and ≥3 attacks/month during the run-in period.[15] As the time-normalised number of HAE attacks during the 6-month treatment period was the primary endpoint of VANGUARD, equal distribution of baseline attack rates was necessary to ensure that any observed differences in efficacy between the treatment arms could be attributed to garadacimab and not to disparities in baseline attack rates.[15 19,20]

A10. In Section B.2.6.7 of the CS, a post-hoc pooled analysis of the VANGUARD and CSL312_3002 studies was conducted in people who were randomised to garadacimab in VANGUARD and rolled over to the CSL312_3002 study (n=36). The company stated that the baseline demographics and HAE history characteristics for these people was presented in Appendix E and was similar to the VANGUARD ITT population and CSL312_3002 ATS population. However, they do not appear to be presented in

Appendix E. Please can the company present these baseline demographics and HAE history characteristics.

Apologies for the cross-referencing error. The baseline characteristics and HAE history characteristics for this subpopulation are available in Appendix O provided as part of the Company Submission.

Additional results/analysis

A11. Please complete the following table for the ITT population in the VANGUARD trial.

The results presented in

Table 5 show the EQ-5D-5L (VAS and HSV) and AE-QoL outcomes for the ITT population in VANGUARD.

Table 5. EQ-5D and AE-QoL change from baseline scores (ITT population, VANGUARD)

	Garadacimab					
	Mean at baseline	**Mean at end of treatment**	**Change score (95% CI)**	**P value**	**Mean difference (95% CI) versus placebo**	**P value**
EQ-5D-5L VAS score	N=37	N=38	N=			
EQ-5D-5L HSV score	N=37	N=38	N=			
AE-QoL	N=34	N=34	N=			
	38.75	11.72	-26.47			
	Placebo					
VAS score	N=24	N=23	N=		N/A	N/A
HSV score	N=24	N=23	N=		N/A	N/A

	Garadacimab					
AE-QoL	N=22	N=21	N=			
	43.65	39.37			N/A	N/A

A12. Please complete the following table for people experiencing ≥2 HAE attacks per month in the VANGUARD trial:

The results presented in Table 6 show the EQ-5D-5L (VAS and HSV) and AE-QoL outcomes for the subpopulation of patients experiencing ≥2 attacks per month in VANGUARD.

Table 6. EQ-5D and AE-QoL change from baseline scores (patients experiencing ≥2 HAE attacks per month at baseline, VANGUARD)

	Garadacimab					
	Mean at baseline	**Mean at end of treatment**	**Change score (95% CI)**	**P value**	**Mean difference (95% CI) versus placebo**	**P value**
EQ-5D-5L VAS score	N=	N=	N=			
EQ-5D-5L HSV score	N=	N=	N=			
AE-QoL	N=	N=	N=			
	Placebo					
VAS score	N=	N=	N=		N/A	N/A
HSV score	N=	N=	N=		N/A	N/A
AE-QoL	N=	N=	N=		N/A	N/A

	Garadacimab					
	[redacted]	[redacted]	[redacted]	[redacted]		

A13. Please present subgroup analysis of the primary study outcome of VANGUARD based on the specific LTP people received prior to the trial. Please present for the ITT and ≥2 HAE attacks per month subgroup.

This request involves subgrouping the relatively small VANGUARD ITT into several post-hoc subgroups by baseline attack freqeuncy and/or LTP therapy, resulting in extremely small patient numbers as demonstrated in response to questions A2 and A3. As discussed during the clarification call on 10 December, in a rare disease setting where the ITT population from the pivotal trial is N=64, this type of subgrouping does not produce population sizes sufficient to draw meaningful conclusions. Moreover, even in the event that these population sizes had have been larger, the impact of prior LTP use is expected to be limited by the inclusion of a 1-month washout period in the trial design of VANGAURD.

As such, we have not presented this requested data as the patient numbers preclude its suitability to inform decision-making.

A14. Please present the following figures (including numbers at risk) for the ≥2 HAE attacks per month subgroup in the VANGUARD/CSL312_3002 pooled population:

a) **Figure 13. Percentage reduction in time-normalised number of HAE attacks per month, monthly time windows (VANGUARD/CSL312_3002 pooled population)**

The data referenced in Question A14 comes from a post-hoc analysis provided as supportive evidence of the long-term efficacy in patients who were randomised to garadacimab treatment in the VANGUARD study and subsequently rolled over into the CSL312-3002 OLE study (n=36). This subpopulation contains patients who have received monthly 200 mg garadacimab throughout both studies and thus those patients who have been on the licensed dosage of garadacimab for the longest period of time. The analysis requested in this question involves subgrouping this post-hoc subgroup further to 23 patients. Whilst we have provided these data, and the analyses are demonstrated to be broadly consistent with Figure 13 and Figure 14 of the company submission, CSL Behring express caution in the use of this data for decision making.

Figure 2 below shows the percentage reduction in time-normalised number of HAE attacks per month for the pooled VANGUARD/CSL312_3002 subpopulation who experienced ≥2 HAE attacks at baseline (n=23). Patients who were treated with garadacimab during VANGUARD and rolled over into CSL312_3002 were followed for up to [redacted] months. The percent reduction in monthly attack rates compared to Run-In/baseline remained higher than [redacted]% throughout the studies, with no indication of decline in percent reduction over time, suggesting that that garadacimab is able to

maintain efficacy over time. These results are aligned with observations from the full pooled subpopulation (n=36).

Figure 2. Percentage reduction in time-normalised number of HAE attacks per month, monthly time windows (VANGUARD/CSL312_3002 pooled population who experienced ≥2 HAE attacks at baseline)

Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema; q4wk, once every 4 weeks; SC, subcutaneous.
VANGUARD/CSL312_3002 pooled population includes all rollover patients from the CSL312_3001 (VANGUARD) study into CSL312_3002, who received monthly 200 mg garadacimab in VANGUARD and CSL312_3002.
The percentage reduction in the time-normalised number of HAE attacks is calculated within a patient as:
100 * [1 – (time-normalised number of HAE attacks per month during Treatment Period/time-normalised number of HAE attacks per month during Run-In Period)].
One month is equal to 28 days.

b. Figure 14. Kaplan-Meier curve for time to first HAE attack after Day 1 (VANGUARD/CSL312_3002, pooled population)

Figure 3 below shows the Kaplan-Meier curve with 95% confidence interval (95% CI) for the time-to-first HAE attack after study Day 1 for the pooled VANGUARD/ CSL312_3002 subpopulation who experienced ≥2 HAE attacks at baseline (n=23).

This subpopulation contains patients who have received monthly 200 mg garadacimab throughout both studies and thus those patients who have been on the licensed dosage of garadacimab for the longest period of time.

As shown in Figure 3, the efficacy of garadacimab in prolonging the time to first attack was maintained through to the latest data cut-off of CSL312_3002. Median time to first attack was [redacted] with [redacted]% of patients remaining attack-free after two years of treatment.

As expressed for A14a, CSL Behring does not consider these data appropriate for decision-making, since these results are based on a relatively small sample size consisting of a post-hoc subgroup within a post-hoc subgroup.

Figure 3. Kaplan-Meier curve for time to first HAE attack after Day 1 (VANGUARD/ CSL312_3002 pooled population who experienced ≥2 HAE attacks at baseline)

Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema.
VANGUARD/CSL312_3002 pooled population includes all rollover patients from the CSL312_3001 (VANGUARD) study into CSL312_3002, who received monthly 200 mg garadacimab in VANGUARD and CSL312_3002.
Note: the numbers above show the number of patients at risk.

NMA

A15. Please provide additional justification for the use of the disease-specific AE-QoL measure in the NMA in preference to the standard EQ-5D.

CSL Behring would like to clarify an assumption made in the question regarding the non-inclusion of EQ-5D in the NMA network. The non-inclusion of EQ-5D and, conversely, the inclusion of AE-QoL in the NMA was not based on the preference for a disease specific measure. The EuroQol 5-Dimension (EQ-5D) scale was not

considered an outcome of interest in the NMA for several reasons outlined below. If these limitations were not present then the feasibility of EQ-5D as an outcome of interest in the NMA would have been further explored.

Availability of any evidence to facilitate comparisons:

The comparators of interest to this appraisal that are present in the base-case NMA are as follows: lanadelumab, berotralstat and Cinryze.

In the same manner as was observed in TA606, supportive clinical evidence for Cinryze is derived from the CHANGE study. In TA606 EQ-5D was not explored as an outcome in the NMA, despite presumed access to IPD to facilitate this network. EQ-5D is not presented as an outcome in the public domain as part of the aggregate data presented in the CHANGE pivotal study publication. In the absence of publicly reported RCT evidence for Cinryze or Berinert IV, EQ-5D could not be considered as an outcome in the NMA for these comparisons.

Lack of sufficient data, where any is present:

The timing of HRQoL assessments is of particular importance when considering the spontaneous nature of the attacks HAE patients experience and their frequency in the case of this recommendation (≥2 attacks per month).

In the VANGAURD study for garadacimab, EQ-5D-5L data was collected for Visit Days 1, 91 and 182.[14] Similarly, as described in TA606, the EQ-5D data from the HELP trial were collected at limited timepoints (Days 0, 98 and 182). In TA738 for berotralstat, the APEX-2 study is described as administering EQ-5D-5L questionnaires at weeks 4,8,12,18 & 24.[21]

As such, and in all cases, very few of the EQ-5D questionnaires coincided with an ongoing or recent attack.[22] Specifically, in VANGUARD, just 2 out of 52 (3.85%) EQ-5D-5L responses recorded during any Visit Day were associated with an ongoing HAE attack. For this analysis, “during” was defined as completing the EQ-5D-5L questionnaire within seven days of an HAE attack.[14] Similarly, as described in TA606, only two patients completed EQ-5D-5L questionnaires while experiencing an attack in the HELP trial.[22] Such limitations were also seen in the APeX-2 study for

berotralstat, with TA738 reporting that the collection of EQ-5D data was limited and not aligned with the onset of HAE attacks.[21]

Therefore, in the absence of sufficient and meaningful EQ-5D trial data for garadacimab and key comparators, it was not deemed useful for decision-making to present an NMA of EQ-5D outcomes, with literature based utilities viewed as the best source of data for the economic modelling. This is the same conclusion arrived at in two prior NICE HAE appraisals, and the SLR informing the NMA did not retrieve any relevant and more contemporary RCT evidence for the included comparators that might otherwise change this conclusion. Therefore, AE-QoL data is presented to maximise the utilisation of relevant RCT evidence for garadacimab and its comparators, in the interest of full transparency and in recognition of the importance of comparing the efficacy of treatments in improving HRQoL. AE-QoL is a disease-specific measure which offers an alternative, and by design, patient-centric insight into the quality of life for patients with HAE. In contrast to the EQ-5D, the AE-QoL was frequently administered and commonly reported amongst comparator trials so was feasible for inclusion in the NMA.

Summary of approach and context from prior NICE HTA:

- In both TA606 (lanadelumab) and TA738 (berotralstat) decisions were not made on the basis of EQ-5D evidence from the respective pivotal studies.
- In TA606/TA738 final committee recommendations were made on the basis of the same literature source that CSL Behring are utilising in this appraisal (Nordenfelt et al 2014).[23]
- The rationale for the exclusion of EQ-5D from the NMA, is the same as that agreed upon in TA606. The number of EQ-5D observations that coincide with ongoing attacks is very small and limits the usefulness of conclusions made from an EQ-5D NMA.
- When considering comparators considered in the base-case (lanadelumab, Berinert IV, Cinryze, Berotralstat) the clinical systematic literature review informing the NMA included no further RCT evidence beyond that presented in TA606 or TA738 that would make this network more feasible to construct.

A16. Priority: Please present a table of the following studies used in the NMA: VANGUARD, CSL312_2001, COMPACT, APeX-1, APeX-2, APeX-J, HELP, and CHANGE. This should include:

- **A summary of the inclusion criteria**
- **Intervention/comparator**
- **Number of patients**
- **Study design details, including:**
    - **How attacks were recorded and reported**
    - **How severity was graded**
    - **Access to acute treatments during the trial**
    - **Whether patients could treat themselves or had to go to the study site**
- **Outcomes measured relevant to the NMA (including timepoints).**
- **Please also note where any trial presented subgroup analysis based on the number of HAE attacks per month at baseline.**

A summary of all requested details above for the studies used in the NMA is provided in Table 7 except for the outcomes measured (including timepoints), which are provided separately in Table 8.

As discussed during the 10th December clarification call and confirmed by the EAG via email on the 12th December, this response makes no reference to APeX-1 as it did not include the intervention (berotralstat) at a licensed dose and was therefore excluded from the NMA base case and scenario analysis with Cinryze. Further, please note that SC Berinert is not considered relevant to the decision problem. However, given its inclusion in the base case NMA, detail to answer this question has been provided for COMPACT. As outlined in Section B.2.10.1 of the company submission, the NMA has been developed to suit the needs of several countries in seeking recommendations with their respective HTA authorities.

Study designs were generally comparable across all studies of interest, except for COMPACT and CHANGE, which involved cross-over at 16 weeks and 12 weeks, respectively. As cross-over introduces significant heterogeneity, pre-crossover data

from COMPACT was included in the NMA, while the CHANGE study was excluded from the base case as no pre-crossover data were available.[24]

Although differences in trial duration were noted, clinical expert feedback during the feasibility analysis indicated that a minimum of 1 month (4 weeks) is sufficient to assess the time-normalised attack rate outcomes, while attack-free outcomes require at least 3 months (12 weeks). Therefore, as illustrated in Table 8, the differences in trial duration were not considered a concern, as all studies included in the NMAs allowed adequate time to observe changes against placebo, exceeding what clinicians viewed as the minimum needed for time-normalised attack rate outcomes and attack-free outcomes.[24]

The event of an HAE attack was patient-reported and investigator-confirmed across all studies of interest, except for CHANGE, which has already been identified as a source of heterogeneity and excluded from the base case analyses.

The grading of attack severity was not consistently reported across studies. However, of the available information, VANGUARD and CSL312_2001 had the same definitions for attack severity, considering impact on daily activities, need for rescue medication and need for medical assistance.[14,25] The HELP study used similar topics to determine disease severity but the exact definitions differed slightly.[26] Across these three studies, attack severity was patient-reported and investigator-confirmed.[14,25] In contrast, details from the APeX studies on the definition of attack severity were not identified, but it was reported in TA738 that attack severity in the APeX-2 study was patient-reported and self-diagnosed.[21]

An NMA feasbility assessement was conducted to identify and address inter-study heterogeneity. While Cinryze introduced some heterogeneity due to differences in study design, population, and outcome definitions, clinical experts did not consider the heterogeneity identified among the studies included in the base case NMA to be significant enough to deem the NMA infeasible. Though residual heterogeneity and differences in outcome definitions remained, these were not deemed to threaten the validity of the overall findings. Overall, despite some heterogeneity across studies, the NMA provides a feasible and robust approach to deriving comparative data for

garadacimab against key comparators of interest in the absence of head-to-head trials.

Table 7. Overview of studies used in the NMA

	VANGUARD[14]	CSL312_2001[25]	COMPACT[27]	HELP[26]	APeX-2[28]	APeX-J[29]	CHANGE[30,31]
Study design	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm with cross-over	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Single-country • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Single-country • Double-blind • Randomised • Placebo-controlled • Cross-over
Intervention(s) *Bolding denotes licensed dosage*	• **Garadacimab 200 mg once monthly (n=39)**	• Garadacimab 75 mg Q4W (n=9) • **Garadacimab, 200 mg Q4W (n=8)** • Garadacimab 600 mg Q4W (n=7)	• SC Berinert 0.08 mL/kg (40 IU/kg) twice weekly (n=45) • **SC Berinert 0.12 mL/kg (60 IU/kg) twice weekly (n=45)**	• **Lanadelumab 300 mg Q2W (n=27)** • **Lanadelumab 300 mg Q4W (n=29)** • Lanadelumab 150 mg Q4W (n=29)	• Berotralstat 110 mg daily (n=41) • **Berotralstat 150 mg daily (n=40)**	• Berotralstat 110 mg daily (n=6) • **Berotralstat 150 mg, daily (n=7)**	• **Cinryze 1,000 IU twice weekly** with cross-over to placebo (n=11)
Comparator	Placebo (n=29)	Placebo (n=8)	Placebo (n=90)	Placebo (n=41)	Placebo (n=40)	Placebo (n=6)	Placebo with cross-over to intervention (n=11)
Inclusion criteria	• Male or female • 18 to 69 years • Type I or II HAE • ≥3 HAE attacks during the 3 months before screening[a] • At least an average of 1 HAE attack per month during Run-in period	• Male or female • 18 to 65 years • Type I or II HAE • ≥4 HAE attacks over 2 consecutive months, within the 3 months prior to screening or initiation of previous HAE prophylaxis	• Male or female • ≥12 years • Type I or II HAE • ≥4 HAE attacks over a consecutive 2-month period that required acute treatment[b] • ≥2 HAE attacks within any consecutive 4-week period, which required acute treatment, medical attention or caused significant functional impairment	• Male or female • ≥12 years • Type I or II HAE • ≥1 HAE attack per 4 weeks as confirmed during the run-in period	• Male or female • ≥12 years • Type I or II HAE • ≥2 attacks per month in the first 56 days of run-in period	• Male or female • ≥12 years • Type I or II HAE • ≥2 attacks per month in the first 56 days of run-in period	• Male or female • ≥6 years • Confirmed HAE • History of ≥2 attacks per month

	VANGUARD[14]	CSL312_2001[25]	COMPACT[27]	HELP[26]	APeX-2[28]	APeX-J[29]	CHANGE[30,31]
Total number of patients (including those randomised to unlicensed doses)	N=64	N=32	N=90	N=125	N=121	N=19	N=22
How HAE attacks were recorded and reported	• Attacks were patient-reported and investigator-confirmed • Patient recorded details of HAE attack in an electronic diary • The investigator was able to ask clarifying questions to assist in their assessment of whether an attack occurred and its severity	• Attacks were patient-reported and investigator-confirmed • Patient recorded details of HAE attack in an electronic diary • The investigator was able to ask clarifying questions to assist in their assessment of whether an attack occurred and its severity	• Attacks were patient-reported and investigator-confirmed • The investigator reviewed the electronic diary at each trial visit	• Attacks were patient-reported and investigator-confirmed • During the study, patients were instructed to contact the study site within 72 hours of the onset of an attack. Attack details were assessed by trained site personnel following HAE Attack Assessment and Reporting Procedures and confirmed by the site investigator	• Attacks were patient-reported and investigator-confirmed • Patients recorded the frequency, duration, location, functional impact, and any treatment of HAE attacks experienced in the previous 24 hours in an electronic diary daily. • Investigators contacted patients within 2 business days of each reported attack to discuss and evaluate the event.	• Attacks were patient-reported and investigator-confirmed • Details of attacks were recorded by the patient in an electronic diary. Within approximately 2 business days of the end of each attack, patients were contacted by the investigator to discuss the attack.	• Attacks were patient-reported, investigator confirmation was not mentioned • Patients were given diary cards and instructed to document all HAE attacks on a daily basis, documenting their symptoms over the previous 24 hours

	VANGUARD[14]	CSL312_2001[25]	COMPACT[27]	HELP[26]	APeX-2[28]	APeX-J[29]	CHANGE[30,31]
						• An independent expert (an experienced HAE treater in Japan) was selected by the sponsor to review all reported angioedema attacks. The electronic diary and any investigator-collected information were used by the independent expert to either confirm or reject the attack.	
How attack severity was graded	• Mild attacks were defined as having little-to-no effect on the patient's ability to perform daily activities and might not have necessarily required rescue medication but might have required treatment with other concomitant medications (eg, analgesics). • Moderate attacks were defined as having caused difficulty in performing daily activities or might have required assistance to perform these activities and the use of rescue medication was probable. • Severe attacks were defined as having caused substantial limitations in the patient's ability to perform daily activities, might have required medical assistance, and required the use of rescue medication		Details not published	• Mild attacks were defined as transient or mild discomfort [<48 hours]; no medical intervention/therapy required • Moderate attacks were defined as mild to moderate limitation in activity; some assistance required; no or minimal medical intervention/therapy required	Details not published	Details not published	N/A as not included in the NMA

	VANGUARD[14]	CSL312_2001[25]	COMPACT[27]	HELP[26]	APeX-2[28]	APeX-J[29]	CHANGE[30,31]
				• Severe attacks were defined as marked limitation in activity, assistance required; medical intervention/therapy required, hospitalisation possible • Life threatening attacks were defined as extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalisation or hospice care probable			
Access to on-demand treatment during the trial	The following on-demand HAE therapies were permitted at any time during the study for the treatment of HAE attacks: • Plasma-derived or recombinant C1-INH • Icatibant • Ecallantide	The following on-demand HAE therapies were permitted at any time during the study for the treatment of HAE attacks: • Plasma-derived or recombinant C1-INH • Icatibant • Ecallantide	Patients were permitted to use intravenous C1 inhibitor concentrate, icatibant, ecallantide, or fresh-frozen plasma as a rescue medication for on-demand treatment of attacks	Treatment of attacks followed the site investigator's standard of care, which could include intravenous C1 inhibitor, icatibant, or ecallantide	Patients had access to and ability to use one or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH).	Patients had access to and ability to use an acute treatment for angioedema events approved by the Japan Ministry of Health, Labor, and Welfare (plasma-derived C1-INH or icatibant).	All patients with acute attacks of angioedema were eligible for rescue treatment with C1-INH[29].

	VANGUARD[14]	CSL312_2001[25]	COMPACT[27]	HELP[26]	APeX-2[28]	APeX-J[29]	CHANGE[30,31]
Site of treatment administration	The first dose and the first 3 subsequent injections were administered by the patients or caregiver at the study site under supervision by the investigator or delegate. Subsequent doses were self-administered with or without supervision of the investigator or delegate.	All subcutaneous doses of investigational product were self-administered under supervision of the investigator or delegate at the study site.	Patients were trained to administer the injections at home.	Treatment was administered at the study site by the principal investigator or qualified site personnel.	Patients took study drug doses at home with the exception of study drug that was administered under Investigator (or designee) supervision during scheduled on-treatment clinic visits	Patients took study drug doses at home with the exception of study drug that was administered under Investigator (or designee) supervision during scheduled on-treatment clinic visits	The study drug was administered intravenously and only under medical supervision
Subgroup analyses by baseline attack rate	No published data available; post-hoc analyses for ≥2 attacks per month were presented in the company submission	No data available	No published data found	No published data found	No published data found	No published data found	No published data found

For all studies except VANGUARD and CSL312_2001, information provided is based on publicly available sources; as such, some details were not available. APeX-1 is not included in this table as it did not include the intervention (berotralstat) at a licensed dose and was therefore excluded from the NMA base case and scenario analysis with Cinryze.

[a] For participants taking any prophylactic HAE therapy during the 3 months before screening, ≥3 HAE attacks may be documented over 3 consecutive months before commencing the prophylactic therapy.

[b] For participants taking any prophylactic HAE therapy in the 3 months before the screening visit, ≥4 HAE attacks can be documented over any consecutive two-month period before commencing the prophylactic therapy.

Abbreviations: HAE, hereditary angioedema; IU, international units; N/A, not applicable; Q2W, once every two weeks; Q4W, once every 4 weeks.

Table 8. Summary of outcomes measured for the NMA and timepoint of measurement for each study

Outcome	VANGUARD	CSL312_2001	COMPACT	HELP	APeX-2	APeX-J	CHANGE
Time-normalised number of HAE attacks	26 weeks	12 weeks	16 weeks (prior to cross-over)	26 weeks	24 weeks	24 weeks	12 weeks
Time-normalised number of HAE attacks requiring on-demand treatment	26 weeks	12 weeks	16 weeks (prior to cross-over)	26 weeks	24 weeks	24 weeks	-
Time-normalised number of moderate and/or severe attacks	26 weeks	12 weeks	16 weeks (prior to cross-over)	26 weeks	24 weeks	24 weeks	-
Proportion of attack-free patients	26 weeks	12 weeks	16 weeks (prior to cross-over)	26 weeks	24 weeks	-	-
Attack free days per month	26 weeks	12 weeks	16 weeks (prior to cross-over)	26 weeks	-	-	-
Any TEAEs	26 weeks	12 weeks	16 weeks (prior to cross-over)	26 weeks	24-week plus 30 days	-	-
Change from baseline in AE-QoL total score	26 weeks	-	-	26 weeks	24 weeks	24 weeks	-

APeX-1 is not included in this table as it did not include the intervention (berotralstat) at a licensed dose and was therefore excluded from the NMA base case and scenario analysis with Cinryze.
Values in cells denote the time period over which the outcome was measured during the study. Green cells = included in base case or scenario analysis with Cinryze. Red cells = not included in base case or scenario analysis with Cinryze.
Abbreviations: NR, not reported; TEAE, treatment-emergent adverse event.
Source: CSL Behring 2024 (NMA report).[24]

A17. Priority: Please justify the use of FE NMA for all sensitivity analysis. What evidence is there of minimal between study heterogeneity (include comparison of study design types and baseline characteristics and outcomes in placebo arm)?

The systematic literature review (SLR) identified a paucity of trials in HAE that led to sparse evidence networks due to few randomised controlled trials (RCTs) informing each treatment comparison. Further, a relatively small number of patients were included in each trial. Therefore, as was also observed in TA606, FE models were preferred over using random effects models for these analyses as the latter is likely to produce less reliable results in the absence of a credible informative prior. Fixed effect models can provide more precise estimates of treatment effect in the absence of significant heterogeneity between trials. This is demonstrated by the consistency in credible intervals from the fixed effect NMA results with those in published trial results, where available (Table 9). Please note that it was not feasible to compare trial results vs. NMA results for garadacimab or berotralstat because relevant trials for these therapies were pooled in the NMA.

Furthermore, although heterogeneity was identified in patient characteristics during the feasibility analysis, the extent of this heterogeneity was generally minimal. Across comparators, baseline HAE attack rate (during run-in) ranged from 2.3 to 5.2 attacks per month, mean age at baseline ranged from 39.6 to 44.1 years, the percentage of female patients ranged from 56.3% to 78.9%, and mean body mass index (BMI) ranged from 28.05 kg/m^2 to 29.0 kg/m^2. History of anxiety and history of depression were not publicly available for all comparators. Based on these ranges, it is reasonable to assume that the included studies are sufficiently similar as to not preclude analysis via NMA using fixed effect models.

As such, due to the sparsity of the networks and to ensure consistency across all analyses, fixed effect models were preselected as the primary approach for all outcomes in the base case analyses. However, for completeness and to ensure robustness, sensitivity analyses using random effects models were also presented for each outcome in Section B.2.10.2 of the company submission. Additional sensitivity analyses, such as the exclusion of phase 2 studies, were performed exclusively with fixed-effect models. This approach ensured that each sensitivity

analysis altered only one aspect of the base case, whereas using random-effects models would introduce an additional variable, thereby changing two elements simultaneously.

Lastly, the methods employed in the analyses were robust based on the data currently available and followed best practices as described in the NICE Evidence Synthesis DSU TSD series (NICE TSD 2). The robustness of our analyses is indicated by the consistency in results among the base case and sensitivity analyses, as described in Section B.2.10 of the company submission, as well as the consistency between the observed and estimated results from the direct (RCT) evidence and the indirect (NMA) estimated effects (Table 9).

Table 9. Overview of trial results and fixed effect NMA results for interventions assessed in the NMA

Outcome	Results for Comparator vs Placebo							
	Garadacimab 200 mg		Lanadelumab 300 mg Q2W		Lanadelumab 300 mg Q4W		Berotralstat 150 mg	
	Result from VANGUARD/ CSL312_2001	Result from base case NMA	Result from HELP	Result from base case NMA	Result from HELP	Result from base case NMA	Result from APeX-2/ APeX-J	Result from base case NMA
Time-normalized number of HAE attacks, rate ratio (95% CI)	NA (trials pooled in NMA)	[redacted]	0.13 (0.07 to 0.24)	[redacted]	0.27 (0.18 to 0.41)	[redacted]	NA (trials pooled in NMA)	[redacted]
Time-normalized number of HAE attacks requiring on-demand treatment, rate ratio (95% CI)	NA (trials pooled in NMA)	[redacted]	0.13 (0.07 to 0.25)	[redacted]	0.26 (0.16 to 0.41)	[redacted]	NA (trials pooled in NMA)	[redacted]
Time-normalized number of moderate and/or severe HAE attacks, rate ratio (95% CI)	NA (trials pooled in NMA)	[redacted]	0.17 (0.08 to 0.33)	[redacted]	0.27 (0.16 to 0.46)	[redacted]	NA (trials pooled in NMA)	[redacted]
Proportion of attack-free patients, hazard ratio (95% CI)	NA (trials pooled in NMA)	[redacted]	NA (not reported as hazard ratio)	[redacted]	NA (not reported as hazard ratio)	[redacted]	NA (not reported as hazard ratio)	[redacted]
Attack-free days per month	NA (trials pooled in NMA)	[redacted]	4.7 (3.2 to 6.2)	[redacted]	4.3 (2.8 to 5.8)	[redacted]	NA	[redacted]
Any TEAEs, hazard ratio (95% CI)	NA (trials pooled in NMA)	[redacted]	NA	[redacted]	NA	[redacted]	NA (not reported as hazard ratio)	[redacted]
Change from baseline in AE-QoL total score	NA	[redacted]	−16.57 (−28.53 to −4.62)	[redacted]	−12.66 (−24.51 to −0.80)	[redacted]	NA (trials pooled in NMA)	[redacted]

Abbreviations: AE-QoL = Angioedema Quality of Life; CI = credible interval; NA = not available; NMA = network meta-analysis; Q2W, once every two weeks; Q4W, once every 4 weeks; TEAEs = treatment-emergent adverse events.

A18. Priority: Please present the following figures reporting the results of the NMA but excluding Phase 2 studies:

a) **Figure 16: Summary of results from fixed effect NMAs**

b) **Figure 17: Summary of results from random effect NMAs**

A summary of results excluding phase 2 studies for fixed effect NMAs and random effect NMAs is presented in Figure 4.

However, given that HAE is a rare disease with limited randomsied controlled trials and patient numbers, CSL Behring considers the base case NMA, which includes all evidence where patients were randomised to the licenced dose of study treatment, to be the most robust source of comparative efficacy. It is important to note that following a systematic literature review (SLR) and thorough feasibility assessment, the only phase 2 study included in the base case NMA was the CSL312_2001 study, as outlined below:

- The objective of the NMA was to estimate the comparative efficacy, safety, and impact on quality of life of LTP treatments including garadacimab for adolescent/adult patients with HAE, whose disease is type I or II. The base case NMA considered only licensed dosages for the interventions of interest. The APeX-1 study, a phase 2 RCT, did not investigate a licenced dosage of berotralstat and thus was excluded from the base case NMAs. The other phase 2 RCT identified in the SLR, CSL312_2001, assessed three dosages of garadacimab, only one of which is licenced. Therefore, only the licenced dosage from CSL312_2001 was included in the base case NMA.
- Before conducting the NMAs, a feasibility assessment was performed to evaluate clinical heterogeneity across the evidence base. This assessment identified that 'treatment period 2' of CSL312_2001 used an open-label, non-controlled design. To minimize bias and uncertainty, treatment period 2 was excluded from the NMA. Instead, only data from randomized patients receiving the licensed dosage of garadacimab during treatment period 1 of CSL312_2001 were included in the NMAs
- For full transparency, a sensitivity analysis including all licensed and unlicensed dosages was conducted. Therefore APeX-1 was included in the context of a sensitivity analysis.
- An additional sensitivity analysis was conducted by removing the phase 2 studies. For this sensitivity analysis, CSL312_2001 was the only phase 2 study excluded, as the phase 2 APeX-1 RCT examined only unlicenced dosages and was already excluded from the base case NMA.

In conclusion, the base-case NMA makes best use of the available clinical evidence in a transparent manner whilst approaching the inclusion of this phase 2 evidence with a fair, considered and evidence-based approach to any potential bias.

Figure 4. NMA results excluding phase 2 studies

Abbreviations: BIW, twice weekly; CrI, credible interval; HR, hazard ratio; IV, intravenous; NR, not reported; QM, once monthly; QD, once daily; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RR = rate ratio; SC, subcutaneous.
Dark blue fill indicates garadacimab 200 mg QM is significantly superior vs the comparator; light blue fill indicates garadacimab 200 mg QM is numerically superior vs the comparator; light orange fill indicates garadacimab 200 mg QM is numerically inferior vs the comparator; grey fill indicates data were not available for the comparator to perform a pairwise comparison.
* RR <1 implies that garadacimab performs better than comparator. † Fixed effect results for this outcome are aligned with the outcomes from the scenario analysis including Cinryze. ‡ HR >1 implies that garadacimab performs better than comparator. # Mean difference >0 implies that garadacimab performs better than comparator. § HR <1 implies that garadacimab performs better than comparator. ** Mean difference <0 implies that garadacimab performs better than comparator.
Source: CSL Behring Data on File, NMA report (2024).[24]

A19. Please justify the appropriateness of assuming proportional hazards in the time to first attack NMA.

As confirmed by via email on the 12th December, this question should now be superseded by the below wording:

"Please justify the appropriateness of assuming proportional hazards when applying the proportion of attack-free patients NMA to estimate the time to first attack in the model."

The NMA was able to produce a singular comparative metric for the endpoint of proportion of attack-free patients in the form of the hazard ratio at month 6. In the absence of data at different time points, there is no other alternative but to use the month 6 hazard ratio value to construct the comparators time to first HAE attack curves over time.

In effect, given the relationship between HAE attack rates and proportion of attack free patients as established in the response to question B4, the proportional hazards assumption would imply that patients are subject to the same underlying risk of attacks overtime. This is an approportiate assumption considering the long-term evidence of prophylactic technologies such as garadacimab, lanadelumab and berotralstat in their respective submissions.

ML-NMR

A20. Priority: Please present a ML-NMR for proportion of attack-free patients using the risk difference metric for proportion of attack free patients.

The ML-NMR was undertaken using the multinma package in R, developed by David Phillippo, member of the DSU and author of the seminal works introducing multilevel network meta regression. The package was created in accordance with his ongoing academic progress in applying Bayesian frameworks to networks of individual patient and aggregated data and is the most developed ML-NMR solution available at present. The most recent multinma package (0.7.2) does not support the risk difference metrics for the negative binomial regression.

We understand the EAG's request suggesting that risk difference metric might be able to provide as a working alternative to the continuity-correction method currently

utilised to address the underlying issue. However, while some adjustments to outputs from the base package have been discussed with the author, including the risk difference would mean major updates that are not possible to be implemented and validated in a limited time-frame. Furthermore, we are also concerned that given the temperamental nature of binomial regressions, the existing issues may still not be resolved through the risk difference analysis.

A21. Priority: Please provide ML-NMR for all outcomes removing the phase 2 garadacimab trial (CSL312_2001).

As outlined and agreed with the EAG on the 10th December clarification call, CSL Behring will not fulfil this request.

ML-NMR for all outcomes removing the phase II garadacimab trail (CSL312_2001) will be infeasible to provide. Holding practical feasibility of the request to one-side, CSL Behring do not believe that, were this task achievable, it would be informative for the EAG or committee to consider. The rationale for this conclusion is that the existing ML-NMR of larger sample size already experiences divergent transition issues related to the underlying negative binomal regressions for the count (time-normalised) outcomes (see also repsonse to B13). As a result, and as previously communicated to the EAG, the endpoint rate ratios from these ML-NMR models are less reliable. As such, CSL Behring does not plan on including them in the cost-effectiveness model to preclude exposing decision making to results that are unreliable. Removing the phase II trial will cause a 18.75% decrease in the sample size of the garadacimab patients, which serve as the sole source of individual patient level data in the networks.

In order to minimise the chance of divergent transition trajectories within the Bayesian framework, it is crucial to maximise the sample size across all analyses. By reducing the sample size of garadacimab patients even further, these issues of divergent transition trajectories for count outcomes are only served to be exacerbated. In the same way, it would be expected that this analysis would also hinder the reliability of those endpoints, which were able to achieve convergence in the pooled population.

Section B: Clarification on cost-effectiveness data

Effectiveness

B1. Priority: Curve fits for time to first HAE attack are currently only provided for the pooled population and it is unclear what the company intends the base case to be.

a) **The CS indicates the parametric curves provide a better fit to the data, but the Excel file uses constant attack rates. Please clarify your intended base case.**

Section B.3.3.3 and Appendix J of the CS explains how the standard formula of Equation 1 used to calculate constant attack rates underestimated the time to first HAE attack of garadacimab patients when compared to VANGUARD trial data. As a result of this, we conducted a survival analysis, similar to that seen in TA606 to explore if parametric curves may provide a better fit for the data.

In this analysis, curves were intentionally fitted to the outcome of time to first HAE attack for garadacimab-naïve patients who are a subgroup of the open label extension CSL312_3002 study instead of only patients on garadacimab from VANGUARD trial. The intention behind this was to increase sample size (n=90 vs n=39) and the duration over which the curve fitting exercise could be examined. since this not only allowed us to use a larger sample size (n=90 vs n=39). However, the analysis (also labelled as ‘calibrated attack rates’ in the model) showed that there is a plateau in the time to first HAE attack outcomes towards the tail end of the observation period which suggested that the number of HAE attacks will keep on decreasing eventually leading to a situation where a portion of patients on treatment will never have their first HAE attack. This result is unrealistic, insofar as, none of the therapies under consideration are curative in nature and was found to be inconsistent with all other methods used to quantify attack rates.

Hence, results from the survival analyses did not inform any cost-effectiveness analysis. The intended base case was informed by constant attack rates for the first 24 cycles with average attack rate reduction carried forward for cycle 25 and beyond (derived from pooled VANGUARD/CSL312_3002: patients who rolled-over from

VANGUARD and received 200 mg garadacimab throughout VANGUARD and CSL312_3002 [n=36]).

b) Could you please provide the KM survival curves (with numbers at risk) and the fitted curves, the fit of the curves to the observed hazard function and the goodness-of-fit statistics for the time to first HAE attack for each of the sub-populations listed below, in a new version of the model, which enables selection of the source of data to be used for the fitted survival curve?

- **Phase 3 VANGUARD: garadacimab and placebo**
- **Phase 2 CSL312_2001**
- **CSL312 study-naïve**

Phase 3 VANGUARD: garadacimab and placebo

As can be seen in associated Kaplan-Meir curve in Figure 5 most people in *Phase 3 VANGUARD: garadacimab and placebo study* (n=39, 25 respectively) experienced HAE attacks in the first few weeks of the study – mainly the placebo patients. Figure 6 and Figure 7 provide the basis for the visual inspection of the fitted curves in relation to the associated KM curves and strongly support the conclusions found in appendix J (covering garadacimab-naïve patients; n=90), having a similar visual likeness and both having the gamma curves as the best fit.

Table 10 provides the goodness of fit statistics for the Phase 3 VANGUARD.

Table 10. Goodness of fit statistics for the Phase 3 VANGUARD: garadacimab and placebo study

Model	Rank - garadacimab	Rank - placebo	AIC - garadacimab	BIC - garadacimab	AIC - placebo	BIC - placebo
Exponential	7	7	146.64	148.30	972.55	973.77
Weibull	2	4	90.43	93.76	-144.96	-142.52
Log-normal	3	3	90.97	94.29	-161.39	-158.96
Log-Logistic	4	2	91.11	94.44	-172.04	-169.60
Gompertz	6	6	140.04	143.37	7.16	9.60
Generalized Gamma	5	1	91.74	96.73	-229.88	-226.22

Gamma	1	5	89.76	93.09	-129.05	-126.61

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion. Note, rank follows AIC.

Figure 5. Phase 3 VANGUARD, time to first HAE Attack after Day 1 with 95% Confidence Interval (CSL312 200mg and Placebo Subjections in Treatment Period 1)

Figure 6. CSL312_3001 Garadacimab Survival Curves Comparison

Figure 7. CSL312_3001 Placebo Survival Curves Comparison

Phase 2 CSL312_2001

As agreed during the clarification call on 10th December, the provision of analysis for this study is of lower priority. As has been explained in response to A18, the phase-2 study is included in a limited and considered fashion in the base-case NMA. Specifically, the pooling only includes those patients who were randomised to the dose of garadacimab under consideration in this appraisal, during part 1 of the study.

In the Phase 2 CSL312_2001 trial (n=35), all placebo patients had their first HAE attack within a short amount of time. On the other hand, there was only [redacted] HAE attack observed after Day 1, for the treatment group. Given these points, it was judged that fitting parametric curves to these observations would not provide meaningful insights. Considering the more restricted population of patients of CSL_2001 who meet the eligibility criteria for inclusion in the base-case NMA, this analysis is likely to have yielded even less useful results. Please see Figure 8, for the corresponding KM survival curves.

Figure 8. Phase 2 CSL312_2001, time to first HAE Attack after Day 1 with 95% Confidence Interval (CSL312 200mg and Placebo Subjections in Treatment Period 1)

There were 8 patients on placebo, of which [redacted] had an attack on Day 0. Thus, number at risk in the placebo arm was [redacted].

CSL312 study-naïve

As can be seen in associated Kaplan-Meir curve in Figure 9 most people in CSL312 study-naïve (n=69) who experienced an HAE attack did so in the first few weeks of the study, however the remaining people mostly continued to be attack free over the time horizon. Figure 10 provide the basis for the visual inspection of the fitted curves in relation to the associated KM curve which supports the conclusions found in appendix J (covering garadacimab-naïve patients; n=90), having a similar visual likeness and gamma curves being a good fit.

Table 11 provides the goodness of fit statistics for the sub population.

Table 11. Goodness of fit statistics for the CSL312 study-naive patients

Model	Rank AIC	Rank BIC	AIC	BIC
Exponential	7	7	365.74	367.97
Weibull	4	4	176.92	181.39
Log-normal	2	2	175.72	180.19
Log-Logistic	5	5	177.51	181.98
Gompertz	6	6	326.43	330.90

Generalized Gamma	1	1	156.06	162.76
Gamma	3	3	176.53	181.00

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion.

Figure 9. CSL312 study-naïve, time to first HAE Attack after Day 1 with 95% Confidence Interval

Figure 10. CSL312_3002 Survival Curves Comparison

c) Please provide the fit of the curves to both the observed hazard function and the survivor function for the pooled data currently used in the submission

Please see the data provided in appendix J for the observed survivor function used in the submission. Hazard functions have not been utilised in the model to generate the analyses and have therefore not been provided.

B2. Priority: Attack rates may have different sources depending on the treatment, the period under analysis, and the user choice.

a) **In relation to the source of attack rates in the first 24 months (cells C6:D8 of the "Inputs – Transitions" sheet of the cost-effectiveness model), can you confirm that, for the comparators, the source of the "Constant attack rates" and of the "Poisson" transition methods is the same, specifically the attack rates ratio from the NMA applied to the baseline placebo rate (cells C21:G27 of the "Inputs – Efficacy" sheet of the model)? In the case of the Poisson why not fit the regression to the placebo data and apply the NMA to that?**

In relation to the source of attack rates in the first 24 months, for the comparators, the source of the "Constant attack rates" and of the "Poisson" transition methods is the same, being the attack rate multiplied by the comparators rate ratios. Additionally, comparator technologies are also not affected by the user choice of the attack rates when the Poisson regression option or Average attack rate reduction carried forward (AARRCF) methods are selected for cycle 25 and beyond. This is because CSL Behring does not have access to comparators IPD data which would have allowed altering attack rates for comparator technologies based on a Poisson regression or AARRCF.

Table 21 of the CS presents the Poisson regression outcomes for the placebo arm data. However, the regression output when used to predict attack rates did not produce results with face validity. Please see the response to question B9e.

b) **For cycle 25 of the comparators, was it intended to input the Last Observation Carried Forward (LOCF) regardless of the selection (e.g. Average attack rate reduction carried forward (AARRCF), or Poisson)? This is causing clear bias in the base case as the garadacimab rate is dropping by more than 50% while the comparators remain constant.**

For cycle 25 and onwards for the comparators, ideally, we wanted to input the AARRCF or Poisson for all technologies. However, due to lack of IPD data for the comparators, their attacks rates remained informed by aggregate level derived LOCF while AARRCF and Poisson can be used to inform attack rates for garadacimab when selected by the user. Hence, no bias has been introduced when applying the AARRCF methodology for cycle 25 and beyond for garadacimab. This can also be seen from both the methodological and outcome perspectives.

From a methodological perspective, the AARRCF methodology has been used to characterise the developments of HAE attack rates over the long run in previous submissions (TA738)[21], originating initially as an EAG recommendation. Furthermore, the population that has been used to inform the analysis i.e. pooled VANGUARD/CSL312_3002 subpopulation of patients (n=36) received 200mg garadacimab monthly in both studies are the patients that have been receiving garadacimab for a considerable amount of time and are well suited to provide maintenance of treatment effect insights. This is described in detail in Section B.2.6.7 of the CS.

From an outcome perspective, the AARRCF values are remarkably consistent with those produced by the Poisson regression analysis over the long run which can be seen when comparing Sections B.3.3.5.1 and B.3.3.5.2 of the CS. The cross-validation of results from both these analyses provides credence to using them for cycle 25 and beyond for garadacimab.

Hence, given the data availability and justifications for using the AARRCF method, no bias has been introduced in the cost-effectiveness analysis. Instead, CSL Behring have aligned their approach as closely as possible to what has been accepted previously for extrapolation in TA606/TA738. The difference that has arisen here is not a consequence of the choice being made as inappropriate, but rather the lack of sufficient IPD.

c) When "Calibrated attack rates" for the first 24 cycles is selected, cells C21:G27 (of the "Inputs – Efficacy" sheet of the model) show a significant attack rate drop from cycle 1 to cycle 2 across all

treatments except lanadelumab (Q4W) and placebo. Can you explain why there is no drop on lanadelumab (Q4W)?

Cells C21:G27 (of the “Inputs – Efficacy” sheet) do not depend on the choice of ‘source of attack rates for first 24 months’ setting in the “Inputs – Transitions” sheet.

However, when ‘Calibrated attack rates’ are selected in the “Inputs-Transitions” sheet, then except for placebo, there is a drop in the attack rates from cycle 1 to cycle 2 across all treatments which includes lanadelumab (Q4W) too. Please see ‘Attack rate table’ in the “Inputs – Transitions” sheet.

As outlined in Appendix J, the survival analysis was originally not conducted on the placebo arm due to extremely limited survival. Therefore, there are no ‘Calibrated attack rates’ present in the cost-effectiveness model for placebo, meaning attack rates for placebo do not change with the user settings.

B3. On page 1 of Appendix J (as cited in Section B.3.3.3 of the submission), it is indicated that the expression 1 – e[redacted] is used to calculate the survival in each successive cycle. Could you please confirm whether the value [redacted] represents the rate parameter? If so, please provide the detailed calculations that resulted in this value.

The [redacted] value represents the rate parameter as calculated by multiplying VANGUARD ITT population placebo-arm time-normalised number of HAE attacks and garadacimab NMA-based rate ratio (2.01*[redacted]).

B4. On page 5 of Appendix J (as cited in Section B.3.3.3 of the submission), it is stated that the hazard ratio for the proportion of patients who were attack-free on IV Cinryze and IV Berinert has been assumed to be as large as the relative increase in HAE attack rate ratios between lanadelumab Q4W and IV Cinryze/IV Berinert. Can you provide further justification for this assumption and conduct sensitivity analysis to this assumption?

The justification of this assumption is purely mathematical. Let F(r,x,t) be the function that denotes the proportion (or probability) of attack free patients at any point in time x, by the attack rate r, and the time scalar t. It follows, F(r,x,t) can be expressed by Equation 1.

Equation 1. Proportion of attack free patients as a function of time, HAE attack rates and the time scalar

$$F(r, x) = (1 - (1 - e^{-rt}))^{x}$$

It reads that the proportion of attack free patients (without their first HAE attack) is equal to unity, minus the probability of having a HAE attack, exponentiated by the amount of time x, since to be without an attack at month x you must not have suffered an attack in any of the preceding months in multiplicative process. (The probability of having an attack follows the standard formula outlined in Section B.3.3.2).

Equation 1 provides clear insight, into the relationship between the HAE attack rates and the proportion of patients attack free at any point in time. Thereby, in absence of the hazard rate which provides the relative efficacy metric among treatments for the endpoint of proportion of patients who were attack-free, the next best alternative was to approximate the unknown hazard rate based on the known difference in time-normalised number of HAE attack rate ratios.

Overall, to approximate the difference in the output, the difference in the input was examined. The relative increase/decrease of any of the rate ratios could have been chosen, but lanadelumab Q4W was the closest match in efficacy to IV Cinryze and by extension IV Berinert.

Please see Figure 11, which includes two IV Cinryze, gamma based, survival curves. Derived as plus or minus 20% of the original hazard rate for the n=90 population.

Figure 11. Calibrated time to first HAE attack survival probability - IV Berinert/ IV Cinryze upper and lower sensitivity analysis

B5. Can you comment on the use of severity data drawn naively from individual trials rather than from a network meta-analysis (NMA). This would not appear robust given the different definitions used across trials. Further to this point:

a) Please amend the base case to use the NMA to inform these parameters

The attack severity data drawn naively from individual trials is an appropriate way to include this in the cost-effectiveness model. The strength of this approach is that it takes into account the relative severity of attacks i.e. mild, moderate, severe and laryngeal attacks. As seen throughout the CS, various outcomes such as quality-of-life and resource use varied by attack severity. So, although the definitions used across the trials were not identical (Table 7), they are sufficiently similar to be compared and do not pose a significant issue for the cost-effectiveness analysis.

However, even if the definitions used across the trials were quite heterogenous and could not be compared, then too the NMA approach suggested by the EAG could not be regarded as a solution. This is because although the NMA does report the outcomes of time-normalised number of HAE attacks and those of the

moderate/severe severities separately, it is still unable to adjust for the different definitions of attack severities across trials. This is similar to the case outlined in response to question B11a wherein the use of the NMA approach would result in all technologies conforming to a singular attack severity profile and applying a relative metric to the common severity profile.

For context, TA606 assigned the same attack severities for lanadelumab and C1-INHs, and TA738 used naïve trial data to inform attack severities for berotralstat and placebo. They both did not use an ITC to inform these parameters.

Overall, acknowledging the difference in the attack severity definitions across trials is a better modelling approach than the standardisation imposed by the NMA alternative, the base case has not been amended any further.

b) Please also provide a scenario which assumes an equal split of severity across treatments either as a whole or for treatments with a similar mechanism of action (e.g. lanadelumab and garadacimab; Cinryze and Berinert).

The scenario (using the updated model) which assumes an equal split of severity across treatments with a similar mechanism of action has the following grouping, where berotralstat and placebo remain unchanged:

- Garadacimab base – assumed by lanadelumab Q2W & Q4W
- Berinert base – assumed by Cinryze

Please see Table 12 for the associated cost-effectiveness results.

Table 12: Equal severity split across groups of treatments scenario analysis, pairwise cost-effectiveness outcomes

	Garadacimab versus pairwise			
	Inc. Costs	Inc. QALYs	INMB	ICER
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

B6. Priority: The CS (Section B.3.3.1) states: “The technology-specific NMA based rate ratio for the outcome of time-normalised number of HAE attacks is applied to the baseline number of attacks experienced by placebo patients of VANGUARD to arrive at the number of HAE attacks per cycle by technology.” Please explain why baseline was used rather than data for placebo observed during the trial.

This is a typographical error. The mean time-normalised number of HAE attacks per month as observed for the placebo arm over the course of the pivotal VANGUARD trial has been used, with the technology-specific NMA rate ratios, to arrive at the number of HAE attacks per cycle by technology. This is the ‘Constant attack (LOCF)’ method.

B7. Priority: Could you please comment on the efficacy of patients who continue treatment with berotralstat after 3 months in the economic model? These patients are responders by definition and will have lower attack rates than the overall population in the trial.

Additionally, could you update the model to base the efficacy of responders on data for responders-only from the APeX-2 trial after 3 months. Check the NICE submission for berotralstat for this information.

If this data is redacted, could you provide a scenario analysis where the efficacy of berotralstat after 3 months is equal to:

- **Lanadelumab Q2W**
- **Garadacimab**

CSL Behring have conducted a rigorous interrogation of published literature sources and do not believe that efficacy data for those patients who satisfy the continuation rule for berotralstat exists in the public domain. Therefore, the efficacy of patients who continue treatment with berotralstat after 3 months in the economic model is derived from relative efficacy estimates originating from the NMA.

In TA738 the EAG concluded that the attack rates for berotralstat responders would not improve over time as stated on p.41 of the EAG report:

“Furthermore, looking at the observed monthly attack rates for *responders* (n=*), there is no obvious trend towards efficacy increasing further with longer follow-up beyond month 3 (Figure 4).”

Hence, the suggested scenario by EAG of equating berotralstat’s responder efficacy to the levels of lanadelumab Q2W or garadacimab is unrealistic. This is because in case of lanadelumab the published Watt et al. (2023) NMA study demonstrated that “lanadelumab 300mg administered every 2 weeks or every 4 weeks was associated with statistically significantly higher effectiveness versus berotralstat 150mg once daily” whereas for garadacimab, the NMA conducted by CSL Behring also supports the same conclusion i.e. garadacimab’s relative efficacy is significantly higher than berotralstat see Section 2.10 in CS.

However, it may be reasonable to assume that those patients that meet the continuation rule i.e. continue taking berotralstst beyond 3 months may in fact have slightly lower attack rates than the aggregate attack rate informed by responders and non-responders. But, as stated in the conclusion above by EAG on TA738, this attack rate for berotralstst responsders cannot improve further beyond what is observed at month 3 timepoint.

Due to the redactions of the values discussed, CSL Behring does not know the true attack rate for berostralstat responders beyond month 3. However, to reflect the possibility of marginal improvements in the attack rate amongst the berotralstat responders beyond month 3, we have provided in Table 13 results corresponding to the attack rate being equal to a 50% reduction in HAE attack rates from baseline ([redacted] attack rate) over the long-run. However, the results should be interpreted with caution given the lack of evidence on this matter alongside the fact that the continuation rule is only checked at a single timepoint at month 3 leaving a potential for the attack rate of responders to increase over time.

Table 13. Marginal improvements to berotralstat responders pairwise cost-effectiveness outcomes

Garadacimab versus Berotralstat			
Inc. Costs	Inc. QALYs	INMB	ICER
[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

The results demonstrate that marginal improvements in the attack rate amongst the berotralstat responders beyond month 3 do not alter the cost-effectievness conclusions and geneally have a small impact.

Overall, given the limited impact of the scenario on cost-effectievenes outcomes, uncertainty with respect to the true attack rates amongst berostralstat responders beyond month 3 and the robustness of the relative efficacy estimates derived from the NMA in CS, CSL Behring's modelling approach is the most appropriate for decision making.

B8. Priority: The model currently assumes that the effectiveness of lanadelumab patients who switch from Q2W to Q4W reduces to equal that of patients who started on Q4W in the HELP trial. This does not seem to make sense as only patients able to maintain equal effectiveness between Q2W and Q4W make the switch. Please amend the model to assume that the effectiveness of people who switch to Q4W is maintained at the same level as the effectiveness of Q2W.

CSL Berhing believe that by attributing lanadelumab Q4W's efficacy to correspond with its efficacy estimates as informed by the NMA, we have taken the most methodologically rigorous approach possible..

The question statement is consistent with lanadeluamb's SmPC, that in those patients who are stably attack free on treatment, a dose reduction may be considered. Thereby, it may be reasonable that in the immediate short run, the efficacy among the two treatments may be approximated as roughly equal.

However, in the long run, once the steady state concentration levels consistent with the dosing of lanadelumab Q2W are naturally lowered to the steady state concentration levels with the dosing of lanadelumab Q4W, the efficacy of the treatment would be consistent with the NMA estimates of lanadelumab Q4W efficacy. These are likely to be lower because, lanadelumab Q4W is half the potency of the biweekly option.

Furthermore, this approach is strictly aligned to the approach of the submitting company in TA606 for lanadelumab. Please see clarification response to question B10 of TA606 which we have copied below for convenience:

> "B10. CS, document B, section B.3.3. When patients switch from lanadelumab every 2 weeks (q2w) to every 4 weeks (q4w) in the model, estimates based on the q4w arm of the HELP-03 trial are applied. However, the q4w arm of this RCT was in patients previously naïve to lanadelumab. It is unclear whether the RCT experience with q4w reflects the likely experience when switching patients whose disease is controlled with q2w to q4w. Is there any other evidence about the effectiveness of a switching policy as in the model? If so, please provide details.
>
> *While there is no evidence yet on the effectiveness of a switching policy, we believe the approach in the economic model is most reflective of the label and conservative as patients switch to the q4w regimen when they are stably attack free and lanadelumab has reached the steady state, while at the point of switching, the effectiveness of the q4w arm is applied, assuming lanadelumab still has to reach its steady state after the switch."*

In absence of the above data or any individual patient level data describing the efficacy of short and long run efficacy around lanadelumab switching patterns, the current assumptions are the most relevant for decision making.

B9. The following issues with the Poisson regression require clarification.

a) **Please justify why only data from VANGUARD and not the extension study was used in the Poisson regression. Please present either sensitivity analysis or validation using the extension study data.**

The reason why data from VANGUARD and not the extension study was used in the Poisson regression was to preserve randomisation and allow a robust comparison to the placebo attack rates. Although including the extension study in the Poisson regression analysis would have increased the sample size and the observation period, randomisation would have not been upheld. Therefore we have not presented sensitivity analysis or validation using the extension study data.

b) The Poisson model looks to be a poor fit – consider using a zero-inflated Poisson model instead. In addition, please justify the lack of imputation for missing data.

Thank you for the suggestion of considering using a Zero-inflated Poisson (ZIP) model. The R package 'pscl' has been tasked with running the regression specification found in Figure 12.

Figure 12. Zero-inflated Poisson model specification of the 'Previous cycle' family of attacks for the sixth cycle

```
zip_model <- zeroinfl(
NEVENTS_T6 ~ NEVENTS_T5 | 1,
data = data_filtered,
subset = (TIMEx == 6 & ARMx == 1),
dist = "poisson")
```

Table 14 contains the regression outputs and summary statistics for the ZIP model. Notably, the residual deviance values are the same. However, the ZIP model suffered a higher dispersion test value of 1.4856 compared to the Poisson dispersion test value of 1.4454. This is likely because the ZIP necessitates the use of the data intensive binomial with a logit link function for the subset of patients that have zero observations, further dispersing rather than consolidating the outputs of the BFGS optimisations. This is evident in the size of the standard error for the fitted intercept (binomial with logit link), which is contributing to its insignificance statistically.

In summary, the ZIP did not produce an improved fit relative to the Poisson regression.

Table 14. Zero-inflated Poisson model results of the 'Previous cycle' family of attacks for the sixth cycle

Model and coefficient	Mean and significance level	Standard error	Lower 95% confidence interval	Upper 95% confidence interval
Garadacimab – AIC: 40.5646; residual deviance: 22.345; dispersion test value; 1.4856				
Fitted intercept (Poisson with log link)	[redacted]	[redacted]	[redacted]	[redacted]
Fitted previous cycle number of attacks (Poisson with log link)	[redacted]	[redacted]	[redacted]	[redacted]
Fitted intercept (binomial with logit link)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion

The reasons for not imputing the missing data are that due to anonymisation, the cause of the missing data is unknown. Imputing data would have involved applying prespecified assumptions which may have not overcome the benefit of the marginally increased degrees of freedom.

c) In the cost-effectiveness model (cells C115 to D140 of the “Inputs – Transitions” sheet) a steep increase can be seen in cycle 4 in the attack rate using the Poisson regression, followed by a sudden drop in the same variable in cycle 5. The initial increase in cycle 4 is not seen when the “Calibrated attack rates” option is selected. Can you please provide a justification for these figures?

The reason for not seeing an attack rate increase with the ‘Calibrated attack rates’ is because this setting corresponds to providing information on attack rates based on the survival analysis in which parametric extrapolations smooth the implied attack rate.

The cause of the increase in the attack rate at cycle 4 and then a drop in cycle 5 with the ‘Poisson regression’ is because for cycles 1-5 attack rates in the model followed the observed data rather than the predicted values from the Poisson regressions. This has now been updated, such that the individual regressions for cycles 1-5 provide the predicted attack rates for the relevant cycles. The main cycle 6 regression continues to provide the basis for extrapolating attack rates for cycle 6

and beyond. Please see Figure 13 comparing observed and Poisson predicted (for both ‘Previous’ and ‘All previous’) HAE attack rates over the trial period.

Figure 13. Observed and Poisson predicted number of HAE attack rates for garadacimab

d) Table 19 (Section B.3.3.4) of the submission shows the baseline characteristics of patients in the Poisson regression analysis. Can you please provide the source for all inputs?

The source of these baseline characteristics is the VANGUARD pivotal study.As discussed and agreed on the 10th December clarification meeting, provision of this IPD is not feasible and will not be provided.

e) Please provide equivalents to Table 20 and Figure 19 for the placebo arm.

Table 20 of the CS shows the goodness-of-fit statistics for the various garadacimab Poisson regressions. The judgment of the parsimonious regression specification for every cycle was determined by the goodness-of-fit statistics for the garadacimab

arm, and for each comparable cycle, the same regression specification was used for the placebo regression to enhance comparability. This means the variety of regressions displayed in Table 20 of the CS do not currently exist for the placebo arm. Due to the limited time available, the planning, coding, interpretation and presentation of 24 new placebo regressions has not been undertaken. Please see the goodness-of-fit statistics for the existing placebo regressions in Table 15.

Table 15. Goodness of fit metrics for the placebo 'Previous cycle' Poisson regressions

Cycle	AIC	Residual deviance	Dispersion test
1	68.703	14.878	0.6539
2	68.406	19.358	0.8660
3	63.519	15.299	0.6388
4	72.043	25.125	1.1444
5	68.362	15.942	0.9059
6	56.995	16.381	0.7001

Abbreviations: AIC, Akaike information criterion.

Please see the observed and predicted number of HAE attacks figure (Figure 14) for the placebo arm. This figure provides visual justification as to why the placebo regressions were not used to for quantifying attack rates over time in the cost-effectiveness model. This is because the predicted values did not match the observed values over the trial horizon.

Figure 14. Observed and Poisson predicted number of HAE attack rates for placebo

f) On page 118 (Section B.3.3.4) of the submission, it is stated that the ‘Previous cycle’ family of regression models was chosen over the ‘All previous cycles’ family of regression models to derive the Poisson regression analysis. Can you please provide a scenario in which the ‘All previous cycles’ family of regression models is used.

The ’All previous cycles’ family of regression models has been added to the cost-effectiveness model as a selectable option. However, as seen in Figure 15, the predictions from this set of regressions tend towards a lower number of HAE attacks over time. Although such results would be favourable for garadacimab’s cost-effectiveness, CSL Behring maintains the stance outlined in Section B.3.3.4, of the CS, that the ‘Previous cycle’ family of regressions is to be the preferred.

g) On page 122 in the last paragraph of Section B.3.3.5.2 it is stated that the Poisson regression can be used to predict the number of HAE attacks at any cycle. Can you please provide a plot of the number of HAE attacks over a 30-year time horizon.

Figure 15 is a plot of the number of the garadacimab HAE attack rate over a 25-cycle horizon. Both regression families tend towards constant HAE attack rates rapidly, so a shorter time horizon has been presented to ease the readability of the figure.

Figure 15. Poisson predicted number of HAE attack rates for garadacimab over an extended horizon

B10. Page 122 (Section B.3.3.5.1) of the submission states that a rate of [redacted] attacks per cycle is used for patients with the ≥2 attack per month at baseline. However, the model in cell I107 of the “Inputs – Transitions” sheet shows [redacted]. Can you confirm which is correct? Please provide the calculations used to derive value.

Page 122 (Section B.3.3.5.1) of the CS contains a typographical error. The attack rate per cycle used for patients with the ≥2 attack per month at baseline is [redacted]. The [redacted] value corresponds to the attack rate per cycle used for ITT patients at baseline. Please see the calculations below.

- [redacted] = 2.01*(1-[redacted])
- [redacted] = [redacted]*(1-[redacted])

B11. AE probabilities are drawn naively from trials rather than using the NMA.

a) Please justify this approach or amend the model to use the NMA

If AE probabilities were to be derived using the NMA then this would necessitate the use of a baseline technology with a relevant comparative metric to be applied across all treatments, in this case, the hazard ratio. This would mean that comparators would inherit the adverse event profile of the baseline technology, which may not be a suitable assumption to work with. For example, as an oral therapy, berotralstat would have adverse events relating to injection site reactions which would be inappropriate.

Hence, overall, the use of the NMA for modelling adverse events would be imposing stricter and not necessarily more relevant insights into decision making, especially given that adverse events have a low impact on cost-effectiveness outcomes as demonstrated by DSA outcomes

b) AE probabilities in Table 2 of Appendix R do not match what is presented in Table 2 of Appendix F (referred to in Section B.2.11.3 of the submission). For example, no upper respiratory tract infections are included for garadacimab. Please rectify.

Thank you for observing the difference between these two tables, however, they should not be the same, as these two sets of data were derived from different studies. Table 2 in Appendix R reported data from VANGUARD (CSL312_3001), and Table 2 in Appendix F reported data from the OLE CSL312_3002 study. To clarify, only AE probabilities from VANGUARD were incorporated in the CEM. In the submission B.3.4.4 section, “Appendix R reports the probability of various adverse events by technology as a naïve comparison utilising data straight from the original sources *which* was used in the base case, such as the relevant pivotal trials.”

Thank you for pointing out the exclusion of upper respiratory tract infections for garadacimab in Appendix R and in the model. We have now amended this and assigned the 10.26% probability of viral upper respiratory tract infection to upper respiratory tract infection which should have been the case instead. All cost-effectiveness results provided in response to the clarification questions now account for this minor change.

B12. Please justify assuming a gradual switch between lanadelumab Q2W and Q4W over a year when a clinical advisor to the EAG indicates that a faster switch is more common. Alternatively, please revise the model.

The Dorr et al. (2023) paper states that following a one-year period of observation, only 45% of patients progress to the Q4W schedule of lanadelumab. The SmPC states that lanadelumab patients should be initiated on Q2W. The key unknown is the pace of the schedule switching over the course of the year.

As explained in the answer to question B29e, assuming a linear or gradual progression over time is the simplest and least imposing approach compared to alternatives. Additionally, alternative extreme scenarios, such as having all patients switch at the start or end of the year, have little effect on the results due to the lifetime horizon of the decision problem.

Nevertheless, to investigate the effect of potential faster transition to Q4W on lanadelumab, a scenario has been investigated, where instead of 1 year gradually, it takes 3 months for all 45% of patients to progress to the Q4W schedule on lanadelumab. The results of that scenario are provided in Table 16, where it is

evident that the increase of the pace of that transition has neglegible impact on the results.

Table 16: 3 months to 45% of patients transitioning to Q4W Lanadelumab scenario results

Garadacimab versus Lanadelumab			
Inc. Costs	Inc. QALYs	INMB	ICER
[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

B13. Priority: can you please provide a model with the option of choosing the NMA from the original submission, or the results from the multi-level network meta regression (including new analysis excluding the Phase 2 trial requested)? Please also provide the updated tables in the economic section of the submission.

As discussed in the response to question A21 and agreed during the 10th December clarification meeting with the EAG, the new analysis excluding the Phase 2 trial from the ML-NMR has not been undertaken.

Furthermore, as outlined by email communication on 21st November 2024, CSL Behring does not plan to provide an updated cost-effectiveness model following the post-submission delivery of Appendix T – Multi-level network meta regression addendum for the following reasons:

The only endpoints of the ML-NMR that are compatible with the cost-effectiveness model are the count outcomes of:

- Time-normalised number of HAE attacks
- Time-normalised number of Moderate/Severe HAE attacks
- Time-normalised number of HAE attacks requiring on-demand treatment

Suspecting overdispersion as a potential issue, Section 3.1 of the addendum described the use of the negative binomial as the basis for the individual level likelihood as a mitigating solution. The negative binomial is generally better suited in

achieving convergence in the event of plausible data limitations. However, due to unavailability of individual patient level data, any potential overdispersion in the comparator trials also could not be addressed.

Overall, the Monte Carlo Markov Chain algorithm using the negative binomial distribution to predict relative efficacy had difficulties in determining the transition trajectories for the count endpoint models, and as such these endpoint outcomes are to be considered less reliable than NMA estimates. Hence, CSL Behring does not believe that the decision-making process would be aided any further by using input estimates at this level of reliability.

B14. Priority: the model states that discontinuation rates are taken from Buttergereit et al. (2024) for non-oral treatments assuming linear discontinuation rates over 40 years for non-oral treatments and from clinical opinion for oral treatments.

a) **Please provide the Buttergereit et al. (2024) reference.**

Buttgereit T, Vera Ayala C, Aykanat S, Weller K, Gutsche A, Maurer M, Magerl M. The real life experience goes on: update after 4 years on the first cohort treated with lanadelumab at our center. Front Immunol. 2024 May 10;15:1405317. doi: 10.3389/fimmu.2024.1405317. PMID: 38799421; PMCID: PMC11116806.

This has been included in the reference pack to be sent with the clarification question responses.

b) **Please justify the assumption of linear discontinuation referencing data from the literature (e.g. trials). Are the reasons for discontinuation equally likely to occur over a 40-year time horizon?**

Over a four-year period, the two discontinuations discussed in Buttergereit et al. (2024) were due to a major career change resulting in fewer HAE attack triggers, and self-reported intolerance to various foods which manifested as the occurrence of angioedema and wheals (p.2). The multi-centre review of LTP by Mendivil et al. (2023) used to inform discontinuation of C1-INHs, reports a variety of potential

reasons why patients may discontinue prophylaxis. What is understood is that the causes of discontinuation are varied.

In TA606 it was assumed that 8.8% of patients would discontinue both lanadelumab and Cinryze at cycle 7. This was based on data from the HELP-03 study and facilitated by a claim of there being no evidence of a difference between the discontinuation rates of lanadelumab and Cinryze. When questioned by the EAG (then ERG), the submitting company explained that the rationale behind this assumption was “due to a lack of long-term data to base an assumption upon”.

The existing approach builds on TA606 by providing a long-term source of discontinuation data, whilst maintaining, in the absence of a similar source for Cinryze/Berinert IV, the assumption of equal discontinuation rates for these non-oral products.

Apart from when continuation rules are embedded within a prescribing policy (as exists for berotralstat), there is no systematic way to determine who would discontinue which treatment when and why. Although one cannot prove that discontinuations are exactly equally likely to occur over a 40-year time horizon, linear discontinuation rates are the least imposing assumption that can reasonably quantify these broad possibilities.

c) Please provide reassurance that death is not being double-counted with discontinuation.

Death is handled by a separate calculation mechanic to discontinuations in the engines. Additionally, since there are no technology-related mortality risks, there is no possibility of death being double-counted.

d) Why was the discontinuation rate for berotralstat informed by clinical opinion rather than data and how was this information sourced?

In order to find a suitable source for the proportion of patients who discontinue berotralstat at month 3, CSL Behring undertook regular and rigorous desk research beyond the provided systematic literature reviews. In the absence of a published evidence clearly definining this input, we sought insight from three UK HAE expert

KOLs. Clinical expert opinion and clinical information from the APeX trial[28] were used together to arrive at what were at the time the most robust estimates of discontinuation rates for berotralstat, leveraging both clinical findings and real-world practice generalisability. This has been discussed in Section B.3.5.1.4 of the CS which states that “Based on this feedback and clinical information from the APeX trial, the proportion of patients that discontinue berotralstat treatment due to lack of efficacy and/or tolerability was estimated”.

The question posed to the clinical experts was “*In your clinical experience, what proportion of patients discontinue berotralstat due to failure to meet the continuation rule (i.e. treatment is stopped if the number of attacks per month does not reduce by at least 50% after 3 months)*?”. For full details of the responses to this question, please refer to the report included in the reference pack accompanying the company submission, titled 'UK Primary Research Report: Clinical Expert Opinion on the Treatment of Adults with Hereditary Angioedema'.

Whilst responding to these clarification questions, CSL Behring have become aware of data from an abstract by Elbashir et al. (2024).[32] This UK audit of real-world berotralstat use reports discontinuation trends over a 24-month period in 18 immunology centres with data collected from 164 patients. Of these patients, 33% (54 patients) discontinue berotralstat.The reasons for discontinuation include: treatment ineffectiveness, adverse effects, pregnancy, patient preference, enrolment in a clinical trial and loss of contact. The largest contributing factor to discontinuation is reported treatment ineffectiveness which resulted in 20% of patients discontinuing (32/164). The discontinuations reported are for the full 24 month time period and are not further disaggregated to see the discontinuation at month 3. In the absence of this data, we continue to assume that all berotralstat discontinuation is captured at month 3, per TA738.

To explore the impact of this change we present a further sensitivity analyses of only 33% of berotralstat failing to meet the continuation rule as seen in Table 17. By contrast, the base case value of [redacted] is conservative for garadacimab.

Table 17. Elbashir et al. (2024) audit estimates of berotralstat continuation rates pairwise cost-effectiveness outcomes[32]

Garadacimab versus berotralstat			
Inc. Cost	Inc. QALYs	INMB	ICER
[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

Cost and resource use

B15. Can you please provide the rationale for choosing the cost and healthcare resource use studies in section B.3.5?

Section B.3.5 of the CS states that “To support the cost-utility analysis, the following studies have been chosen from the SLR and listed below.” The SLR identified the relevant healthcare resource use studies which were used in the cost-effectiveness analysis.

The cost information for resource use and technology pricing applied in the cost-effectiveness analysis were obtained from BNF and NHS Schedule of Reference costs.

B16. Vial sharing was not included in the analysis. Can you provide economic results that include vials wastage referencing Hatswell et al.[33]?

Long term prophylaxis treatments are not weight based so whilst in principle wastage should be considered in economic modelling, in this case there is a limited scope for the possibility of drug wastage, and so vial sharing is considered of limited relevance.

For completeness, the prophylactic form of IV Berinert has been assumed to follow the same dosing as IV Cinryze which is not weight based. The adjunct indication of IV Berinert for the treatment of actue HAE attacks is weighted based as per the SmPC.

In this submission we have followed the same approach as was accepted in TA606. Specifically, utilising the assumption vial sharing or storage is not possible for IV treatments. We believe this assumption remains reasonable “given the rarity of the

disease and the fact that patients tend to self-administer at home, making it unlikely any vial sharing would occur in practice." as mentioned on p.168 in TA606[22].

Quality of life

B17. Can you please provide the rationale for choosing the health-related quality-of-life studies in B.3.4?

The rationale for HRQoL study selection in B.3.4 was that the SLR search strategies were set to identify all relevant health-related quality-of-life studies. The table below outlines some further reasoning for these studies being included.

Study	**Reason for inclusion**
Nordenfelt et al. (2014) – A retrospective study of HAE patients (n=103) from a Swedish registry captured by the Sweha-Reg census. The study captured patient EQ-5D-5L responses for both the attack-free state and the last HAE attack	The study population was from Sweden, but the U.K. crosswalk value set for EQ-5D-5L was used
Aygören-Pürsün et al. (2016) – A cross-sectional study of HAE patients (n=111) from Spain, Germany and Denmark captured by the HAE European Burden of Illness survey. The study captured EQ-5D-3L responses for all respondents for the period of acute attacks and between attacks.	HAE-BOIS-Europe survey responses were manually cross walked to the respective EQ-5D domain severity level
Itzler et al. (2024) – A panel study of HAE patients on long-term prophylaxis (n=159) from the United States, Australia, Canada, the United Kingdom, Germany and Japan conducted by MarketCast International. The study reported AE-QoL and Angioedema Control Tests results per attack-free durations of <1 month, 1-6< months and ≥6 months (n=67, 43 and 45, respectively).	This study examined the relationship between the duration of attack-free periods and health-related quality of life (HRQoL) in patients with hereditary angioedema (HAE). The study population was from the USA, Australia, Canada, UK, Germany, Japan and used AE-QoL for HRQoL
Lo et al. (2022) – A vignette study of HAE patients and carers and clinical expert (n=15, 5 and 1, respectively) from England. The study reports the vignette development and time-trade off (TTO) results for attack-free, attack and care provision for HAE attack states.	Used utility data from the UK, which is directly applicable to the NICE submission

In summary the studies in the above table contained relevant patient reported utility data from either UK patients or data that had been mapped from a patient reported outcome measure for HAE to the EQ-5D.

For the health-related quality-of-life studies eliciting general population utilities, we have used the recommended DSU sources such as Hernandez Alva et al. (2020)[34].

B18. Priority: Please conduct an analysis to demonstrate the impact of being attack free according to the number of months attack free based on trial data for the AE-QOL and EQ-5D. Please present analysis using both the index and domain scores.

Please may the EAG find in the reference pack Visit Day 182 responses for the index and domain scores for AE-QoL and ED-5D-5L questionnaires, stratified by 30-day HAE attack-free periods.

Although the trial was not powered to inform differences according to the number of months attack free using the AE-QoL and EQ-5D, the results are aligned to the claims that the quality of life of HAE patients improve the longer they are attack free.

For example, the AE-QoL Total Score for garadacimab patients improved i.e. attack-free 30 Days prior to Visit Day 182 (n=[redacted]) was [redacted] and HAE attack-free since Baseline (all 182 days) (n=[redacted]) was [redacted]. Similarly, for EQ-5D-5L, index scores for garadacimab patients improved i.e. attack-free 30 Days prior to Visit Day 182 was [redacted] and HAE attack-free since Baseline (all 182 days) [redacted].

Similar patterns of improvement in the domain scores are observed for the individual AE-QoL and EQ-5D domain scores.

Overall, the modelling assumptions and more broadly the model structure are substantiated by both the analysis conducted and the literature such as Itzler et al. (2024)[35].

B19. Please comment on whether use of the Nordenfelt equation, which includes the number of attacks in the previous cycle, double counts benefits with the way attack freedom utility improvements are applied

As pointed out by the EAG , we acknowledge that the Nordenfelt equation does include the number of attacks in the previous cycle. However, it is worth clarifying that this is not the number of attacks in the previous cycle for patients *in a particular Markov state*, but *for all alive patients in the cohort.* Therefore, patients in the model who enjoy attack freedom over a longer period (as reflected by being in a Markov

state with longer attack freedom) have the same baseline utility as patients who just experienced an attack in the previous cycle, thus not accounting for differential utility benefit accumulated by a patient based on their duration of attack freedom. The probability is applied in a separate step where the utility is extrapolated to represent that attack freedom, linearly progressing it to the general population utility.

Additionally, it is valuable to point out that Nordenfelt equations do not differentiate between patients who are attack free for 1 month, versus for 6 months, and it is that benefit which the adjustment to general population utility is aimed at measuring. For the above reasons, we do not consider that double-counting utility benefit is an issue in this instance.

B20. Priority: Please justify the assumptions in relation to caregiver impact, given that the study used as a reference was conducted only shortly after lanadelumab became available and before the availability of berotralstat. Expert advice to the EAG is that, since the availability of these treatments, the vast majority of attacks can be self-managed with no requirement for carer input.

Before answering this question, it should be noted that additional clarity regarding the request was provided to CSL Behring on the 12th December, as follows:

> *"The question is to do with caregiver disutility. The study referenced in our question (and which the company use for the utility for caregivers of 0.762) is: Lo SH, Lloyd A, Elkhalifa S, Sisic Z, van Nooten FE. Time Trade-Off Utilities for Hereditary Angioedema Health and Caregiver States. Pharmacoecon Open. 2022;6(2):231-239. The TTO exercises were conducted in June 2020 in this study."*

We thank the EAG for this additional clarity and provide our response below.

The question asked assumes that the presence of effective prophylaxis does two things

1) Reduces the number of HAE attacks of any kind that a person with HAE may experience

2) Reduces the number of HAE attacks that warrant caregiver support that a person with HAE may experience

Whilst 1) could be true, the cited value of 0.762 refers to the TTO utility ascribed to a carer whilst caring for somone having an attack and not to the experience of caring for a patient wholistically. Whilst the carer experience as a whole may now involve fewer attacks, there is no evidence to suggest that those attacks that do occur are any less burdensome to patient/carer.

CSL Behring are not aware of any published evidence to support the assumption that effective prophylaxis reduces the severity of breakthrough attacks. In fact, the final advice document for berotralstat, recieved in TA738, states clearly that the impact “[the] impact [of berotralstat] on attack severiy is not known”.

The inclusion of caregiver input for adults has already been confined to those most severe of attacks which are most likely to require caregiver support and least likely to be self-managed. Furthermore, in an effort to validate the claim made that most attacks are self-resolved without caregiver input, CSL Behring have sought informal insight from three expert HAE KOLs. In all instances, it was confirmed that the impact of HAE attacks still has a substantial burden on carers, particularly where those attacks occur in adolescents.

B21. Priority: Please justify the assumption that both parents of a child with HAE act as carers with the same impact on quality of life

Contrary to the statement made within the question, it is not assumed that both parents are acting as carers for a child with HAE, as in reality this orthodox family structure is far from universal. Therefore, the value of 1.46 caregivers had been taken from ONS data[36] as the number of carers taking care of a child with HAE. To examine the importance of this input, a scenario with just one parent being involved in caregiving has been provided in Table 18 below (with the updated model). This shows negligible difference from the base case results.

Table 18: One person as the caregiver scenario results

Garadacimab versus Lanadelumab			
Inc. Cost	Inc. QALYs	INMB	ICER

[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

B22. Priority: The general population utility was calculated using the Ara and Brazier (2010) equation. Given HAE may affect people of all ages, use of the distribution of the age at baseline may be more appropriate than using all patients starting at the same mean age. Please supply either the individual age and sex data from the trial or a distribution fitted to these within the model and reconfigure the model to use this data to predict general population utilities and mortality. Please refer to the Lee et al. paper[37] to conduct that analysis.

Further clarity regarding this question from the EAG was provided via email on the 12th December.

> *"On the clarification call it was noted that the company would probably not have time to do the calculation we suggested in B22. This was for two reasons: data confidentiality and the complexity of the calculation.*
>
> *With regard to the first point, age and sex data are normally listed in a typically CSR, so confidentiality should not, we hope, be an issue. With regard to the calculation itself, the paper that describes the method provides an "easy to use R script and VBA function" in its Supplementary material (The Impact of the Approach to Accounting for Age and Sex in Economic Models on Predicted Quality-Adjusted Life-Years | Applied Health Economics and Health Policy), so maybe that will open up the opportunity to do the work"*

Whilst we really appreciate the extra clarity, there appears to have been a miscommunication here in the notes taken from the call, which we would like to resolve. We understand that this could have been facilitated without use of IPD and do not recognise this as a reason to not fulfill the request. The second reason that is given is more closely aligned to the discussion of the 10th December clarification meeting. It was duly recognised that CSL Behring have been given a substantial 83 questions to return to the EAG and that avenues to reduce this burden should be explored where possible. The confirmation we had sought from the EAG was

whether this analysis could be deemed as lower priority, insofar as, they had confirmed during the call that this analysis comes from a paper that is recently published and not yet recommended as an approach in any DSU TSD. Whilst we are grateful for you pointing us towards the R and VBA code, we note that this is one among many requests that require data generation, quality control and formal interpretation of results. It has not been feasible to conduct this analysis.

Supportive rationale as to why we believe that this analysis is likely to be of low impact for decision making is provided below: It is indeed true that HAE may affect people of all ages, but from the perspective of cost-effectiveness results, it is the differential effect between treatments which is the important driver of the outcomes. Age and gender are not considered to be treatment effect modifiers, hence their effect is expected to have no material impact on the cost-effectivenes conclusions. Additionally, with no mortality differences between the treatment arms, changes in general population utility applied to both treatment arms will have negligible effect on the cost-effectiveness results. The impact of simillar changes in age has been investigated in the scenario analyses, showing no significant changes in the results, which leads us to conclude that the proposed adjustments will have no material effect on the cost-effectiveness conclusions.

Sensitivity analysis

B23. Priority: Please amend the PSA to include all modelled variables, to use data from the primary data sources to reflect uncertainty and to account for correlation between variables appropriately where this exists (e.g. NMA and utility regression).

a) **Please include the following variables in the PSA (they're currently missing from it):**

- **Proportion of patients remaining on primary prophylaxis**
- **Average attack rate reduction carried forward value**
- **HAE disutility of an attack on caregiver disutility**
- **Poisson regression coefficients**

To answer this question, we have addressed each of the named variables in turn.

Proportion of patients remaining on primary prophylaxis: Except for berotralstat, this has now been included in the PSA and assigned the beta distribution, since proportions need to be bounded by 0 and 1. CSL Behring believes that due to heterogeous estimates of proportion of patients meeting the continuation rule of berotralstat this uncertainty is better examined as a scenario analyses rather than being subjected to probabilisitc sensitivity.

Average attack rate reduction carried forward value: Due to the percentage reduction in time-normalised number of HAE attacks in monthly windows being valued close to 1, the beta condition of $\sigma^2<\mu(1-\mu)$ did not generally hold meaning the AARRCF values were not probabilistic in their entirety. To alleviate this issue, all percentage reduction parameters have been assigned the lognormal distribution, with a manual cap so that these values do not exceed a 100% reduction in time-normalised number of HAE attacks.

HAE disutility of an attack on caregiver disutility: the Lo et al. (2022) study reports results for n=15 and the standard deviation of the 'Caregiver state while caring for someone having an HAE attack' being 0.303. The beta distribution has been replaced with the lognormal distribution to better accommodate these uncertainty statistics and to avoid complications usually associated with using the beta distribution mentioned above. Please note, that caregiver disutility is calculated as the difference between a fixed estimate of general population and the health state value reported by Lo et al. (2022)

Poisson regression coefficients: Both the 'Previous' and 'All Previous' family of Poisson regressions have been fully implemented in the PSA. We apologise for any inconvenience caused.

b) Gamma has been applied for disutility of an attack. This may or may not be appropriate, but it's not working, because the mean is so small that the disutility drawn is 0 every time

We agree that the gamma distribution is appropriate for utilities, as noted in Drummond et al. (2015).[38] The mean disutility values for mild, moderate, and severe attacks are in *Table 23: Summary of utility values of cost-effectiveness analysis respectively of the submission*. As observed, none of these means are close to zero.

Unfortunately, we are unable to explain or resolve this discrepancy based on the available information, as it does not align with the details provided in the model. For further clarification, please refer to the parameters sheet cell Z227:Z284.

Given the nature of B23c, it appears that your inquiry may relate to the disutilities of adverse events (AEs). If that is the case, we kindly refer you to the corresponding response. Additionally, we have reviewed that no other disutilities/utilities consistently give a value of zero across the random draws.

c) **The PSA also isn't functioning for the disutilities of AEs. An IFERROR formula is holding those inputs constant in the PSA**

The mean disutilities of adverse events are so small that the disutility drawn is 0 every time, in turn causing the IFERROR to hold the inputs constant in the PSA. Hence, they have now been de facto excluded from the PSA

d) **Please amend the PSA so that data from the original data source / publications are used to reflect uncertainty rather than making assumptions. For your NMA, please use the CODA samples. Other areas we have noted making inappropriate assumptions are clinical inputs, utilities, AEs.**

The NMA parameter standard deviations (Parameters – R49:R60) now follow the CODA samples. Thank you for the suggestion. The updated uncertainty statistics are broadly similar to previously used values from the body of the NMA report, but the CODA samples have generally decreased the uncertainty statisitc values. Please note, the time-normalised number of HAE attacks CODA samples amount to 160,000 iterations, and time-normalised number of HAE attack requring on-demand amount to 240,000 iterations.

Additionally, we conducted a review of uncertainty staitistics reporting from the relevant sources for clinical inputs and utilities present in the original submission. This exercise confirms the lack of suitable uncertainty statistics to inform the cost-effectiveness model for the clinical, utility and adverse events inputs. Adverse events are no longer part of the PSA (see B23c). In the absence of suitable data for the

bounds of uncertainty for particular parameters, the original assumptions used in the model are the most appropriate.

e) **The PSA and deterministic results in the CS did not align well. Once corrections are made, please assess whether these are now consistent and, if not, please provide commentary on what is driving any difference**

A side-by-side comparison of the deterministic and probabilistic results show that they are aligned. For example, total QALYs are within a 0.01 difference or less. As such, during the 10th December clarification meeting, further detail was sought regarding the source of the inconsistency that provides the background to this question. The sources of inconsistency mentioned by the EAG were:

- QALY gain in the DSA vs the PSA

Relevant corrections were made to the DSA following the checks conducted as part of the response to question B23a. The DSA now benefits from a narrower (more precise) estimates of uncertainty.

B24. Can you please justify the use of the lognormal function for rates and rate ratios, but use the gamma distribution for the mean duration of attacks?

The lognormal distribution is routinely recommended for rates and rate ratios, for example, please see Drummond et al. (2015).[38]

The gamma distribution was chosen for mean duration of attacks as it is strictly positive. The normal distribution may be plausible; however, it is not strictly positive. In turn, there is no risk of duration of attacks being negative with the gamma distribution, which avoids any illogical sample draws.

Validation

B25. Priority: Please present the impact of alterations made to the model structure compared to prior appraisals one by one. Please present the changes in total costs, total QALYs, increment costs, incremental QALYs and ICER. For example:

- **Separating out laryngeal attacks**

- **Including tunnel states to capture time spent attack free**

The cost-effectiveness model is flexible with respect to many structural assumptions, allowing the examples posed by the questions to be explored in analyses as follows:

- Request 1: Laryngeal attacks have been incorporated as part of severe attacks since they were originally modelled separately.
- Request 2: Tunnel state length has been set to one, meaning the model is reduced to a 'alive – attack', 'alive – no attack', 'death' structure i.e., no tunnel states

Please see

Table **19** and Table 20 for the associated cost-effectiveness results. Request 1 has very small cost-effectiveness implications, whilst Request 2 adds to garadacimab's gain over the comparators.

Table 19. Alteration request 1 - combined laryngeal with severe attacks

Garadacimab versus Incremental (berotralstat)			
Inc. Cost	Inc. QALYs	INMB	ICER
[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

Table 20. Alteration request 2 - no tunnel states

Garadacimab versus Incremental (berotralstat)			
Inc. Cost	Inc. QALYs	INMB	ICER
[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality adjusted life year(s)

B26. Priority: Please provide a comparison of the predicted time to first attack in the model to the observed data for placebo

Please refer to results from question B1b, where the curves have been provided for this comparison.

B27. Please provide validation of the economic model versus the outcomes seen in previous economic models

Due to redactions of previous economic models, the outcomes from this model cannot be compared to them.

However, one way to compare the different HAE models in this case is by examining the ranking of variables of the deterministic sensitivity analysis (DSA). This outcome serves as a reliable measure of validation, since it reflects both the inputs and outputs of an economic analysis. As shown in Table 21, the same categories of parameters have a comparable ranking impact on variations in the cost-effectiveness outcomes across all three HAE submission models. Parameters related to HAE attack rates are generally the most impactful across all three HAE submissions, since all cost-effectiveness models are HAE attack based.

Table 21. Validation of economic model outcomes through comparison of DSA parameter ranks (descending) across NICE HAE submissions

Table 41 of TA738 (DSA results)	**Table 40 of CS (DSA against berotralstat)**	**Figure 24 of TA606 (DSA results)**	**Table 39 of CS (DSA against lanadelumab)**
Baseline attack rate (SoC)	Attack rate requiring on-demand treatment - ≥2 attacks per month	Attacks at baseline – Placebo	Rate ratio for the requirement of on-demand treatment - Garadacimab
SoC: proportion of attacks treated	Rate ratio for the requirement of on-demand treatment - Berotralstat	Intercept – Placebo	Rate ratio for the requirement of on-demand treatment - Lanadelumab
Berotralstat price per cycle	Number of on-demand administration per moderate attack	Intercept – Lanadelumab 300mg Q4W	Rate ratio - Garadacimab

Berotralstat compliance	Number of on-demand administration per mild attack	Attacks previous cycle - Placebo	Attack rate requiring on-demand treatment - ≥2 attacks per month
Berotralstat: reduction of attack rate from baseline, from month 12	Rate ratio for the requirement of on-demand treatment - Garadacimab	Attacks at baseline – Lanadelumab 300mg Q4W	Rate ratio for the requirement of on-demand treatment - Lanadelumab (Q4W)
SoC: Firazyr cost per attack	Rate ratio - Garadacimab	% attacks treated	Number of on-demand administration per moderate attack
SoC: proportion of attacks treated with Firazyr single dose	Nordenfelt et al. (2014) intercept	RR Cinryze IV	Rate ratio - Lanadelumab
SoC: Berinert cost per attack	Attack rate - ≥2 attacks per month	Attacks at baseline – Lanadelumab 300mg Q2W	Nordenfelt et al. (2014) intercept
SoC: proportion of patients requiring second dose of Firazyr	Number of on-demand administration per severe attack	Intercept - Lanadelumab 300mg Q2W	Proportion of males
SoC: proportion of attacks treated with Berinert single dose	Duration over the impact of an attack is felt (days)	Hospitalisation duration	Number of on-demand administration per mild attack

Abbreviations: DSA, deterministic sensitivity analysis; IV, intravenous; kg, kilograms; Q4W, every 4 weeks; Q2W, every 2 weeks; RR, rate ratio; SC, subcutaneous; SoC, standard of care.

B28. Please provide evidence of quality control checks undertaken

The EAG is kindly requested to review the provided evidence of the quality control checks undertaken in June 2024, corresponding to the first draft of the cost-effectiveness model (where errors are most likely to occur).

Following the clarification questions process, minor changes to the cost-effectiveness model were also conducted which the EAG may review within the new quality control checklist (December 2024).

Both quality control checklists include a broad set of modelling ‘black box’ tests that required us to conduct a full review of formuals and VBA code.

Potential model errors

B29. We have noted a number of potential model errors which we would request are explained or corrected.

a) **Cells BW9: BW1159 across all Engines seem to be wrong. To rectify, we would suggest switching formula 1 for formula 2**

    1. **=(SUM(AR10:AX10)*'Inputs - Resource use'!$F$19+SUM(AY10:BD10)*'Inputs - Resource use'!$G$19)*$N10**

    2. **=(AR10*'Inputs - Resource use'!$F$19+SUM(AS10:BD10)*'Inputs - Resource use'!$G$19)*$N10**

Cells BW9:BW1159 across all engines are accurate since they are substantiated by Section B.3.5.2.1 which states “Monitoring costs are divided into attack free (AF) i.e. stable patients (defined as living six months without an attack) and patients experiencing a HAE attack.”

Formula 1 correctly applies monitoring costs to the relevant patients, with AR – AX columns being all the patients from the ‘Attack health state’ to the ‘Without month attack 6 health state’. AY – BD columns capture all the patients from the ‘Without month attack 7 health state’ to ‘Without month attack 12 health state’.

Formula 2 proposes that resource use is systematically different for those patients that are in the ‘Attack health state’ and those that are not. Clinical opinion indicated that potential changes to routine monitoring would only occur for stable patients, which Section B.3.5.2.1 defines as those living six months without an attack.

b) The administration training cost of £54 is applied regardless of the number of patients in cycle 0. Please rectify by multiplying it to the health state occupancy at cycle 0.

Administration training costs have now been applied to the number of patients in cycle 0, i.e., the starting cohort.

c) The polarity for all costs and QALYs of the scenarios table is reversed across all comparators – please rectify in the Excel file.

This has been rectified in the Excel file.

d) Administration disutility is being applied per injection, whereas the original source reports a TTO conducted per health state, with the health state described being dependent on the types of injections received. These should therefore be applied per year. Please rectify.

The original Matza et al. (2013) TTO study was conducted with participants being asked to evaluate health states. However, the note under Table 2 of the study reads "This difference score represents the impact of adding each treatment modality to an otherwise identical health state. These values can be interpreted as the "disutility" or utility shift associated with each treatment modality".

Thereby, administration disutility being applied per injection is in line with the study conclusions as the authors also directly report in the abstract "The injection, 30-minute infusion, and 2-hour infusion had mean disutilities of −0.004, −0.02, and −0.04, respectively".

e) Please include the possibility to select at what cycle switching to secondary/tertiary treatments initiates. Assuming patients discontinue linearly until the stopping rule is not realistic.

There is now a possibility to select at what cycle switching to other treatments initiates for all engines. This has been applied in the cost-effectiveness model to reflect the continuation rule of berotralstat at cycle 4 (Month 3).

However, linear discontinuation is the most straightforward and least imposing assumption, relative to alternatives such as step functions and polynomials, which depend on more complex data insights. So, unless concrete continuation rules are available such as the one existing for berotralstat, we concur that linear discontinuation is the most appropriate tool and a realistic option to characterise treatment discontinuation patterns in patients over extended periods.

Section C: Textual clarification and additional points

C1. Please provide Figure 14 with numbers at risk included

The requested figure with numbers at risk included is presented below (Figure 16).

Figure 16. Kaplan-Meier curve for time to first HAE attack after Day 1 (VANGUARD/CSL312_3002, pooled population)

Abbreviation: CSL312, garadacimab; HAE, hereditary angioedema
Note: Shaded areas represent 95% CIs.
Note: Data are from completed study VANGUARD (CSL312_3001) and the [redacted] (IA4) data cut-off from study CSL312_3002, with a median (min, max) duration of exposure of [redacted] months.
Note: pooled population includes patients who were on active treatment in VANGUARD and rolled over into CSL312_3002.

C2. Please clarify whether the numbers in the >=2 attacks subgroup are CON or not (different marking on page 46 to page 47 of CS in Section B.2.2.2.1)

The patient numbers of the ≥2 and ≥8 attacks per month subgroup should be CONFIDENTIAL. To clarify, the section on page 46 of the CS (B.2.2.2.1) should read:

A post-hoc subgroup analysis of the VANGUARD ITT population was performed in patients experiencing ≥2 attacks per month at baseline, which is reflective of the recommended use of berotralstat in the UK (see Section B.1.3.2.2). This subgroup included [redacted] patients in the garadacimab arm and [redacted] patients in the placebo arm. Only [redacted] patients from the VANGUARD study had a baseline attack rate of ≥8 attacks per month (equating to ≥2 attacks per week), precluding the feasibility of a subgroup analysis in a subpopulation that would be reflective of the commissioning policy for C1-INHs and NICE recommendations for lanadelumab (see Section B.1.3.2.2).

C3. Please provide a reference for this statement in Section B.3.3.5 “Furthermore, a review of NICE TAs related to monoclonal antibodies (published between 2019-2024) demonstrated precedence that in the absence of the development of neutralising antibodies, the assumption of extended treatment effect has been widely accepted by committees”

The statement originated from our internal rapid review of literature comprising NICE TAs published between 2019-2024. The findings of this search are data on file, and we will be happy to provide more detailed results of the review if needed.

C4. Please provide references for the study type filters used in the search strategies (for clinical, HRQoL, CEA, and resource costs searches). If published filters were not used, did you do any testing of the effectiveness of the search strings used?

The population search line across all topics included the MeSH or Emtree subject heading for the disease. The free text terms were then developed based on the scope notes of the MeSH and Emtree subject headings, followed by searching Ovid and online to check for any other terms for the disease. Effectiveness testing was then carried out to ensure that papers known to be published about the population of interest were being picked up by the search string.

For the clinical review interventions and comparator terms we followed this same process of searching for subject headings, reviewing the scope notes, searching online and testing.

For the study design search lines, a modified (expanded to include terms for open-label extensions) RCT filter, based on the SIGN search filter for RCTs was incorporated.

For the CEA and resource cost reviews, the outcomes filter was based on the 'Economic (HE) studies' filter from NICE guideline CG181 (https://www.nice.org.uk/guidance/ng238/evidence/appendices-pdf-13254225662) following appropriate testing that papers known to be of relevance were being picked up.

Similarly, the HRQoL review was based on the 'Quality of life and model (QoL) search terms' filter from NICE guideline CG181, with "quality of life" free text term added following the effectiveness testing.

C5. The grey literature tables of the economic searches (Table 6 in Appendix H and Table 6 in Appendix I) both report references found from "SLR handsearch". However, what was hand-searched and how is not described in the methods. Could you please provide some details of the hand-searching performed.

SLRs were identified through the database searches and HTA website search. The hand-searching of the retrieved SLRs involved an assessment of the content of the document to identify which references in the reference list might be relevant against the SLR eligibility criteria tables. A deduplication check of those potential references against the existing database of retrieved results was conducted. After deduplication, abstracts were reviewed for inclusion and if eligible for inclusion, a full text review was conducted for those new references. To ensure thoroughness, while hand-searching an SLR for one topic (e.g., clinical effectiveness) if references appeared relevant to another topic (e.g. HRQoL), then the SLR was also hand-searched for the new topic. In the following table the column "Included references from the SLR hand-search" shows the source of each reference identified.

Table 22. SLRs hand-searched and results

Topic	SLRs hand-searched	Included references from the SLR hand-search
Clinical	SLRs from databases hand-searched (the 16 publications excluded for the reason "Study design – SLR" in Appendix D, Table 10):	(The seven publications of the last row of Appendix D, Table 5): From 239 Bork 2013

	• 11 Agboola F, Lubinga S, Carlson J, Lin GA, Dreitlein WB, Pearson SD. The Effectiveness and Value of Lanadelumab and C1 Esterase Inhibitors for Prophylaxis of Hereditary Angioedema Attacks. Journal of managed care & specialty pharmacy. 2019;25(2):143-8. • 53 Anonymous. CADTH Canadian Drug Expert Committee Recommendation: Lanadelumab (Takhzyro - Shire Pharma Canada ULC): Indication: For the routine prevention of attacks of hereditary angioedema (HAE) in adolescents and adults. 2019. • 55 Anonymous. Clinical Review Report Lanadelumab (Takhzyro): (Shire Pharma Canada ULC): Indication: For routine prevention of attacks of hereditary angioedema in adolescents and adults. 2020. • 56 Anonymous. Pharmacoeconomic Review Report: Lanadelumab (Takhzyro): (Shire Pharma Canada ULC): Indication: For the routine prevention of attacks of hereditary angioedema in adolescents and adults. 2020. • 62 Anonymous. Berotralstat (Orladeyo): CADTH Reimbursement Recommendation: Indication: For routine prevention of attacks of hereditary angioedema in adults and pediatric patients 12 years of age and older. 2023. • 63 Berotralstat (Orladeyo): CADTH Reimbursement Review: Therapeutic area: Hereditary angioedema (HAE) • 147 Beard N, Frese M, Smertina E, Mere P, Katelaris C, Mills K. Interventions for the long-term prevention of hereditary angioedema attacks. The Cochrane database of systematic reviews. 2022;11:CD013403. • 240 Bork K, Steffensen I, Nemet A, Morrison A, Van Den Hoef G, Barnes D. A systematic review of the efficacy and safety of a purified, pasteurised C1 inhibitor concentrate for the treatment of patients with type i or II hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2009;64(SUPPL. 90):281. • 239 Bork K, Steffensen I, Machnig T. Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: a systematic literature	• SLR1: Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. International archives of allergy and immunology. 2010 Jul 27;154(1):81-8. • SLR6: Czaller I, Visy B, Csuka D, Füst G, Tóth F, Farkas H. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2010 Sep 1;152(1):44-9. • SLR11: Lovsin, Z. Guzej, M. Vok, I. Kramar, J. Ravnikar B. C-1 esterase inhibitor prophylaxis for delivery in hereditary angioedema. Journal of Obstetrics and Gynaecology. 1999 Jan 1;19(5):537-8. • SLR12: Tallroth GA. Long-term prophylaxis of hereditary angioedema with a pasteurized C1 inhibitor concentrate. International archives of allergy and immunology. 2011 Mar 1;154(4):356-9. <u>From 147 Beard 2022 CD013403</u> • SLR5: Craig T, Zaragoza-Urdaz R, Anderson J, Li H, Paes K, Ren H, Juethner S. Response to lanadelumab is not affected by race and ethnicity: findings from phase 3 studies. Journal of Allergy and Clinical Immunology. 2021 Feb 1;147(2):AB21. <u>From 963 Maurer 2022</u> • SLR8: González-Quevedo T, Larco JI, Marcos C, Guilarte M, Baeza ML, Cimbollek S, López-Serrano MC, Piñero-Saavedra M, Rubio M, Caballero T. Management of Pregnancy and Delivery in Patients With Hereditary Angioedema Due to C1 Inhibitor Deficiency. Journal of investigational allergology & clinical immunology. 2016 Jan 1;26(3):161-7.

	review. Allergy and asthma proceedings. 2013;34(4):312-27. • 262 Burnham K, Reinert JP. Thromboembolic Risk of C1 Esterase Inhibitors: A Systematic Review on Current Evidence. Expert review of clinical pharmacology. 2020;13(7):779-86. • 352 Costantino G, Casazza G, Bossi I, Duca P, Cicardi M. Long-term prophylaxis in hereditary angio-oedema: a systematic review. BMJ open. 2012;2(4). • 365 Craig T, Pursun EA, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organization Journal. 2012;5(12):182-99. • 944 Maurer M, Abuzakouk M, Al-Ahmad M, Al-Herz W, Alrayes H, Al-Tamemi S, et al. Consensus on diagnosis and management of Hereditary Angioedema in the Middle East: A Delphi initiative. The World Allergy Organization journal. 2023;16(1):100729. • 963 Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygoren-Pursun E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy: European Journal of Allergy and Clinical Immunology. 2022;77(7):1961-90. • 1029 Nicola S, Rolla G, Brussino L. Breakthroughs in hereditary angioedema management: a systematic review of approved drugs and those under research. Drugs in context. 2019;8:212605. • 1182 Rosi-Schumacher M, Shah SJ, Craig T, Goyal N. Clinical manifestations of hereditary angioedema and a systematic review of treatment options. Laryngoscope investigative otolaryngology. 2021;6(3):394-403. <u>SLRs from grey literature included for hand-search:</u> • NICE. Berotralstat for preventing recurrent attacks of hereditary angioedema. Available from: https://www.nice.org.uk/guidance/ta738 • NICE. Lanadelumab for preventing recurrent attacks of hereditary	• SLR13: Hahn J, Nordmann-Kleiner M, Trainotti S, Hoffmann TK, Greve J. Successful long-term prophylactic treatment with subcutaneous C1 esterase inhibitor in a patient with hereditary angioedema. Journal of Pharmacy Practice. 2020 Dec;33(6):907-11.

	angioedema. Available from: https://www.nice.org.uk/guidance/ta606 • SMC. Conestat alfa (Ruconest®) is accepted for use within NHSScotland. Available from: https://scottishmedicines.org.uk/medicines-advice/conestat-alfa-ruconest-fullsubmission-74511/ • SMC. Icatibant acetate (Firazyr®) is accepted for use within NHS Scotland. Available from: https://scottishmedicines.org.uk/medicines-advice/icatibant-firazyr-resubmission-47608/ • SMC. Lanadelumab (Takhzyro®) is accepted for restricted use within NHSScotland. For routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. Available from: https://scottishmedicines.org.uk/medicines-advice/lanadelumab-takhzyro-full-smc2206/ • SMC. Berotralstat (Orladeyo®) is accepted for restricted use within NHSScotland. Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Available from: https://scottishmedicines.org.uk/medicines-advice/berotralstat-orladeyo-full-smc2405/ • AWMSG. C1-esterase inhibitor (Berinert®): C1-esterase inhibitor (Berinert) is recommended as an option for use within NHS Wales for the treatment of acute episodes of hereditary angioedema type I and II. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/c1-esterase-inhibitor-berinert/ • AWMSG. Icatibant acetate (Firazyr®): Icatibant acetate (Firazyr) is recommended as an option for use within NHS Wales for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1 esterase-inhibitor deficiency. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/icatibant-acetate-firazyr/	

	• AWMSG. C1 inhibitor (human) (Cinryze®) is recommended as an option for use within NHS Wales for the treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE); routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of HAE, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/c1-inhibitor-human-cinryze/ • CADTH. Berotralstat (Orladeyo) (Last Updated: Apr 27, 2023) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/berotralstat *(also identified in database searches – IDs)* • CADTH. Lanadelumab (Takhzyro) (Last Updated: Jan 9, 2020) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/lanadelumab *(also identified in database searches – IDs 62, 63)* • CADTH. Drug Therapies for the Long-Term Prophylaxis of Hereditary Angioedema Attacks (Last Updated: Dec 19, 2019) Hereditary angioedema (HAE) is associated with often unpredictable attacks. Available from: https://www.cadth.ca/drug-therapies-long-term-prophylaxis-hereditary-angioedema-attacks • CADTH. Icatibant (Firazyr) (Last Updated: Mar 4, 2014) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/icatibant	
Economic evaluations and costs and resource use	SLRs from databases hand-searched (the seven publications excluded for the reason "Study design (SLR)" in Appendix I, Table 10): • 101 Craig TJ, Cribbs K, Czado S. EE529 Characterizing Attack-Related Health Utility in Hereditary Angioedema.	(The 12 publications of the last row of Appendix I, Table 6): From 103 Craig 2023: • SLR19: Bowen K, Sahli B, Gleason P.P. Hereditary Angioedema (HAE) Real-World Prophylactic and On-demand Treatment Cost in a 15 Million

	Value in Health. 2023;26(6 Supplement):S156. • 102 Craig TJ, Cribbs K, Czado S. EE286 A Systematic Review of Socioeconomic Burden in Hereditary Angioedema. Value in Health. 2023;26(6 Supplement):S111. • 103 Craig TJ, Cribbs K, Czado S. EE405 A Systematic Review of Healthcare Resource Utilization and Direct Medical Costs in Hereditary Angioedema. Value in Health. 2023;26(6 Supplement):S133-S4. • 105 Crossley O, Bodke A, Knott C, Samuels E, Tang M. EE399 Exploring the Economic Consequences of Caring for Patients With Rare Diseases: A Systematic Literature Review. Value in Health. 2023;26(12 Supplement):S127. • 184 Kanchanasurakit S, Kositamongkol C, Kengkla K, Saokaew S, Phisalprapa P. HPR131 Benefit Package of Universal Coverage Scheme for Hereditary Angioedema (HAE) Caused by C1 Esterase Inhibitor Deficiency (C1-INH). Value in Health. 2022;25(12 Supplement):S255-S6. • 202 Liu S, Zhi Y. Hereditary angioedema: A Chinese perspective. Allergy: European Journal of Allergy and Clinical Immunology. 2018;73(Supplement 105):726-7. • 308 Tachdjian R, Lahue B, Cribbs KA, Fang DIK, Czado S, Goga L, et al. Current State of Health Economic Models in Hereditary Angioedema. Value in Health. 2023;26(12 Supplement):S68-S9. <u>SLRs from grey literature included for hand-search:</u> • NICE. Berotralstat for preventing recurrent attacks of hereditary angioedema. Available from: https://www.nice.org.uk/guidance/ta738 • NICE. Lanadelumab for preventing recurrent attacks of hereditary angioedema. Available from: https://www.nice.org.uk/guidance/ta606 • SMC. Conestat alfa (Ruconest®) is accepted for use within NHSScotland. Available from: https://scottishmedicines.org.uk/medicines-advice/conestat-alfa-ruconest-fullsubmission-74511/ • SMC. Icatibant acetate (Firazyr®) is accepted for use within NHS Scotland.	Commercially Insured Population: Comparison of C-1 Inhibitor (Haegarda®) versus Lanadelumab (Takhzyro®) Treated Members. 2020 • SLR23: Riedl MA, Banerji A, Manning ME, Burrell E, Joshi N, Patel D, Machnig T, Tai MH, Watson DJ. Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States. Orphanet journal of rare diseases. 2018 Dec;13:1-7. <u>From 101 Craig 2023:</u> • SLR24: Tyson C, Relan A, Adams P, Haynes A, Magar R. Cost-effectiveness model for on-demand treatment of hereditary angioedema (HAE) attacks. Journal of Drug Assessment. 2019 Sep 3;8(S1):22-. <u>From QoL 49 Banerji 2013:</u> • SLR17: Huang SW. Results of an on-line survey of patients with hereditary angioedema. InAllergy and asthma proceedings 2004 Mar 1 (Vol. 25, No. 2, pp. 127-132). OceanSide Publications; 1999. • SLR18: Javaud N, Karami A, Stirnemann J, Pilot F, Branellec A, Boubaya M, Chassaignon C, Adnet F, Fain O. Bradykinin-mediated angioedema: factors prompting ED visits. The American journal of emergency medicine. 2013 Jan 1;31(1):124-9. • SLR21: Kreuz W, Rusicke E, Martinez-Saguer I, Aygören-Pürsün E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. Transfusion. 2012 Jan;52(1):100-7. <u>From Clinical 239 Bork 2013:</u> • SLR14: Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for

	Available from: https://scottishmedicines.org.uk/medicines-advice/icatibant-firazyr-resubmission-47608/ • SMC. Lanadelumab (Takhzyro®) is accepted for restricted use within NHSScotland. For routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. Available from: https://scottishmedicines.org.uk/medicines-advice/lanadelumab-takhzyro-full-smc2206/ • SMC. Berotralstat (Orladeyo®) is accepted for restricted use within NHSScotland. Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Available from: https://scottishmedicines.org.uk/medicines-advice/berotralstat-orladeyo-full-smc2405/ • AWMSG. C1-esterase inhibitor (Berinert®): C1-esterase inhibitor (Berinert) is recommended as an option for use within NHS Wales for the treatment of acute episodes of hereditary angioedema type I and II. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/c1-esterase-inhibitor-berinert/ • AWMSG. Icatibant acetate (Firazyr®): Icatibant acetate (Firazyr) is recommended as an option for use within NHS Wales for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older, with C1 esterase-inhibitor deficiency. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/icatibant-acetate-firazyr/ • AWMSG. C1 inhibitor (human) (Cinryze®) is recommended as an option for use within NHS Wales for the treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE); routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent	hereditary angioedema and associated quality of life benefits. European Journal of Dermatology. 2009 Mar 1;19(2):147-51. • SLR20: Kreuz W, Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, Klingebiel T. Impact of the Frankfurt HAE therapy protocol on Health-Related Quality of Life (HRQoL) in 50 patients with Hereditary Angioedema (HAE). Journal of Allergy and Clinical Immunology. 2009 Feb 1;123(2):S116. From Clinical 963 Maurer 2022: • SLR25: Christiansen SC, Davis DK, Castaldo AJ, Zuraw BL. Pediatric hereditary angioedema: onset, diagnostic delay, and disease severity. Clinical pediatrics. 2016 Sep;55(10):935-42. • GL131: Nordenfelt P, Nilsson M, Lindfors A, Wahlgren CF, Björkander JF. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. Allergy Asthma Proc. 2017;38(6):447-455. • GL132: Prior N, Remor E, Pérez-Fernández E, Caminoa M, Gómez-Traseira C, Gayá F, Aabom A, Aberer W, Betschel S, Boccon-Gibod I, Bouillet L. Psychometric field study of hereditary angioedema quality of life questionnaire for adults: HAE-QoL. The Journal of Allergy and Clinical Immunology: In Practice. 2016 May 1;4(3):464-73. From 'NICE. Lanadelumab for preventing recurrent attacks of hereditary angioedema. Available from: https://www.nice.org.uk/guidance/ta606' • SLR38: Longhurst HJ, Dempster J, Lorenzo L, Buckland M, Grigoriadou S, Symons C, Bethune C, Fabien V, Bangs C, Garcez T. Real-world outcomes in hereditary

	attacks of HAE, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/c1-inhibitor-human-cinryze/ • CADTH. Berotralstat (Orladeyo) (Last Updated: Apr 27, 2023) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/berotralstat • CADTH. Lanadelumab (Takhzyro) (Last Updated: Jan 9, 2020) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/lanadelumab • CADTH. Drug Therapies for the Long-Term Prophylaxis of Hereditary Angioedema Attacks (Last Updated: Dec 19, 2019) Hereditary angioedema (HAE) is associated with often unpredictable attacks. Available from: https://www.cadth.ca/drug-therapies-long-term-prophylaxis-hereditary-angioedema-attacks • CADTH. Icatibant (Firazyr) (Last Updated: Mar 4, 2014) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/icatibant	angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. Allergy, Asthma & Clinical Immunology. 2018 Dec;14:1-1.
Quality of life	<u>SLRs from databases hand-searched (the 11 publications excluded for the reason "Study design – SLR" in Appendix H, Table 9):</u> • 49 Banerji A. The burden of illness in patients with hereditary angioedema. Annals of Allergy, Asthma & Immunology. 2013 Nov 1;111(5):329-36. • 66 Beard N, Frese M, Smertina E, Mere P, Katelaris C, Mills K. Interventions for the long-term prevention of hereditary angioedema attacks. Cochrane Database of Systematic Reviews. 2022(11). • 78 Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, Keith P, Lacuesta G, Waserman S, Yang B, Aygören-Pürsün E. The International/Canadian hereditary angioedema guideline. Allergy, Asthma & Clinical Immunology. 2019 Dec;15:1-29.	<u>(The five publications of the last row of Appendix H, Table 6):</u> <u>From QoL 553 Savarese 2021</u> • SLR34: Savarese L, Bova M, De Falco R, Guarino MD, De Luca Picione R, Petraroli A, Senter R, Traverso C, Zabotto M, Zanichelli A, Zito E. Emotional processes and stress in children affected by hereditary angioedema with C1-inhibitor deficiency: a multicenter, prospective study. Orphanet Journal of Rare Diseases. 2018 Dec;13:1-8. <u>From QoL 97 Bork 2021</u> • GL141: Caballero T, Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Wait S, Boysen HB. The humanistic burden of hereditary

	• 79 Betschel S, Badiou J, Binkley K, Hébert J, Kanani A, Keith P, Lacuesta G, Yang B, Aygören-Pürsün E, Bernstein J, Bork K. Canadian hereditary angioedema guideline. Allergy, Asthma & Clinical Immunology. 2014 Dec;10:1-8. • 97 Bork K, Anderson JT, Caballero T, Craig T, Johnston DT, Li HH, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2021;17(1):40. • 98 Bork K, Steffensen I, Machnig T. Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: a systematic literature review. InAllergy & Asthma Proceedings 2013 Jul 1 (Vol. 34, No. 4). • 145 Caballero T, Lleonart-Bellfill R, Pedrosa M, Ferrer L, Guilarte M. Expert Review and Consensus on the treat-to-Target Management of Hereditary Angioedema: from scientific evidence to clinical practice. Journal of Investigational Allergy and Clinical Immunology, 2023, vol. 33, issue. 4, p. 238-249. 2023 Jul 26. • 180 Craig TJ, Cribbs K, Czado S. EE529 Characterizing Attack-Related Health Utility in Hereditary Angioedema. Value in Health. 2023 Jun 1;26(6):S156. • 418 Magerl MA, Riedl MA, Newcomer SD, Supina D, Krishnarajah G. The Predictability of Attacks in Patients with Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2018 Feb 1;141(2):AB57. • 553 Savarese L, Mormile I, Bova M, Petraroli A, Maiello A, Spadaro G, Freda MF. Psychology and hereditary angioedema: a systematic review. InAllergy and Asthma Proceedings. 2021:42;1. • 578 Tachdjian R, Lahue B, Cribbs KA, Fang DI, Czado S, Goga L, Desai V, Rautenberg T, Schwander B. EE94 Current State of Health Economic Models in Hereditary Angioedema. Value in Health. 2023 Dec 1;26(12):S68-9.	angioedema: results from the Burden of Illness Study in Europe. Asthma Proc. 2014;35(1):47–53. <u>From QoL 66 Beard 2022</u> • HS1: Ohsawa I, Honda D, Suzuki Y, Fukuda T, Kohga K, Morita E, Moriwaki S, Ishikawa O, Sasaki Y, Tago M, Chittick G. Oral berotralstat for the prophylaxis of hereditary angioedema attacks in patients in Japan: a phase 3 randomized trial. Allergy. 2021 Jun;76(6):1789-99. • SLR26: Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, Busse PJ, Anderson J, Magerl M, Martinez-Saguer I, Davis-Lorton M. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. Jama. 2018 Nov 27;320(20):2108-21. <u>From economic 103 Craig 2023</u> • GL140: Javaud N, Bouillet L, Rabetrano H, Bitoun A, Launay D, Lapostolle F, Reuter PG, Martin L, Vicaut E, Fain O, Adnet F. Hereditary angioedema: Clinical presentation and socioeconomic cost of 200 French patients. The Journal of Allergy and Clinical Immunology: In Practice 2018;7(1):328–330.

	SLRs from grey literature included for hand-search: • NICE. Berotralstat for preventing recurrent attacks of hereditary angioedema. Available from: https://www.nice.org.uk/guidance/ta738 • NICE. Lanadelumab for preventing recurrent attacks of hereditary angioedema. Available from: https://www.nice.org.uk/guidance/ta606 • SMC. Conestat alfa (Ruconest®) is accepted for use within NHSScotland. Available from: https://scottishmedicines.org.uk/medicines-advice/conestat-alfa-ruconest-fullsubmission-74511/ • SMC. Icatibant acetate (Firazyr®) is accepted for use within NHS Scotland. Available from: https://scottishmedicines.org.uk/medicines-advice/icatibant-firazyr-resubmission-47608/ • SMC. Lanadelumab (Takhzyro®) is accepted for restricted use within NHSScotland. For routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. Available from: https://scottishmedicines.org.uk/medicines-advice/lanadelumab-takhzyro-full-smc2206/ • SMC. Berotralstat (Orladeyo®) is accepted for restricted use within NHSScotland. Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Available from: https://scottishmedicines.org.uk/medicines-advice/berotralstat-orladeyo-full-smc2405/ • AWMSG. C1-esterase inhibitor (Berinert®): C1-esterase inhibitor (Berinert) is recommended as an option for use within NHS Wales for the treatment of acute episodes of hereditary angioedema type I and II. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/c1-esterase-inhibitor-berinert/ • AWMSG. Icatibant acetate (Firazyr®): Icatibant acetate (Firazyr) is recommended as an option for use within NHS Wales for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults,	

	adolescents and children aged 2 years and older, with C1 esterase-inhibitor deficiency. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/icatibant-acetate-firazyr/ • AWMSG. C1 inhibitor (human) (Cinryze®) is recommended as an option for use within NHS Wales for the treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with hereditary angioedema (HAE); routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of HAE, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/c1-inhibitor-human-cinryze/ • CADTH. Berotralstat (Orladeyo) (Last Updated: Apr 27, 2023) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/berotralstat • CADTH. Lanadelumab (Takhzyro) (Last Updated: Jan 9, 2020) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/lanadelumab • CADTH. Drug Therapies for the Long-Term Prophylaxis of Hereditary Angioedema Attacks (Last Updated: Dec 19, 2019) Hereditary angioedema (HAE) is associated with often unpredictable attacks. Available from: https://www.cadth.ca/drug-therapies-long-term-prophylaxis-hereditary-angioedema-attacks • CADTH. Icatibant (Firazyr) (Last Updated: Mar 4, 2014) Project Line: Reimbursement Review Project Status: Complete. Available from: https://www.cadth.ca/icatibant	

C6. Table 26 (Section B.3.4.5.5) of the submission shows a disutility per cycle of 0.037 for garadacimab. Could you please correct this to 0.0037 as indicated in the model?

Table 23 is a replica of Table 26 of the CS with the updated values.

Table 23. Administration disutility variables by technology

Technology	Administration route	Disutility per admin	Disutility per cycle
Garadacimab	Autoinjector pen	0.004	0.0037*
Lanadelumab (Q2W)	Subcutaneous	0.004	0.008
Lanadelumab (Q4W)	Subcutaneous	0.004	0.004
Berotralstat	Oral	0	0
Berinert	Intravenous	0.02	0.16
Cinryze	Intravenous	0.02	0.16

Abbreviations: Q2W; Once every two weeks; Q4W, Once every four weeks. *Asterisks refers to the fact that garadacimab follows a once monthly (QM) pattern.

C7. Please provide Table 1 in Appendix R but repeated for >=3 attacks per month, >=4 attacks per month, >=5 attacks per month, >=6 attacks per month

Table 24 to Table 27 show monthly results split by attack frequency for the requested rates (all patient subgroups were followed for at least 27 months). Although the observed numbers are small, particularly in the higher attack rates, Garadacimab is consistently effective in reducing the number of attacks which is maintained throughout the time horizon.

For context, the percentage reduction in the time-normalized number of HAE attacks was calculated within a subject as: 100 * [1 – (time-normalized number of HAE attacks per month during the Treatment Period ÷ time-normalized number of HAE attacks per month during the Run-In Period)], with one month defined as 28 days.

Table 24. Percentage reduction in time-normalised HAE attacks with ≥3 HAE attacks per month

Month	Number observed	Mean (SD)	Median	1st Quartile; 3rd Quartile	Minimum-Maximum	95% CI (mean)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Source: ADEFFWIN; Produced: 09DEC2024 18:41; Program: t_hae_mnth_ge3.sas

Table 25. Percentage reduction in time-normalised HAE attacks with ≥4 HAE attacks per month

Month	Number observed	Mean (SD)	Median	1st Quartile; 3rd Quartile	Minimum-Maximum	95% CI (mean)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation.
Source: ADEFFWIN; Produced: 09DEC2024 18:41; Program: t_hae_mnth_ge3.sas

Table 26. Percentage reduction in time-normalised HAE attacks with ≥5 HAE attacks per month

Month	Number observed	Mean (SD)	Median	1st Quartile; 3rd Quartile	Minimum-Maximum	95% CI (mean)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation.
Source: ADEFFWIN; Produced: 09DEC2024 18:41; Program: t_hae_mnth_ge3.sas

Table 27. Percentage reduction in time-normalised HAE attacks with ≥6 HAE attacks per month

Month	Number observed	Mean (SD)	Median	1st Quartile; 3rd Quartile	Minimum-Maximum	95% CI (mean)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation.
Source: ADEFFWIN; Produced: 09DEC2024 18:41; Program: t_hae_mnth_ge3.sas

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NICE 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]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	**Angela Metcalfe**
2. Name of organisation	Hereditary Angioedema UK
3. Job title or position	Chief Executive Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Advocacy Group, Registered Charity 1152591 HAE UK, core funding by unrestricted grants from pharmaceutical companies as well as patients/members fundraising intiatives such as running marathons etc.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes, £35,000 core funding to the charity to support and help HAE Patients in 2023 from CSL Behring
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	**We are the patient advocacy and support group**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hereditary Angioedema, a well-documented genetic inability to produce C1 Esterase Inhibitor, a blood plasma protein and needs an urgent re-referral to Immunology. The result of this deficiency is that the patient develops gross, intensely painful swellings of subcutaneous tissues which can be anywhere in the body. At best these are uncomfortable and unsightly, at worst, such as a laryngeal swelling, they can be fatal. It is estimated that, before treatments were available, up to 35% of HAE sufferers died from laryngeal swellings. It could also be Acquired Angioedema which will give normal C1 readings. When attacks occur, patients describe the pain as 'feeling as though their skin is about to split' or that their 'abdomen swells so I feel as though I should explode'. Swollen hands make it impossible to hold a cup or glass or undress to use the toilet; swollen feet make it impossible to wear shoes, let alone walk. Swollen abdomens lead to intense and excruciating pain, making it impossible to wear 'normal' clothes, bend over or sit down. Liken this if you will to a women's abdomen swelling in a matter of hours to the similar size of that of being 8 months pregnant. Obviously with children, their ability to describe pain is somewhat hit and miss and can be anything from 'tummy ache' to 'I feel sick', or 'my throat hurts'. A child will quickly become agitated, in pain and possibly vomit, have diarrhoea, have swellings or a combination of all. It is absolutely imperative that a child receives treatment (usually IV administered in hospital) as quickly as possible. Attacks are absolutely debilitating in that onset is rapid over literally a few hours. Many patients have home therapy such as injecting themselves with their medication and whilst this starts to work immediately, swellings make take two to three days, and in extreme cases, up to a week to disappear. After attacks patients describe feeling utterly drained and suffering what they call flu-like symptoms of extreme fatigue.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Good but extremely restricted in ability to prescribe due to guidance not being regularly updated**
8. Is there an unmet need for patients with this condition?	Yes, guidance on prescribing needs to be regularly updated as more is learned about the condition. All patients should be able to live attack free if they are well managed and many cannot due to not being able to access appropriate medication.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Ability to transport – non refrigeration – and ease of use of applicator as a sub cut device**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All patients with Herediatary Angioedema could potentially benefit from this technology, possibly only restricted by but not solely due to co-morbidities

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	Travel – whether in this country or abroad – can be severely restricted for patients with Hereditary Angioedema. This technology enables travel as the product does not have to be refrigerated and is a small portable device. Anxiety is one of the biggest issues that triggers an attack so for a patient knowing that they are permanently able to travel/carry this product helps to reduce anxiety.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Easily transportable and doesn't require constant refrigeration • Reduces anxiety allowing patients to travel as technology is small and portable • It is a one stop medication to administer for any HAE attack • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE 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]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society for Immunology Clinical Immunology Professional Network (BSI-CIPN)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes – [redacted] (completing sections 1-5) A specialist in the treatment of people with this condition? Yes – [redacted] (Completing sections 6 -23)
5a. Brief description of the organisation (including who funds it).	The BSI-CIPN is a professional network hosted within the British Society for Immunology, a learned society. The BSI-CIPN is an integrated and impactful professional network for individuals working within clinical immunology. The network includes over 150 professionals working in the clinical immunology field, including clinical immunologists, allergists, healthcare scientists, pharmacists and specialist nurses. The BSI-CIPN is funded through the British Society for Immunology, which has a range of income streams which can be viewed in our 2022/23 annual report here. BSI-CIPN events and training also have some sponsorship from industry partners which is detailed below. The BSI-CIPN also has some ringfenced funding as a result of a merger with the UK Primary Immunodeficiency Network in 2022.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]

If so, please state the name of manufacturer, amount, and purpose of funding.

		BSI		BSI Trading	
CSL Behring (Berinert)		40,000	Grant for training programme for immunology nurses mapped to the BSI-CIPN nursing competency framework	29,000	Sponsorship of BSI-CIPN 2024 conference
CSL Behring (Berinert)				28,000	Sponsorship of BSI-CIPN 2023 conference
Maxwellia (tranexamic acid)	Nil				
Mylan (tranexamic acid)	Nil				
Pharming Group N.V (Ruconest)				35,500	Sponsorship of BSI-CIPN 2024 conference
Rivopharm (tranexamic acid)	Nil				
Sovereign Medical (tranexamic acid)	Nil				
Takeda (Cinryze, lanadelumab)		40,000	Grant for training programme for immunology nurses mapped to the BSI-CIPN nursing competency framework	49,495	Sponsorship of BSI-CIPN 2024 conference
Tillomed Laboratories (tranexamic acid)	Nil				
BioCryst Pharmaceuticals (berotralstat		22,000	Grant for training programme for immunology nurses mapped to the BSI-CIPN nursing competency framework		

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim of treatment is to prevent episodes of swelling in patients with hereditary angioedema. Episodes of swelling occur in hereditary angioedema, and can be life threatening if affecting the airway, or result in morbidity and functional disability if affecting limbs or abdomen.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in frequency and severity of attacks. There is no consensus agreement as to what the minimum amount of frequency and/or severity reduction would be considered clinically significant. The previous NICE assessment on berotralstat used a 50% reduction in attack frequency (without accounting for severity) to allow continuation of treatment. A lower reduction in attack frequency can also be clinically significant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is. The most effective licensed treatments (from trial results) are only accessible to patients with 2 or more attacks per week, on oral medication. Patients with 2 or more attacks per month but fewer than 2 attacks per week have access to a licensed therapy that has shown lower reduction in attack frequency in the trials. Patients with fewer than 2 attacks per month have no access to any effective licensed prophylactic treatments. They have to rely on treatments like androgens (not licensed for any indication in the UK, with potential long-term side effects) or tranexamic acid (ineffective in most patients). Children and young people often have fewer attacks than adults and have more limited treatment options available due to not meeting access criteria or being below the licensed age for treatment. Attacks are still significant, and can result in missing school and lower educational attainment.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment is divided into acute on-demand treatment and long-term prophylaxis (LTP). The acute on-demand treatments are icatibant and C1 inhibitor. The available licensed therapies for LTP are C1 inhibitor, lanadelumab and berotralstat. NHSE commissioning policy and NICE TA limit the use of C1 inhibitor and lanadelumab to patients with 2 or more attacks per week, while on oral medication. The dosing interval of lanadelumab can be increased if the condition is stable. NICE TA limit the use of berotralstat to patients with 2 or more attacks per month, with a discontinuation criteria if attack frequency does not improve by at least 50%. For patients with <2 attacks per month or <2 attacks per week who do not respond to berotralstat, the remaining options are androgens (not licensed for any indication in the UK, with potential long-term side effects) or tranexamic acid (ineffective in most patients).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHSE commissioning policies and NICE TAs determine access to licensed therapies for patients with these conditions. The most recent published international guidelines are the 2021 WAO/EAACI guidelines for HAE. These guidelines recommend aiming for complete control of disease and normalising patient lives. The guidelines do not use an attack frequency criteria for determining when LTP should be used, and so NHSE commissioning policy and NICE TA supersede the guidelines in relation to when LTP can be offered.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Access to treatments are determined by NHSE commissioning policies and NICE TAs, resulting in a defined population of patients currently eligible for these LTP medications. Care of patients with HAE rests with specialised immunology/allergy centres commissioned by NHSE.
9c. What impact would the technology have on the current pathway of care?	This will depend on what access criteria are for the technology. For patients with <2 attacks per week, there are no other approved modern licensed therapies of similar efficacy in England – so approval for usage in that group would give patients access to a potentially more effective therapeutic option.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used for LTP, for the same indication as the other agents available for LTP. Access criteria will determine which patients are eligible to be treated with this technology.
10a. How does healthcare resource use differ between the technology and current care?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, there are no other approved modern licensed therapies of similar efficacy in England. For this group of patients, if LTP results in better control of disease, this will reduce the need for rescue on-demand therapy, and any emergency department visits for treatment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist immunology clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, there are no other approved modern licensed therapies of similar efficacy in England. For this group of patients, the technology would be expected to provide more clinically meaningful benefits compared with current available options, particularly if current available options are ineffective or not tolerated.
11a. Do you expect the technology to increase length of life more than current care?	This is difficult to predict. Mortality from HAE is primarily due to airway swelling, that is untreated or not treated quickly enough. There are available on-demand therapy options for treatment of acute swelling. Although prevention of swelling may reduce the risk of airway swelling, mortality is expected to be relatively low anyway due to the availability of on-demand therapies.
11b. Do you expect the technology to increase health-related quality of life more than current care?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, the technology has a better reduction in attack frequency compared to current approved options available to that group of patients. For patients with <2 attacks per month, there are no available effective licensed therapies at all. For these groups of patients, the technology is likely to result in the most increase in HRQoL.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no obvious reason to expect the technology to be more or less effective in any subgroups of people with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This will depend on which mediation the patient is using for current care and the effectiveness of the current medication the patient is using. If the patient is using IV injections or fortnightly subcutaneous injections for LTP, or frequent injectable on-demand therapies, then the technology will be easier for patients compared to current care.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is likely to depend on access criteria, similar to the other medications that have NICE TAs or NHSE commissioning policies. Additional testing is unlikely to be needed.
15. Do you consider that the use of the technology will result in any	N/A

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, the technology has a better reduction in attack frequency compared to approved options available to that group of patients. For patients with <2 attacks per month, there are no approved effective licensed therapies at all in England. For these groups of patients, the technology is likely to result in the most increase in HRQoL as there is no approved highly effective LTP options available to that group of patients.
16a. Is the technology a 'step-change' in the management of the condition?	The technology is a highly effective LTP agent given as a subcutaneous injection every 4 weeks. There is already another LTP agent given subcutaneously, but more frequently. The technology would be considered as a slight improvement in terms of administration compared to current therapies in the current management, rather than a major step-change. It should be noted that the most effective licensed injectable LTP agents are restricted to patients with 2 or more attacks per week, so this treatment is a potential "step-change" in management for patients who do not meet the criteria for access to the most effective LTP agents or where available oral agents are ineffective or not tolerated. The technology utilises a different drug target compared to existing technologies. This is useful where current technologies are ineffective in an individual patient.
16b. Does the use of the technology address any	This will depend on the access criteria for the technology. For patients with <2 attacks per week, the technology has a better reduction in attack frequency compared to commissioned options available to that group of patients.

particular unmet need of the patient population?	For patients with <2 attacks per month, there are no commissioned effective licensed therapies at all. For those groups of patients, there is an unmet need, and more so, if oral therapies inadequately control the disease or are not tolerated.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment side effects from the trial data suggest that it was generally well-tolerated, so should not have significant impact on management of the condition.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Patients in the trials are likely
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Attack frequency, use of rescue medication, attack severity, quality of life, safety. These were measured in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We are not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	We are not aware of any.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA606 and TA738?	There is published data on the comparator treatments since the NICE TAs, showing the real-world experience with those therapies.
21. How do data on real-world experience compare with the trial data?	There is no real-world experience of this technology in the UK.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Children and young people often have fewer HAE attacks compared to adults, as attack frequency often increases with age. Access criteria based purely on attack frequency may disadvantage children and young people, who can be significantly affected despite having attack frequencies below current access criteria.
22b. Consider whether these issues are different from issues with current care and why.	The issues relating to children and young people also affect current care.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There remains an unmet need for long-term prophylaxis for people with HAE, as current access criteria limit the use of effective licensed therapies, resulting in a group of patients that would benefit from LTP, but are unable to access it. • Depending on what access criteria is approved for the technology, this could meet some of the unmet need. • Children and young people are a particular group of patients with more limited access to treatment options. • The new technology also utilises a different drug target to existing technology, and will have a role in existing patients who have not responded to current approved technologies.

Thank you for your time.

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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists and Frimley Park Hospitals
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 13000 members worldwide. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	no
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim of treatment is to prevent episodes of swelling in patients with hereditary angioedema. Episodes of swelling occur in hereditary angioedema, and can be life threatening if affecting the airway, or result in morbidity and functional disability if affecting limbs or abdomen.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in frequency and severity of attacks. There is no consensus agreement as to what the minimum amount of frequency and/or severity reduction would be considered clinically significant. The previous NICE assessment on berotralstat used a 50% reduction in attack frequency (without accounting for severity) to allow continuation of treatment. A lower reduction in attack frequency can also be clinically significant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is. The most effective licensed treatments (from trial results) are only accessible to patients with 2 or more attacks per week, on oral medication. Patients with 2 or more attacks per month but fewer than 2 attacks per week have access to a licensed therapy that has shown lower reduction in attack frequency in the trials. Patients with fewer than 2 attacks per month have no access to any effective licensed prophylactic treatments. They have to rely on treatments like androgens (not licensed for any indication in the UK, with potential long-term side effects) or tranexamic acid (ineffective in most patients). Children and young people often have fewer attacks than adults and have more limited treatment options available due to not meeting access criteria or being below the licensed age for treatment. Attacks are still significant, and can result in missing school and lower educational attainment.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment is divided into acute on-demand treatment and long-term prophylaxis (LTP). The acute on-demand treatments are icatibant and C1 inhibitor. The available licensed therapies for LTP are C1 inhibitor, lanadelumab and berotralstat. NHSE commissioning policy and NICE TA limit the use of C1 inhibitor and lanadelumab to patients with 2 or more attacks per week, while on oral medication. The dosing interval of lanadelumab can be increased if the condition is stable. NICE TA limit the use of berotralstat to patients with 2 or more attacks per month, with a discontinuation criteria if attack frequency does not improve by at least 50%. For patients with <2 attacks per month or <2 attacks per week who do not respond to berotralstat, the remaining options are androgens (not licensed for any indication in the UK, with potential long-term side effects) or tranexamic acid (ineffective in most patients).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHSE commissioning policies and NICE TAs determine access to licensed therapies for patients with these conditions. The most recent published international guidelines are the 2021 WAO/EAACI guidelines for HAE. These guidelines recommend aiming for complete control of disease and normalising patient lives. The guidelines do not use an attack frequency criteria for determining when LTP should be used, and so NHSE commissioning policy and NICE TA supersede the guidelines in relation to when LTP can be offered.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Access to treatments are determined by NHSE commissioning policies and NICE TAs, resulting in a defined population of patients currently eligible for these LTP medications. Care of patients with HAE rests with specialised immunology/allergy centres commissioned by NHSE.
9c. What impact would the technology have on the current pathway of care?	This will depend on what access criteria are for the technology. For patients with <2 attacks per week, there are no other approved modern licensed therapies of similar efficacy in England – so approval for usage in that group would give patients access to a potentially more effective therapeutic option.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used for LTP, for the same indication as the other agents available for LTP. Access criteria will determine which patients are eligible to be treated with this technology.
10a. How does healthcare resource use differ between the technology and current care?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, there are no other approved modern licensed therapies of similar efficacy in England. For this group of patients, if LTP results in better control of disease, this will reduce the need for rescue on-demand therapy, and any emergency department visits for treatment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist immunology clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is required to introduce the technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, there are no other approved modern licensed therapies of similar efficacy in England. For this group of patients, the technology would be expected to provide more clinically meaningful benefits compared with current available options, particularly if current available options are ineffective or not tolerated.
11a. Do you expect the technology to increase length of life more than current care?	This is difficult to predict. Mortality from HAE is primarily due to airway swelling, that is untreated or not treated quickly enough. There are available on-demand therapy options for treatment of acute swelling. Although prevention of swelling may reduce the risk of airway swelling, mortality is expected to be relatively low anyway due to the availability of on-demand therapies.
11b. Do you expect the technology to increase health-related quality of life more than current care?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, the technology has a better reduction in attack frequency compared to current approved options available to that group of patients. For patients with <2 attacks per month, there are no available effective licensed therapies at all. For these groups of patients, the technology is likely to result in the most increase in HRQoL.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no obvious reason to expect the technology to be more or less effective in any subgroups of people with HAE.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This will depend on which mediation the patient is using for current care and the effectiveness of the current medication the patient is using. If the patient is using IV injections or fortnightly subcutaneous injections for LTP, or frequent injectable on-demand therapies, then the technology will be easier for patients compared to current care.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is likely to depend on access criteria, similar to the other medications that have NICE TAs or NHSE commissioning policies. Additional testing is unlikely to be needed.
15. Do you consider that the use of the technology will result in any	N/A

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, the technology has a better reduction in attack frequency compared to approved options available to that group of patients. For patients with <2 attacks per month, there are no approved effective licensed therapies at all in England. For these groups of patients, the technology is likely to result in the most increase in HRQoL as there is no approved highly effective LTP options available to that group of patients.
16a. Is the technology a 'step-change' in the management of the condition?	The technology is a highly effective LTP agent given as a subcutaneous injection every 4 weeks. There is already another LTP agent given subcutaneously, but more frequently. The technology would be considered as a slight improvement in terms of administration compared to current therapies in the current management, rather than a major step-change. It should be noted that the most effective licensed injectable LTP agents are restricted to patients with 2 or more attacks per week, so this treatment is a potential "step-change" in management for patients who do not meet the criteria for access to the most effective LTP agents or where available oral agents are ineffective or not tolerated.

	The technology utilises a different drug target compared to existing technologies. This is useful where current technologies are ineffective in an individual patient.
16b. Does the use of the technology address any particular unmet need of the patient population?	This will depend on the access criteria for the technology. For patients with <2 attacks per week, the technology has a better reduction in attack frequency compared to commissioned options available to that group of patients. For patients with <2 attacks per month, there are no commissioned effective licensed therapies at all. For those groups of patients, there is an unmet need, and more so, if oral therapies inadequately control the disease or are not tolerated.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment side effects from the trial data suggest that it was generally well-tolerated, so should not have significant impact on management of the condition.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Patients in the trials are likely
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Attack frequency, use of rescue medication, attack severity, quality of life, safety. These were measured in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We are not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	We are not aware of any.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA606 and TA738?	There is published data on the comparator treatments since the NICE TAs, showing the real-world experience with those therapies.
21. How do data on real-world experience compare with the trial data?	There is no real-world experience of this technology in the UK.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Children and young people often have fewer HAE attacks compared to adults, as attack frequency often increases with age. Access criteria based purely on attack frequency may disadvantage children and young people, who can be significantly affected despite having attack frequencies below current access criteria.
22b. Consider whether these issues are different from issues with current care and why.	The issues relating to children and young people also affect current care.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There remains an unmet need for long-term prophylaxis for people with HAE, as current access criteria limit the use of effective licensed therapies, resulting in a group of patients that would benefit from LTP, but are unable to access it. • Depending on what access criteria is approved for the technology, this could meet some of the unmet need. • Children and young people are a particular group of patients with more limited access to treatment options. • The new technology also utilises a different drug target to existing technology, and will have a role in existing patients who have not responded to current approved technologies. •

Thank you for your time.

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NICE 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]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? Yes An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify): CRG Member
5a. Brief description of the organisation (including who funds it).	The Clinical Reference Group is an advisory body to NHS England and provides expert opinion on service commissioning, specification and governance. It is a part of NHSE and its resources funded by NHSE.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are World Allergy Organization and European Academy of Allergy and Clinical Immunology guidelines used for the treatment of hereditary angioedema (https://onlinelibrary.wiley.com/doi/10.1111/all.15214), these are supplemented by national commissioning guidance and a treatment algorithm (awaiting NHSE approval).
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a clear pathway of care for acute and prophylactic therapy. The minimum threshold has been set by currently available and commissioned medicines (2 treatable attacks per month). There is broad consensus amongst treating professionals that when patients consistently suffer attacks, they should be treated acutely and patients with regular attacks should receive prophylaxis aiming for zero attacks on therapy.
8. What impact would the technology have on the current pathway of care?	There is a high degree of heterogeneity in expressivity of HAE, assumed to be due to variation in expression of key regulators of the complex pathway that leads to bradykinin production. Whilst many patients are well served by current therapies, not all respond and the thresholds for treatment preclude a number of patients from receiving alternative agents. The new medicine proposed here would increase the number of patients able to potentially live without the fear of attacks of HAE that affect quality of life, access to work and employment and may also be fatal.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	The medicine would be available only to patients with HAE1/2 (a rare disease) who are under the care of a recognised and accredited Immunology centre. The use would therefore be highly restricted (appropriately).
10. Will the technology be used (or is it already used) in the same way	This medicine would be an addition to the current care, without major modification to care pathways.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The new medicine would provide an additional treatment option for patients who are either intolerant of, fail to respond to or ineligible for current long term prophylaxis options. Garadacimab would potentially reduce healthcare utilisation for such patients, because of the regular ED attendances and additional hospital visits to OPA for review for patients who experience regular attacks.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be restricted to secondary/tertiary care Clinical Immunology services only.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Patient training in self injection would be needed (or parents for >12 year old children) but would occur within units who already provide such training for other HAE medications (LTP and acute therapies).
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No additional testing over and above current diagnostic tests to establish the diagnosis of HAE would be required.
11. What is the outcome of any evaluations or audits of the use of the technology?	Phase 3 clinical trial provides evidence of efficacy.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Equality of access is age based (due to the proposed licence indications), but would not occur based on protected characteristics in the proposed scope.
12b. Consider whether these issues are different from issues with current care and why.	N/A

Thank you for your time.

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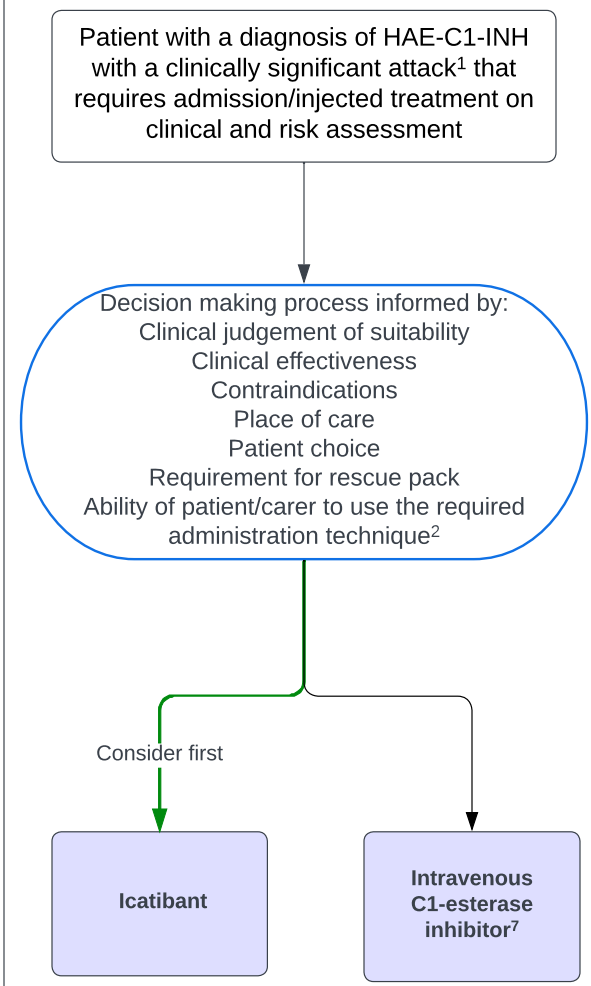
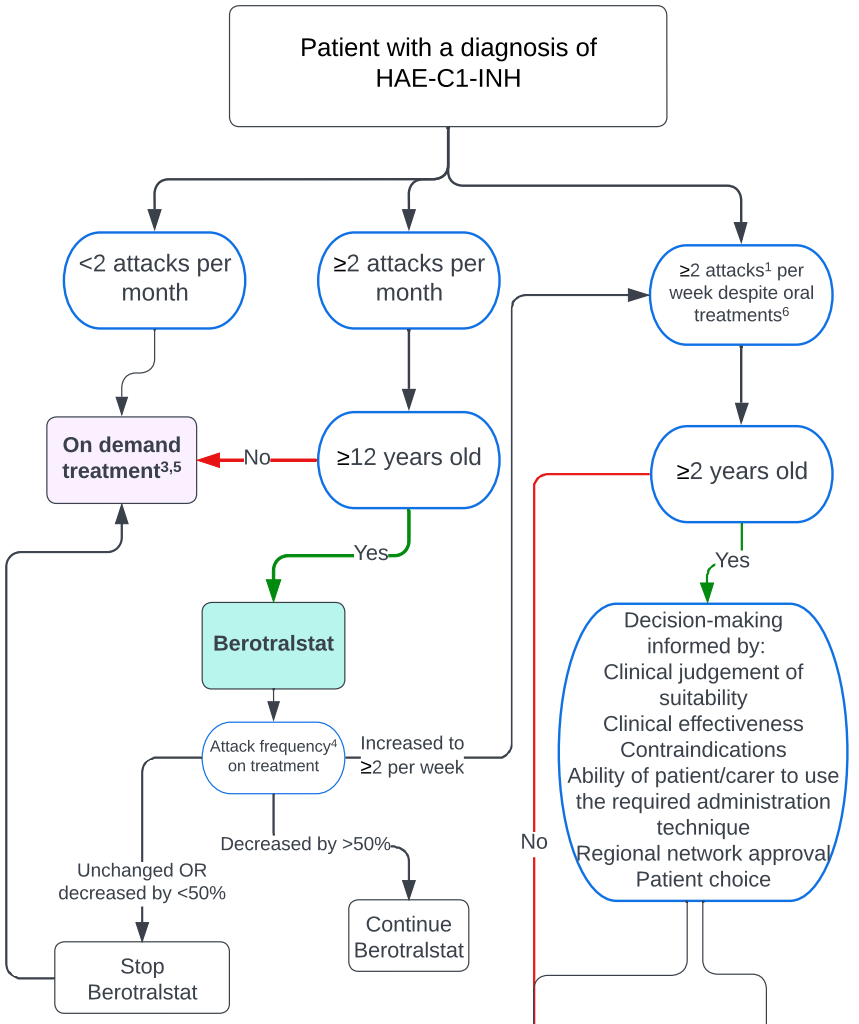
Commissioned treatment options for patients with Hereditary Angioedema secondary to C1 esterase inhibitor deficiency (HAE-C1-INH)

- This algorithm provides a framework to aid decision-making for angioedema specialists and patients
- The algorithm is informed by the regulatory status, NICE technology appraisal (TA) guidance and NHS England (NHSE) clinical commissioning policies. Relevant clinical commissioning policies/TAs should be consulted for further details
- All patients with a diagnosis of HAE-C1-INH should be under the care of specialised immunology centres as outlined in the service specification. HAE-C1-INH is classified as per the IUIS Phenotypical Classification
- For special circumstances including pregnancy and lactation, please refer to individual product Summary of Product Characteristics
- Where plasma products are used, patients need to be consented to potential risks associated with these products
- This algorithm is not intended to guide management during critical events including airway threatening or life threatening emergencies

On demand treatments



Long-term prophylactic treatments



Pre-procedure prophylaxis:
Patients with HAE-C1-INH are eligible for prophylaxis with C1-esterase inhibitor before undergoing dental, medical, obstetric or surgical procedures

Key

NHSE policy	NICE TA	In tariff/ NHSE policy

[1] The lanadelumab TA refers to clinically significant attacks as defined by i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. Frequency should be calculated over a period of at least 56 days.
[2] This includes securing venous access for C1-esterase inhibitors, and ability to reconstitute doses from multiple vials.
[3] Some adult patients are treated with androgens as oral prophylactic treatment. However, evidence is limited and accessing treatment is difficult so this is not recommended as first line for patients newly starting on prophylaxis. Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate; if established patients do cease treatment with androgen therapy then review the need for any prophylaxis. An individualised assessment to withdrawal of androgens and commencing new prophylaxis should be taken. If a historical attack frequency is documented, it can be used as the basis for selecting other prophylaxis treatment options.
[4] Berotralstat should be stopped if, after 3 months of treatment, attack frequency has not reduced by at least 50% compared to baseline.
[5] Some patients, including children under 12, are treated with tranexamic acid however evidence is limited.
[6] Patients who are unable to tolerate oral medications are also eligible for lanadelumab/intravenous C1-esterase inhibitor.
[7] In appropriate cases and where available, licensed recombinant products should be considered in preference to plasma-derived products in the treatment of acute attacks.

Commissioned treatment options for patients with Acquired Angioedema secondary to C1 esterase inhibitor deficiency (AAE-C1-INH)

- This algorithm provides a framework to aid decision-making for angioedema specialists and patients
- The algorithm is informed by the regulatory status, NICE technology appraisal (TA) guidance and NHS England (NHSE) clinical commissioning policies. Relevant clinical commissioning policies/TAs should be consulted for further details
- All patients with a diagnosis of AAE-C1-INH should be under the care of specialised immunology centres as outlined in the service specification, alongside relevant specialist team involved in management of underlying condition. AAE-C1-INH is classified as per the IUIS Phenotypical Classification
- For special circumstances including pregnancy and lactation, please refer to individual product Summary of Product Characteristics
- Where plasma products are used, patients need to be consented to potential risks associated with these products
- This algorithm is not intended to guide management during critical events including airway threatening or life threatening emergencies

On demand treatments

Patient with a diagnosis of AAE-C1-INH with a clinically significant attack[1] that requires admission/injected treatment on clinical and risk assessment

Decision making process informed by:
Clinical judgement of suitability
Clinical effectiveness
Contraindications
Place of care
Patient choice
Requirement for rescue pack
Ability of patient/carer to use the required administration technique[2]

Consider first

- **Icatibant**
- **Intravenous C1 -esterase inhibitor[4]**

Long-term prophylactic treatments

Patient with a diagnosis of AAE-C1-INH

MDT and relevant specialist input to diagnose and treat the underlying cause of AAE. If additional treatment required:

- <2 attacks per week → **Tranexamic acid[3]**
- ≥2 attacks per week → **Intravenous C1 -esterase inhibitor**

Pre-procedure prophylaxis:
Patients with AAE-C1-INH are eligible for prophylaxis with C1-esterase inhibitor before undergoing dental, medical, obstetric or surgical procedures

Key

- NHSE policy
- In tariff

[1] A clinically significant attacks as defined by i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. Frequency should be calculated over a period of at least 56 days.
[2] This includes securing venous access for C1-esterase inhibitors, and ability to reconstitute doses from multiple vials.
[3] Some adult patients are treated with androgens as oral prophylactic treatment. However, evidence is limited and accessing treatment is difficult so this is not recommended as first line for patients newly starting on prophylaxis. Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate; if established patients do cease treatment with androgen therapy then review the need for any prophylaxis. An individualised assessment to withdrawal of androgens and commencing new prophylaxis should be taken. If a historical attack frequency is documented, it can be used as the basis for selecting other prophylaxis treatment options.
[4] In appropriate cases and where available, licensed recombinant products should be considered in preference to plasma-derived products in the treatment of acute attacks.

Current Commissioning Position at Time of Publication

The algorithm describes the key criteria for accessing commissioned treatments.

Two of the commissioned treatments are via NICE TAs:

- Berotralstat for preventing recurrent attacks of hereditary angioedema (Technology appraisal guidance [TA738])(2021) https://www.nice.org.uk/guidance/ta738
- Lanadelumab for preventing recurrent attacks of hereditary angioedema (Technology appraisal guidance [TA606])(2019) https://www.nice.org.uk/guidance/ta606

NHS England has also published two clinical commissioning policies:

- Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult)(April 2013) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/09/b09-p-b.pdf
- Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II (2016) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/16045_FINAL.pdf

NICE 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]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Friday 2 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Comments received during engagement 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating hereditary angioedema and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Scott Hackett
2. Name of organisation	University Hospitals of Birmingham
3. Job title or position	Consultant paediatric immunologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hereditary angioedema? ☐ A specialist in the clinical evidence base for hereditary angioedema or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for hereditary angioedema?	To reduce attacks significantly, to zero if possible and to ensure no fatalities. A cure would be the ideal

(For example, to prevent attacks, reduce symptoms of an attack, to provide a cure)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount)	As the disease is unpredictable and due to this is very distressing for some. Reducing attacks to any level will reduce the anxiety. Certainly those with fairly frequent attacks have significantly more morbidity so at least a 50% reduction is Ok but near complete resolution is better. I do not agree with the WAO premise that patients should be 100% abolished in 100% of all patients as treatment are not without side effects including how they are administered
10. In your view, is there an unmet need for patients and healthcare professionals in hereditary angioedema?	The lack of a good oral treatment / prophylaxis (does not require a needle) particularly for children for both treatment and prophylaxis and especially in those with infrequent attacks. Most new medications are not licensed for children under 12 years of age, but even for those over 12 they need more than 2 attacks per month to qualify or 8 for Lanadelumab
11. How is hereditary angioedema currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care? • When would the technology be used when there are existing treatment options and what factors would influence the order of treatments (For example, first-line, second-line, before or after existing options)	The new pathway (hyperlinked below), that I help draft for England is good but I had to argue that tranexamic acid is still part of this for children as they have little else apart from needles etc. 'Gene therapy' if safe may be a game changer if safe, but I would not advise yet until we have more long-term safety data from adults.

Please note: NHS England recently published a new algorithm for commissioned treatment options for hereditary angioedema.	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This will depend upon the number of attacks patients need to have before they qualify for this therapy. If 2+/month then would be a good addition. If they need to have 8 or more then not sure needed as Lanadelumab works very well in this group in the majority
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	See above
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Children that cannot take tablets e.g with ASD. If they tolerate injections can be used as an infrequent prophylaxis otherwise dissolvable tablets or liquids are needed It is not clear from the Vanguard study the number of patientns under 17 years of age
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	For Garadacimab which is SC but monthly this will have the same issues for any needle therapy in children

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing as all will have HAE 1 or 2 The rule will likely still be age and the number of significant attacks which for children is too big a hurdle
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	This will only help if able to be given to all children and if they require fewer attacks before started
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology will be another medication that we can use if other prophylaxis do not work. None are 100% effective. Where we place this will depend upon the number of attacks needed to start. If fewer then may come before other established treatments 1/3 or more of patients only had a 50% or less reduction in symptoms if my calculations are correct
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are not a significant concern, equal and same side effects in placebo group as treatment group, but should not be ignored. All the medications come with side effects that we risk benefit all the time

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	They are transferrable to the UK Transferrable if number of attacks is stated
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No new data for those under 12 years olds. The Vanguard study does not quantify the number of children in this study. Cannot even find a median age
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA606 and TA738?	No
23. How do data on real-world experience compare with the trial data?	Very good data for Berotralstat and Lanadelumab post marketing shows that side effects and effectivity much the same as the studies. Need to for all new drugs going forward
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	Under 12 year old not included Patients who have had severe episodes but do not qualify for prophylaxis due to the number of episodes

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Uncertainty around the treatment pathway for people with HAE. This is about what treatments are available currently for HAE in the NHS. EAR section 2.3.4 and 2.4. Following the recent publication of the NHS England HAE Algorithm please confirm the expected	

positioning of garadacimab in the treatment pathway for HAE (see the final row of this table with 'Other information from the NICE technical team' for further information).	
Key issue 2: Methods and trials used in the indirect treatment comparison. This is about the methods used to compare garadacimab with other treatment options and which clinical trial evidence should be used for garadacimab. EAR section 3.4.1.4-5 and 3.4.2.3-4.	
Key Issue 3: Methods and data used to estimate treatment effectiveness. This is about the methods and data used to	

estimate how well garadacimab works in treating HAE compared with other treatment options, including when predictions about longer terms effects of treatment are being made. EAR section 4.2.6.3.	
Key Issue 4: The handling of berotralstat stopping rule. This is about the methods used to estimate what proportion of people taking berotralstat stop treatment due to it not working well enough. EAR section 4.2.6.5.	
Key Issue 5: The handling of lanadelumab switch between Q2W and Q4W. This is about the methods used to estimate what proportion of people move from taking	

lanadelumab once every 2 weeks to once every 4 weeks. EAR section 4.2.6.6. We would be particularly interested to hear whether this stopping rule is used in clinical practice and the proportion of patients who switch to the once every 4 weeks regimen.	
Key Issue 6: The calculation of patient utilities. This is about how HAE affects a person's health related quality of life (HRQoL), and the methods used to calculate this. EAR section 4.2.2.	
Are there any important issues that have been missed in EAR?	
Other information from the NICE technical team	Some important information relevant to the evaluation has been confirmed since the company submission and EAG report were received by NICE: 1. In January 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) approved garadacimab, as being indicated for 'routine prevention of recurrent attacks of hereditary

	angioedema (HAE) in adult and adolescent patients aged 12 years and older'. The following are links to the Summary of Product Characteristics for garadacimab as a pre-filled pen SmPC or pre-filled syringe SmPC. 2. In February 2025, NHS England published a new algorithm for commissioned treatment options for hereditary angioedema. This can be found online at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf.

NICE National Institute for Health and Care Excellence

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE 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]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Part 1: Treating hereditary angioedema and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Sorena Kiani
2. Name of organisation	Royal Free London NHS Foundation Trust
3. Job title or position	Consultant Immunologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hereditary angioedema? ☐ A specialist in the clinical evidence base for hereditary angioedema or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No link
8. What is the main aim of treatment for hereditary angioedema?	Normalisation of life by reduction of attacks to near zero. Improvement in quality of life: reduction in morbidity Prevention of death

(For example, to prevent attacks, reduce symptoms of an attack, to provide a cure)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount)	A clinically significant reduction in attack numbers is different for different patient depending on their baseline attacks. A reduction in attack numbers 50% of baseline is probably noticeable by patients and hence clinically significant but reduction in number of attacks to almost zero has been achieved by modern medications, setting the standard of care that patients expect.
10. In your view, is there an unmet need for patients and healthcare professionals in hereditary angioedema?	The need for prophylaxis should be based on a variety of parameters not just attack numbers. A single attack could be laryngeal and result in asphyxiation and hence should have a larger impact on decision making with regards to the need for prophylaxis. An abdominal attack could render the individual unable to work or perform daily activities of life for up to one week even if treated with on-demand medication promptly. Such attacks should be considered as having more weight when deciding on prophylaxis. Injectables carry a burden of method of treatment. Some patients continue to experience trauma when using injectables.
11. How is hereditary angioedema currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The pathway of care is well defined. Please refer to https://www.england.nhs.uk/wp-content/uploads/2025/02/hereditary-amd-acquired-angioedema-algorithms.pdf for the NHS algorithm. The WAO/EAACI guideline https://pubmed.ncbi.nlm.nih.gov/35006617/ but in the UK we are not able to follow this guideline when prescribing prophylaxis as in thy UK the number of attacks is considered the most important determining factor based on NHS England commissioning

• When would the technology be used when there are existing treatment options and what factors would influence the order of treatments (For example, first-line, second-line, before or after existing options) Please note: NHS England recently published a new algorithm for commissioned treatment options for hereditary angioedema.	If if covers patients with lower number of attacks (e.g. 1 or 2 attacks per months) who are clinically eligible for prophylaxis, it would provide a solution for a significant unmet need
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology would be used in the same way as the current care but will cover more patients or patients who have not responded to oral prophylaxis with Berotralstat. It should be used in specialist clinics under the supervision of immunologist who are currently managing HAE patients There is no need for additional investments in facilities or equipment. The training will be minimal and the same as the training needed for patients receiving other subcutaneous drugs for HAE. One of the acute treatments is given subcutaneously and all patient should be trained to administer that so they would have transferable skill.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I do not expect the technology to increase length of life more that the current care unless it is given to people who are not eligible for the current care or not responding to current available prophylaxis.. I do not expect the technology to increase health related quality of life more than current care unless it is given to patients who are currently either not receiving prophylaxis due to being considered not eligible or not responding to current available prophylaxis.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I assume “general population” refers to patients with HAE. It is possible that the technology is more effective in some patients but no evidence for this has been demonstrated. If patient who fail to respond to other prophylactic medications are given this new technology, we might see some in who this technology is more effective. There is also no date who may not respond to this technology.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is comparable to one of the available technologies, Lanadelumab which is also injectable via the subcutaneous route. Lanadelumab is given every 2 weeks then the frequency is reduced to once a month. Majority of patients remain stable on monthly injections but some continue to need fortnightly administrations. The assessed technology is a monthly subcut injection. There is no data on whether it would be safe or more efficacious if it was used every fortnight in non- or poor-responers
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The technology has not been made available for use. The experience with this technology is purely within a clinical trial which was not conducted in the UK. We do not have any experience with it in the UK and commissioning criteria has not been set for UK immunologists to use its rules for stopping or starting. The licensing does not require any addition monitoring or testing but as it is a new medicine and it has only been used in “64 (39 drug 25 placebo) adult and paediatric patients with HAE, who experienced at least who experienced at least 2 attacks during the run-in period, which lasted up to 2 months”, it needs to be monitored closely and any ADR reported but a responsible clinician would also do routine blood tests baseline and at 3 or 6 monthly intervals at least for the first year. This is not a requirement of market authorisation but I personally think, is good practice in a rare disease when a medication has been used in very few people.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	Yes. This is the case with all HAE prophylactic drugs. It is difficult to capture the psychological benefits in patients who start feeling confident about their lives after a year or two of not having any attacks.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The target is new but biologically in close relationship to previously proven targets for this disease. So far, it is achieving the levels of efficacy as the best in class but more experience is needed to see if it is superior to the other available treatments. This is also the case with safety; as safe as the best in class but only tested in a limited number of patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The drug safety was comparable to placebo. The side effect or adverse events, based on 39 patients receiving the drug, would not affect management and patients' QoL.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Patients who had a baseline of 2 attacks per months were recruited. This is the criteria for using oral prophylaxis with Berotralstat in the UK. Most important outcomes were reduction in number of attacks, attack free days, and a meaningful improvement in quality of life measurements which were all reported. I am not aware of any ADRs which were reported since the trial.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, I am not.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA606 and TA738?	No
23. How do data on real-world experience compare with the trial data?	I am not aware of any real-world experience data being collected or published.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	No as far as I can think. HAE is found equality in all races and equally distributed amongst men and women. The drugs could be used in any eligible patient regardless of their race or sex. No adverse impact on disabled people

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Uncertainty around the treatment pathway for people with HAE. This is about what treatments are available currently for HAE in the NHS. EAR section 2.3.4 and 2.4. Following the recent publication of the NHS England HAE Algorithm please confirm the expected	The available treatment and the pathways stated in sections 2.3.4 and 2.4 reflect the current HAE management in the UK

positioning of garadacimab in the treatment pathway for HAE (see the final row of this table with 'Other information from the NICE technical team' for further information).	
Key issue 2: Methods and trials used in the indirect treatment comparison. This is about the methods used to compare garadacimab with other treatment options and which clinical trial evidence should be used for garadacimab. EAR section 3.4.1.4-5 and 3.4.2.3-4.	No comments
Key Issue 3: Methods and data used to estimate treatment effectiveness. This is about the methods and data used to	No comments

estimate how well garadacimab works in treating HAE compared with other treatment options, including when predictions about longer terms effects of treatment are being made. EAR section 4.2.6.3.	
Key Issue 4: The handling of berotralstat stopping rule. This is about the methods used to estimate what proportion of people taking berotralstat stop treatment due to it not working well enough. EAR section 4.2.6.5.	Agree with EAG analysis
Key Issue 5: The handling of lanadelumab switch between Q2W and Q4W. This is about the methods used to estimate what proportion of people move from taking	I agree with the clinical advisor mentioned in section 4.2.6.6 that a faster switch to every 4 weeks is more common than 45% reported by the study mentioned in this section. In addition, a significant proportion of patients also switch to every 6 or 8 weeks in real-world.

lanadelumab once every 2 weeks to once every 4 weeks. EAR section 4.2.6.6. We would be particularly interested to hear whether this stopping rule is used in clinical practice and the proportion of patients who switch to the once every 4 weeks regimen.	
Key Issue 6: The calculation of patient utilities. This is about how HAE affects a person's health related quality of life (HRQoL), and the methods used to calculate this. EAR section 4.2.2.	I am not able to comment on the statistical models used as this is not my expertise. The quality-of-life effects of HAE are difficult to measure as apart from these effects during attacks, HAE affects QoL during the periods between attacks. This is because of either prolonged physical (eg. prolonged abdominal discomfort for a number of days after attacks) and emotional debility caused by a recent attack, in addition to the loss of confidence, anxiety and uncertainty about when the next attack may come and disrupt their lives. When effective prophylaxis is used, patients regain their confidence with time. The more effective the treatment, the more likely they can become confident and enjoy a better quality of life.
Are there any important issues that have been missed in EAR?	Please see above
Other information from the NICE technical team	Some important information relevant to the evaluation has been confirmed since the company submission and EAG report were received by NICE: 1. In January 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) approved garadacimab, as being indicated for 'routine prevention of recurrent attacks of hereditary

	angioedema (HAE) in adult and adolescent patients aged 12 years and older'. The following are links to the Summary of Product Characteristics for garadacimab as a pre-filled pen SmPC or pre-filled syringe SmPC. 2. In February 2025, NHS England published a new algorithm for commissioned treatment options for hereditary angioedema. This can be found online at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf.

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with hereditary angioedema. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on F**riday 2 May 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Comments received 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.

Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with hereditary angioedema

Table 1 About you, hereditary angioedema, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with hereditary angioedema? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with hereditary angioedema? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Hereditary Angioedema UK (HAE UK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / **was a contributor** to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience**: As a trustee of**

	HAEUK I have met many patients from across the UK at patient meetings and shared their experiences of this disease. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with hereditary angioedema? **If you are a carer (for someone with hereditary angioedema) please share your experience of caring for them**	I inherited Type 1 HAE from my mother and was therefore familiar with the condition. First presentation for me was aged 14 ([redacted]) with abdominal pain due to intestinal swelling. In those days there were no specific treatments. For those unfortunate enough to suffer with laryngeal swelling in those times the outcome was often fatal. Since those early days I have had somewhere between four to eight episodes of swelling per annum. Stanozolol was introduced as prophylaxis, this had little effect and the drug was discontinued. After a frightening episode of upper airways obstruction due to laryngeal oedema in which I ended up in Intensive Care I was commenced on Danazol as prophylaxis, the effectiveness of which has been uncertain, and I was also commenced on the anti-bradykinin agent Icatabant which has largely been effective in aborting an attack. In the event of Icatabant failure I have C1 esterase inhibitor which I self-administer by iv injection. This is always effective. I consider myself lucky in that the episodes are relatively infrequent compared to many with the condition. Before the days of effective treatment, I learned to just to put up with attacks in the knowledge that things would settle after about forty eight hours Stress is a well-recognised trigger and attacks often occurred when travelling abroad and as a student at exam times.

	Things have improved enormously since the introduction of drugs to abort the attacks. Despite this the future for the treatment of HAE across the board lies in the development and wider use of effective prophylaxis particularly for those with frequent attacks whose quality of life can be adversely affected.
7a. What do you think of the current treatments and care available for hereditary angioedema on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a** - Treatment has progressed in recent years, particularly in terms of drugs to abort attacks, namely the anti-bradykinin agent Icatabant and the use of C1 Inhibitor. The standard prophylaxis treatments, androgens and antifibrinolytics, are of doubtful effectiveness. However, there is progress in this area with kallikrein inhibitors and the latest development of the factor X11 inhibitor and these agents are without doubt more effective than their predecessors. These drugs need to reach a certain threshold of attack frequency before they are prescribed. I hope that with time this will not apply. Most of these drugs are administered by subcutaneous injection or iv injection. Some patients struggle to self-administer and this can be a problem occasionally requiring an expensive trip to A&E. Some patients live a considerable distance from a hospital that offers care for HAE patients. **7b** - Despite advances in treatment, the burden of HAE remains heavy for patients. Attacks can be very disabling; the frequency can be very variable from patient to patient. The disease is rare (1:50000) and therefore is not understood by employers, teachers' friends and family. Because HAE is so rare some GPs and A&E staff are unfamiliar with this disease leading to delays in treatment or diagnosis. All these things have a significant effect on quality of life which is ongoing.
8. If there are disadvantages for patients of current NHS treatments for hereditary angioedema (for	Current commonly used prophylaxis is of doubtful help. Androgens may have significant side effects. C1 inhibitor is extracted from human plasma and although

example, how they are given or taken, side effects of treatment, and any others) please describe these	the risk of transmission of viral disease should be extremely low there is a very slight possibility. Thrombosis is also a rare side effect. In some extreme case C1 is used as prophylaxis. As described in 7a, most treatments are by either subcutaneous or iv injection. Not all patients are able to self-administer.
9a. If there are advantages of garadacimab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does garadacimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a -** The development of newer prophylactic drugs is very encouraging for HAE patients. I hope that wider use will become available. As far as I am aware the latest, garadacimab, has had encouraging results with few serious side effects, importantly no effect on blood clotting. Also, it is a monthly injection and there are no storage temperature restrictions. Whether it is head and shoulders better than the alternatives remain to be seen. Very much the point is that each patient will react differently to any drug and therefore the greater the number of alternatives can only be a good thing. Any measure that reduces the number of attacks will improve all areas of quality of life. **9b** - Increase in the number of prophylaxis alternatives. This will be good for patients. **9c** – As 8, 9a and 9b above.
10. If there are disadvantages of garadacimab over current treatments on the NHS please describe these. For example, are there any risks with garadacimab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As a new drug garadacimab any disadvantages will become apparent with wider use. Improved prophylaxis is so important in HAE it is my view that currently the advantages outweigh any disadvantages.

11. Are there any groups of patients who might benefit more from garadacimab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	None.
12. Are there any potential equality issues that should be taken into account when considering hereditary angioedema and garadacimab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	None.
13. Are there any other issues that you would like the committee to consider?	Can I ask you to be aware that after a lifetime with HAE and with a medical background I am well adjusted to it all. The views that I have expressed are primarily based on my experience as a trustee for HAEUK and with ten years in this role I have attended many patient meetings which has enabled me to understand the many facets of HAE and how it affects lives of those who suffer from this rare disease. Thank you for considering the points that I have made.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Effective prophylaxis is the most important aspect in the development of HAE treatment.
- As such I fully support the introduction of garadacimab as a means to achieve this.
- Current state of knowledge suggests that it is a safe and easy to use drug.

Thank you for your time.

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

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Author contributions

Alex Allen	Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report
Valdemar Dias Do Espirito Santo	Critical appraisal of the company's economic evidence and analysis, conducted additional economic analyses, and drafted sections of the report
Jemma Perks	Critical appraisal of the company's network meta-analysis and drafted sections of the report
Alan Lovell	Project manager. Critical appraisal of the company's literature search strategies, drafted sections of the report, and editorial input.
Maxwell S Barnish	Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report
Frank Grimsey Jones	Conducted additional economic analyses and quality assurance of the economic modelling
Dawn Lee	Project director. Conducted additional economic analyses and drafted sections of the report

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Abbreviations

Acronym	Definition
AARRCF	Average attack rate reduction carried forward
A&E	Accident and Emergency
AE	Adverse event
AE-QoL	Angioedema Quality of Life Questionnaire
AgD	Aggregated patient level data
ATS	All treated patients
BMI	Body mass index
C1-INH	C1-inhibitor
CASP	Critical Appraisal Skills Programme
CEA	Cost effectiveness analysis
CFB	Change from baseline
CI	Confidence interval
CLS312	Garadacimab
COVID	Coronavirus disease
cPAS	Confidential Comparator Patient Access Scheme
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DNA	Deoxyribonucleic acid
DARE	Database of Abstracts of Reviews of Effects
EAG	External Assessment Group
EMA	European Medicines Agency
EOS	End-of-study
EoT	End of treatment
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ESS	Explained sum of squares
FDA	Food and Drug Administration
FE	Fixed effect
GARA	Garadacimab
H01, H02	First and second hierarchical test, respectively
HAE	Hereditary angioedema

Acronym	Definition
HAEG	Haegarda
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly specialised technologies
HSUV	Health-state utility value
HTA	Health Technology Assessment
IADL	Instrumental activities of daily living
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
INHB	Incremental net health benefit
IPD	Individual patient data
ISPOR	Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LOCF	Last observation carried forward
LTP	Long-term prophylaxis;
LYG	Life years gained
MCID	Minimal clinically important different
MD	Mean difference
ML-NMR	Multi-level network meta regression
N	Number
N/A	Not applicable
NE	Not evaluable
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
NR	Not reported
OLE	Open label extension
ONS	Office for National Statistics
ORL	Orladeyo

Acronym	Definition
PAS	Patient access scheme
PBO	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2W	Administered every two weeks
Q4W	Administered every four weeks
QA	Quality assessment
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
ROB	Risk of bias
RR	Rate ratio
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-6D	Short-form 6-dimension
SGART	Subject's Global Assessment of Response to Therapy
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TA	Technology Appraisal
TAK	Takhzyro
TEAE	Treatment-emergent adverse events
UK	United Kingdom
UKHLS	UK Household Longitudinal Study
US	United States
VAS	Visual analogue scale

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, and 1.5.

Broadly speaking the key clinical issues related to uncertainties regarding the current treatment pathway – and the position of garadacimab in it – and the methods used by the company in their indirect treatment comparison. In terms of cost effectiveness issues, the EAG noted concerns with how the company estimated long-term treatment effectiveness; the assumptions made for effectiveness following the berotralstat stopping rule; assumptions regarding effectiveness of different dosages of lanadelumab, and the choice of utility data for patients.

Table 1: Summary of key issues

ID	Summary of issue	Report sections
#1	Uncertainty around the treatment pathway for people with HAE	2.3.4 and 2.4
#2	Methods and trials used in the indirect treatment comparison	3.4.1.4, 3.4.1.5, 3.4.2.3, 3.4.2.4, and Appendix B
#3	Methods and data used to estimate treatment effectiveness	4.2.6.3
#4	The handling of berotralstat stopping rule	4.2.6.5
#5	The handling of lanadelumab switch between Q2W and Q4W	4.2.6.6
#6	The calculation of patient utilities	4.2.2

Abbreviations: HAE, hereditary angioedema; Q2W, administered every two weeks; Q4W, administered every four weeks

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Population	≥2 per month	≥2 per month ≥2 per week	4.2.4
Comparator	All comparators presented regardless of whether available for the ≥2 per month population or not	≥2 per month - berotralstat ≥2 per week – lanadelumab and IV C1-INHs	4.2.3
Methods and data used to estimate treatment effectiveness	First 24 cycles – constant attack rates 25th cycle onwards – AARRCF for intervention and LOCF for comparators Relative effectiveness – rate ratios from the fixed effects NMA including Phase 2 trials	First 24 cycles – trial attack rates 25th cycle onwards – AARRCF from cycles 12-24 assuming same proportional change for comparators Relative effectiveness – rate ratios from the fixed effects NMA excluding Phase 2 trials	4.2.6.4 and 4.2.6.5
Berotralstat effectiveness	Berotralstat effectiveness after the 3rd month is equal to that of the first 3 months, even though patients who did not have an attack rate reduction ≥50% would discontinue treatment	Berotralstat effectiveness after the 3rd month equal to that of lanadelumab Q2W	4.2.6.5
Lanadelumab switch between Q2W and Q4W	Stable patients switching to Q4W dosage have the same effectiveness as patients initiating treatment on Q4W	Stable patients switching to Q4W dosage have the same effectiveness as Q2W	4.2.6.7
Attack severity and duration	Attack severity varies between active treatments based on naïve data from trials and observational studies The impact of attacks on HRQoL lasts beyond the duration of attack (7 days)	Attack severity is the same for active treatments The impact of attacks on HRQoL lasts for the duration of attack (to be consistent with source of attack utilities; [redacted] days)	4.2.6.8 and 4.2.9.6

	Company's preferred assumption	EAG preferred assumption	Report Sections
Attack-free patient quality of life	Nordenfelt equation with intercept based on mean EQ-5D today and linear return to general population utilities over 6 months	Nordenfelt equation with intercept of 1 and no additional return to general population utilities	4.2.2
Carers utilities	1.46 carers per household Disutility of 0.145	1 carer per household Disutility of 0.018	4.2.9.9
Administration disutilities	Scenario analysis only. Assumes additive impact of each administration on HRQoL	Included. Impact of each additional administration on HRQoL decreases	4.2.9.10
Resource use	Monitoring costs lower after 6 months of attack freedom was noted in the report but not implemented in the model One training visit for non-oral treatments	Monitoring costs lower after 6 months of attack freedom implemented in model Two training visits for non-oral treatments No involvement from family physician or home nurse in treating attacks, reduced A&E visits and inpatient hospitalisation, increased ENT consultations	4.2.10

Abbreviations: AARRCF, average attack rate reduction carried forward; C1-INHs, C1-inhibitor; HAE, hereditary angioedema; NMA, network meta-analysis; Q2W, administered every two weeks; Q4W, administered every two weeks

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology was modelled to affect QALYs by:

- Reducing the number of HAE attacks which have a direct impact on patient quality of life (key model driver) and carer quality of life, which is assumed to be the case for carers of children and patients experiencing severe attacks
- Increasing the time spent attack-free: patients are assumed to return to general population quality of life after six months

- Reducing the severity of attacks relative to most comparators – this was based on a naïve comparison of data from a variety of sources which used varying descriptions of severity

Overall, the technology was modelled to affect costs by:

- Changing the costs of long-term prophylaxis relative to comparator treatments
- Reducing the costs of treating acute attacks, both in terms of drug costs and health-care resource use

The modelling assumptions that had the greatest effect on the ICER were:

- The population and relevant comparator – garadacimab is not-cost effective when compared to no prophylaxis (which was also the case for lanadelumab in TA606). The EAG tested this in scenario analysis in the ≥2 attacks per month population following berotralstat. Cost-effectiveness also varies between the ≥2 attacks per month population, where berotralstat is the only treatment recommended by NICE, and the ≥2 attacks per week population, where lanadelumab is the treatment most commonly used
- The duration applied to quality of life impacts for each HAE attack
- The assumption that the effectiveness of berotralstat responders beyond the third month is equal to that of the pooled population (including both responders and non-responders)
- The assumption that lanadelumab taken at a Q4W dosage after being stable on the Q2W dosage has the same effectiveness as the lanadelumab Q4W population from the **HELP-03** trial, who did not try lanadelumab Q2W
- The assumption of constant attack rates for the first 24 cycles followed by a reduced attack rate using AARRCF for garadacimab and a maintained constant attack rate using LOCF for comparators
- The assumption that quality of life returns to that of the general population over six months of attack freedom, and the method used to apply disease related quality of life data from Nordenfelt et al
- The assumption that attack severity is reduced with garadacimab relative to lanadelumab and berotralstat

Economic analysis results are presented without the application of any severity modifier, which the EAG agreed was not relevant to this case.

1.3. The decision problem: summary of the EAG's key issues

Key Issue 1: Uncertainty around the treatment pathway for people with HAE

Report sections	**2.3.4, 2.4 and 4.2.3**
Description of issue and why the EAG has identified it as important	There is uncertainty regarding the current treatment pathway for people with HAE as, at the time of writing**,** the updated NHSE algorithm has not been published. This is a key issue because the current treatment pathway is unclear, and it is therefore uncertain where garadacimab can be positioned, and what the relevant comparator treatments are. In people with HAE who have ≥2 attacks per month, the EAG understood first-line treatment to be berotralstat. Garadacimab could be positioned as an alternative at first-line or at second-line as an alternative to no LTP. In people with HAE who have ≥2 attacks per week, oral treatment (predominantly berotralstat) is first-line. Garadacimab could be positioned at second-line as an alternative to lanadelumab or IV C1-INHs. Selection of second-line treatment is based on efficacy, tolerability, and safety, with most people initiating treatment currently receiving lanadelumab rather than IV C1-INHs. People for whom garadacimab is not effective may be treated with lanadelumab; if lanadelumab is also ineffective, patients may be treated with IV C1-INHs. In the company base case, lanadelumab, Cinryze and Berinert were included as comparators for the ≥2 attacks per month population in the company's economic analysis. This did not reflect the EAG's understanding of the treatment pathway.
What alternative approach has the EAG suggested?	The EAG detailed a treatment pathway, with potential positioning for garadacimab, based on NHS policy, NICE guidance, and advice from clinical experts. The EAG provided separate cost-effectiveness analyses for the ≥2 attacks per month and ≥2 attacks per week populations. The EAG provided scenario analysis exploring the cost-effectiveness of garadacimab as a second-line treatment after berotralstat in the ≥2 attacks per week population.
What is the expected effect on the cost-effectiveness estimates?	≥2 attacks per month subgroup: 1st line berotralstat + 2nd line garadacimab vs 1st line berotralstat + no prophylaxis (after EAG corrections): ICER of [redacted].
What additional evidence or analyses might help to resolve this key issue?	The pathway detailed by the EAG was based on clinical practice and NICE guidance as it currently stands. However, when the NHSE algorithm for treatment of people with HAE has been published it will resolve any uncertainty regarding the current treatment pathway and help clarify the positioning of garadacimab. Additional data on the effectiveness of multiple lines of LTP.

Abbreviations: C1-INH, C1-inhibitor; EAG, External Assessment Group; HAE, hereditary angioedema; LTP, long-term prophylaxis; NHSE, NHS England; NICE, National Institute for Health and Care Excellence.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 2: Methods and trials used in the indirect treatment comparison

Report sections	**3.4.1.4, 3.4.1.5, 3.4.2.3, 3.4.2.4, and Appendix B**
Description of issue and why the EAG has identified it as important	The company reported several indirect treatment comparisons (ITCs). The results differed, in some cases substantially, depending on the methods used and the inclusion of the phase 2 garadacimab trial (**CSL312_2001**). The company preferred the FE NMA where **CSL312_2001** was included in the model. However, based on the model fit and heterogeneity between garadacimab trials, the EAG preferred the FE NMA where **CSL312_2001** was removed. The company also presented a ML-NMR leveraging IPD and aggregate data from RCTs to adjust for between study differences. The EAG accepted that the ML-NMR offered distinct methodological benefits in capturing and adjusting for heterogeneity and contextual factors that a standard NMA may overlook. However, the EAG had concerns regarding the pooling of heterogenous garadacimab trials as a single trial, testing of covariates, and the inclusion of only a single covariate in the final model for the principal efficacy outcomes. This is a key issue because the ITC results used in the model impact on the cost-effectiveness estimates.
What alternative approach has the EAG suggested?	The EAG have used the best fitting NMA (FE with **CSL312_2001** removed) as their base case. They have also provided scenario analysis using the results from the ML-NMR in the model.
What is the expected effect on the cost-effectiveness estimates?	≥2 attacks per month subgroup: • Impact of phase 2 trial removal: The effect was only in the garadacimab arm in which the cost increased by [redacted] and the incremental QALYs by [redacted] QALYs • Scenario with ML-NMR: incremental costs were reduced in the comparison with garadacimab vs berotralstat by around [redacted]. Incremental QALYs were reduced by [redacted] ≥2 attacks per week subgroup: • Impact of phase 2 trial removal: The impact was minimal in terms of costs or QALYs in the garadacimab arm [redacted] and null in the comparators • Scenario with ML-NMR: Cost for comparators are reduced by [redacted] and QALYs were increased by [redacted] to [redacted] for comparators.
What additional evidence or analyses might help to resolve this key issue?	At the clarification stage, the EAG requested the ML-NMR be carried out without the phase 2 garadacimab trial (**CSL312_2001**). This would have addressed a key concern of the EAG over the ML-NMR methods while retaining its benefits in terms of capturing and adjusting for heterogeneity and contextual factors.

Abbreviations: EAG, External Assessment Group; FE, fixed effect; IPD, individual patient data; ITC, indirect treatment comparison; ML-NMR, multi-level network meta regression; NMA, network meta-analysis.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

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

Report sections	**4.2.6.3, 4.2.6.4**
Description of issue and why the EAG has identified it as important	The company used constant attack rates, derived from the time-normalised numbers of HAE attacks and the NMA, for the first 24 cycles of treatment across all treatments. The company then used the average attack rate reduction carried forward (AARRCF) to extrapolate long-term effectiveness for garadacimab and LOCF for the comparators. Long-term effectiveness is uncertain for all treatments due to a lack of long-term data. However, the EAG considered that attack rates were relatively stable following the first 6 months of treatment within the open-label extension (OLE) study (median [min, max] duration on treatment of [redacted] months), although caution should be taken not to over-interpret this data, which comes from a post-hoc analysis based on a small sample. The EAG did not support the company's approach for two reasons. First, it does not fit the data well as attack rates were not constant within the VANGUARD trial (attack rates reduced over time). Second, the use of different assumptions for garadacimab and comparators in the long-term introduced bias. In the company base case this bias amounted to a reduction in attack rates for garadacimab between cycles 24 and 25+ that was not applied to comparator treatments where rates were kept constant. This resulted in a more favourable ICER for garadacimab relative to comparators than would be expected had the same assumption been applied to all treatments.
What alternative approach has the EAG suggested?	To use observed attack rates from the OLE for the first 24 cycles. Then apply the FE NMA for time-normalised HAE attack rates to differentiate treatments and derive expected comparator outcomes. For long-term extrapolation, to use a "partial AARRCF" methodology based on garadacimab attack rates between cycles 12 and 24, again applying the FE NMA to differentiate treatments and derive expected comparator outcomes.
What is the expected effect on the cost-effectiveness estimates?	≥2 attacks per month subgroup: • Extrapolation of attack rates: [redacted] in incremental costs by [redacted] and a QALY [redacted] of incremental QALYS of [redacted] • Different source of attack rates in 1st 24 cycles: [redacted] in incremental costs by [redacted] and incremental QALYs [redacted] of [redacted] ≥2 attacks per week subgroup • Extrapolation of attack rates: Garadacimab arm [redacted]%; comparators no impact • Different source of attack rates in first 24 cycles: garadacimab and lanadelumab had a [redacted] in costs but while garadacimab had a small increase of [redacted], lanadelumab had an increase of [redacted]

Report sections	**4.2.6.3, 4.2.6.4**
What additional evidence or analyses might help to resolve this key issue?	Additional long-term effectiveness data.

Abbreviations: AARRCF, average attack rate reduction carried forward; CS, company submission; EAG, External Assessment Group; FE, fixed effect; HAE, hereditary angioedema; LOCF, last observation carried forward; NMA, network meta-analysis; OLE, open label extension

Key Issue 4: The handling of berotralstat stopping rule

Report sections	**2.5, 4.2.6.5**
Description of issue and why the EAG has identified it as important	Berotralstat requires patients to discontinue treatment if they do not achieve a reduction in HAE attack rate greater than 50% by month 3. However, to calculate extrapolated efficacy, the company used data from the entire berotralstat patient population from the first three months. This included both those who did not meet this threshold (i.e. those participants for whom berotralstat was not effective, and therefore who would discontinue using berotralstat), and those who did achieve a 50% or greater reduction. This is a key issue because the company's base case underestimates berotralstat effectiveness. This underestimation substantially impacts the ICER for the ≥2 attacks per month population.
What alternative approach has the EAG suggested?	As data for the effectiveness of berotralstat responders from TA738 was redacted, the EAG assumed in its base case that the efficacy of patients beyond month 3 is the same as that of lanadelumab administered every two weeks (Q2W). This was based on clinical expert advice that responders to berotralstat generally have a high level of response.
What is the expected effect on the cost-effectiveness estimates?	≥2 attacks per month subgroup – Changes only occurred in the berotralstat arm. The incremental cost reduced by [redacted] and incremental QALYs were reduced by [redacted] QALYs
What additional evidence or analyses might help to resolve this key issue?	Data on the effectiveness of berotralstat following application of the stopping rule at 3 months.

Abbreviations: CS, company submission; EAG, External Assessment Group; HAE, hereditary angioedema; Q2W, Administered every two weeks

Key Issue 5: The handling of lanadelumab switch between Q2W and Q4W

Report sections	**4.2.6.7, 4.2.6.6**
Description of issue and why the EAG has identified it as important	Lanadelumab's SmPC states that patients receiving lanadelumab every two weeks (Q2W) can reduce their administration frequency to every four weeks (Q4W) if they are "stably attack free". The SmPC notes this is a particular consideration for patients with low body weight. The clinical rationale behind this is that some patients may not require Q2W dosing to achieve optimal clinical benefit.

Report sections	**4.2.6.7, 4.2.6.6**
	However, the CS used effectiveness data from the **HELP-03** trial, where Q4W patients had never received Q2W, to model the long-term effectiveness of stable patients who switch from Q2W to Q4W. This data includes patients who would not be suitable for switching in practice. Similar to Key Issue 4, this is a key issue because it underestimates the effectiveness of the lanadelumab arm, thereby lowering the garadacimab ICER.
What alternative approach has the EAG suggested?	The EAG assumed that the effectiveness of the Q2W population was the same as that of the Q4W population based upon clinical expert advice and observational study analysis, which found that allowing patients to increase their dose interval did not impact effectiveness with ~75% of those increasing their dose interval to Q4W not needing to return to the Q2W dose.
What is the expected effect on the cost-effectiveness estimates?	≥2 attacks per week subgroup – lanadelumab arm cost increased by [redacted] and QALY gains increased by [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional clinical evidence on the impact of switching from Q2W to Q4W.

Abbreviations: CS, company submission; EAG, External Assessment Group; HAE, hereditary angioedema; Q2W, administered every two weeks; Q4W, administered every four weeks; SmPC, Summary of product characteristics

Key Issue 6: The calculation of patient utilities

Report sections	**4.2.2, 4.2.9**
Description of issue and why the EAG has identified it as important	Consistent with prior appraisals, the CS used data from Nordenfelt et al (2014) to estimate the impact of attacks on health-related quality of life (HRQoL). However, the company assumed that the impact of attacks on quality of life lasts for 7 days, based upon clinical opinion to the company that the impact of an attack lasts for longer than the actual attack duration ([redacted] in the VANGUARD trial). This is inconsistent with prior appraisals and how the attack-related quality of life decrements were calculated from the published papers; inflating the impact of attack on HRQoL [redacted] times. The company then also assumed that HRQoL was dependent on time spent attack-free, in addition to the direct impact of attacks on HRQoL, and that a patient's quality of life would return to the same as a member of the general population linearly over 6 months. In contrast to this assumption, AE-QoL results from VANGUARD showed improvement within the first month of treatment followed by stabilisation. Clinical advice to both the company and EAG also indicated that a patient's quality of life was unlikely to ever return to the same as a member of the general population. Finally, the EAG noted that the correct application of the regression equation from Nordenfelt et al (2014) is unclear, and that the

Report sections	**4.2.2, 4.2.9**
	intercept co-efficient used by the company (and in prior appraisals) is not in fact an intercept but is instead the mean EQ-5D today reported in the paper. It is also unclear over what time period the decrement per previous attack should be applied. This is a key issue because applying a longer attack utility decrement has a major impact on the ICER (particularly in the comparison to berotralstat). The method of application of utilities outside of an attack also has a moderate impact on ICER results.
What alternative approach has the EAG suggested?	The EAG made some amendments to the company's base case to test the impact of these issues: • Applied the impact of an attack only to the duration of an attack • Assumed that the benefit from attack freedom would be incurred after the first month through the application of the Nordenfelt (2014) equation, rather than through the use of the company's tunnel state methodology, which assumed a linear increase over 6 months • Assumed an intercept of 1 rather than using the mean EQ-5D today when applying the Nordenfelt (2014) paper
What is the expected effect on the cost-effectiveness estimates?	≥2 attacks per month subgroup (garadacimab vs. berotralstat) • Reducing the attack length to the trial attack duration resulted in incremental QALYs reducing to [redacted] (comparison with corrected company base case) • Removal of tunnel states resulted in incremental QALYs reducing by [redacted] • Application of the Nordenfelt (2014) an intercept of 1 for the Nordenfelt equation reduced incremental QALYs by [redacted] (comparison with corrected company base case) ≥2 attacks per week subgroup • Reducing the attack length to the trial attack duration resulted in QALY gains for C1-INHs of [redacted] - [redacted], lanadelumab had a QALY gain of [redacted] and garadacimab gained [redacted] (comparison with corrected company base case). • Removal of tunnel states had a moderate impact on garadacimab and lanadelumab in terms of QALYs [redacted] and [redacted] respectively) (comparison with corrected company base case) • Application of the Nordenfelt (2014) an intercept of 1 for the Nordenfelt equation resulted in QALY gains ranging between [redacted] for IV C1-INHs. Lanadelumab and garadacimab had QALY gains of [redacted] and [redacted] respectively (comparison with corrected company base case)
What additional evidence or analyses might help to resolve this key issue?	Clarification on how the regression from the Nordenfelt (2014) paper should be applied. The EAG have contacted the corresponding author but have not yet received a response.

Report sections	**4.2.2, 4.2.9**
	Data showing how attack freedom impacts on quality of life. Data showing how long the impact of an attack lasts on quality of life and how the magnitude of that impact varies over time.

Abbreviations: CS, company submission; EAG, External Assessment Group; HAE, hereditary angioedema; HRQoL, Health-related quality of life

1.6. Summary of EAG's preferred assumptions and resulting ICER

Table 3: Summary of EAG's preferred assumptions and ICER: ≥2 attacks per month population compared to berotralstat

Scenario	**Incremental cost**	**Incremental QALYs**	**ICER garadacimab vs berotralstat**
Company's base case			
Using model submitted with clarification questions	[redacted]	[redacted]	[redacted]
EAG corrected company base case			
Cumulative	[redacted]	[redacted]	[redacted]
Calibrated attack rate error	[redacted]	[redacted]	[redacted]
Utility implementation errors	[redacted]	[redacted]	[redacted]
Tunnel states	[redacted]	[redacted]	[redacted]
PSA fixes	[redacted]	[redacted]	[redacted]
EAG's preferred base case			
Cumulative (deterministic)	[redacted]	[redacted]	[redacted]
Cumulative (probabilistic)	[redacted]	[redacted]	[redacted]
Berotralstat responders increased effectiveness	[redacted]	[redacted]	[redacted]
Attack severity aligned with garadacimab	[redacted]	[redacted]	[redacted]
Attack rate extrapolation method aligned across treatments	[redacted]	[redacted]	[redacted]
NMA FE excluding phase 2 trials	[redacted]	[redacted]	[redacted]
Attack rates from trial (cycle 0-24)	[redacted]	[redacted]	[redacted]
No utility tunnel states	[redacted]	[redacted]	[redacted]
Amended application of Nordenfelt equation	[redacted]	[redacted]	[redacted]
Administration disutility included	[redacted]	[redacted]	[redacted]
Administration disutility for IV treatments source	[redacted]	[redacted]	[redacted]
Attack length ([redacted] days)	[redacted]	[redacted]	[redacted]

Scenario	Incremental cost	Incremental QALYs	ICER garadacimab vs berotralstat
One caregiver	[redacted]	[redacted]	[redacted]
Reduced caregiver disutility value	[redacted]	[redacted]	[redacted]
Increased training costs	[redacted]	[redacted]	[redacted]
Amended resource use rates	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; FE, fixed effects; ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, network meta-analysis; QALY, quality adjusted life year; PSA, probabilistic sensitivity analysis

Table 4: Summary of EAG's preferred assumptions and ICER: ≥2 attacks per week population compared to lanadelumab

Scenario	Incremental cost	Incremental QALYs	ICER garadacimab vs lanadelumab
Company's base case			
Using model submitted with clarification questions	[redacted]	[redacted]	[redacted]
EAG corrected company base case			
Cumulative	[redacted]	[redacted]	[redacted]
Calibrated attack rate error	[redacted]	[redacted]	[redacted]
Utility implementation errors	[redacted]	[redacted]	[redacted]
Tunnel states	[redacted]	[redacted]	[redacted]
PSA fixes	[redacted]	[redacted]	[redacted]
EAG's preferred base case			
Cumulative (deterministic)	[redacted]	[redacted]	[redacted]
Cumulative (probabilistic)	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W instantaneous switch	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W effectiveness = Q2W	[redacted]	[redacted]	[redacted]
Attack severity aligned with garadacimab	[redacted]	[redacted]	[redacted]
Attack rate extrapolation method aligned across treatments	[redacted]	[redacted]	[redacted]
NMA FE excluding phase 2 trials	[redacted]	[redacted]	[redacted]
Attack rates from trial (cycle 0-24)	[redacted]	[redacted]	[redacted]
No utility tunnel states	[redacted]	[redacted]	[redacted]
Amended application of Nordenfelt equation	[redacted]	[redacted]	[redacted]

Scenario	Incremental cost	Incremental QALYs	ICER garadacimab vs lanadelumab
Administration disutility included	[redacted]	[redacted]	[redacted]
Administration disutility for IV treatments source	[redacted]	[redacted]	[redacted]
Attack length ([redacted] days)	[redacted]	[redacted]	[redacted]
One caregiver	[redacted]	[redacted]	[redacted]
Reduced caregiver disutility value	[redacted]	[redacted]	[redacted]
Increased training costs	[redacted]	[redacted]	[redacted]
Amended resource use rates	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; FE, fixed effects; ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, network meta-analysis; QALY, quality adjusted life year; PSA, probabilistic sensitivity analysis

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by CSL Behring in support of garadacimab (Andembry®) for preventing recurrent attacks of hereditary angioedema in people aged 12 and over.

2.2. Critique of the company's description of the underlying health problem

The company's description of the underlying health problem is presented in CS Section B.1.3.1. Hereditary angioedema (HAE) is a rare chronic genetic disorder characterised by recurrent and unpredictable inflammation and swelling of the skin (cutaneous oedema) and submucosa (submucosal oedema) resulting from inherited or spontaneous mutations in the contact system pathway.[1,2] The estimated global prevalence of HAE ranges between 1:50,000 and 1:100,000.[2,3] HAE can be classified into subtypes, although they are clinically indistinguishable.[2]

- HAE type 1 (HAE-1) results from a failure to synthesise C1-inhibitors (C1-INHs) and is characterised by low levels of normal-functioning C1-INHs, accounting for ~85% of all cases of HAE.
- HAE type 2 (HAE-2) results from the synthesis of abnormal C1-INH protein and is characterised by normal levels of low-functioning C1-INHs, accounting for ~15% of all cases of HAE.
- HAE type 3 (oestregen-dependent)[4] is extremely rare and there is a paucity of data for this population.

HAE may be slightly more common in females than males (58% female according to Yong et al.[5]), although clinical advice was that there is no clearly discernible clinical demographic for HAE and that no specific ethnicity is more prone to HAE. Of people with HAE, 81% are adults, 9% are adolescents and 10% are children <12 years of age.[5]

Diagnosis is primarily based on clinical presentation during an attack, confirmed by history and investigations.[2] Most attacks are spontaneous and not prompted by triggers. Nevertheless, various triggers have been identified, including emotional stress, local trauma (accidents, or associated with dental, medical, or surgical procedures) and infections.[2,6,7]

The symptom burden associated with HAE attacks is substantial. People with HAE may experience disfiguration, severe pain, inability to perform daily activities, and feelings of fear and anxiety.[8,9] There is some evidence that there is caregiver burden associated when people have severe HAE attacks,[8,10] although clinical experts consulted by the EAG considered that additional caregiver burden is only expected for paediatric patients. Overall mortality in HAE is similar to the general population. However, HAE attacks leading to laryngeal oedema pose a risk of asphyxiation if this occurs in the absence of timely medical treatment.[11,12] Death due to laryngeal attacks mainly occurs where HAE is undiagnosed or untreated.[11,13]

2.3. Critique of the company's overview of current service provision

Garadacimab is a fully human, recombinant immunoglobulin G4 (IgG4)/lambda monoclonal antibody and specific inhibitor of activated Factor XII (FXIIa).[14] The mechanism of action is by blocking the cascade of events leading to a HAE attack. It does this by preventing the activation of pre-kallikrein to kallikrein and the subsequent generation of bradykinin, which is associated with the inflammation and swelling observed during HAE attacks.[14]

The comparator drugs have different mechanisms of action. Berotralstat is an inhibitor of plasma kallikrein.[15] Plasma kallikrein is a serine protease that cleaves high-molecular-weight-kininogen (HMWK), releasing bradykinin, a potent vasodilator that increases vascular permeability. In patients with HAE due to C1-INH deficiency or dysfunction, normal regulation of plasma kallikrein activity is impaired, which leads to uncontrolled increases in plasma kallikrein activity and bradykinin release, resulting in HAE attacks consisting of swelling (angioedema). Lanadelumab also works inhibiting active plasma kallikrein proteolytic activity. Increased plasma kallikrein activity leads to angioedema attacks in patients with HAE through the proteolysis of HMWK to generate cleaved HMWK and bradykinin. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in people with HAE.[16] IV C1-INHs inhibit the complement system by binding C1r and C1s, two of the active enzyme subunits of the first component of the complement system (C1) in the classical pathway, as well as to mannose-binding lectin-associated serine proteases in the lectin pathway. The primary substrate of the activated C1 enzyme is C4; uninhibited C1 results in diminished C4 levels. C1 is the most important inhibitor of contact activation and regulates the contact system and the intrinsic coagulation pathway by binding to and inactivating kallikrein and factor XIIa. Because these pathways are part of enzyme amplification cascades, without C1-esterase inhibitor, spontaneous or trigger-induced activation of these pathways can lead to unopposed activation and swelling.

The recommended dose of garadacimab is an initial loading dose of 400 mg administered as two 200 mg subcutaneous (SC) injections on the first day of treatment followed by a monthly dose of 200 mg. The intended method of administration is single-use pre-filled pen (autoinjector device). After training by a healthcare provider it can be self-administered or administered by a caregiver.[14] The clinical effectiveness evidence presented in the submission does not use the autoinjector device but rather a pre-filled syringe – although clinical expert advice to the EAG was that this difference in method of administration is unlikely to make any meaningful difference to safety or efficacy. The company also referenced a narrative review that discussed the differences between prefilled pens, prefilled syringes, and electromechanical devices in the context of the administration of biologics for arthritis.[17] The review concluded that both prefilled syringes and autoinjector pens assist people with self-injection, and both are extremely useful and valued options for people who self-inject.

The company's overview of current service provision is presented in CS Section B.1.3.2. Currently, there are three main approaches[18] to the management of HAE:

- Acute treatment during a HAE attack
- Short-term prophylaxis as a preventative measure before planned events that may be a trigger
- Long-term prophylaxis (LTP) for the routine prevention of recurrent attacks.

2.3.1. Acute treatment

Acute treatment is given during a HAE attack. People with frequent HAE attacks typically carry acute treatment with them outside the house. Treatment options in the UK include icatibant (Firazyr), intravenous (IV) C1-INHs (IV Berinert/Cinryze), and recombinant IV C1-INHs (Ruconest). Some treatments used for acute treatment, including IV Berinert and Cinryze, are also used for LTP.[19]

2.3.2. Short-term prophylaxis

There are planned events, such as medical procedures that can provoke HAE attacks. For these, people can use short-term prophylaxis (STP) before the event. Busse et al. (2022)[20] stated that short-term prophylaxis is indicated when people are at increased risk of having an attack, associated with known triggers, such as invasive dental or medical procedures or stressful life events. They noted that STP with a single dose of C1-INH (1 to 12 hours prior to the stressor) or a short course of anabolic steroids (started 5–7 days before the event and

continued for 2 to 5 days after) may be appropriate. As garadacimab is not indicated for STP and its use is relatively rare, STP was not further assessed in this appraisal.

2.3.3. Long-term prophylaxis

At the time of this appraisal, the treatments used for LTP in people with HAE were plasma kallikrein inhibitors (lanadelumab or berotralstat) or C1 esterase inhibitors (C1-INHs, such as IV Berinert, SC Berinert, or Cinryze). People could also use attenuated androgens or antifibrinolytics, such as tranexamic acid, for LTP. The results of a survey undertaken by the UK HAE network in 2018 found that 45% of people with HAE were on LTP.[5] This consisted of 53% of adults and 24% of adolescents (12 to <18 years old). However, one of the authors of the survey, Patrick Yong, in his role as clinical expert for the EAG, noted that the survey was carried out prior to lanadelumab receiving marketing authorisation and a recommendation from NICE. Therefore, the numbers may not represent the current proportions of people on LTP in the UK.

2.3.4. NHS treatment pathway for LTP

The EAG requested clarification on the treatment pathway for people with HAE from NHS England (NHSE). In response, NHSE stated that they were working on an algorithm for hereditary angioedema which was still in progress and was expected to be published in early 2025. The algorithm will consider three scenarios:

- People with less than 2 attacks per month (acute treatment)
- People with 2 or more attacks per month and (acute treatment; berotralstat positioned here)
- People with 2 or more attacks per week (lanadelumab positioned here, C1-INHs)

However, until it is published there will be uncertainty regarding the NHS treatment pathway for people with HAE. The EAG therefore presented NHS policy and NICE guidance as it currently stands, alongside advice from their clinical experts.

NHS policy and NICE guidance restricts access to LTP treatment by attack frequency as follows:

- TA738[21] recommends berotralstat as an option for preventing recurrent HAE attacks in people aged 12 and over who have ≥2 attacks per month. Treatment should be stopped if there is not a 50% reduction in attacks after 3 months.

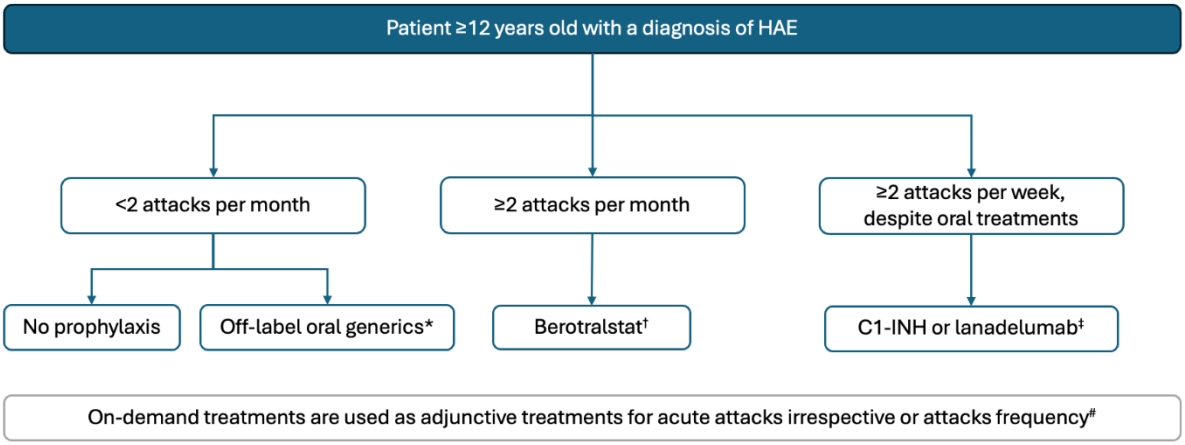
- TA606[22] recommends lanadelumab as an option for preventing recurrent HAE attacks in people aged 12 and over who have ≥2 clinically significant attacks per week over 8 weeks despite oral preventive therapy (i.e. berotralstat or historically attenuated androgens or antifibrinolytics).

- NHS England[23] reimburses plasma derived IV C1-INHs (Cinryze and off-label IV Berinert) for prophylactic treatment of HAE in people who have failed or are intolerant to oral prophylaxis and experience ≥2 clinically significant attacks per week.

For people experiencing fewer than two attacks per month, LTP options were restricted to oral generic therapies, namely attenuated androgens (e.g. danazol or oxandrolone) and antifibrinolytics (i.e. tranexamic acid).[24] However, clinical advice to the EAG is that these treatments are rarely used in routine UK practice.

The current LTP pathway in England was summarised in the CS in Figure 7 in Document B. It has been reproduced below in Figure 1. It was notable that a treatment that has been shown to be effective for LTP, but was not included in this appraisal, is SC Berinert, which is a subcutaneous (SC) C1-INH. Clinical advice to the EAG was that SC Berinert (Haegarda) cannot be routinely commissioned in the NHS and can only be used if people were previously on IV Berinert. However, the EAG understood that it would be a relevant comparator if consultants could readily prescribe it. SC Berinert (Haegarda) was a comparator in the company's network meta-analysis (NMA) and multi-level network meta regression (ML-NMR).

Figure 1: Current LTP option pathway for people with HAE aged >=12 in England as presented in the CS (reproduced from Figure 7, Doc B)



Abbreviations: C1-INH, C1-Inhibitor; CS, company submission; HAE, hereditary angioedema; LTP, long-term prophylaxis
Notes:
* Off-label oral generics include tranexamic acid and attenuated androgens

† As per the TA738 NICE guidance, treatment with berotralstat is stopped if the number of attacks per month does not reduce by at least 50% after 3 months.9
‡ Decision-making of treatment choice is informed by: clinical judgement of suitability, clinical effectiveness, contraindications, ability of patient/carer to use the required administration technique, regional network approval and patient choice.
# On-demand therapy (the on-demand use of C1-INHs or icatibant) is used as an adjunct therapy in all patients for the treatment of acute attacks, irrespective of attack frequency or concurrent use of LTP options.

Internationally recognised HAE guidelines by WAO/EAACI (2021)[2] recommend plasma-derived C1INHs, berotralstat and lanadelumab as first-line LTP options with androgens used only as a second-line option; antifibrinolytics are not recommended. The guideline does not limit treatment based on number of attacks people had. Rather, it encourages shared decision. However, the guideline does not consider the cost of treatment and noted that "cost and access may also be an issue for patients".

2.4. Positioning of garadacimab

Lack of evidence of the efficacy and tolerability of current LTP options formed the central argument of the company's rationale for unmet need. Clinical advice to the EAG questioned this rationale, given that lanadelumab has been demonstrated to have high efficacy. The unmet need is instead that the most effective treatment is currently restricted to those with ≥2 attacks per week due to its high cost. Thus, the most effective treatment (lanadelumab) is not available to people with HAE who have fewer than two attacks per week.

The company partially addressed this unmet need as they seek a recommendation in people who have ≥2 attacks per month. However, the EAG noted two unmet needs not addressed in the CS. Firstly, the company did not present an economic case in people who have ≥2 attacks per month, for whom berotralstat has failed. Currently this population have no further LTP options. The EAG have rectified this, as noted in the positioning of garadacimab detailed below. Secondly, the company is not seeking a recommendation in people with <2 attacks per month, for whom LTP is limited to off-label oral generics. This continues to be a population with HAE with an unmet need.

The company's proposed positioning for garadacimab is summarised in Figure 8 in Document B. It is positioned alongside lanadelumab in the population with ≥2 attacks per week and alongside berotralstat in the ≥2 attacks per month population.

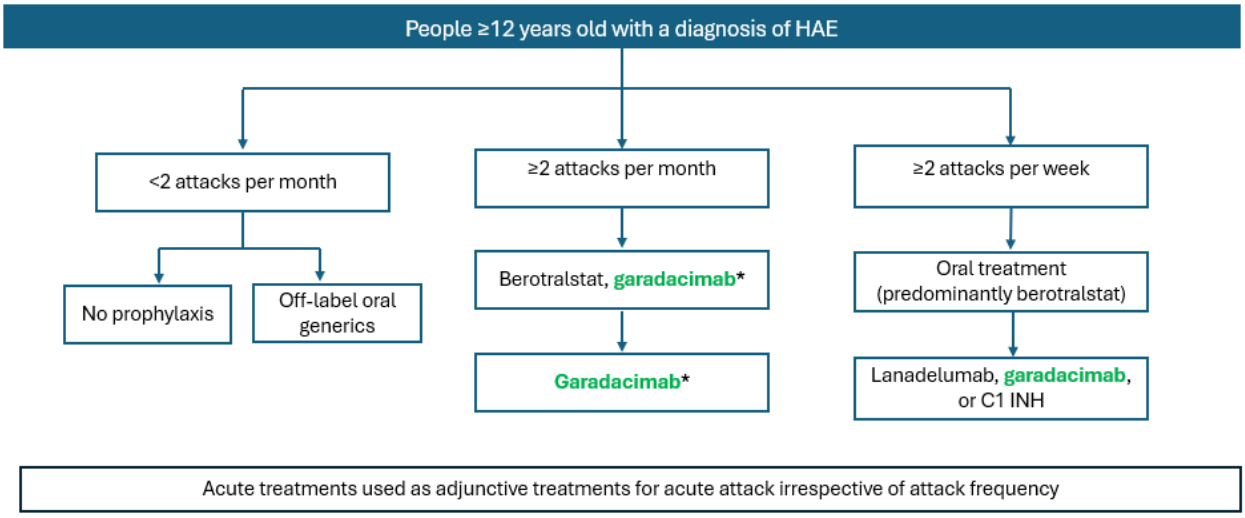
However, it was unclear to the EAG whether the positioning of garadacimab, as presented by the company, was fully reflective of the current care pathway. Clinical expert advice to the EAG

was that, if adopted in routine clinical practice, garadacimab would most likely be used in the following cases:

- In people with ≥2 attacks per month, garadacimab could either be offered first-line as an alternative to berotralstat, or second-line in people for whom berotralstat failed.
- In people with ≥2 attacks per week, garadacimab could be offered to people for whom oral treatment (predominantly berotralstat) had failed and compete with lanadelumab to be the main treatment for this population.

The EAG has updated the possible positioning of garadacimab based on this advice (Figure 2).

Figure 2: The EAG's positioning of garadacimab based on advice from clinical experts on the current NHS treatment pathway



Abbreviations: C1-INH, C1-Inhibitor; HAE, hereditary angioedema.

Note: * Garadacimab has been placed in two possible treatment pathway locations for people with ≥2 attacks per month.

2.5. Stopping criterion

As noted in Section 2.3.4, TA738 recommended that berotralstat treatment should be stopped if there is not a 50% reduction in attacks after 3 months.[21] The NHSE clinical commissioning policy for IV C1-INHs stated that if treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic IV C1-INHs should be discontinued and alternative therapy options considered.[23] The EAG asked

NHSE about any stopping rules linked to treatment with lanadelumab and they said that there are none. The EAG was also unaware of any stopping rule related to LTP with garadacimab.

2.6. Critique of company's definition of decision problem

The company's decision problem, along with the EAG's commentary, is presented in Table 5. The EAG considered the decision problem to be reasonably well-aligned to the NICE scope and that any deviations were justified.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People 12 years and over with hereditary angioedema	People 12 years and over with hereditary angioedema experiencing ≥2 attacks per month at baseline	The company has optimised its positioning to patients experiencing ≥2 attacks per month as this reflects the commissioning landscape for novel LTP therapies which restrict by baseline attack frequency.	This optimised population is aligned to the understood treatment pathway in the UK.
Intervention	Garadacimab	Garadacimab	N/A	The intervention in the submission matches the final scope. Marketing authorisation was granted for people aged 12 years and older with HAE on 24th January 2025.
Comparator(s)	Established clinical management for preventing attacks of hereditary angioedema which may include: • C1-esterase inhibitors (this includes Cinryze, Berinert and Ruconest) • Attenuated androgens • Antifibrinolytics • Lanadelumab for people eligible for preventative	• Plasma-derived, intravenous C1-esterase inhibitors (Cinryze and IV Berinert) • Lanadelumab for people eligible for preventative C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat	An extensive rationale is provided. In summary, antifibrinolytics, attenuated androgens, Ruconest and SC Berinert have not been included as comparators in the decision problem, as they are not considered part of current SoC in the NHS.	The EAG considered it appropriate not to consider these comparators given they are not routinely used in the NHS for LTP.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	C1-esterase inhibitor treatment in line with NHS England's commissioning policy • Berotralstat			
Outcomes	• Angioedema attacks (including frequency, severity, location and duration) • Attack-free period • Time to first attack • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	• Angioedema attacks (including frequency, severity, location and duration) • Attack-free period • Time to first attack • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	N/A	The outcomes in the CS match those in the scope. Clinical advice to the EAG was that all these outcomes were of clinical value and that there was not one outcome that is necessarily more important than the others.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be			The cost effectiveness of treatments was expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness was sufficiently long to reflect any differences in costs

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			or outcomes between the technologies being compared. Costs were considered from an NHS and Personal Social Services perspective
Subgroups	No subgroups stated	No subgroups stated	N/A	Although no subgroups are listed in the company decision problem table, the CS presents data for the ≥2 attacks per month subgroup which is the company's target population. Exploratory cost-effectiveness analysis is presented in the ≥2 attacks per week subgroup although the sample size in the VANGUARD trial was insufficient to consider clinical effectiveness in this subgroup or any of the other subgroups of key interest in the trial.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Special considerations including issues related to equity or equality	N/A	CSL Behring does not believe that the draft remit or scope will exclude people protected by equality legislation. However, of note, the IV C1-INHs included in the decision problem (Cinryze and IV Berinert) are derived from human plasma which may result in their lower uptake among groups who have religious or spiritual beliefs against receiving treatments derived from human plasma. As such, consideration should be given to treatment options available for people with these beliefs 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.	The NICE scope did not list any particular equity concerns.	Clinical advice to the EAG was that there are likely no major equity or equality issues, although females who have HAE may experience more severe symptoms due to hormonal influences. There was, however, no evidence of a substantial gender difference in prevalence.

Abbreviations: C1-INH, C1-inhibitor; DNA, deoxyribonucleic acid; EAG, External Assessment Group; HAE, hereditary angioedema; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SoC, standard of care; UK, United Kingdom

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of the SLR

The company undertook a systematic literature review (SLR) to identify clinical effectiveness evidence for garadacimab and its comparators. Initial searches were conducted in April 2024 and updated in August. Searches were conducted in MEDLINE ALL, Embase, the Cochrane Library databases and Centre for Reviews and Dissemination (CRD) database. The strategies used were suitable for the scope, and broad enough to retrieve observational and real-world studies for the intervention and relevant comparators, which was necessary for the economic modelling. The database searches were complemented by grey literature and registry searches, both of which were well reported.

The EAG considered the screening and data extraction methods to be appropriate. The risk of bias assessment was conducted using the York CRD checklist for randomised controlled trials (RCTs) and the CASP cohort studies checklist for non-randomised and non-controlled studies. The EAG considered the tool selection reasonably appropriate, although no explanation was offered why these tools were used in preference to the more common Cochrane Risk of Bias 2 and ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tools. It would have been appropriate if the company had presented a pairwise meta-analysis as data from two garadacimab RCTs (**VANGUARD** and **CSL312_2001**) were used in the company's preferred network meta-analysis.

Table 6: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D1.1	The EAG considered the searches to be appropriate and well-aligned to the scope.
Inclusion criteria	Appendix D (Table 6)	The EAG considered the inclusion criteria to be appropriate and well-aligned to the scope.
Screening	Appendix D (pp.16-17)	Independent dual screening was conducted following NICE and PRISMA guidance. The EAG considered this to be appropriate.
Data extraction	Appendix D (p.17)	Standardised extraction tables were used. Data were extracted by one reviewer and checked by a second reviewer. While this is not the gold standard independent dual data extraction, the EAG considered it reasonably appropriate.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Tool for quality assessment of included study or studies	Appendix D (Tables 22 and 23)	Risk of bias assessment was conducted using the York CRD checklist for RCTs and the CASP cohort studies checklist for non-randomised and non-controlled studies. The EAG considered the tool selection reasonably appropriate, although no explanation was offered why these tools were used in preference to the more common ROB.2 and ROBINS tools. However, there was no information available about whether the risk of bias assessment was conducted by two independent reviewers.
Evidence synthesis	B.2.8	It would have been appropriate if the company had presented a pairwise meta-analysis as data from two garadacimab RCTs (**VANGUARD** and **CSL312_2001**) were used in the company's preferred network meta-analysis. A network meta-analysis (NMA) was conducted to compare the efficacy of garadacimab with berotralstat, lanadelumab and plasma-derived IV C1-INHs. This is critiqued in Section 3.3.

Abbreviations: CASP, critical appraisal skills programme; CRD, Centre for Reviews and Dissemination; CS, Company submission; EAG, External Assessment Group; IV, intravenous; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCTs, randomised controlled trials; ROB, risk of bias.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described three trials (detailed in Table 7):

- **VANGUARD** (CSL312_3001; NCT04656418)[25]
- **CSL312_2001** (NCT03712228)[26]
- **CSL312_3002** (NCT04739059)[27,28]

The company noted in Section B.2.2.1 of the CS that, given the availability of robust phase 3 data from **VANGUARD**, **CSL312_2001** was not further discussed in the submission. However, **CSL312_2001** was used in the network meta-analysis (NMA) and in the multi-level network meta regression (ML-NMR). Also, 35 participants rolled over from **CSL312_2001** to the open label extension (OLE) study (**CSL312_3002**).

Table 7: Clinical evidence included in the CS (adapted from Table 6, Doc B)

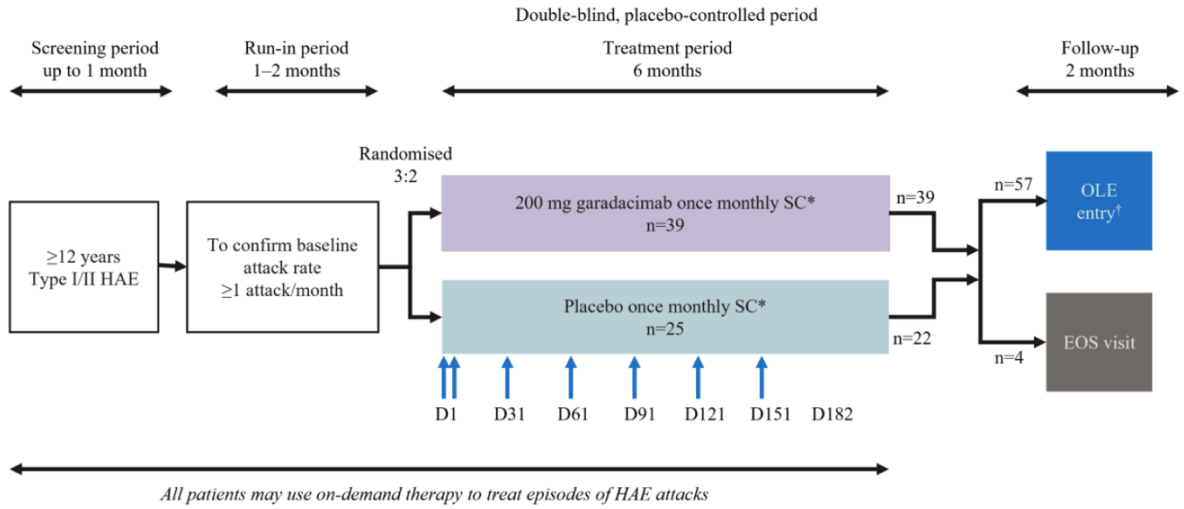
Study name and acronym	Study design	Population	Intervention	Comparator
VANGUARD (CSL312_3001; NCT04656418)	Phase 3, multicentre, double-blind, RCT[b]	People aged ≥12 years with HAE-1 or HAE-2 who experienced ≥3 HAE attacks during the 3 months prior to screening	Garadacimab 200 mg SC injection (pre-filled syringe), once per 28 days (n=39)	Placebo SC once per month (n=25)
CSL312_2001 (NCT03712228)	Phase 2, dose-finding study[a]	People aged 18–65 years old with HAE who either: • HAE-1/HAE-2: experienced ≥4 HAE attacks over 2 months during the 3 months prior to screening - HAE-3: experienced ≥1 HAE attack during the 3 months prior to screening"	Garadacimab SC injection (pre-filled syringe) • Garadacimab 75 mg Q4W (n=9) • Garadacimab, 200 mg Q4W (n=8) Garadacimab 600 mg Q4W (n=7)	Placebo SC once per 28 days (n=8)
CSL312_3002 (NCT04739059)	Phase 3b, multinational, multicentre, open-label study[c]	People aged ≥12 years with HAE-1 or HAE-2 who experienced ≥3 HAE attacks during the 3 months prior to screening	Garadacimab 200 mg SC injection (pre-filled syringe), once per 28 days (n=161)	N/A

Abbreviations: HAE, hereditary angioedema; LTP, long term prophylaxis; Q4W, once every 4 weeks; RCT, randomised controlled trial; SC, subcutaneous.
Notes:
[a] Phase 2 study designed to determine efficacy and further evaluate safety.
[b] Phase 3 study designed to confirm efficacy/ effectiveness, monitor side effects, compare it with standard or similar interventions, and collect information about safety.[29]
[c] Phase 3b study designed to gather additional data, such as best use of the drug in real-world settings, patient subpopulations, long-term outcomes, and safety.

3.2.2. Description and critique of the design of the studies

The pivotal trial for this submission was **VANGUARD**,[25] a phase 3, double-blind, randomised, placebo-controlled trial where the intervention arm were treated with garadacimab 200 mg as a SC injection using a pre-filled syringe for six months (Figure 3). The study was conducted in 28 sites across seven countries, although none of the sites were in the UK. However, the EAG was unaware of any rationale to suggest that the trial would have limited generalisability to NHS care. At the end of the treatment period, people either entered a two-month follow-up period or the **CSL312_3002** OLE study.

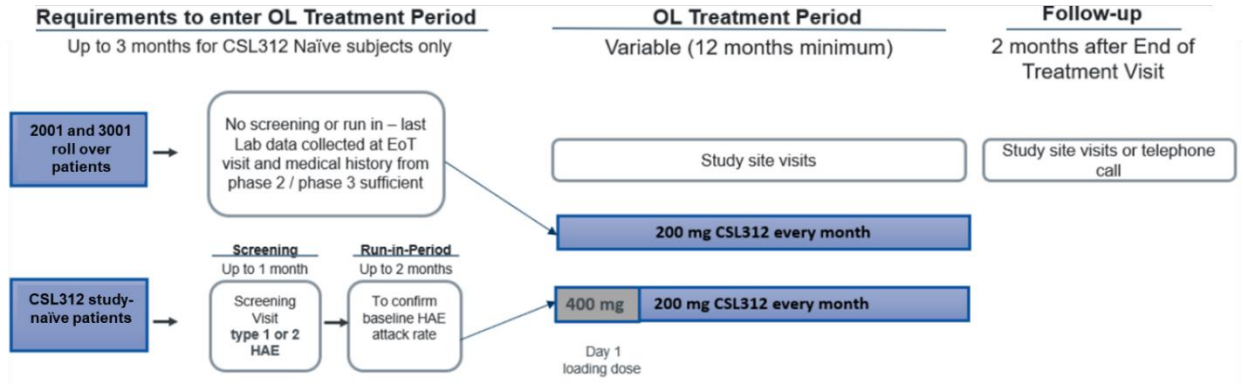
Figure 3: VANGUARD (CSL312_3001) phase 3 study design (reproduced from Figure 9, Doc B)



Abbreviations: D, study day; EOS, end-of-study; HAE, hereditary angioedema; OLE, open-label extension; SC, subcutaneous.
Notes: The 2-month follow-up period started 3 months post-last treatment dose.
*Patients received a 400-mg loading dose of garadacimab (2x 200 mg) or volume-matched placebo as first dose.
†Entry into phase 3b CSL312_3002 OLE study.

The **CSL312_3002** (NCT04739059)[27,28] is an ongoing Phase 3b, open-label trial in people aged ≥12 years with HAE experiencing ≥1 attack per month (N=161; Figure 4). This trial included people previously enrolled in **VANGUARD** and **CSL312_2001** (Phase 2), as well as eligible people who were not previously enrolled in the garadacimab trials. The objective of **CSL312_3002** (OLE) was to evaluate the long-term safety and efficacy of garadacimab 200 mg once monthly. The trial operated across 47 sites in 14 countries (none in the UK) and all participants were treated with garadacimab 200 mg SC for a median [redacted] months at the latest data cut-off ([redacted]).

Figure 4: CSL312_3002 study design (reproduced from Figure 10, Doc B)



Abbreviations: CLS312, garadacimab; EoT, end of treatment; HAE, hereditary angioedema; OL, open-label.

3.2.2.1. Population

The study randomised 65 people, aged 12 years or older, with HAE-1 or HAE-2 who experienced at least three HAE attacks during the 3 months before screening, to garadacimab or placebo. The randomisation was stratified by the person's age (≤17 years and >17 years) and, for adults, baseline attack rate observed during the run-in period (1 to <3 per month and ≥3 per month). However, the population recruited to **VANGUARD** and **CSL312_3002** (OLE) were required to have had experienced ≥3 HAE attacks during the three months before screening. This requirement was not specified in the final scope issued by NICE.

Trial eligibility criteria

The eligibility criteria for **VANGUARD** and the garadacimab-naïve patients in **CSL312_3002,** the OLE trial, were identical:

- Male or female aged ≥12 years
- Diagnosis of HAE-1 or HAE-2, confirmed by the following criteria:
  - Documented clinical history consistent with HAE,
  - C1-INH functional activity <50% of normal, and
  - C4 antigen concentration below the lower limit of the reference range (0.16–0.38 mg/mL)
- Experienced ≥3 HAE attacks during the three months before screening

- Participated in the run-in period for ≥1 month and experienced ≥1 attack per month in the study run-in period

The key exclusion criteria were:

- Concomitant diagnosis of other forms of angioedema (e.g. idiopathic or acquired HAE)
- Use of monoclonal antibodies (i.e. lanadelumab) ≤3 months before the run-in period
- Use of oestrogen-containing medications with systemic absorption ≤4 weeks before the run-in period
- Use of C1-INH products, androgens, antifibrinolytics, or other small molecule medication (i.e. berotralstat) for routine prophylaxis against HAE ≤2 weeks prior to the run-in period

The EAG's clinical experts agreed that the trial eligibility criteria were appropriate. They indicated that the criteria were similar to the lanadelumab trials and that this was reassuring as lanadelumab is the treatment most commonly offered to the subgroup of people with severe HAE (≥2 attacks per week). The EAG's experts considered that given a minimum three-month washout period for lanadelumab, it was reasonable to assume prior treatment did not influence the trial results. The trial did not include people with HAE-3, but the EAG understood this type of HAE to be extremely rare, representing a very small subset of the HAE population.

Baseline characteristics

The baseline characteristics of the **VANGUARD** intention-to-treat (ITT) population and the ≥2 attacks per month **VANGUARD** subgroup are detailed below in Table 8. The EAG's clinical experts stated that the participants recruited to the trial were similar to the people they see in their practices. The treatment arms were different in some baseline characteristics such as, mean age, sex, number of HAE attacks ≤3 months before screening, and the proportion of people who had previously had laryngeal attacks. The EAG's clinical experts did not consider the differences between the arms in either the ITT population or the ≥2 attacks per month subgroup to offer any meaningful benefit to either treatment arm. During the three months before entering the run-in period, all [redacted] ([redacted]%) people who were receiving LTP for HAE prophylaxis discontinued their prophylactic treatments. [redacted] people in the garadacimab arm received either C1-INHs ([redacted] people), berotralstat ([redacted] people), lanadelumab ([redacted] people), tranexamic acid ([redacted] people), danazol ([redacted]), or desloratadine ([redacted]). [redacted]

people in the placebo arm received either C1-INHs ([redacted] people), berotralstat ([redacted] people), tranexamic acid ([redacted]), or danazol ([redacted]).

Table 8: Baseline characteristics of participants in VANGUARD (adapted from Table 1, Appendix E)

	VANGUARD ITT population			≥2 attacks/month subgroup (VANGUARD subgroup)		
	Gara	Placebo	Total	Gara	Placebo	Total
N	39	25	64	[redacted]	[redacted]	[redacted]
Demographic characteristics						
Age at screening (years) Number observed Mean (SD) Median (min, max)	39 43.3 (17.5) [redacted]	25 37.8 (12.8) [redacted]	64 41.2 (15.9) [redacted]	[redacted]	[redacted]	[redacted]
Age at diagnosis, n (%) <18 18 to <40 40 to <65 ≥65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%) Female Male	 24 (61.5) 15 (38.5)	 14 (56.0) 11 (44.0)	 38 (59.4) 26 (40.6)	[redacted]	[redacted]	[redacted]
BMI at screening, kg/m^2 Number observed Mean (SD)	 39 27.9 (6.0)	 25 28.4 (7.6)	 64 28.1 (6.6)	[redacted]	[redacted]	[redacted]
Baseline weight (kg), n (%) <50 50 to <75 75 to <100 ≥100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%) White Other	 33 (84.6) 6 (15.4%)	 22 (88) 3 (12%)	 55 (85.9) 9 (14.1%)	[redacted]	[redacted]	[redacted]
HAE history						
HAE type, n (%) 1 2 3	 34 (87.2) 5 (12.8) –	 22 (88.0) 3 (12.0) –	 56 (87.5) 8 (12.5) –	[redacted]	[redacted]	[redacted]

	VANGUARD ITT population			**≥2 attacks/month subgroup (VANGUARD subgroup)**		
	Gara	Placebo	Total	Gara	Placebo	Total
Patients on prophylactic therapy ≤3 months before screening, n (%)	14 (35.9)	7 (28.0)	21 (32.8)	[redacted]	[redacted]	[redacted]
Number of HAE attacks ≤3 months before screening or at the start of prophylaxis				[redacted]	[redacted]	[redacted]
Number observed	39	25	64			
Mean (95% CI)	8.6 (6.3, 10.9)	9.3 (6.4, 12.2)	8.9 (7.1, 10.6)			
History of laryngeal attacks, n (%)	21 (53.8)	17 (68.0)	38 (59.4)	[redacted]	[redacted]	[redacted]
Location of HAE ≤3 months before screening, n (%)*				[redacted]	[redacted]	[redacted]
Cutaneous (extremities)	30 (76.9)	20 (80.0)	50 (78.1)			
Abdominal	30 (76.96)	18 (72.0)	48 (75.0)			
Cutaneous**	13 (33.3)	8 (32.0)	21 (32.8)			
Throat, larynx, or tongue	3 (7.7)	2 (8.0)	5 (7.8)			
Peripheral†	1 (2.6)	0	1 (1.6)			

Abbreviations: BMI, body mass index; CI, confidence interval; Gara, garadacimab; HAE, hereditary angioedema; ITT, intention-to-treat; kg, kilogram; max, maximum; min, minimum.
* Up to three locations could be selected per patient.
** head/face/lip/neck
† As described by the investigator using the free text option in the person's eDiary.

The baseline characteristics of the participants in **CSL312_3002** (OLE) were presented in Table 8 in Document B. The EAG's clinical experts considered that the participants recruited to the trial were a reasonable representation of the people they saw in their practices.

Dropouts

The company presented CONSORT diagrams for **VANGUARD** and **CSL312_3002** (OLE) in Figures 1 and 2 in Appendix N of the CS. Sixty-five people were randomised in **VANGUARD** and 64 people received treatment. Thirty-nine people were assigned to garadacimab and 25 people to placebo. There were no drug or study discontinuations in the garadacimab arm and three study discontinuations in the placebo arm. The reasons given for study discontinuation were lack of efficacy for one person and HAE attacks for two people. Sixty-one people completed the study and 57 went on to join the OLE trial (**CSL312_3002**).

At the clarification stage (A4) the company expanded on how missing data in **VANGUARD** was addressed. In people who discontinued the study early after being continuously treated for the first 30 days of the treatment period, the observation was terminated by the Early Termination Visit. The use of time-normalised data minimised bias by calculating the primary endpoint based on HAE attacks reported up to the Early Termination Visit. As such, it was assumed that the attack rate for patients who discontinued the study after 30 days of the treatment period, but before the end of the study, was comparable to the attack rate observed in people who completed the full six-month treatment period. The company noted in their response that in the VANGUARD study, discontinuation rates were low. All people (100%) in the garadacimab arm and 22/25 people (88%) in the placebo arm completed the full six months of treatment.

CSL312_3002 (OLE) recruited 35 people from the phase 2 trial (**CSL312_2001**), 57 people from **VANGUARD**, and 79 people who were not involved in previous trials of garadacimab. One-hundred and sixty-one people received treatment and had a median (min, max) duration of treatment of [redacted] ([redacted], [redacted]) months by the [redacted] data cut-off. At that point, [redacted] people had discontinued treatment:

- [redacted] people discontinued due to study site being terminated by the sponsor;
- [redacted] people discontinued due to physician decision;
- [redacted] people withdrew from the study;
- [redacted] people discontinued due to adverse event (AE);
- [redacted] discontinued due to pregnancy;
- [redacted] due to lack of efficacy;
- [redacted] was lost to follow-up.

It was notable to the EAG that only one person discontinued due to AE and no people discontinued due to lack of efficacy. However, the EAG was aware that “withdrawal due to physician decision” and “people withdrew from the study” could be linked to lack of efficacy.

3.2.2.2. Intervention

In **VANGUARD** and in CSL-study-naïve people in **CSL312_3002**, participants received a 400 mg loading dose of garadacimab SC as two 200 mg injections, followed by additional self-

administered (or caregiver-administered) monthly doses of 200-mg garadacimab SC. This dose is in line with the company's marketing authorisation and with the treatment pathway in the UK.

3.2.2.3. Comparator

In **VANGUARD** people received a volume-matched placebo on day one of the treatment period, followed by five additional self-administered (or caregiver-administered) monthly doses of subcutaneous volume-matched placebo.

3.2.2.4. Outcomes

The outcomes relevant to the final scope by NICE reported in **VANGUARD**, the **VANGUARD** ≥2 attacks per month subgroup, and **CSL312_3002** (OLE) are summarised in Table 9. However, as noted in Table 7, **CSL312_3002** (OLE) did not have a control arm and all participants were treated with garadacimab.

Table 9: Outcomes reported in the included trials of garadacimab

	VANGUARD ITT	VANGUARD ≥2 attacks per month	CSL312_3002[a]
Angioedema attacks: frequency	✓	✓	✓
Angioedema attacks: severity	✓	✓	✓
Angioedema attacks: location [b]	×	×	×
Angioedema attacks: duration [b]	×	×	×
Attack-free period	✓	✓	✓
Time to first attack	✓	✓	✓
Need for acute treatment	✓	✓	✓
Mortality	✓	✓	✓
Adverse effects of treatment	✓	×	✓
Health-related quality of life (for patients and carers)	✓ EQ-5D-5L and AE-QoL (for patients)	✓ EQ-5D-5L and AE-QoL (for patients)	×

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; ITT, Intention-to-treat.

[a] No comparator arm. All participants used garadacimab.

[b] The proportion of patients with laryngeal attacks and the duration of angioedema attacks is included within later economic analysis but not clinical reporting

While the outcomes reported from **VANGUARD** and **CSL312_3002** (OLE) addressed most of the outcomes detailed in the final scope issued by NICE, the EAG noted that the location and duration of HAE attacks were not reported. However, the EAG's clinical experts were not concerned by this omission. They considered these outcomes to be adequately represented by reporting the number of HAE attacks requiring acute treatment, and the number of moderate and/or severe HAE attacks. They observed that, to many people with HAE, reducing the number of moderate or severe attacks is more important than reducing the overall number of attacks. People with HAE have systems in place and can cope with mild attacks and go about their day-to-day activities despite such attacks. However, moderate or severe attacks can be substantially more debilitating and potentially life-threatening. The outcomes collected in **VANGUARD** and **CSL312_3002** (OLE) are detailed in Table 10.

Table 10: Outcomes collected in VANGUARD and CSL312_3002 (adapted from Table 6, Doc B)

	VANGUARD	CSL312_3001
Primary outcomes	The primary endpoint was the investigator-assessed time normalised number of HAE attacks during the 6-month treatment period (Days 1 to 182). Symptoms of an HAE attack were recorded in a person's electronic diary and then assessed by the investigator at each monthly visit to confirm whether the symptoms represented an HAE attack.	The primary endpoint was TEAEs
Secondary endpoints	Three secondary efficacy endpoints comparing garadacimab 200 mg with placebo were tested in the following hierarchical order: • Percentage reduction in the monthly number of HAE attacks from baseline to the end of the treatment period • Number of people who were attack-free at the end of the treatment period • Percentage of people rating therapy as "good" or better with the SGART at the end of the treatment period Additional secondary efficacy endpoints were: • Attack rate reductions compared with the run-in period (defined as ≥50%, ≥70%, ≥90%, or 100% reduction) • Attack rates over prespecified timepoints (Month 1 to 3, Month 4 to 6, Month 1 to 6) • Number of attacks per month requiring rescue medication, and number of moderate or severe attacks per month	• Time-normalised number of HAE attacks • Percentage reduction in the number of HAE attacks per month compared with the run-in period (defined as ≥50%, ≥70%, ≥90%, or 100% reduction) • For people previously treated with garadacimab, the run-in period considered for this outcome was from their initial study (VANGUARD or CSL312_2001) • Time-normalised number of HAE attacks requiring on-demand/acute treatment • Time-normalised number of moderate or severe HAE attacks
Exploratory endpoints	• Time to first HAE attack • AE-QoL and EQ-5D-5L	• Time to first HAE attack (in garadacimab-naïve people)
Safety endpoints	• TEAEs • Deaths	See primary outcome

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HAE, hereditary angioedema; ITT, Intention-to-treat; SGART, Subject's Global Assessment of Response to Therapy; TEAEs, treatment-emergent adverse events.

3.2.2.5. Critical appraisal of the design of the studies

Critical appraisal for the **VANGUARD**, **CSL312_2001**, and **CSL312_3002** (OLE) was presented in D1.3 of the CS. For the RCTs (**VANGUARD**, **CSL312_2001**), the company used a critical appraisal checklist adapted from the CRD's guidance for undertaking reviews in health care.[30] The minimum criteria for assessment of risk of bias in RCTs were followed. The company answered yes/no/not clear to each of the seven criteria but offered no reasoning for this assessment. In addition, no overall risk-of-bias judgement was made for each study. Given these limitations it was not clear from the assessment presented how the risk of bias in studies caused by inadequacies in study design, conduct, or analysis may have led to the treatment effect being over or underestimated.

The company used a critical appraisal checklist adapted from Critical Appraisal Skills Programme (CASP) – "Making sense of evidence: 12 questions to help you make sense of a cohort study"[31] – for the non-randomised study (**CSL312_3002**). The checklist was focussed on assessing comparative non-randomised studies and had limited relevance to a single arm trial. However, the EAG recognised that there are no validated checklists for single arm trials and adapting a cohort checklist was acceptable. The company answered yes/no/not clear to each of the seven criteria but offered no reasoning for this assessment. Given the lack of reasoning offered for each of the criteria, it was not clear from the assessment presented, how the risk of bias caused by inadequacies in study design, conduct, or analysis may have influenced the treatment effect. However, the EAG understood that open-label, uncontrolled studies, are at an increased risk of bias as it is not possible to determine to what extent changes in the outcomes are due to reasons other than the treatment.

3.2.3. Description and critique of the results of the studies

In this section, the EAG report the efficacy and safety results from **VANGUARD** and **CSL312_3002** (OLE).

The efficacy results presented are from the final data cut-off at six months from **VANGUARD** (N=65). The results in the ≥2 attacks per month subgroup in **VANGUARD** (n=39) are reported alongside the ITT results. The EAG recognised this subgroup as most relevant to the optimised population the company was addressing in their submission.

Efficacy evidence is also presented from the [redacted] data cut-off of **CSL312_3002**, which included 161 people with a median (min, max) duration of treatment of [redacted] ([redacted], [redacted]) months.

A summary of all the efficacy results for the ITT population and ≥2 attacks per month subgroup is presented in Table 11.

3.2.3.1. Number of HAE attacks

After six months of treatment in **VANGUARD** (ITT), the mean (95% CI) number of attacks per month was 0.27 (0.05, 0.49) in the garadacimab arm and 2.01 (1.44, 2.57) in the placebo arm. The relative difference in means (95% CI) was −86.5% (−95.7, −57.8; p<0.001). The EAG interpreted this as strong evidence that treatment with garadacimab will result in people having substantially fewer HAE attacks when compared to placebo. [redacted] with the ITT population, **VANGUARD** found a [redacted] for garadacimab [redacted] placebo in the ≥2 attacks per month subgroup ([redacted]*). The results from **CSL312_3002** (OLE) were [redacted] to the garadacimab arm in **VANGUARD**.

3.2.3.2. Reduction from baseline in the number of HAE attacks

At the end of the 6-month treatment period in **VANGUARD**, the ITT population treated with garadacimab experienced a 90.7% (95% CI: 83% to 98%) mean reduction in attacks from baseline, which was significantly greater compared to a reduction of 20.2% (95% CI: 2% to 38%) with placebo (p<0.0001). The results in the **VANGUARD** ≥2 attacks per month subgroup [redacted] ITT population and the results from **CSL312_3002** (OLE) were [redacted] to the garadacimab arm in **VANGUARD**.

3.2.3.3. Proportion of patients achieving attack freedom

The proportion of patients achieving attack freedom (95% CI) was 61.5% (45.9% to 75.1%) in the garadacimab arm and 0% (0% to 13.8%) in the placebo arm in the **VANGUARD** ITT population (p<0.001). The proportion achieving attack freedom was [redacted] in the ≥2 attacks per month subgroup treated with garadacimab ([redacted]%). The results from **CSL312_3002** (OLE) were [redacted] to the garadacimab arm in **VANGUARD**. The EAG considered it notable that over half of the people in the garadacimab arm achieved attack freedom over six months in **VANGUARD,** compared to zero people in the placebo arm.

3.2.3.4. Number of HAE attacks requiring on-demand/acute treatment

In **VANGUARD** (ITT), the mean (95% CI) number of attacks requiring acute therapy per month was 0.23 (0.02 to 0.45) in the garadacimab arm and 1.86 (1.26 to 2.46) in the placebo arm. The relative difference in means was −87.5% (p<0.001). The EAG interpreted this as strong evidence that treatment with garadacimab would lead to a reduction in the use of acute therapy

when compared to placebo. Consistent with the ITT population, **VANGUARD** found a [redacted] for [redacted] in the ≥2 attacks per month subgroup ([redacted]). The results reported from **CSL312_3002** (OLE) were [redacted] to the garadacimab arm in **VANGUARD**. The company also reported that in **VANGUARD**, [redacted]% of HAE attacks in people treated with garadacimab required acute treatment compared with [redacted]% in people treated with placebo.

3.2.3.5. Number of moderate or severe HAE attacks

In **VANGUARD** (ITT), the mean (95% CI) number of moderate and/or severe HAE attacks per month was 0.13 (0.03 to 0.22) in the garadacimab arm and 1.35 (0.86 to 1.84) in the placebo arm. The relative difference in means was −90.4% (p<0.001). Consistent with the ITT population, **VANGUARD** found a [redacted] for garadacimab [redacted] placebo in the ≥2 attacks per month subgroup ([redacted]). The results reported from **CSL312_3002** (OLE) were [redacted] the garadacimab arm in **VANGUARD**. The EAG interpreted this as strong evidence that treatment with garadacimab would lead to a reduction in the number of moderate or severe HAE attacks when compared to placebo. The EAG's clinical experts also noted that a reduction in moderate or severe attacks is the most important outcome of treatment for many people with HAE.

3.2.3.6. Time to first HAE attack

In **VANGUARD**, time to first HAE attack for 75% of patients was ≥72 days for garadacimab compared with ≥5 days for placebo. The median time to first attack was not estimable for garadacimab (more than 50% of patients were attack-free during the 6-month treatment period) and was 11 days for placebo. In people who were previously naïve to garadacimab in **CSL312_3002**, the median time to first attack was ~[redacted] ([redacted]).

Table 11: Clinical effectiveness results from the included clinical trials (reproduced from Table 10, Doc B)

	VANGUARD				CSL312_3002		Pooled VANGUARD/CSL312_3002
	ITT population		≥2 attacks per month		ATS population	Gara-naïve subpopulation	Patients who received gara throughout both studies
	Gara (n=39)	Placebo (n=24)	Gara (n=[redacted])	Placebo (n=[redacted])	Gara (n=161)	Gara (n=90)	Gara (n=36)
Number of evaluable patients, n (%)	39 (100.0)	24 (96.0)[a]	[redacted]	[redacted][a]	161 (100.0)	90 (100.0)	36 (100.0)
Mean (95% CI) number of HAE attacks per month at baseline	3.07 (2.41, 3.73)	2.52 (2.13, 2.91)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of HAE attacks							
Mean (95% CI) number of attacks per month	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (95% CI) number of attacks per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	p<0.001		[redacted]		N/A	N/A	N/A
Relative difference in means (95% CI); p-value	−86.5% (−95.7, −57.8); p<0.001		[redacted]		N/A	N/A	N/A
Reduction from baseline in monthly HAE attacks							
Mean reduction in monthly HAE attacks in the treatment period vs. the run-in period[b], % (95% CI)	90.7% (83.4, 97.9)	20.2% (2.2, 38.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	<0.001		[redacted]		N/A	N/A	N/A
Proportion of patients achieving attack freedom (i.e. 100% reduction in HAE attacks from baseline)							
Proportion of patients, % (95% CI)	61.5% (45.9, 75.1)	0.0% (0.0, 13.8)	[redacted] (NR)	[redacted] (NR)	[redacted]	[redacted] (NR)	[redacted] (NR)
p-value	p<0.001		[redacted]		N/A	N/A	N/A
Number of HAE attacks requiring on-demand/acute therapy							
Mean (95% CI) number of attacks per month	0.23 (0.02, 0.45)	1.86 (1.26, 2.46)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	VANGUARD				CSL312_3002		Pooled VANGUARD/CSL312_3002
	ITT population		≥2 attacks per month		ATS population	Gara-naïve subpopulation	Patients who received gara throughout both studies
	Gara (n=39)	Placebo (n=24)	Gara (n=[redacted])	Placebo (n=[redacted])	Gara (n=161)	Gara (n=90)	Gara (n=36)
Mean (95% CI) number of attacks per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	<0.001		[redacted]		N/A	N/A	N/A
Relative difference in means	−87.5%		[redacted]		N/A	N/A	N/A
Number of moderate or severe HAE attacks							
Mean (95% CI) number of attacks per month	0.13 (0.03, 0.22)	1.35 (0.86, 1.84)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (95% CI) number of attacks per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	<0.001		[redacted]		N/A	N/A	N/A
Relative difference in means	−90.4%		[redacted]		N/A	N/A	N/A
Time to first HAE attack							
Median (min, max) time to first attack after Day 1 of treatment, days	NE [redacted]	11 [redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]

Abbreviations: ATS, all treated patients; CI, confidence interval; gara, garadacimab; H01, first hierarchical test; H02, second hierarchical test; HAE, hereditary angioedema; ITT, intention-to-treat; max, maximum; min, minimum; N/A, not applicable, NE, not evaluable; NR, not reported.

Note: results are presented for the entire treatment period, defined as Days 1–182 for the VANGUARD study (6 months), and up to the latest data cut-off ([redacted]) for the CSL312_3002 study (with a median [min, max] treatment duration of [redacted]). For the pooled analyses, the median (min, max) treatment duration was [redacted] ([redacted], [redacted]) months.

[a] One patient in the placebo group stayed in the treatment period <30 days and was excluded from the analysis, as per the clinical study protocol.

[b] For roll-over patients, the Run-in Period of the previous study was used to determine the baseline attack rate.

3.2.3.7. Maintenance of treatment effect

The company conducted a post-hoc pooled analysis of **VANGUARD** and **CSL312_3002** (OLE) in people who were randomised to garadacimab in VANGUARD and rolled over to **CSL312_3002** (OLE) (n=36). This resulted in a population of 36 people who had been treated with garadacimab for a median (min, max) of [redacted] ([redacted]) months. The company provided baseline characteristics for this subpopulation in Table 1 in Appendix O. The baseline demographics and HAE history characteristics for these people were similar to the **VANGUARD** ITT population and the **CSL312_3002** (OLE) all treated patients (ATS) population. Results from the post-hoc analysis did not find evidence of waning of treatment effect after two years of treatment. However, the EAG caution that this was a post-hoc analysis based on a small sample.

Figure 5: Percentage reduction in time-normalised number of HAE attacks per month, monthly time windows (VANGUARD/CSL312_3002 pooled population; reproduced from Figure 13, Doc B)

Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema; no., number; Q4W, once every 4 weeks; SC, subcutaneous; time-norm., time-normalised.

Notes: The percentage reduction in the time-normalised number of HAE attacks was calculated within a patient as: 100*[1–(time-normalised number of HAE attacks per month during treatment period/time-normalised number of HAE attacks per month during run-in period)]. 1 week is equal to 7 days, 1 month is equal to 28 days. Pooled population includes patients who were on active treatment in VANGUARD and rolled over into CSL312_3002. Data are from completed study VANGUARD (CSL312_3001) and the latest ([redacted], IA4) data cut-off from study CSL312_3002, with a median (min, max) duration of exposure of [redacted] ([redacted]) months.

The company also presented post-hoc pooled analysis of 36 people from **VANGUARD** and **CSL312_3002** (OLE) for the time to first HAE attack after Day 1 (Figure 6). The company noted that the efficacy of garadacimab in prolonging the time to first attack was maintained through to the latest data cut-off of **CSL312_3002** (OLE), with median time to first attack not reached as

most people remained attack-free ([redacted]%). However, the EAG again caution that this was a post-hoc analysis based on a small sample.

Figure 6: Kaplan-Meier curve for time to first HAE attack after Day 1 (VANGUARD/CSL312_3002, pooled population; reproduced from Figure 3, clarification response)

Abbreviation: CSL312, garadacimab; HAE, hereditary angioedema.

Notes: Shaded areas represent 95% CIs. VANGUARD/CSL312_3002 pooled population includes all rollover patients from the CSL312_3001 (VANGUARD) study into CSL312_3002, who received monthly 200 mg garadacimab in VANGUARD and CSL312_3002. Note that the numbers above show the number of patients at risk.

3.2.3.8. Patient-Reported Outcome Measures

The patient-reported outcomes (PROs) collected in **VANGUARD** were EQ-5D-5L, the Angioedema QoL (AE-QoL) questionnaire, and the Subject's Global Assessment of Response to Therapy (SGART), and the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire. The EAG's clinical experts stated that EQ-5D-5L and AE-QoL were both validated for HAE and routinely reported in trials. The company presented results for EQ-5D-5L, AE-QoL, and SGART in Document B of the CS, and the EAG will concentrate on these PROs in this section.

EQ-5D-5L

The EAG have judged the differences between the treatment arms using minimally important differences (MIDs) reported in Cheng at al. (2024).[32] Cheng et al. recommended an MID of 6.5 for EQ-5D-5L VAS and 0.04 for EQ-5D-5L HSUV.

At baseline, there were differences in mean EQ-5D-5L domain scores, visual analogue scale (VAS) and overall health-state utility values (HSUVs) between the treatment arms in the **VANGUARD** ITT population and the subgroup who had ≥2 HAE attacks per month. The company stated in Section B.2.6.8.1 of the CS that the baseline EQ-5D-5L scores were comparable between garadacimab and placebo treatment arms and, given the proximity to the MIDs published in Cheng at al. (2024), the EAG accepted this.

Garadacimab demonstrated a [redacted] placebo in EQ-5D-5L VAS score in the ITT population (Table 12). The mean difference and 95% confidence interval [redacted] the published MID. Garadacimab also demonstrated a [redacted] in EQ-5D-5L HSUV score [redacted] placebo where the mean difference [redacted] the published MID. The EAG interpreted this as strong evidence that garadacimab [redacted] in quality of life in people with HAE who have at least one attack per month.

Table 12: EQ-5D change from baseline scores (ITT population, VANGUARD, adapted from Table 5, clarification response)

	Garadacimab					
	Mean (95% CI) at baseline	**Mean (95% CI) at end of treatment**	**Change score (95% CI)**	**P value**	**Mean difference (95% CI) versus placebo**	**P value**
EQ-5D-5L VAS score	N=37	N=38	N=[redacted]			
EQ-5D-5L HSUV score	N=37	N=38	N=[redacted]			
	Placebo					
EQ-5D-5L VAS score	N=24	N=23	N=[redacted]		N/A	N/A
EQ-5D-5L HSUV score	N=24	N=23	N=[redacted]		N/A	N/A

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HSUV, health-state utility values; ITT, Intention-to-treat; VAS, Visual Analogue Scale.

At the clarification stage (A12), the company reported EQ-5D-5L results for the **VANGUARD** subgroup who had ≥2 HAE attacks per month at baseline. The results, presented in Table 13, were [redacted] to the results in the ITT population. Garadacimab demonstrated a [redacted] placebo in EQ-5D-5L VAS score. The mean difference and 95% confidence interval [redacted] the published MID. Garadacimab again demonstrated a [redacted] in EQ-5D-5L HSUV score over placebo, where the mean difference [redacted] the published MID. The EAG interpreted this as evidence that garadacimab provides a [redacted] in quality of life in the people who have ≥2 HAE attacks per month.

Table 13: EQ-5D change from baseline scores (patients experiencing ≥2 HAE attacks per month at baseline, VANGUARD, adapted from Table 6, clarification response)

	Garadacimab					
	Mean at baseline	**Mean at end of treatment**	**Change score (95% CI)**	**P value**	**Mean difference (95% CI) versus placebo**	**P value**
EQ-5D-5L VAS score	N=[redacted]	N=[redacted]	N=[redacted]		[redacted]	
EQ-5D-5L HSUV score	N=[redacted]	N=[redacted]	N=[redacted]		[redacted]	
	Placebo					
EQ-5D-5L VAS score	N=[redacted]	N=[redacted]	N=[redacted]		N/A	N/A
EQ-5D-5L HSUV score	N=[redacted]	N=[redacted]	N=[redacted]		N/A	N/A

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HSUV, Health-state utility values; VAS, Visual Analogue Scale.

Angioedema QoL

The AE-QoL questionnaire is a disease-specific instrument to assess QoL impairment in people with recurrent angioedema attacks. This was reported in the ITT population in the CS and in the

≥2 HAE attacks per month subgropup at the clarification stage. The results, in both the ITT population and the ≥2 HAE attacks per month subgroup, are presented below in Table 14. The placebo arm had [redacted] AE-QoL scores at [redacted] indicating [redacted] quality of life. It was unclear to the EAG whether this made the placebo arm harder to treat but noted that the difference at baseline was unlikely to bias the results in favour of the garadacimab arm.

The **VANGUARD** results demonstrated a [redacted] for garadacimab [redacted] placebo for AE-QoL, [redacted] ITT population [redacted] subgroup who had ≥2 HAE attacks per month. The EAG interpreted this as complementary evidence, to the EQ-5D-5L results, of the [redacted] of garadacimab in quality of life.

Table 14: AE-QoL change from baseline scores (ITT population/ people experiencing ≥2 HAE attacks per month at baseline, VANGUARD, adapted from Table 5 & 6, clarification response)

	Mean (95% CI) at baseline	Mean (95% CI) at end of treatment	Change score (95% CI)	P value	Mean difference (95% CI) versus placebo	P value
	Garadacimab					
ITT population	N=34	N=34	N=[redacted]			
	38.75 [redacted]	11.72 [redacted]	-26.47 [redacted]	[redacted]	[redacted]	[redacted]
≥2 HAE attacks per month subgroup	N=[redacted]	N=[redacted]	N=[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo					
ITT population	N=22	N=21	N=[redacted]			
	43.65 [redacted]	39.37 [redacted]	[redacted]	[redacted]	N/A	N/A
≥2 HAE attacks per month subgroup	N=[redacted]	N=[redacted]	N=[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; CI, confidence interval; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HSUV, Health-state utility values; ITT, Intention-to-treat; VAS, Visual Analogue Scale.

Subject's Global Assessment of Response to Therapy

The overall response to treatment with the investigational product was self-assessed by the trial participants using the Subject's Global Assessment of Response to Therapy (SGART) tool. The ratings used in SGART were:

- None: Worse or no response at all, not acceptable
- (1) poor: Very little response, not acceptable
- (2) fair: Some response, acceptable but could be better
- (3) good: Good response, acceptable
- (4) excellent: Excellent response, as good as can be imagined

The company did not comprehensively report SGART but stated that at the end of treatment (Day 182), the most frequently rated response to therapy in patients treated with garadacimab was "excellent" (65.8%) or "good" (15.8%), and in the placebo arm was "none" (41.7%). A significantly higher proportion of patients in the garadacimab group rated their response to therapy as "good or better" (81.6%) compared to 33.3% in the placebo arm ($p<0.0001$).

3.2.3.9. Pre-specified subgroups

In **VANGUARD**, the pre-specified subgroup analyses assessed several outcomes for (1) all people and (2) Japanese people. The company stated that the Japanese subgroup analysis was done to support with the regulatory approval process in Japan, and not because they expected a different efficacy profile for Japanese people. The EAG's clinical experts were not aware of any robust reasoning why the efficacy or safety of garadacimab would be altered by a person's ethnic background. The company also said subgroup analysis for adolescents (12-17 years old) and adults were conducted. The company stated in Section B.2.7.1 that the results in this subgroup were consistent with results observed in the overall study population. The EAG would have preferred for these data to be presented but recognised the adolescent subgroup was very small (n=5).

3.2.3.10. Safety

The company presented safety outcomes for **VANGUARD** in Appendix F of the CS and safety for **CSL312_3002** (OLE) in Section B.2.11 in Document B.

Extent of exposure

All 39 people in the garadacimab 200 mg arm in **VANGUARD** received all [redacted] scheduled SC injections (total of [redacted] injections), with a median duration of exposure of [redacted] years (range [redacted] to [redacted]) and a total exposure of [redacted] patient-years in the garadacimab arm. There were no user errors or device malfunctions, and all injections administered the full volume of investigational product.

In the [redacted] data cut-off in **CSL312_3002** (OLE), [redacted]% and [redacted]% of people had ≥12 and ≥18 months of exposure to garadacimab, respectively, with a median (min, max) duration of exposure of [redacted] ([redacted], [redacted]) months. The total garadacimab exposure was [redacted]patient-years and there had been no dose adjustments.

Adverse events in VANGUARD ITT population

An overview of adverse events during **VANGUARD** was presented in Table 25, Appendix F. In sum, during the 6-month treatment period, 75 adverse events (AEs) occurred in 25 (64%) of 39 people in the garadacimab arm and 54 adverse events occurred in 15 (60%) of 25 people in the placebo arm. The most common treatment-emergent adverse events (TEAEs) were upper-respiratory tract infections, nasopharyngitis, and headaches. One serious adverse event (SAE), a severe laryngeal attack, occurred in the garadacimab arm. No adverse events of special interest (anaphylaxis, thromboembolic events, or abnormal bleeding) occurred, and there were no deaths or treatment discontinuations due to AEs.

Injection-site reactions occurred in two (5%) people in the garadacimab arm and three (12%) people in the placebo arm. As previously noted, **VANGUARD** used pre-filled syringes to administer garadacimab, but it is expected that a pre-filled pen (autoinjector device) will be used in the NHS. The EAG's clinical experts did not consider using an autoinjector device would necessarily lead to increased injection-site reactions in comparison to using a pre-filled syringe.

The company concluded that the safety profile of garadacimab was similar to placebo, with no major safety signals identified during the study period. However, the EAG noted that there were substantially more moderate AEs in the garadacimab arm than the placebo arm, and the single severe AE occurred in the garadacimab arm. Nevertheless, there was only one SAE in the trial and no adverse events led to study drug discontinuation. In conclusion, while the EAG did not consider the AE profile of garadacimab to be the same as placebo, it accepted that there were no major safety signals identified in **VANGUARD**.

Adverse events in CSL312_3002 extension study

The safety and tolerability of garadacimab was assessed in the full safety analysis population of the phase 3 open-label **CSL312_3002** (OLE; N=161). This was reported in Table 13 in Document B.

At the [redacted] data cut-off, [redacted]% of patients experienced ≥1 treatment-emergent adverse event (TEAEs). [redacted] ([redacted]%) people experienced a mild AE, [redacted] ([redacted]%) people experienced a moderate AE, and [redacted] ([redacted]%) experienced a severe AE. [redacted] ([redacted]%) people discontinued the study due to AEs. A total of [redacted] serious adverse events (SAEs) were reported, which included [redacted] cases of COVID-19, [redacted] HAE attack and [redacted] drug reaction/eruption.[27] The company stated [redacted] SAEs were resolved by the time of the data cut-off and [redacted] were considered to be related to study treatment or led to study discontinuation. There were [redacted] deaths due to TEAEs and [redacted] patients were assessed by the investigator as experiencing an adverse event of special interest (AESI) as per the study protocol. The EAG interpreted this as further evidence that there were no major safety signals linked to treatment with garadacimab.

3.2.4. Conclusions of the clinical effectiveness results

The pivotal, randomized, placebo-controlled trial (**VANGUARD**) recruited a population with HAE who experienced ≥1 attack per month in the study run-in period. The EAG's clinical experts stated that the participants recruited to **VANGUARD** were similar to the people they see in their practices. The company positioned garadacimab as a treatment for people with HAE who have ≥2 attacks per month and people with HAE who have ≥2 attacks per week. In line with this positioning, the company presented baseline characteristics and efficacy data for people in **VANGUARD** who had ≥2 attacks per month at baseline. However, it was unclear how many participants in **VANGUARD** had ≥2 attacks per week, and no baseline characteristics or efficacy data were presented for this subgroup.

The pivotal trial demonstrated that people receiving garadacimab had meaningful reductions in HAE attacks compared to placebo, including moderate or severe attacks, and attacks that required acute treatment. More than half of the people on garadacimab were attack-free the entire 6-month treatment period compared to zero people on placebo. The company conducted a post-hoc pooled analysis in people who were randomised to garadacimab in **VANGUARD** and rolled over to the OLE (**CSL312_3002,** n=36). This analysis did not find evidence of waning of

treatment effect after two years of treatment, although this was a post-hoc analysis based on a small sample.

Garadacimab also demonstrated a clinically important benefit in quality of life (EQ-5D-5L / AE-QoL) when compared to placebo, and the garadacimab trials did not raise any concerns in relation to safety.

In sum, based on the evidence presented, the EAG considered garadacimab to be a safe, effective medication in reducing HAE attacks, and in doing so, it provided a quality-of-life benefit. This may in part be linked to a reduction in a person with HAE's anxiety – that at any time they could be subject to a debilitating, painful and potentially life-threatening attack. There was some evidence that treatment efficacy does not wane after two years, but longer follow-up is required to establish this.

3.3. Critique of trials identified and included in the indirect comparisons

The company presented a network meta-analysis (NMA) and multi-level network meta regression (ML-NMR) in the CS. The NMA was presented in the initial submission, and the ML-NMR was presented seven days later in Appendix T.

The company presented the ML-NMR to *"to supplement the existing NMA used in the company's cost-effectiveness model by further exploring the base case assumption that there is no evidence of treatment effect modification that would necessitate adjustment, be it for garadacimab or the comparator technologies"*.

The company identified trials through a SLR investigating LTP treatments in people with HAE. The SLR was conducted from database inception to April 8, 2024, then subsequently updated on August 5, 2024. The six LTP treatments considered for the analysis were:

- Garadacimab
- Subcutaneous (SC) C1-INHs (SC Berinert/Haegarda)
- Berotralstat (Orladeyo)
- Lanadelumab (Takhzyro) every two weeks
- Lanadelumab (Takhzyro) every four weeks
- Intravenous (IV) C1-INHs (Cinryze/IV Berinert)

The relevant lanadelumab dose for initial treatment of HAE was once every two weeks, as that is understood to be the most effective dose and is the initial dose offered to people with HAE. The EAG's clinical experts advised that people who are stable on lanadelumab every two weeks may have their dose reduced to lanadelumab every four weeks. This is offered to people because it may lead to fewer adverse events with no noticeable change in efficacy. People who do notice a reduction in efficacy may revert to lanadelumab every two weeks. The EAG noted that Magerl et al. (2024) found most people (75.7%) who changed to lanadelumab every four weeks did not return to the lanadelumab every two weeks, and attack frequency rates were reduced (rather than increased) following the switch, which the authors consider to be due to the effect of longer exposure.[33]

As noted by the company in Table 1 in Document B, SC C1-INHs, such as SC Berinert (Haegarda), and are not routinely commissioned in UK practice for the prevention of recurrent HAE attacks, despite having marketing authorisation for this use. Also, SC C1-INHs were not comparators in the final scope issued by NICE. From this point forward in the report, the EAG will refer to "SC Berinert", rather than SC C1-INHs, to prevent any confusion with IV C1-INHs (Cinryze/IV Berinert), which are comparators for this appraisal.

3.3.1. Feasibility Assessment

The company undertook a feasibility assessment to assess the extent of clinical heterogeneity across the studies identified in the clinical SLR. This was reported for the NMA in Section 3.2 of the company's NMA report and, briefly, in Appendix T, in relation to the ML-NMR.

3.3.1.1. Studies included in the indirect comparison

The company included 20 studies (Page 19, Appendix D) in the SLR. Based on eligibility criteria, which were not clearly reported, the company included six trials investigating five LTP treatments in the indirect treatment comparisons (ITC). The company did not identify any RCTs that could be included in the network for IV Berinert. The company noted that the RCT for Cinryze (CHANGE) was a crossover trial.[34] In Section 3.2 of the NMA report the company stated "[redacted]". Therefore, no trials were included in the company's base case ITCs investigating IV C1-INHs (Cinryze/IV Berinert).

The studies included in the ITC are detailed in Table 15. The EAG were not aware of any studies that were incorrectly excluded. All the included studies were multicentre, double-blind,

randomised, placebo-controlled trials. **COMPACT** was a crossover trial, SC Berinert (outside of the NICE scope) versus placebo, but results relevant to the analysis prior to crossover were used in the ITC.

The EAG noted four key differences between the trials in the ITC:

- Five of the trials were phase 3 trials but one garadacimab trial, **CSL312_2001**, was a phase 2 trial. The company noted this inconsistency and presented a sensitivity analysis removing the phase 2 trial in the NMA.
- Five trials recruited people aged at least 12 years old and one trial (**CSL312_2001**) recruited adults who were at least 18 years old.
- Trials differed in terms of the number of HAE attacks participants were required to have at baseline. It was not clear to the EAG whether differences in baseline attack rate made people more or less responsive to treatment. However, it was notable that the ML-NMR only adjusted for baseline HAE attack rate in the time-normalised family of outcomes.
- Inconsistency between the trials in how the severity of attack was graded (Table 15). 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].[35] 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.

Table 15: Trials used in the ITCs presented in the CS (adapted from Table 7, Clarification Response)

	VANGUARD[36]	CSL312_2001[36]	COMPACT[37]	HELP[38]	APeX-2[39]	APeX-J[40]
Study design	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm with cross-over	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Multicenter • Double-blind • Randomised • Placebo-controlled • Parallel-arm	• Single-country • Double-blind • Randomised • Placebo-controlled • Parallel-arm
Study phase	• Phase 3 trial	• Phase 2 trial	• Phase 3 trial	• Phase 3 trial	• Phase 3 trial	• Phase 3 trial
Intervention(s) *Bolding denotes licensed dosage*	• **Garadacimab 200 mg once monthly (n=39)**	• Garadacimab 75 mg Q4W (n=9) • **Garadacimab, 200 mg Q4W (n=8)** • Garadacimab 600 mg Q4W (n=7)	• SC Berinert/Haegarda 0.08 mL/kg (40 IU/kg) twice weekly (n=45) • **SC Berinert/ Haegarda 0.12 mL/kg (60 IU/kg) twice weekly (n=45)**	• **Lanadelumab 300 mg Q2W (n=27)** • **Lanadelumab 300 mg Q4W (n=29)** • Lanadelumab 150 mg Q4W (n=29)	• Berotralstat 110 mg daily (n=41) • **Berotralstat 150 mg daily (n=40)**	• Berotralstat 110 mg daily (n=6) • **Berotralstat 150 mg, daily (n=7)**
Comparator	Placebo (n=29)	Placebo (n=8)	Placebo (n=90)	Placebo (n=41)	Placebo (n=40)	Placebo (n=6)
Inclusion criteria	• Male or female • ≥12 years • Type I or II HAE • ≥3 HAE attacks during the 3 months before screening[a] • At least an average of 1 HAE attack per month during Run-in period	• Male or female • ≥18 years old • Type I or II HAE • ≥4 HAE attacks over 2 consecutive months, within the 3 months prior to screening or initiation of previous HAE prophylaxis	• Male or female • ≥12 years • Type I or II HAE • ≥4 HAE attacks over a consecutive 2-month period that required acute treatment[b]	• Male or female • ≥12 years • Type I or II HAE • ≥1 HAE attack per 4 weeks as confirmed during the run-in period	• Male or female • ≥12 years • Type I or II HAE • ≥2 attacks per month in the first 56 days of run-in period	• Male or female • ≥12 years • Type I or II HAE • ≥2 attacks per month in the first 56 days of run-in period
Total number of patients	N=68	N=32	N=180	N=125	N=121	N=19

	VANGUARD[36]	CSL312_2001[36]	COMPACT[37]	HELP[38]	APeX-2[39]	APeX-J[40]
How HAE attacks were recorded and reported	• Attacks were patient-reported and investigator-confirmed • Patient recorded details of HAE attack in an electronic diary • The investigator was able to ask clarifying questions to assist in their assessment of whether an attack occurred and its severity	• Attacks were patient-reported and investigator-confirmed • Patient recorded details of HAE attack in an electronic diary • The investigator was able to ask clarifying questions to assist in their assessment of whether an attack occurred and its severity	• Attacks were patient-reported and investigator-confirmed • The investigator reviewed the electronic diary at each trial visit	• Attacks were patient-reported and investigator-confirmed • During the study, patients were instructed to contact the study site within 72 hours of the onset of an attack. Attack details were assessed by trained site personnel following HAE Attack Assessment and Reporting Procedures and confirmed by the site investigator	• Attacks were patient-reported and investigator-confirmed • Patients recorded the frequency, duration, location, functional impact, and any treatment of HAE attacks experienced in the previous 24 hours in an electronic diary daily. • Investigators contacted patients within 2 business days of each reported attack to discuss and evaluate the event.	• Attacks were patient-reported and investigator-confirmed • Details of attacks were recorded by the patient in an electronic diary. Within approximately 2 business days of the end of each attack, patients were contacted by the investigator to discuss the attack. • An independent expert (an experienced HAE treater in Japan) was selected by the sponsor to review all reported angioedema attacks. The electronic diary and any investigator-collected information were used by the independent expert to either confirm or reject the attack.

	VANGUARD[36]	CSL312_2001[36]	COMPACT[37]	HELP[38]	APeX-2[39]	APeX-J[40]
How attack severity was graded	• Mild attacks were defined as having little-to-no effect on the patient's ability to perform daily activities and might not have necessarily required rescue medication but might have required treatment with other concomitant medications (eg, analgesics). • Moderate attacks were defined as having caused difficulty in performing daily activities or might have required assistance to perform these activities and the use of rescue medication was probable. • Severe attacks were defined as having caused substantial limitations in the patient's ability to perform daily activities, might have required medical assistance, and required the use of rescue medication		The company stated the details were not published but the EAG has taken the definitions from the lanadelumab appraisal consultation document [ID1268].[41] The overall severity of the patient's attack was determined by the investigator using the following definitions: • Mild: transient or mild discomfort. • Moderate: mild to moderate limitation in activity; some assisatnce required • Severe: marked limitatiion in activity; assistance required	• Mild attacks were defined as transient or mild discomfort [<48 hours]; no medical intervention/therapy required • Moderate attacks were defined as mild to moderate limitation in activity; some assistance required; no or minimal medical intervention/therapy required • Severe attacks were defined as marked limitation in activity, assistance required; medical intervention/therapy required, hospitalisation possible • Life threatening attacks were defined as extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalisation or hospice care probable	Details not published. However, in the NICE appraisal of berotralstat [ID1624], 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 instead proposed the use of more objective measures.[35]	Details not published

	VANGUARD[36]	CSL312_2001[36]	COMPACT[37]	HELP[38]	APeX-2[39]	APeX-J[40]
Site of treatment administration	The first dose and the first 3 subsequent injections were administered by the patients or caregiver at the study site under supervision by the investigator or delegate. Subsequent doses were self-administered with or without supervision of the investigator or delegate.	All subcutaneous doses of investigational product were self administered under supervision of the investigator or delegate at the study site.	Patients were trained to administer the injections at home.	Treatment was administered at the study site by the principal investigator or qualified site personnel.	Patients took study drug doses at home with the exception of study drug that was administered under Investigator (or designee) supervision during scheduled on-treatment clinic	Patients took study drug doses at home with the exception of study drug that was administered under Investigator (or designee) supervision during scheduled on-treatment clinic visits
	No published data available; post-hoc analyses for ≥2 attacks per month were presented in the company submission	No data available	No published data found	No published data found	No published data found	No published data found
Access to on-demand/acute treatment during the trial	The following acute HAE therapies were permitted at any time during the study for the treatment of HAE attacks: • Plasma-derived or recombinant C1-INH • Icatibant • Ecallantide	The following acute HAE therapies were permitted at any time during the study for the treatment of HAE attacks: • Plasma-derived or recombinant C1-INH • Icatibant • Ecallantide	Patients were permitted to use intravenous C1 inhibitor concentrate, icatibant, ecallantide, or fresh-frozen plasma as a rescue medication for acute treatment of attacks	Treatment of attacks followed the site investigator's standard of care, which could include intravenous C1 inhibitor, icatibant, or ecallantide	Patients had access to and ability to use one or more acute medications approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH).	Patients had access to and ability to use an acute treatment for angioedema events approved by the Japan Ministry of Health, Labor, and Welfare (plasma-derived C1-INH or icatibant).

	VANGUARD[36]	CSL312_2001[36]	COMPACT[37]	HELP[38]	APeX-2[39]	APeX-J[40]
Site of treatment administration	The first dose and the first 3 subsequent injections were administered by the patients or caregiver at the study site under supervision by the investigator or delegate. Subsequent doses were self-administered with or without supervision of the investigator or delegate.	All subcutaneous doses of investigational product were self-administered under supervision of the investigator or delegate at the study site.	Patients were trained to administer the injections at home.	Treatment was administered at the study site by the principal investigator or qualified site personnel.	Patients took study drug doses at home with the exception of study drug that was administered under Investigator (or designee) supervision during scheduled on-treatment clinic visits	Patients took study drug doses at home with the exception of study drug that was administered under Investigator (or designee) supervision during scheduled on-treatment clinic visits
Subgroup analyses by baseline attack rate	No published data available; post-hoc analyses for ≥2 attacks per month were presented in the company submission	No data available	No published data found	No published data found	No published data found	No published data found

Abbreviations: C1-INH, C1-Inhibitor; HAE, hereditary angioedema; NICE, National Institute for Health and Care Excellence; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

3.3.1.2. Critical appraisal of the studies used in the indirect comparison

Critical appraisal for **VANGUARD**, **APeX-1**, **APeX-2**, **APeX-J**, **CHANGE**, **COMPACT**, **CSL312_2001**, and **HELP** were presented in D1.3 of the CS. The company used a critical appraisal checklist adapted from the CRD's guidance for undertaking reviews in health care.[30] The minimum criteria for assessment of risk of bias in RCTs were followed. The company answered yes/no/not clear to each of the seven criteria but offered no reasoning for this assessment. In addition, no overall risk-of-bias judgement was made for each study. Given these limitations it was not clear from the assessment presented how the risk of bias in included studies caused by inadequacies in study design, conduct or analysis may have led to the treatment effect being over or underestimated.

3.4. Critique of the indirect comparisons

3.4.1. Network meta-analysis

The EAG presents relevant details of the outcomes, methodology and the results of the company's and EAG's preferred NMA analyses in this section.

3.4.1.1. Outcome measures used in the NMA

The company assessed the feasibility of including efficacy and safety outcomes in in Section 3.2 of the company's NMA report. The outcomes considered feasible for the NMA and the timepoint of measurement for each study are detailed below in Table 16.

The company did not consider either the "time to first HAE attack" or the "patients who had ≤1 attack in 6 months" efficacy outcomes feasible for NMA. While the company did not offer details of why these outcomes were not suitable, this did not concern the EAG unduly as they were not used in the company's economic model and were not required for the EAG's base case. The safety outcomes not considered suitable for NMA were deaths, serious treatment-emergent adverse events (STEAEs), discontinuations due to adverse events, all-cause discontinuations, and hospitalisations.

However, the EAG was concerned about the quality-of-life outcome used in the NMA and requested clarification (A15) from the company on their use of disease-specific AE-QoL measure over the NICE preferred EQ-5D measure. The company responded highlighting limited evidence to facilitate this comparison in the NMA. The EAG noted that the reporting of EQ-5D was incomplete across trials, with heavily redacted outcomes and idiosyncratic reporting. **HELP**

does not present an uncertainty measure around their estimates e.g. standard deviation or confidence intervals at baseline or follow-up and does not present data for the between arm difference. Likewise, **APEX-2** also does not present this data. Without this information the EAG noted that it is not possible to use these studies in an NMA. Completing a NMA using only **COMPACT** and **VANGUARD** between arm differences would be of limited value.

Table 16: Summary of outcomes measured for the NMA and timepoint of measurement for each study (adapted from Table 8, Clarification Response)

Outcome	VANGUARD	CSL312_2001	COMPACT	HELP	APeX-2	APeX-J
Time-normalised number of HAE attacks	26 weeks	12 weeks	16 weeks	26 weeks	24 weeks	24 weeks
Time-normalised number of HAE attacks requiring on-demand/acute treatment	26 weeks	12 weeks	16 weeks	26 weeks	24 weeks	24 weeks
Time-normalised number of moderate and/or severe attacks	26 weeks	12 weeks	16 weeks	26 weeks	24 weeks	24 weeks
Proportion of attack-free patients	26 weeks	12 weeks	16 weeks	26 weeks	24 weeks	-
Attack-free days per month	26 weeks	12 weeks	16 weeks	26 weeks	-	-
Any TEAEs	26 weeks	12 weeks	16 weeks	26 weeks	24-weeks plus 30 days	-
Change from baseline in AE-QoL total score	26 weeks	-	-	-	24 weeks	24 weeks

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; NMA, network meta-analysis; TEAEs, treatment emergent adverse events.

3.4.1.2. Methodology of the network meta-analysis

The methods used for the NMA were reported briefly in Section B.2.10.1.1.2 of the CS and more fully in the company's NMA report.[42] The NMAs were conducted using a Bayesian framework. The company stated their methods were consistent with the Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) series.[43] The company presented results of a fixed-effect (FE) and random-effects (RE) NMA in the CS. In the company's NMA report, they also presented sensitivity analyses, including analyses incorporating all identified dosages (licensed and unlicensed, to increase patient data), sensitivity analysis incorporating the CHANGE trial to allow comparison to Cinryze and an analysis excluding the phase 2 trial (**CSL312_2001**), to increase homogeneity across the network. All sensitivity analyses were conducted using a FE model.

3.4.1.3. Shape of the network

While there was some difference between the networks used for each outcome, the shape of the network stayed the same. An example of the typical shape of the network is presented in Figure 7. Each of the trials compared the intervention to placebo. **HELP**, the lanadelumab trial, compared two doses of the active treatment, leading to a closed loop in the network.

Figure 7: Evidence network for time-normalized number of HAE attacks (reproduced from Figure 4.1, NMA report)

Abbreviations: GARA 200 QM, Garadacimab 200 mg once monthly; HAE, hereditary angioedema; HAEG 60 BIW, SC Berinert/Haegarda (SC C1-INH) 60 IU/kg twice weekly; ORL 150 QD, Orladeyo (berotralstat) 150 mg once daily; PBO, Placebo; TAK 300 mg Q2W, Takhzyro (lanadelumab) 300 mg once every 2 weeks; TAK 300 mg Q4W, Takhzyro (lanadelumab) 300 mg once every 4 weeks.

3.4.1.4. NMA assumptions and requirements

The EAG assessed the network based on the three assumptions underlying all indirect comparisons[44]:

1. All the trials included must be comparable in terms of potential effect modifiers, including trial or patient characteristics (assumption of similarity).
2. There must be no relevant heterogeneity between trial results in pairwise comparisons (assumption of homogeneity).
3. There must be no relevant discrepancy or inconsistency between direct and indirect evidence (assumption of consistency).

Similarity

The EAG discussed the trials in Section 3.3.1.1, and related the following concerns regarding their similarity:

- Five of the trials used in the company's base case NMA were phase 3 trials, but one garadacimab trial (CSL312_2001) was a phase 2 trial.
- Five trials recruited people aged at least 12 years old and one trial (CSL312_2001) recruited adults who were at least 18 years old.
- Each of the trials had different eligibility criteria related to baseline HAE attack rates (except APeX-2/ APeX-J).
- The approaches to grading severity of HAE attacks varied between trials leading to concerns related to the time-normalised number of moderate and/or severe attacks outcome.

Two of the EAG's concerns were related to the inclusion of **CSL312_2001** in the network. This could be addressed by using the sensitivity analysis presented by the company where the phase 2 trial was removed. The third concern was linked to differences in the baseline attack rates of people recruited to each trial. The company sought to address this through adjusting for differences in baseline attack rates in the ML-NMR, although decided against using those results in their economic model. The EAG's fourth concern was related to inconsistent definitions of attack severity used in the trials in the network – these inconsistent definitions disrupt the network's transitivity, introducing a bias in the NMA for the number of moderate and/or severe attacks outcome.

Homogeneity

Homogeneity could be assessed through two comparisons in the company's base case NMA:

- Garadacimab versus placebo (**VANGUARD** and **CSL312_2001**)
- Berotralstat versus placebo (**APeX-2** and **APeX-J**)

The EAG ran head-to-head analyses (Appendix A) for the two comparisons and judged heterogeneity based on the I^2 value. The Cochrane Handbook offered a rough guide to interpretation of I^2.[45]

In the head-to-head analysis of garadacimab versus placebo (**VANGUARD** and **CSL312_2001)** there was substantial heterogeneity between the trials for the number of HAE attacks, HAE attacks requiring on-demand/acute treatment, number of moderate and/or severe HAE attacks, and number of attack-free days using either a FE or RE model. Heterogeneity was low for the proportion of attack-free people and TEAEs. In the head-to-head analysis of berotralstat versus placebo (**APeX-2** and **APeX-J)** heterogeneity was low for all outcomes.

Consistency

There was a single closed loop in the network, connecting two doses of lanadelumab with placebo. No evidence of inconsistency was apparent between direct and indirect evidence within the closed loop.

3.4.1.5. Network meta-analysis model fit

NMAs can be conducted using a fixed effect (FE) or random effects (RE) model. In the NMA report,[42] the company detailed the model fit for the base case and sensitivity analysis for the NMAs run for seven outcomes. The EAG have reproduced this in Appendix B. Better model fit is indicated by lower deviance information criterion (DIC) scores. The company have used the FE analysis for all outcomes in their base case, but this is consistently not the model with the best fit. As noted in Section 3.4.1.4, there was considerable heterogeneity introduced to the network with the phase 2 trial (**CSL312_2001**). The company reported that the model with the best fit for [redacted] is the fixed effect model with the phase 2 trial (**CSL312_2001**) removed and, as such, this is the EAG's preferred NMA model.

3.4.1.6. Network meta-analysis results

The EAG considered the FE analysis that removed the phase 2 trial (**CSL312_2001**) fit the data best and has reported those results. See Section 3.4.1.7 for a summary of the EAG's preferred NMA (FE with phase 2 trial removed) and the company's preferred NMA (FE).

Time-normalised number of HAE attacks

This outcome was used to calculate attack rates in the EAG and company base case. The company presented the results of the FE and RE models in Table 16 of Document B. The NMA forest plot (Figure 8) found [redacted] to have a [redacted] placebo in reducing the number of HAE attacks. Garadacimab (GARA 200 QM) and lanadelumab (twice every 4 weeks; TAK 300 Q2W) were [redacted]. SC Berinert (HAEG

60 BIW) was [redacted] garadacimab or lanadelumab (every two weeks; TAK 300 Q2W). Lanadelumab (every 4 weeks; TAK 300 Q4W) [redacted], as noted in Section 2.3.4, it is not a first-line LTP for people with HAE and instead is utilised as a reduced dose option for people in whom lanadelumab (every 2 weeks) has been effective. Berotralstat (ORL 150 QD) was found to be [redacted] than the other active treatments.

The company also presented a sensitivity analysis for this outcome where they included an outcome form the **CHANGE** trial crossover trial comparing IV C1-INHs (Cinryze) to placebo (Section 4.2.1.4 NMA report). As noted in Section 3.3.1.1, the company stated that [redacted] and the company did not present the input data used from **CHANGE** in the NMA report. However, the company used the estimate of effect for IV C1-INHs (Cinryze) from the sensitivity analysis in the economic analysis. The addition of **CHANGE** to the NMA did not alter the effect estimates for the other active treatments. Cinryze had a [redacted] placebo and close to a [redacted] Berotralstat for the number of HAE attacks. It was [redacted] than garadacimab, Lanadelumab (either dose), or SC Berinert. However, given uncertainty around the validity of the input data, the EAG considered the results of the sensitivity analysis to be highly uncertain.

Figure 8: Forest plot (active treatments vs. PBO) for fixed effect NMA of time-normalized number of HAE attacks with phase 2 trial removed (reproduced from Figure 4.7, NMA report)

Abbreviations: CrI, credible interval; GARA 200 QM, Garadacimab 200 mg once monthly; HAE, hereditary angioedema; HAEG 60 BIW, SC Berinert/Haegarda (SC C1-INH) 60 IU/kg twice weekly; ORL 150 QD, Orladeyo (berotralstat) 150 mg once daily; PBO, Placebo; TAK 300 mg Q2W, Takhzyro (lanadelumab) 300 mg once every 2 weeks; TAK 300 mg Q4W, Takhzyro (lanadelumab) 300 mg once every 4 weeks.

Number of HAE attacks requiring on-demand/acute treatment

This outcome was used to calculate attack rates requiring acute treatment in the company and EAG economic model base cases. The NMA found garadacimab, lanadelumab every two weeks, and SC Berinert to be [redacted] treatments for preventing HAE attacks requiring on-demand/acute treatment. They were each [redacted] for this outcome. Lanadelumab every four weeks was [redacted] and berotralstat was [redacted] However, all the active treatments demonstrated a [redacted] placebo

Proportion of attack-free patients

This outcome was used to calculate calibrated attack rates in the economic model as reported in Appendix J of the CS. It was noted using the company base case analysis. The NMA (Figure 9) found garadacimab (GARA 200 QM), both lanadelumab doses (TAK 300), and SC Berinert (HAEG 60 BIW) demonstrated a [redacted] for proportion of attack-free patients. Berotralstat (ORL 150 QD) demonstrated a [redacted] over placebo.

Given the uncertainty of the estimates [redacted] by the [redacted] the EAG [redacted] consider it appropriate to conclude that garadacimab was [redacted] than the other treatments for proportion of attack-free patients. Notably, the input data for proportion of attack-free patients used in the NMA, were available in Table F.4 of the NMA report; the EAG note that [redacted] have contributed to this uncertainty.

Figure 9: Forest plot (active treatments vs. PBO) for fixed effect NMA of proportion of attack-free patients with phase 2 trial removed (reproduced from Figure 4.7, NMA report)

Abbreviations: CrI, credible interval; GARA 200 QM, Garadacimab 200 mg once monthly; HAE, hereditary angioedema; HAEG 60 BIW, SC Berinert/Haegarda (SC C1-INH) 60 IU/kg twice weekly; ORL 150 QD, Orladeyo (berotralstat) 150 mg once daily; PBO, Placebo; TAK 300 mg Q2W, Takhzyro (lanadelumab) 300 mg once every 2 weeks; TAK 300 mg Q4W, Takhzyro (lanadelumab) 300 mg once every 4 weeks.

Time-Normalized Number of Moderate and/or Severe HAE Attacks

The time-normalized number of moderate and/or severe HAE attacks NMA was not used in the company's economic model; instead, naïve inputs from trials and observational datasets were used. The NMA found all five active treatments to have a [redacted] placebo in reducing the number of moderate and/or severe HAE attacks. Garadacimab was [redacted] than lanadelumab (every two weeks) and SC Berinert, but it was unclear to the EAG whether this was a clinically important difference. Lanadelumab (once every

four weeks) was [redacted], but as noted in Section 3.3, it is not a first-line LTP for people with HAE and is used as a reduced dose for responders to lanadelumab (every two weeks). Berotralstat was found to be [redacted] than the other active treatments. However, as highlighted in Sections 3.3.1.1 and 3.4.1.4 there was inconsistency in the definitions of attack severity used in the trials in the network. Inconsistent definitions of outcomes disrupt the networks transitivity introducing a bias in the NMA.

Attack-free days per month

The NMA found all four active treatments to be [redacted] in increasing the number of attack-free days people experienced per month which was [redacted] SC Berinert was found to be [redacted] than garadacimab or lanadelumab (every two weeks). Garadacimab and lanadelumab (every two weeks) were [redacted] in increasing the number of attack-free days people experienced per month.

Any Treatment-Emergent Adverse Events

The NMA found people on garadacimab and SC Berinert had a [redacted] placebo. People on berotralstat and lanadelumab (once every 4 weeks) had [redacted] TEAEs than people on placebo. The NMA found that people on lanadelumab (every two weeks) had a [redacted] in TEAEs compared to placebo.

Change From Baseline in AE-QoL Total Score

The EAG have reproduced the FE model results in this section. The Angioedema Quality of Life (AE-QoL) questionnaire total score ranges from 0 to 100, with lower scores indicating better quality of life (QoL). The NMA (Figure 10) found garadacimab (GARA 200 QM) to be [redacted] in improving a person's HRQoL, using the AE-QoL scale, than either of the two lanadelumab (TAK 300) doses or berotralstat (ORL 150 QD). However, all active treatments [redacted] a [redacted] placebo in improving people's HRQoL.

Figure 10: Forest plot (active treatment vs. PBO) for fixed effect NMA of change from baseline in AE-QoL total score (reproduced from Figure 4.52, NMA report)

Abbreviations: CrI, credible interval; GARA 200 QM, Garadacimab 200 mg once monthly; HAE, hereditary angioedema; HAEG 60 BIW, SC Berinert/Haegarda (subcutaneous C1-INH) 60 IU/kg twice weekly; ORL 150 QD, Orladeyo (berotralstat) 150 mg once daily; PBO, Placebo; TAK 300 mg Q2W, Takhzyro (lanadelumab) 300 mg once every 2 weeks; TAK 300 mg Q4W, Takhzyro (lanadelumab) 300 mg once every 4 weeks.

3.4.1.7. Summary of results from the FE NMAs

The results from the EAG's preferred NMA (FE with phase 2 trial removed) and the company's preferred NMA (FE) are detailed in Table 17. The EAG's preferred NMA was [redacted] with the company's preferred NMA in the effect estimates for berotralstat, both doses of lanadelumab and SC Berinert. However, there were differences between the analyses in the effect estimates for garadacimab. The estimates of effect for garadacimab were marginally lower for number of HAE attacks, HAE attacks requiring on-demand/acute treatment, number of moderate and/or severe HAE attacks, and attack-free days per month in the NMA using a FE model with phase 2 trial removed. However, the EAG's preferred model found an increased proportion of attack-free people and reduced number of TEAEs. **CSL312_2001** (phase 2 trial) did not report the AE-QoL total score outcome and, as such, could not be used in the NMA.

Table 17: Summary of intervention versus placebo results using a fixed effect NMA with or without the phase 2 trial

Intervention versus placebo	**Garadacimab**	SC Berinert (**Haegarda**)	**Berotralstat (Orladeyo)**	**Lanadelumab 300 Q2W (Takhzyro)**	**Lanadelumab 300 Q4W (Takhzyro)**
NMA (**phase 2 trial removed**): No. HAE attacks, RR (95% CrI)					
NMA: No. HAE attacks, RR (95% CrI)					
NMA (**phase 2 trial removed**): HAE attacks requiring on-demand/acute treatment, RR (95% CrI)					
NMA: HAE attacks requiring on-demand/acute treatment, RR (95% CrI)					
NMA (**phase 2 trial removed**): No. of moderate and/or severe HAE attacks, RR (95% CrI)					
NMA: No. of moderate and/or severe HAE attacks, RR (95% CrI)					
NMA (**phase 2 trial removed**): Proportion of attack-free people, HR (95% CrI)					
NMA: Proportion of attack-free people, HR (95% CrI)					
NMA (**phase 2 trial removed**): attack-free days per month, MD (95% CrI)					
NMA: No. attack-free days per month, MD (95% CrI)					
NMA (**phase 2 trial removed**): Any treatment-emergent adverse events, HR (95% CrI)					
NMA: Any treatment-emergent adverse events, HR (95% CrI)					
NMA: Change in AE-QoL total score, MD (95% CrI)					

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; C1-INH, C1-Inhibitor; CrI, credible interval, HAE, hereditary angioedema; HR, hazard ratio; MD, mean difference; No., number; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RR, rate ratio; SC, subcutaneous.

3.4.1.8. NMA conclusions

The EAG concluded that the NMA model that best fit the included studies in terms of similarity, homogeneity, and consistency, was the FE analysis where the phase 2 trial (**CSL312_2001**) was removed. This conclusion was supported by the model fit presented by the company.

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 the uncertainty of the estimates was demonstrated by the wide and overlapping credible intervals. The NMA found garadacimab, lanadelumab (every two weeks), and SC Berinert to be [redacted] across all of the efficacy outcomes reported. The clinical outcome where garadacimab demonstrated a [redacted] over lanadelumab (every two weeks), and SC Berinert was the number of moderate and/or severe HAE attacks. However, as previously noted, the EAG had concerns related to inconsistency in the definitions of attack severity used in the trials.

The company also presented a sensitivity analysis using a FE NMA for the number of HAE attacks outcome where they included the **CHANGE** trial crossover trial (IV C1-INHs/Cinryze versus placebo). This analysis found IV C1-INHs to be more effective than berotralstat, but less effective than garadacimab, Lanadelumab (either dose), or SC Berinert. However, given uncertainty around the validity of the input data, the EAG considered this estimate to be highly uncertain.

Garadacimab was demonstrated to have [redacted] safety (TEAEs) to placebo and SC Berinert. Berotralstat and lanadelumab (every 4 weeks) were found to result in [redacted] TEAEs than placebo. Lanadelumab (every 2 weeks) was found to result inoffer a [redacted] in TEAEs compared to [redacted] Garadacimab demonstrated a [redacted] in HRQoL, as judged by AE-QoL scale, [redacted] lanadelumab (both doses) and berotralstat.

3.4.2. Multi-level network meta regression

The multi-level network meta regression (ML-NMR) was delivered as an addendum in Appendix T seven days after the EAG received the CS. A ML-NMR leverages individual patient data (IPD) and aggregate data from a network of RCTs to assess the comparative efficacy of multiple treatments, while adjusting for between-study differences.

The company performed an ML-NMR because, despite efforts to minimise bias by excluding insufficiently similar study data, residual heterogeneity between studies included in the NMA reduced the validity of some analyses. A ML-NMR offered distinct methodological benefits in capturing and adjusting for heterogeneity and contextual factors that a standard NMA may overlook. The company also noted that the decision to conduct ML-NMR aligned with the NICE Decision Support Unit (DSU) Technical Support Documents (TSDs), particularly those addressing complex methods in NMA, model-based evidence synthesis, and the need for robust handling of heterogeneity and inconsistency across studies.[46] The company did not state in Appendix T what residual heterogeneity they wished to address though the EAG have noted four concerns related to the similarity of the trials in Section 3.4.1.4 of the report.

The company offered an overview and comparison of the characteristics of ML-NMR and NMA in Appendix T. This has been adapted and presented in Table 18, below. In short, ML-NMR offered a structured approach to account for variability across study-level covariates and allowed adjustment for treatment-by-covariate interactions that may otherwise bias pooled estimates. The company noted that this was particularly valuable when assessing interventions within diverse patient subgroups, which may be the case for this submission.

Table 18: Overview and comparison of possible ITC methods (adapted from Table 2, Appendix T)

Feature	ML-NMR	NMA
Data usage	Uses both IPD and AgD	Primarily uses AgD
Population adjustment	Adjusts for differences in covariates between populations	Assumes patient characteristics are similar enough not to impact on outcomes
Comparison type	Direct and indirect comparison within a network of treatments	Direct and indirect comparison within a network of treatments
Modelling approach	Embeds a probabilistic approach to population adjustment	Relies on the assumption of no difference in the distribution of trial-level effect modifiers
Complexity	High, involves Bayesian statistical inference	Moderate, uses standard statistical methods
Flexibility	High, can include IPD and covariate information from all trials	Moderate, limited by the assumption of similar covariate characteristics

Abbreviations: AgD, aggregated patient level data; IPD, individual patient level data; ML-NMR, multi-level network meta regression; NMA, network meta-analysis.

3.4.2.1. ML-NMR outcomes

The company assessed the feasibility of including efficacy and safety outcomes in the ML-NMR. The assessment of the ML-NMR outcomes was addressed briefly in Section 3.1 of Appendix T.

The ML-NMR explored the following endpoints:

- Time-normalised number of hereditary angioedema HAE attacks
- Time-normalised number of moderate and or/severe HAE attacks
- Time-normalised number of HAE attacks requiring on-demand treatment
- Change from baseline in Angioedema quality of life (AE-QoL) total score
- Any treatment emergent adverse event (TEAE)
- Change from baseline in number of attack-free days per month

The company did not use the "proportion of attack-free patients" as an endpoint (and which was an endpoint conducted in the NMA). The NMA used a continuity correction method to overcome the zero-observation issue in the placebo arm of the garadacimab studies. I.e., no patients in the placebo arm experienced a 100% decline in the HAE attack rate at month 6 relative to the observed baseline number of HAE attacks. The company explored this in the ML-NMR but found that adding constants to zero-observation values on the individual level, was highly specific to which patients the correction was applied to, resulting in inconsistencies and reducing the predictive accuracy and generalisability of the model.

At the clarification stage (A20), the EAG requested the company present a ML-NMR for "proportion of attack-free patients" using the risk difference metric for proportion of attack-free patients. The company stated that they could not undertake this analysis within the limited timeframe. They were also concerned that given the "temperamental nature" of binomial regressions, the existing issues may still not be resolved through the risk difference analysis.

3.4.2.2. ML-NMR methodology

Bayesian ML-NMR models were fitted for each endpoint, using a fixed-effect (FE) model as the base case. The EAG considered this appropriate, given the shape of the network and the sparsity of studies.

Table 3 in Appendix T lists the likelihoods and link functions that were assumed for each endpoint, based on the type of outcome considered. The individual level likelihood for the time-normalised family of outcomes were assumed to follow a negative binomial, due to improvements in convergence. This was because, for the time-normalised number of HAE attacks endpoints, overdispersion was observed. The negative binomial was more suited to account for this at the individual patient level compared to the Poisson likelihood function. Whilst overdispersion was thereby accounted for in **CSL312** trials (**2001** phase II and **3001** pivotal phase III) when pooled together, any potential overdispersion in the comparator trials could not have been addressed due to the unavailability of IPD.

3.4.2.3. ML-NMR covariates

In Section 3.2 (Appendix T), the company stated that the following covariates (in order of expected priority) were adjusted for in the ML-NMR model:

- Baseline HAE attack rate (during run-in)
- Body Mass Index (BMI)
- Age
- Sex

The EAG understood that the covariates should be the treatment effect modifiers for people with HAE. There was no discussion in the CS as to what the various treatment effect modifiers were for this population. Nevertheless, it was notable that the company stated in Section B.2.2.2.1 of the CS that baseline attack rate was not a treatment effect modifier for garadacimab. This was in line with clinical expert opinion from consultant immunologists obtained by the company for the submission and clinical expert opinion from prior NICE appraisals in HAE (TA606 and TA738).[21,22,24] Given the lack of transparent reasoning for the choice of covariates, it was unclear to the EAG whether all of the relevant covariates were tested in the ML-NMR.

Main effects and their interactions with treatment were fitted for each of these covariates within the models. In cases of poor convergence and/or low explained sum of squares (ESS), covariates were removed one-by-one as per the priority order. The following marginal distributions were assumed for each of the covariates:

- Baseline HAE attack rate = Poisson

- BMI = Gamma
- Age = Gamma
- Sex = Bernoulli

The suitability of the distributions was assessed by graphically comparing the fitted parametric density to the empirical distributions observed within the IPD across both trials jointly (**CSL312_2001**, **CSL312_3001**). The EAG noted that supplementary DIC comparisons would support the company's approach to model-selection based on relative fit and complexity.

Given that correlations between covariates in the aggregate-data studies were unavailable, it was assumed that these were the same as the observed correlations in the available IPD. The EAG noted that conducting sensitivity analyses by varying correlation assumptions would have increased the robustness of this estimate. For example, by perturbing correlations within a plausible range, or incorporating uncertainty into the model. This would have provided valuable insight and helped determine if the results were consistent across different scenarios, increasing the confidence in the estimate.

The seven endpoints and the covariates adjusted in the ML-NMR model are listed below (Table 19). Each of the time-normalised family of outcomes was adjusted for HAE attack rate alone.

Table 19: Summary of outcomes derived from ML-NMR (adapted from Table 1, Appendix T)

Endpoint	Final analysis
Time-normalised number of HAE attacks	Fixed effects ML-NMR performed adjusting for baseline HAE attack rate
Time-normalised number of moderate and/or severe HAE attacks	Fixed effects ML-NMR performed adjusting for baseline HAE attack rate
Time-normalised number of HAE attacks requiring on-demand/acute treatment	Fixed effects ML-NMR performed adjusting for baseline HAE attack rate
Proportion of attack-free patients	None – continuity correction did not produce a feasible analysis. See Section 3.4.2.2.
Change from baseline in AE-QoL total score	Fixed effects and random effects ML-NMR performed adjusting for baseline HAE attack rate, BMI, age and sex.
Any treatment emergent adverse event	Fixed effects and random effects ML-NMR performed adjusting for baseline HAE attack rate

Endpoint	Final analysis
Change from baseline in number of attack-free days per month	Fixed effects and random effects ML-NMR performed adjusting for baseline HAE attack rate, BMI, age and sex.

Abbreviations: HAE, hereditary angioedema; ML-NMR, multilevel network meta regression; NMA, network meta-analysis; BMI; Body mass index; AE-QoL, Angioedema quality of life.

3.4.2.4. ML-NMR trial selection

It was not clear from Appendix T which studies were used in the ML-NMR. However, Figures 31 to 33 in Appendix T indicated that **VANGUARD** and **CSL312_2001** were used alongside **HELP** (landadelumab once per 2 weeks and once per 4 weeks), **APeX-2** (berotralstat), **APeX-J** (berotralstat), and **COMPACT** (SC Berinert/Haegarda). These were the studies used in the company's base case FE NMA.

However, in contrast to the NMA, the company treated **VANGUARD** and **CSL312_2001** (phase 2 trial) as a single trial in the ML-NMR ([redacted]). As previously noted, the EAG conducted head-to-head FE and RE meta-analyses of **VANGUARD** and **CSL312_2001** to quantify the heterogeneity between all outcomes of interest (Appendix A). The I^2 in both the FE and RE meta-analyses indicated that there was considerable heterogeneity between the trials, even when accounting for between-study variability. This finding supported the EAG's conclusion that it was inappropriate to treat the pooled results from the two trials as a single arm in the ML-NMR.

At the clarification stage (A21), the EAG requested ML-NMR analyses excluding **CSL312_2001** (phase 2 trial). The company stated in the clarification response that removing **CSL312_2001** would cause a 18.75% decrease in the sample size of the garadacimab patients, which served as the sole source of IPD in the networks. They posited that this reduction would exacerbate issues of divergent transition trajectories for count outcomes. This would hinder the reliability of those endpoints, which were able to achieve convergence in the pooled population.

3.4.2.5. ML-NMR results

Time-normalised number of HAE attacks

The company reported the results for time-normalised number of HAE attacks in Section 4.1 (Appendix T). The ML-NMR found that all the interventions offered a [redacted] placebo for reducing HAE attacks. Lanadelumab (every 2 weeks) and SC Berinert

was found to be [redacted] than garadacimab and lanadelumab (every 4 weeks), but there was [redacted] in the estimates, especially those for garadacimab. However, it was clear from the analysis that berotralstat was [redacted] the other four interventions.

Time-normalised number of moderate and/or severe HAE attacks

The company presented the results from the ML-NMR in Section 4.2 of Appendix T. The ML-NMR found SC Berinert, lanadelumab (every 2 weeks), and garadacimab to offer a [redacted] placebo in preventing moderate or severe HAE attacks. Given the [redacted] around the estimates of effect [redacted] which treatment was most effective. Lanadelumab (every 4 weeks) was [redacted] and the ML-NMR found only a [redacted] placebo.

Time-normalised attacks requiring on-demand/acute treatment

The company presented the results from the ML-NMR in Section 4.3 of Appendix T. The ML-NMR indicated that all the interventions offered a statistically significant benefit over placebo for reducing HAE attacks that required on-demand/acute treatment. The ML-NMR found Lanadelumab (every 2 weeks) and SC Berinert to be the [redacted] treatments with superior point estimates and small credible intervals. Based on the point estimates, garadacimab and lanadelumab (every 4 weeks) were [redacted], and berotralstat (ORL 150 QD) was [redacted] However, there was [redacted] around the garadacimab estimate and it was unclear to the EAG where it stood in the treatment hierarchy.

Change from baseline in number of attack-free days per month

The company presented the results from the ML-NMR in Section 4.6 of Appendix T. The ML-NMR indicated that garadacimab, SC Berinert, lanadelumab (every 2 weeks) and lanadelumab (every 4 weeks) offered [redacted] placebo in increasing the number of attack-free days people with HAE have per month. The [redacted] were garadacimab and SC Berinert, [redacted] either dose of lanadelumab. Berotralstat was not included in this analysis.

Any treatment emergent adverse event

The company presented the results from the ML-NMR in Section 4.5 of Appendix T. The ML-NMR indicated that none of the interventions offered a [redacted] over placebo

for treatment-emergent adverse events (TEAEs). There was [redacted] around to the estimates of effect but lanadelumab (every 2 weeks) was found to [redacted] TEAEs [redacted] garadacimab and berotralstat. Lanadelumab (every 4 weeks) and SC Berinert was found to be [redacted] to placebo for TEAEs

Change from baseline in AE-QoL total score

The company presented the results from the ML-NMR in Section 4.4 of Appendix T. The ML-NMR indicated that garadacimab and lanadelumab (every 2 weeks) offered a [redacted] placebo in decreasing (lower is better) a person's AE-QoL total score. The ML-NMR found garadacimab to be the [redacted] treatment. Lanadelumab (every 4 weeks) and berotralstat were [redacted] but were only [redacted] than placebo. The network did not include SC Berinert.

3.4.2.6. Summary of results from ML-NMRs

The results from the ML-NMR are detailed in Table 20, below. The company stated that the ML-NMR results were more precise than the original NMA for the continuous and binary outcomes (i.e. AE-QoL total score, attack free days per month, and TEAEs). However, these were not included in the cost-effectiveness model. The count data used in the negative binomial regression experienced divergent transition, indicating that the model could not converge to a stable solution. Consequently, the count endpoint rate ratio estimates are unreliable (the count endpoints were number of HAE attacks, HAE attacks requiring on-demand treatment, number of moderate and/or severe HAE attacks). Therefore, the EAG agreed it was not appropriate to use these data in the base case of the economic model.

As noted in Section 3.4.2.4, the EAG requested a ML-NMR excluding the phase 2 trial (**CSL312_2001**). The company reasoned that this would further exacerbate the convergence issues and lead to more unreliable estimates. However, the EAG believed it would have been more appropriate for the company to demonstrate that this analysis was inappropriate for the committee. This is because, as noted by the company, a ML-NMR offers distinct methodological benefits in capturing and adjusting for heterogeneity and contextual factors that a standard NMA may overlook.

Table 20: Summary of intervention versus placebo results using ML-NMR

Intervention versus placebo	Garadacimab	SC Berinert (Haegarda)	Berotralstat (Orladeyo)	Lanadelumab 300 Q2W (Takhzyro)	Lanadelumab 300 Q4W (Takhzyro)
No. HAE attacks, RR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAE attacks requiring on-demand/acute treatment, RR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of moderate and/or severe HAE attacks, RR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of attack-free people, HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. attack-free days per month, MD (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-emergent adverse events, HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in AE-QoL total score, MD (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; C1-INH, C1-Inhibitor; CrI, credible interval, HAE, hereditary angioedema; HR, hazard ratio; MD, mean difference; No., number; Q2W, once every 2 weeks; Q4W, once every 4 weeks; RR, rate ratio; SC, subcutaneous.

3.4.3. Comparison of the NMA and ML-NMR results

The NMA and ML-NMR analyses resulted in [redacted] effect estimates for SC Berinert (outside of the NICE scope), berotralstat, lanadelumab (once every 2 weeks), and lanadelumab (once every 4 weeks). However, the effect estimates for garadacimab varied considerably between analyses, where the NMA found a [redacted] than the [redacted] for the number of HAE attacks, HAE attacks requiring on-demand/acute treatment, and the number of moderate and/or severe HAE attacks. For example, the NMA found a RR (95% CrI) of [redacted] ([redacted]) for the [redacted] whereas the [redacted] found a RR (95% CrI) of [redacted] ([redacted]). However, the NMA and ML-NMR [redacted] of effect for number of attack-free days per month, TEAEs, and change in AE-QoL.

3.4.4. NMA or ML-NMR

The EAG accepted that the ML-NMR adjusted for a baseline HAE attack rate and this was a notable dissimilarity between the trials included in the NMA and the ML-NMR. However, this

was the sole covariate adjusted for in the ML-NMR for the time-normalised family of outcomes. In addition, in the ML-NMR the company treated **VANGUARD** (phase 3 trial) and **CSL312_2001** (phase 2 trial) as a single trial. As noted in Section 3.4.2.4, this was inappropriate given the heterogeneity between all outcomes of interest (Appendix A). Therefore, on balance, the EAG considered the removal of the phase 2 study from the NMA, better addressed the heterogeneity in the network, than the adjustment for a baseline HAE attack rate and inappropriate pooling of the garadacimab trials in the ML-NMR.

3.5. Conclusions of the clinical effectiveness section

The EAG considered garadacimab to be a safe, effective medication in reducing HAE attacks, and in doing so, it provided a quality-of-life benefit. This may be linked to a reduction in a person with HAE's anxiety that at any time they could be subject to a debilitating, painful and potentially life-threatening attack. There was some evidence that treatment efficacy does not wane after two years, but longer follow-up is required to establish long-term effectiveness.

The company presented several ITCs in the CS, FE NMA, FE NMA with the phase 2 trial removed, RE NMA, and a ML-NMR (Key Issue 2). The EAG preferred the best fitting NMA (FE NMA with the phase 2 trial removed) and, as noted in Section 3.4.4, on balance, the EAG considered this NMA better addressed the heterogeneity in the network than the ML-NMR. The ITCs included trials of garadacimab, lanadelumab, berotralstat, and SC Berinert (outside of the NICE scope).

The company presented a sensitivity analysis using a FE NMA for the number of HAE attacks outcome where they included the **CHANGE** trial crossover trial (IV C1-INHs/Cinryze versus placebo). This analysis found IV C1-INHs to be more effective than berotralstat, but less effective than garadacimab, Lanadelumab (either dose), or SC Berinert. However, given uncertainty around the validity of the input data, the EAG considered this estimate to be highly uncertain.

The EAG's preferred ITC (FE NMA with the phase 2 trial removed) found garadacimab to be [redacted] than berotralstat in preventing HAE attacks, including attacks that required acute (on-demand) treatment. The EAG's clinical experts highlighted that it is the prevention of these attacks that is the priority for many people with HAE. It was also found to be [redacted] (TEAEs) to berotralstat and lead to [redacted] HRQoL outcomes.

The NMA found garadacimab and lanadelumab (every 2 weeks) to be [redacted] across all of the efficacy outcomes reported, with the exception of [redacted]. However, the EAG had concerns related to the inconsistency in the definitions of attack severity used in the trials and considered this outcome to be subject to considerable uncertainty. The NMA found people on garadacimab had a [redacted] in quality of life (AE-QoL) than those on either dose of lanadelumab. The EAG noted that this was a [redacted] and it was unclear if it was [redacted] In addition, the NMA found garadacimab was [redacted] than lanadelumab (every 2 weeks).

There was uncertainty regarding the current treatment pathway for people with HAE in the NHS (Key Issue 1). The EAG noted three potential positions for garadacimab in the treatment pathway (Section 2.4) and have offered a rationale on whether each would be appropriate given the clinical effectiveness. In people with HAE who have ≥2 attacks per month, garadacimab would be a good alternative to berotralstat, as it was found to be [redacted] and [redacted]. For the same reasons it could be used second-line, after [redacted] has failed, in people who have ≥2 attacks per month. In people with HAE who have ≥2 attacks per week it would be a suitable alternative to lanadelumab (every 2 weeks) because it demonstrated [redacted] and leads to [redacted] than lanadelumab (every 2 weeks).

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company undertook SLRs to identify evidence on cost-effectiveness, health-related quality of life, and cost and resource use, for garadacimab and its comparators. One search was done for cost-effectiveness and cost and resource use data, and a second search was done for health-related quality of life. In both cases, initial searches were conducted in April 2024 and updated in August 2024.

For both reviews, searches were conducted in MEDLINE ALL, EMBASE (via Ovid.com), The Cochrane Library databases, the Centre for Reviews and Dissemination database, and EconLIT (via Ovid.com). The strategies used were suitable for the scope, with the same population term as found in the clinical searches. The publication type filters were reasonable; the company confirmed during clarification that they used filters based on those used in NICE guideline CG181.[47] The database searches were complemented by grey literature and hand searching of retrieved SLRs.

Table 21: Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G, Appendix I 1.1 (Tables 12-17)	The EAG considered the searches to be appropriate and well-aligned to the scope.
Inclusion criteria	Appendix I 1.1 (Table 18)	The EAG considered the inclusion criteria to be appropriate and well-aligned to the scope.
Screening	Appendix I 1.1 (p. 540)	Independent dual screening was conducted following NICE and PRISMA guidance. The EAG considered this to be appropriate.
Data extraction	(p.540)	Standardised extraction tables were used. Data were extracted by one reviewer and checked by a second reviewer. While this is not the gold standard independent dual data extraction, the EAG considered it reasonably appropriate.
QA of included studies	Appendix I 1.1 (Table 25)	The company QA included cost-effectiveness studies using the

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		Drummond and Jefferson checklist.[48] No information was provided on how many reviewers conducted risk of bias assessment and how any discrepancies were addressed.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

The company's review of economic evaluations identified and extracted twelve studies (described across 15 publications) exploring the cost-effectiveness of prophylactic treatments in HAE. None of the studies were included because, the company reported, they explored different payer perspectives and/or the comparators were not relevant to the decision problem. However, assessment of the usefulness or relevance of individual papers was not provided in the data extraction table. Quality assessment of the economic evaluations used the Drummond and Jefferson (1996)[48] checklist.

The EAG was unclear why the company did not include relevant NICE TAs for prophylactic treatments in HAE, such as TA738 or TA606, in their formal review – although they are discussed elsewhere in the submission.

Table 22: Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix H 1.1	The EAG considered the searches to be appropriate and well-aligned to the scope.
Inclusion criteria	Appendix H 1.1 (Table 7)	The EAG considered the inclusion criteria to be appropriate and well-aligned to the scope.
Screening	Appendix H 1.1 (pp. 15-16)	Independent dual screening was conducted following NICE and PRISMA guidance. The EAG considered this to be appropriate.
Data extraction	Appendix H 1.1 (p. 16)	Standardised extraction tables were used. Data were extracted by one reviewer and checked by a second reviewer. While this is not the gold standard independent dual data extraction, the EAG considered it reasonably appropriate.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
QA of included studies		Quality assessment was not reported.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

The company's review of HRQoL evidence included 124 studies (described across 206 publications), of which 114 studies (190 publications) were extracted. The sixteen publications that were not extracted reported only HRQoL scales. The data extraction table included a column that summarised the usefulness for the evidence review, and its consistency with NICE's scope.

The company selected four HRQoL studies[49-52] to support the cost-utility analysis. No rationale was provided for the prioritisation of these four articles. Two of the studies selected – Nordenfelt et al. (2014) and Lo et al. (2022) – were indeed reported by the company as being of high usefulness. Lo et al. was a vignette study of HAE patients (n=15), carers (n=5) and a clinical expert from England and used a time-trade off approach to estimate HRQoL data. In the case of Nordenfelt et al., although the population studied was 103 HAE patients from Sweden, the U.K. crosswalk value set for EQ-5D-5L was used for the attack-free state and the last HAE attack.

The other two studies selected, however, were not reported by the company as being of high usefulness. Itzler et al. (2024), a panel study of HAE patients on long-term prophylaxis (n=159), was considered of medium usefulness. It used combined data from populations in the USA, Australia, Canada, UK, Germany, and Japan, and reported AW-QoL data. Aygören-Pürsün et al. (2016), was considered by the company to be of low usefulness, as the study population (n=111) was from Spain, Germany and Denmark. It captured EQ-5D-3L responses for the period of acute attacks and between attacks.

It was not immediately clear why three other studies,[53-55] marked up by the company as being of high usefulness, with HRQoL data from the UK, were not selected. Although, on further inspection, the EAG found that they did not contain any useable data.

Table 23: Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix I 1.1 (Tables 12-17)	The EAG considered the searches to be appropriate and well-aligned to the scope.
Inclusion criteria	Appendix I 1.1 (Table 18)	The EAG considered the inclusion criteria to be appropriate and well-aligned to the scope.
Screening	Appendix I 1.1 (p. 540)	Independent dual screening was conducted following NICE and PRISMA guidance. The EAG considered this to be appropriate.
Data extraction	(p. 540)	Standardised extraction tables were used. Data were extracted by one reviewer and checked by a second reviewer. While this is not the gold standard independent dual data extraction, the EAG considered it reasonably appropriate.
QA of included studies		Quality assessment was not reported.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

The company's review of resource use and costs evidence included 138 publications. Of these, 15 publications reported on 12 economic evaluation studies, while the remaining 126 publications (of 103 studies) reported costs and/or resource use. Across the 103 cost and resource use studies, 31 reported both costs and resource use, 21 costs alone and 51 resource use alone. Just eight publications (covering six studies) reported UK data. The data extraction table included a column that summarised the usefulness for the evidence review, and its consistency with NICE's scope.

The company selected two studies from their review to support their cost-utility analysis: Aygören-Pürsün et al (2014)[10] and Helbert et al (2013).[56] However, it is not stated by the company why these publications were prioritised. There is a clear case for including Helbert et al. This was a cross-sectional retrospective study that used secondary care data from Hospital Episode Statistics (HES), primary care data from The Health Improvement Network (THIN) and primary research in five secondary care centres in England and Scotland. The company reported in their data extraction table that this study was regarded as being of high usefulness. Aygören-Pürsün et al., on the other hand, was assessed by the company as being of low usefulness for the review. While another cross-sectional study, its objective was to characterise

resource use associated with HAE from the patient perspective in Spain, Germany and Denmark.

It was not reported why five other studies,[57-61] which were recorded as of high usefulness by company, with costs and resource use data from the UK, were not selected to be used to inform the cost-utility analysis. See Section 4.2.9.7 for an analysis of Longhurst (2018).

4.2. Summary and critique of company's submitted economic evaluation by the EAG

The CS presented the economic results for scenarios with ≥2 attacks per month as the base case and ≥2 attacks per week as an alternative scenario. It is noted in the CS that different comparators apply to different subpopulations, as confirmed by clinical experts and the NHSE Commissioning Policy. Therefore, two base cases should have been presented.

4.2.1. NICE reference case checklist

Table 24: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate and captured the health benefit to patients. The outcomes of carers were captured which is potentially appropriate. However, the EAG does not agree with the magnitude of carer disutility in the economic case and notes these were not included in prior submissions
Perspective on costs	NHS and PSS	NHS and PSS as appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost–utility analysis with fully incremental analysis as appropriate
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	[redacted]. This is long enough for the patient population (mean age of [redacted]) with <2% remaining alive in the models final cycle
Synthesis of evidence on health effects	Based on systematic review	Effectiveness (HAE attack rates) based on NMAs of time-normalised number of attacks using data identified via systematic review. Attack utilities calculated via equation (used in previous submissions) from Nordenfelt et al. (2014). Maximum attack-free utilities based on Ara and Brazier 2010 (general population utilities) calculated with a linear increase between the attack and the 6th

Attribute	Reference case	EAG comment on company's submission
		month without attack. This assumes patients return to general population utility after 6 months which the EAG do not consider appropriate. AEs naively extracted from studies identified via systematic review. Mortality due to HAE attacks assumed to be null which the EAG consider appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Expressed in QALYs. Nordenfelt et al. (2014) used the EQ-5D-5L to measure patient quality of life Carer HRQoL was measured using vignettes weighted with TTO vallues
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported directly by patients in the Nordenfelt et al. (2014) study Carers HRQoL data derived from Lo (2022)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Nordenfelt et al. (2014) EQ-5D-5L with the UK crosswalk value set from Herdman (2011)[62] to estimate utilities
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Per the NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs were primarily based on NHS reference costs 2021 - 2022 as appropriate
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs were discounted at 3.5%

Abbreviations: EQ-5D, EuroQol 5 dimension; HAE, hereditary angiodaema; HRQoL: health-related quality of life; NHS, National Health Service; NMA, network meta-analysis; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal; UK, United Kingdom

4.2.2. Model structure

A three-health state Markov model, with the addition of 6 tunnel states, was submitted by the company. The cycle length was set at 28 days without the use of half cycle correction. The EAG does not object to omitting half-cycle corrections given the relatively short cycle length as it would not be expected to significantly impact the economic analysis.

The analysis was conducted from the perspective of the NHS and PSS and included direct medical costs only over a lifetime horizon.

The model consisted of three primary health states (alive, with and without an attack in that cycle, and dead), with the addition of 6 tunnel states (based on experts' opinion) which track the amount of time since the previous HAE attack for patients. The tunnel states capture improvements in quality of life and associated resource use. The addition of tunnel states the main difference between this model and previous ones appraised by NICE in this therapeutic area (NICE TA606 and TA738). The model is shown in Figure 17 (page 107) of the CS.

The company justified the structure of the model with:

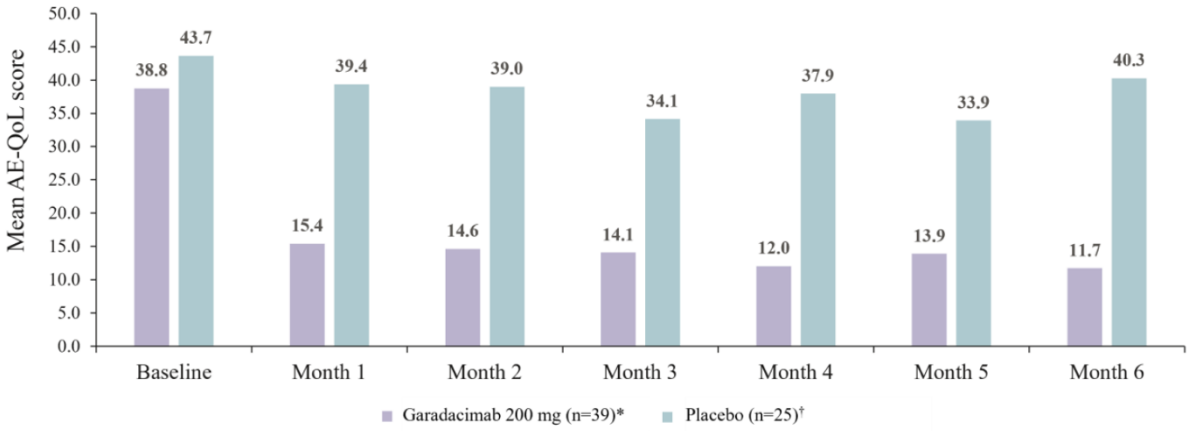
- the intention to reflect the natural history of patients with HAE
- the intention to add memory properties to the model
- the intention to follow similar approaches to those taken in previous TAs: NICE TA606 (lanadelumab) and TA738 (berotralstat)
- the impacts on HRQoL and on resource use in the attack-free health state, with the existing literature
- the available data for the comparators.

As noted, the decision model includes tunnel states that allow patients to accrue different QALYs depending on the duration they remain attack-free. For example, in the 6-cycle tunnel, for each cycle patients remain attack-free, they experience an additional 0.031 utility gain compared to the previous attack-free cycle, until reaching the maximum general population utility. Clinical experts consulted by the EAG noted the lack of evidence for this assumption. Although one expert mentioned that six cycles might be reasonable to reach a maximum attack-free utility, despite acknowledging that patients would never reach the general population quality of life due to the ongoing worry of carrying rescue medication, having to be aware of the nearest hospital, and customs regulations when traveling. The reasonableness of HRQoL assumptions will be further discussed in Section 4.2.9

AE-QoL, as measured within the **VANGUARD**, indicates that the most significant impact on HRQoL occurs within the first month after treatment, regardless of the treatment arm (Figure 11). This 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.)

Figure 11: Mean AE-QoL questionnaire total scores observed at Month 1–6 in patients treated with garadacimab and placebo



Abbreviation: AE-QoL, Angioedema Quality of Life Questionnaire

The EAG disagreed with the company's base case tunnel approach because AE-QoL indicates that the impacts of attack freedom are felt within the first month following an attack. Furthermore, clinical advisors to both the EAG and company stated that they would not expect patient quality of life to fully return to that of the general population. Therefore, the EAG's base case included no tunnel states for quality of life – as is the case with models from previous appraisals in HAE. The company followed a request to test model sensitivity by removing the tunnel states (CQ B25), resulting in a reduction of the incremental cost from [redacted] to [redacted] in the comparison with berotralstat. However, tunnel elimination increased the incremental QALYs from [redacted] to [redacted]. Consequently, the INMB reduced from [redacted] to [redacted]. The impact for other comparisons was not presented.

4.2.3. Intervention, comparators and treatment pathway

The intervention of interest in the economic case is the garadacimab, as described in section 2.3.

Four comparators were included in the economic section in the CS:

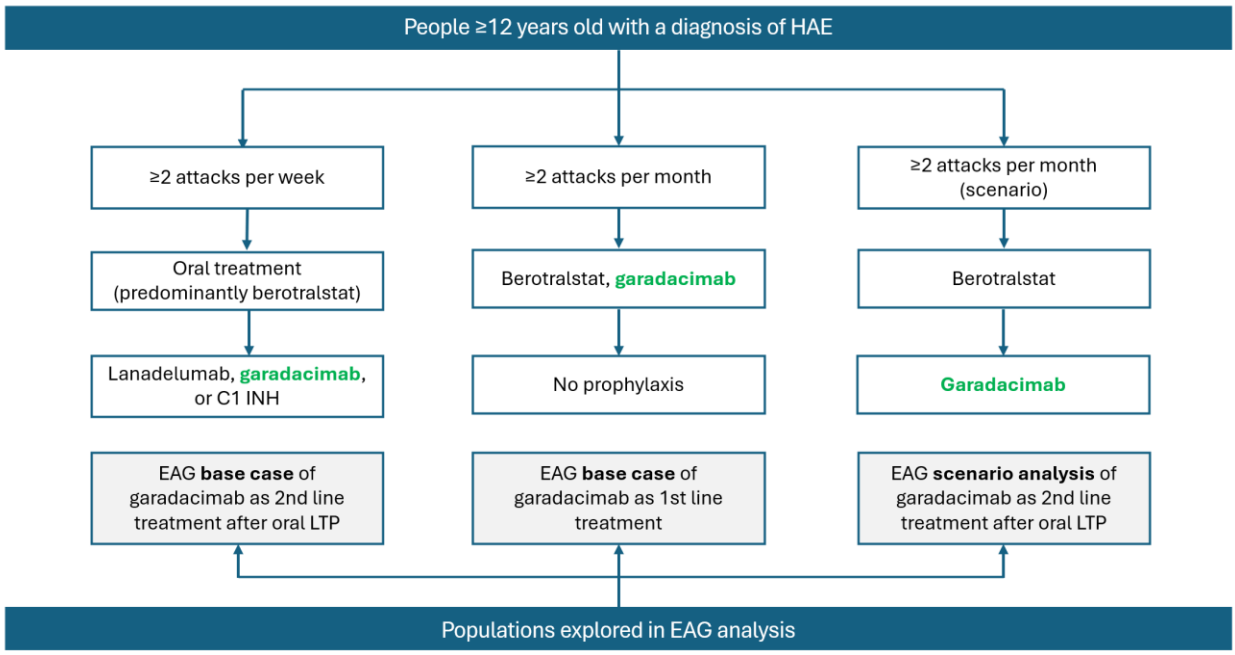
- Oral berotralstat
- SC lanadelumab

- IV Berinert
- Cinryze

The NICE scope included other comparators that were not included in the economic case, namely Ruconest, attenuated androgens, antifibrinolytics, and SC Berinert. The NHSE commissioning policy and the opinions of clinical experts supported the company's reasoning that Ruconest, attenuated androgens, antifibrinolytics, and SC Berinert are not appropriate comparators.

As noted in Section 4.2.4, the choice of comparator depends on the number of attacks experienced prior to treatment as seen in Section 2.3.4. Figure 12 describes the alternative EAG analyses for each population subgroup.

Figure 12: EAG analyses of population subgroups



Abbreviations; C1 INH, C1-inhibitor; EAG, External Assessment Group; LTP, long-term prophylaxis

Apart from the subgroup of patients who suffer ≥2 attacks per week, berotralstat is the single comparator for the subgroup of patients who have ≥2 attacks per month (although this was not made clear in the CS). This was further confirmed by both EAG clinical experts, and therefore was the EAG base case comparator for this subgroup. Patients for whom berotralstat is not

effective do not have any other options from the more recent LTP therapies. Consequently, subsequent treatment is modelled as “no prophylaxis”.

Consistent with the NHSE Commissioning Policy – which stipulates that oral prophylaxis should be tried before other forms of treatment (currently only applicable to the subgroup of patients who experience ≥2 attacks per week) – the EAG also included a scenario in which garadacimab is given to patients for whom berotralstat has not worked effectively and who therefore have no other prophylaxis option. In this scenario, **VANGUARD** data is still used to model effectiveness which implies that, if berotralstat were administered as a previous therapy and there was no wash-out before the run-in phase, the incremental effectiveness of garadacimab seen in the **VANGUARD** trial would remain intact.

The NHSE Commissioning Policy states that patients who experience ≥2 attacks per week should first attempt an oral medication. If that is not effective, patients may be given the choice of lanadelumab or C1-INHs. If the submitting company’s intention was to follow this policy, it implicitly assumed that the incremental efficacy of lanadelumab and garadacimab would remain unchanged if no wash-out of berotralstat or other oral treatments was undertaken before the **VANGUARD** and **HELP** trials. The EAG accepted this approach, consistent with TA606, and considered lanadelumab and C1-INH as the base case comparators for patients with ≥2 attacks per week. The EAG’s understanding of expected second-line treatments for this subgroup based upon clinical expert input is described in Table 25. As data for the effectiveness of lanadelumab and Berinert specifically as subsequent treatments is not available, the EAG followed the company’s approach of assuming patients do not receive prophylaxis after their first-line treatment in the base case. The EAG additionally provide scenario analysis exploring the impact of subsequent treatment.

Table 25: Treatment pathway for patients with ≥ 2 attacks per week

1st line treatment	2nd line treatment
Garadacimab	Lanadelumab
Lanadelumab	Berinert*
Cinryze	Lanadelumab
Berinert	

Note: *Chosen over Cinryze because Berinert market share in the first quarter of 2024 was [redacted] compared with [redacted] for Cinryze

4.2.4. Population

The patient population in the economic analysis is people aged ≥12 years who require routine prevention of recurrent attacks of HAE and experience ≥2 attacks per month prior to treatment. The company justified this population for the base case as it reflects the current clinical commissioning of LTP.

Clinical expert opinion and information provided in the CS (see Figure 8 on page 40) suggest that the choice of comparator depends on the number of attacks per month in two subgroups of patients as follows:

- Subgroup of patients with ≥2 attacks per month and who have not received treatment with oral LTP (henceforth "≥2 attacks per month")
- Subgroup of patients with ≥2 attacks per week and who have received treatment with oral LTP (henceforth "≥2 attacks per week")

In line with the existing commissioning landscape, which limits LTP therapy based on baseline attack frequency, and the company's presented analysis, people who experienced fewer than two attacks per month were excluded from the economic case.

The EAG supported this approach since each subgroup's comparators are unique to that subgroup (see Section 4.2.4).

4.2.5. Perspective, time horizon and discounting

Costs and outcomes were discounted at 3.5% annually, and therefore aligned with NICE guidance. The economic analysis adopted the perspective of the NHS and PSS in England and Wales for costs and outcomes, with a lifetime horizon.

4.2.6. Treatment effectiveness and extrapolation

The clinical parameters and variables included in the cost-effectiveness analysis were sourced from the ITCs and trial outcomes described in Section 3.3.

4.2.6.1. Demographics

The base case demographic variables in the cost-effectiveness analysis are shown in Table 26. Both EAG clinical experts did not see any issues with the **VANGUARD** demographics.

Table 26: Demographics of the cost-effectiveness analysis population (reproduced from Table 15, CS)

Category: mean (standard deviation)	≥2 attack per cycle subgroup of VANGUARD			Value used in the economic analysis
	Garadacimab 200mg (n=[redacted])	Placebo (n=[redacted])	Total (n=[redacted])	
Gender, Male (%)	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Weight at screening (kg)	[redacted]	[redacted]	[redacted]	General pop. weight ([redacted] at start of the model)
Baseline number of HAE attacks	≥ 2 per month subgroup: [redacted] ≥ 2 per week subgroup: [redacted]			As per VANGUARD

Abbreviations: kg, kilogram; mg, milligram; pop., population

Notes: The sources of RCPCH growth charts and NHS Digital (2022)[63-65] have been used across the model to predict weight at each age. The growth (or decline) between two sets of ages happens in a linear fashion

Source: Table UK 14.1.3.1.1 of CSL312_3001.

4.2.6.2. Attack rates in the cost-effectiveness model

In the company's analysis rate ratios were derived from the FE NMA, including Phase 2 trials, with effectiveness of the ITT population in the analysis assumed to be generalisable to both subgroups (see Table 11). This assumption is line with the previous TAs and is considered reasonable as forest plots did not show the number of attacks at baseline to be a treatment effect modifier.

Data for Cinryze were taken from the FE NMA sensitivity analysis. IV Berinert was assumed to be equally effective to Cinryze. The company justified this assumption as they are *"essentially the same protein"*, both intravenous, and with the lack of RCT data for human C1-INH treatments. Threshold analysis on IV Berinert's rate ratio was presented to explore the uncertainty around this assumption. The EAG agreed with this approach.

Each technology's rate ratio of time-normalised number of HAE attacks was applied to the mean number of attacks experienced per month by placebo participants of **VANGUARD** to arrive at the number of HAE attacks per cycle by technology. A similar approach was used to calculate the number of HAE attacks requiring adjunct on-demand treatments.

Table 27: HAE attack rate ratios and per cycle HAE attack rates (company base case)

Technology	Placebo arm HAE time-normalised attack rate for the ≥2 attack per month population of VANGUARD: [redacted]		Placebo arm HAE time-normalised attack rate for the ≥2 attack per week population of VANGUARD: [redacted]
	HAE attack rate, rate ratio	Resulting HAE attack rate per cycle	Resulting HAE attack rate per cycle
Garadacimab	[redacted]	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
HAE attacks and per cycle HAE attack rates that require on-demand treatment			
Garadacimab	[redacted]	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema; ITT, intention-to-treat; Q2W, every two-week dose; Q4W, every four-week dose

Note: outcome not available for Berinert, so assumed the same rate ratio Cinryze.

Source: NMA multiplied by baseline attack rate. Information taken from the economic model.

The EAG, for its base case, preferred to use the FE NMA without the phase 2 studies (see discussion in Section 3.3.1.1) as it provided an improved model fit (Table 28). The EAG also presented a scenario analysis using the ML-NMR.

Table 28: HAE attack rate ratios and per cycle HAE attack rates (EAG base case: excluding Phase 2 studies)

Technology	HAE attack rate, rate ratio	Placebo arm HAE time-normalised attack rate for the ≥2 attack per month per cycle population of VANGUARD: [redacted]	Placebo arm HAE time-normalised attack rate for the ≥2 attack per week per cycle population of VANGUARD: [redacted]
Garadacimab	[redacted]	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	Not included in the base case for this subgroup of patients	[redacted]
Lanadelumab Q4W	[redacted]		[redacted]
Berotralstat	[redacted]	[redacted]	Not included in the base case for this subgroup of patients
Berinert	[redacted]	Not included in the base case for this subgroup of patients	[redacted]
Cinryze	[redacted]		[redacted]
HAE attacks and per cycle HAE attack rates that require on-demand treatment			
Garadacimab	[redacted]	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	Not included in the base case for this subgroup of patients	[redacted]
Lanadelumab Q4W	[redacted]		[redacted]
Berotralstat	[redacted]	[redacted]	Not included in the base case for this subgroup of patients
Berinert	[redacted]	Not included in the base case for this subgroup of patients	[redacted]
Cinryze	[redacted]		[redacted]

Abbreviations: HAE, hereditary angioedema; ITT, intention-to-treat; Q2W, every two-week dose; Q4W, every four-week dose
Note: outcome not available for Berinert, so assumed the same rate ratio Cinryze.
Source: NMA multiplied by baseline attack rate. Information taken from the economic model.

4.2.6.3. Treatment effect: Application of the attack rates in the model

Depending on the cycle number, the CS outlined several approaches to determine each comparator's transition probabilities to the attack-free tunnel states and attack numbers within the attack health state. These were as follows:

- **First 24 cycles**
  - Constant attack rates *(used in company base case)*
  - Calibrated attack rates (included in Appendix J)
  - Poisson regression

- **Cycle 25 onwards**
  - Constant attack rates (Last Observation Carried Forward (LOCF)). Not described in the CS but available in the model
  - Average attack rate reduction carried forward (AARRCF) *(used in company base case)*
  - Poisson regression

We describe below details of the model for the first 24 cycles, then how the model worked for cycle 25 onwards.

4.2.6.4. First 24 cycles

Constant attack rates

In the company base case, HAE attack rates (see Table 27) were converted to calculate the proportion of patients experiencing at least one attack each cycle using the cumulative distribution function (CDF) of the exponential distribution. This assumes a constant rate of attacks across the 24 cycles.

Table 29: Probability of HAE attack based on standard formula attack rates per cycle

Technology	Probability of attack (≥2 attacks per month)	Probability of attack (≥2 attacks per week)
Garadacimab	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	[redacted]
Lanadelumab Q4W	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]
Berinert	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Abbreviations: Q2W, every two-week dose; Q4W, every four-week dose

Source: economic model.

For tunnel states, the "probabilities of no attack" were simply calculated as 100% minus the probabilities from Table 29.

To calculate the occupancy in each of the tunnel states the company investigated whether assuming a constant probability of experiencing an attack dependent on time to first attack was

reasonable. When comparing the prediction using an exponential attack rate, based upon the probability of an attack calculated previously (see Table 29), the company concluded that use of a constant transition probability across tunnel states underestimated the proportion remaining in the attack-free state for garadacimab (Figure 13). As seen in Figure 14, the EAG believed that the constant attack rate did not fit the data well. This methodology was chosen as the company's base case.

Figure 13: Kaplan-Meier curve for time to first HAE attack after Day 1 (CSL312_3002, garadacimab-naïve population) versus time to first HAE attacks using the standard formula

Abbreviations: CSL312, garadacimab; HAE, hereditary angioedema
Notes: Shaded areas represent 95% CIs. 200 mg garadacimab-naïve patients (n=90) include those who are newly enrolled in CSL312_3002 (n=69) or those who previously received placebo in VANGUARD (n=21) make up the red line. The number above the x-axis shows the number of patients at risk
Source: 3002 subgroup of those who were previously naïve to garadacimab (n=90)

Calibrated attack rates

To mitigate the underestimation of constant attack rates, the company fitted standard parametric curves, as per TSD 14,[66] to the outcome time to first HAE attack for garadacimab as observed in open label extension **CSL312_3002** study. This group of patients was selected as it represented the longest available follow-up. The analysis also followed the strict survival criterion of any HAE attack, after day one, being considered as an event. In the CS, the company did not fit a curve to placebo participants as *"nearly all placebo patient experienced at least one HAE attack within the first two cycles*". The company provided the fit for placebo curves following the CQs (question B1b).

Figure 14 shows the visual inspection of the fitted curves in relation to the associated Kaplan-Meier curve. The Akaike and Bayesian Information Criterion (AIC/BIC) statistical tests of fit can be found on the Table 22, page 131 of the CS.

Figure 14: Comparison of fitted survival curves over time

Source: Figure 21 (page 130 of the CS)

The company deemed the gamma curve as the best overall fit, as shown by the AIC/BIC statistical tests. Although, visually, the Gompertz curve followed the KM curves closer in the early cycles of the analysis and the exponential was the worst fit. The company considered the lognormal curve to be the most externally valid based on naïve comparison to data from the **HELP-03** trial for lanadelumab Q2W (44.4% remained attack-free at 6 months vs 55.0% with the gamma curve and 50.8% with the lognormal). The EAG considered this type of naïve comparison of external validity to be problematic, given the differences in study designs and populations.

The company then applied a hazard ratio calculated based upon the NMA for the proportion of attack-free patients to the garadacimab curve to determine comparator outcomes. The EAG considered the NMA for this endpoint to be less reliable than the NMA conducted for number of HAE attacks due to low event rates. For example, the comparison to berotralstat was based upon just three events; see table F.4 on page 139 of the NMA report.

The proportion of attack-free patients for Cinryze (and IV Berinert) was not available to calculate the hazard ratio to apply in the model. It was instead calculated using the relative increase in HAE attack rate ratios between lanadelumab Q4W and Cinryze/IV Berinert. The company considered this to be the best approach as the two parameters are intrinsically linked through HAE attack rates. The EAG considered this strategy to be appropriate.

The calibrated attack rate methodology was used in scenario analysis rather than the company base case (in version 1 of the CS). This was because the company were concerned that this method resulted in a plateau in the time to first HAE attack towards the tail end of the observation period (Figure 14), which may not be clinically plausible as it suggests the number of attacks diminishes over time. Expert advice to the EAG was that, in their experience with lanadelumab and berotralstat, there is a proportion of patients who don't appear to have attacks after starting treatment, and that they would expect to see something similar with garadacimab. They noted, however, that long-term data would be needed to confirm that patients are able to remain fully attack-free, as there always remains a possibility of breakthrough attacks. They also note that lower attack rate reporting over time could be due to patients becoming more confident and not reporting minor symptoms as attacks, particularly with regards to abdominal symptoms.

Poisson regression

The third methodology presented by the company was the use of a Poisson regression. This was presented due to its use in the TA606 submission. Poisson regression is a statistical model used for count data, where the response variable represents the number of times an event occurs. The model uses a log-linear approach, where the logarithm of the expected count is a linear combination of predictor variables (see Equation 2 on page 135 of the CS).

Baseline patient characteristics (age above or below 40, sex and weight above or below 75kg), baseline number of attacks, and number of attacks in the previous cycle were considered as explanatory variables in the analysis. The selection of explanatory variables was not described in the CS. A series of models were run for cycles 1 to 6, as shown in Table 20 (page 118) of the CS. This also provided the AIC values for each family of tested models. The model from cycle 6 was used to extrapolate beyond the trial horizon, as it was supported by the most mature data.

There were 2 regression models options: the "Previous cycle no. of attacks family" and the "All previous cycles no. of attacks family". The company chose the "Previous cycle no. of attacks

family" of regression models because, despite having the second lowest AIC, the "All previous cycles no. of attacks family" had only one variable above the 5% significance level. The “All previous cycles no. of attacks family” was therefore considered less relevant. Moreover, the company stated that the ‘Previous cycle’ family of regression models presented consistently better results on the residual deviation and dispersion tests of fit. Non-linearity and heteroskedasticity were not flagged as issues during the visual inspection of residuals of both the ‘Previous cycle’ and ‘All previous cycles’ families. Therefore, the ‘Previous cycle’ was deemed as the best regression model. The company further supported the use of the ‘Previous cycle no. of attacks family’ claiming it included fewer variables than the ‘All previous cycles no. of attacks family’, hence reducing the possibility of overfitting the placebo regression due to the large number of explanatory variables.

The observed and Poisson predicted mean number of HAE attacks over the trial horizon for garadacimab and placebo from **VANGUARD** are shown in Figure 15 and

Abbreviations: CS, company submission; HAE, hereditary angioedema

Figure 16 (obtained following an EAG request), respectively.

The company concluded that the Poisson regression coefficients were valid predictors of the number of attacks within the observation period. This was because, despite the challenges of limited degrees of freedom and zero-value observations, there was only a small difference between the observed and predicted number of HAE attacks per cycle.

Visual inspection by the EAG of the model fit in the garadacimab and placebo arms revealed that the model underestimates the number of mean attacks in both cases, particularly in the placebo arm. Furthermore, the number of HAE attacks seems to plateau in the garadacimab arm, but not in the placebo arm, where it may show the beginning of a trend to decrease beyond cycle 6. This was not in line with clinical expectation.

Figure 15: Observed and Poisson predicted mean number of HAE attacks over the trial horizon (CQ Response B9c)

Abbreviations: CS, company submission; HAE, hereditary angioedema

Figure 16: Observed and Poisson predicted number of HAE attack rates for placebo (CQ Response Figure 14)

Abbreviations: CQ, clarification question; HAE, hereditary angioedema

EAG's position on the best approach to model the first 24 cycles

Each method has its own strengths and weaknesses. The company's base case used a constant attack rates approach, which assumes an underlying exponential distribution. However, this approach does not fit the data well – as seen in Figure 14. In comparison, the Poisson method fits the data better than the constant attack rates approach, but it consistently underestimates the mean number of attacks. Although not used in the model, the EAG considered the Poisson method to be a particularly poor fit for the data in the placebo arm.

The calibrated attack rate with no tunnel states (see section 4.2.2 for more details) approach may mitigate the issue with assuming constant attack rates when the trial data shows this not to be the case. However, this approach relies on modeling cumulative time to the first attack probabilities, from which garadacimab attack rates are then back-calculated. These rates are then used to determine the comparator's attack rates through a hazard ratio relative to garadacimab (derived from the fixed effects NMA of the proportion of attack-free patients and available on Figure 4.26 page 62 of the NMA report). The EAG was concerned about both the

hazard ratio and the use of cumulative time to the first attack probabilities. In relation, to the use of the hazard ratio, for berotralstat, this strategy may have given biased results due to it being based on relatively sparse data (just 3 events; see table F.4 on page 139 of the NMA report). In relation to using cumulative probabilities for the time until the first attack, this use is problematic because these probabilities will always tend to zero over time due to their cumulative nature. It should be noted that the main reason the company did not choose the calibrated rates approach was that long-term projections showed ever-diminishing probabilities of having an attack, which was considered unrealistic. Furthermore, as will be described in the subsequent section, using approaches such as Last Observation Carried Forward (LOCF) or the average attack rate reduction carried forward AARRCF (especially the former) with cumulative time to first attack would bias the extrapolation. Although it is accepted that the attack rate may drop over time, using cumulative time to first attack effectively pushes the first 24-cycle curve downwards artificially.

Table 30 shows the impact of using constant attack rates compared with the companies calibrated attack rates versus the more stable attack rates calculated directly from the trial results.

Table 30: Transition probabilities: Company base case vs. EAG base case in the ≥2 attacks per month population

	Company base case		**Calibrated attack rate (gamma distribution)**		**EAG Base case**	
Cycle	Garadacimab probability of no-attacks at cycle	Garadacimab implied attack rate (placebo value of [redacted])	Garadacimab probability of no-attacks at cycle	Garadacimab implied attack rate	% reduction in time-normalised HAE attacks	Garadacimab attack rate (placebo value of [redacted])
0	[redacted]	[redacted]				
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Company base case		Calibrated attack rate (gamma distribution)		EAG Base case	
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema; SD, standard deviation.
Source; CSL312_3001[36], CSL312_3002[67]. Information taken from the economic model.

Table 30 and Figure 13 (page 111) demonstrate how converting attack rates into probabilities (company base case) leads to an overestimation of the attack rate, as discussed in section B.3.3.3 of the CS (page 116). The calibrated approach, which estimates attack rates based on the proportion of attack-free patients, also has major limitations due to low event numbers. For example, the **APEX-2** study (which supported the attack rates for berotralstat), only recorded 3 events (see table F.4, page 139 of the NMA report). The EAG preferred to use the attack rates directly from the garadacimab trials (detailed in Appendix R of the submission, including the OLE study **CSL312_3002**) and the NMA for the time-normalised number of HAE attacks. This EAG preferred option prevents overestimation of attack rates by avoiding the conversion into probabilities associated with constant attack rates. It also eliminates the need for the cumulative time to the first attack variable (used in the calibrated attack methodology), which had face validity issues regarding long-term effectiveness. Additionally, it avoids the necessity to fit distribution models, as seen in the Poisson approach, which resulted in a poor fit in the placebo arm.

4.2.6.5. Long-term effectiveness in the cost-effectiveness model

Average attack rate reduction carried forward (AARRCF) – company base case

In the company base case, attack rates beyond the trial period (i.e. beyond the 24th cycle) were modelled through the AARRCF methodology for garadacimab (also used in TA738), and the use of constant attack rates for all comparators. The company justified this approach by stating that it had no IPD data on the comparators to pursue either the Poisson regression or AARRCF. The EAG considered the use of different methods to garadacimab and the comparators as inappropriate. Table 31 shows methods for extrapolation options for garadacimab and the comparators in the model.

Table 31: Methods options for extrapolation from the 25th cycle onwards

	Garadacimab	**Comparators**
25th cycle onwards	Base case – AARRCF Scenario 29 - LOCF Scenario 30 - Poisson	Base case (only option) - LOCF

AARRCF Average attack rate reduction carried forward; LOCF Last Observation Carried Forward

In relation to AARRCF for garadacimab, the average percent reduction in the number of HAE attacks (Table 30) from **CSL312_3002** (OLE) pooled population (e.g. ongoing garadacimab OLE study) was carried forward. The average percent reduction in the number of HAE attacks for all patients over the time horizon amounted to [redacted]% (calculated by averaging the attack reductions across the trial duration – see Figure 5), producing a garadacimab HAE attack rate of [redacted] attacks per cycle for patients with the ≥2 attacks per month baseline.

Constant attack rate's (LOCF)

In the constant attack rate (LOCF) approach, the rates in cycle 24 are simply applied to all subsequent cycles for all treatments. This method was included in the model but not described in the CS. The EAG considered this method less robust than using the average of the last cycles to account for any trends in the data. It should be noted that this is the sole strategy employed for all comparators. If the company had used LOCF in their base case, the attack rate would have increased from [redacted] to [redacted].

Poisson regression

In the Poisson regression approach, the equation used to calculate the attack rate across the trial duration was also used to calculate attack rates beyond the trial duration for garadacimab only (NICE submission TA606 used this method). This resulted in the stabilization of the number of HAE attacks over time at a constant of approximately [redacted] attacks per cycle. However, the EAG noted that the Poisson regression did not provide a good fit to the data from **VANGUARD** (see Section 4.2.6.4) and therefore did not consider this approach reliable.

The company chose AARRCF for its base case as although AARRCF and Poisson regression produced similar results, AARRCF was the preferred in TA738 and had the benefit of simplicity.

EAG's position on long term effectiveness

The EAG's preferred approach to long term garadacimab effectiveness was the use of a "partial AARRCF". This was performed using garadacimab attack rates between cycles 12 and 24 and the FE NMA of proportion of attack-free patients excluding Phase 2 trials. As shown in Table 32 cycles 12 and 24 were chosen as attack rates in this period and are stable enough to be extrapolated. This method provided a similar difference between treatments in long-term attack rate to the LOCF method and a similar value to using the LOCF method with time-varying trial data and is used in the EAG base case (Table 32).

Table 32: Comparison of Cycle 25 extrapolation methods

Treatment	Average attack rate reduction carried forward (AARRCF) – only applies to garadacimab	Average rate ratio using LOCF	Average rate ratio using LOCF and trial data	Average rate ratio using 12-24 AARRCF and trial data
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
IV C1-INHs	[redacted]	[redacted]	[redacted]	[redacted]
On Demand	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AARRCF, average attack rate reduction carried forward; LOCF, last observation carried forward

Source: EAG corrected company economic model, amends applied to the company base case

Clinical advisors to the EAG had not observed any mechanisms causing resistant to LTP in the long-term in practice. They noted that patients who have responded to treatment generally tend to do well and that there is a proportion of patients that they have observed who appear to remain attack-free, although long-term data is lacking. Given this the assumption of no treatment effect waning and the differences in attack rates between treatments being maintained in the long-term term would appear reasonable.

Berotralstat effectiveness in the long term

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. The CS extrapolated the efficacy data from the entire population, including those who did not meet this threshold, to those who did achieve a 50% or greater reduction. The EAG disagreed with this approach because the pooled attack rates from responders and non-responders are higher than those of berotralstat responders alone, underestimating the long-term benefit of berotralstat. The rate ratio for berotralstat derived from the base case NMA is [redacted]. Given that the berotralstat stopping rule requires a minimum attack rate reduction of 50%, using a rate ratio of [redacted] would mean no patients had reached the minimum level to continue taking berotralstat beyond the third month. However, this is not reflected in the model, as there are patients beyond the 3rd cycle. In other words, it is acceptable to have a rate ratio higher than 0.5 in the first three months (as there is a pool of patients reaching the 50% threshold and others not reaching it) but having it after the first three months should result in no patients continuing beyond that time point.

Data on the impact of the stopping rule on effectiveness was unfortunately redacted in TA738 and the company involved in that submission did not agree to supply the data when this was requested by NICE.

Following clarification, the company presented a scenario where the berotralstat HAE attack rate was reduced by an arbitrary 50% from the baseline of [redacted] attacks per month (CQ B7). However, the company noted that these results should be interpreted with caution due to the lack of evidence on this matter. The EAG would note that this is the minimum response required to continue on berotralstat, and it would be expected that responders will on average have a lower attack rate. Additionally, the continuation rule is only checked at a single timepoint (month 3), which leaves the potential for the attack rate of responders to increase over time.

To address this bias in the absence of the data from TA738, the EAG assumed in its base case that the efficacy of patients beyond month 3 is the same as lanadelumab Q2W. This aligns with clinical advice to the EAG that when patients respond to berotralstat they can do very well. For completeness, the EAG also conducted a scenario analysis in which berotralstat efficacy was set to halfway between the effectiveness of lanadelumab Q2W and berotralstat during the first three months.

At factual accuracy check stage, Elbashir (2024)[68] was suggested by the company as a possible alternative source to inform the efficacy of berotralstat after month 3. [redacted]. The source has a number of limitations, however. The fact that it is a poster means there is limited information presented on the methodology followed. Also, [redacted] It also appears that the study includes patients who would not have been subject to the stopping rule applied following NICE recommendation in TA738, as data collection started in November 2020[69] whereas TA738 was published in October 2021. [redacted] compared to 54 patients who discontinued. However, the timing of the discontinuation is not known. This source was therefore included only in scenario analysis rather than the EAG base case. [redacted]. After 24 months we calculated the attack rate as the average of months 12 – 24. The discontinuation rate from this paper was also implemented in this scenario, in the absence of any other data, it is assumed all discontinuation took place at the 3-month stopping rule.

4.2.6.6. Discontinuation rates

Discontinuation rates were sourced naively, largely from observational data sources. No detail was provided on how the sources were identified.

Garadacimab discontinuation was taken from the most solid source, **CSL312_3002** (OLE), in which [redacted] patients remained enrolled in the latest data cut. The continuation patterns

were normalised to a 40-year period over which discontinuation may occur. This was modelled with a 1.9% discontinuation rate (e.g. 1-[redacted]) based upon the [redacted] datacut, normalized to 40 years. This resulted in a 40-year discontinuation rate of[redacted], which translated into a per cycle discontinuation rate of [redacted] per cycle. The EAG agreed with this approach.

The rate of discontinuation for lanadelumab was sourced from Buttergereit et al. (2024),[70] which showed that a total of 32 out of 34 patients continued lanadelumab over a 4-year real-world observation period. In the economic model, 5.88% (1-32/34) of patients discontinued every four years, resulting in a 45.5% linear lanadelumab discontinuation rate (both Q2W and Q4W) across 40 years. This resulted in a per cycle discontinuation rate of 0.087% per cycle.

The source of C1-INHs discontinuation rates was unclear in the CS. The company state that they took this from a multi-centre review of LTP which showed that only one out of 47 C1-INH patients discontinued treatment due to ineffectiveness over 15 months. In response to clarification questions they mention a publication by Mendivil (2023).[71] The EAG could not identify the source of the one in 47 from this paper. This was modelled through the linear extrapolation of the 15 months discontinuation rate, resulting in a 40-year discontinuation of 50.25%. This translated into a per cycle discontinuation rate of 0.10% per cycle. IV Berinert and Cinryze were assumed to have no difference in discontinuation rates. The NHSE Commissioning Policy includes a stopping rule stating that if IV C1-INHs are ineffective after two months (defined as a lack of reduction in attack frequency despite optimized treatment), then treatment with prophylactic IV C1-INHs should be discontinued and alternative therapy options should be considered. This was not included in the company analysis. The EAG also did not include this within its analysis due to 1) a lack of data on the proportion that would be stopped and 2) this comparator being given lower priority as lanadelumab is the more frequently used treatment in the ≥2 attacks per week population.

As previously noted, a discontinuation rule was applied that stated that the prophylactic use of berotralstat should be discontinued if there is a less than 50% reduction in the HAE attack rate after three months of treatment initiation. This was based upon the recommendation in TA738. It was assumed that [redacted] of patients on berotralstat discontinue treatment after three months, based on clinical expert's feedback and clinical data from the Apex trial. It was not clear how the clinical trial data was used to calculate the proportion. This was modelled by applying a linear discontinuation of [redacted] per cycle, resulting in a total discontinuation rate of [redacted] across three cycles. Unlike the previous treatments, long term discontinuation was not included in the

economic model for berotralstat. The EAG are not aware of any evidence which might inform whether or not this is realistic. Since the discontinuation rates at three months are not available, the EAG used the company's base case rate of [redacted]. Additionally, the EAG considered four scenarios with discontinuation rates of 20%, 60%, and 80, and a 51% discontinuation that occurred at week 24 from Zuraw et al (2021).[39] In response to clarification regarding the berotralstat discontinuation rate (CQ B16), a scenario with a 33% discontinuation rate, based on data from Elbashir et al. (2024),[68] was presented.

Overall, per cycle discontinuation rates seemed very similar across all non-oral treatments ranging between 0.1% for IV C1-INHs and [redacted] for garadacimab. The EAG therefore provided scenario analysis to test the impact of assuming equal discontinuation rates for these treatments, given the lack of a NMA for this outcome.

4.2.6.7. Lanadelumab switch: from lanadelumab Q2W to Q4W

In terms of posology, lanadelumab's SmPC states a starting dose of 300mg every two weeks and a dose reduction to 300mg every four weeks in patients who are stable and attack-free on treatment. The company assumed that 45% of patients would switch to Q4W by the end of the first year of treatment. This was based on real-world evidence from the Dorr et al. (2022)[72] study, which examined data on patients from centres in the UK (the EAG contacted the authors to ask if any newer data were available – the first author confirmed that no new data is available, but that the research team is considering an update). The company noted that TA606 for lanadelumab reported an expected rate of dose switching of 76.9% of patients by the end of the first year. However, this figure was not used, as it was based on the proportion of the Q2W cohort that remain attack-free from day 70 to day 182 (a period of 112 days, about ~3.7 months) and not data on switching rates in practice. This was modelled by applying a 45% rate of switching to patients starting on Q2W linearly spread across one1 year (e.g. 3.45% every cycle in the first1st 13 cycles).

In terms of the speed of switch, one EAG clinical advisor explained that a faster switch is more common (e.g., in less than a year). Therefore, following the CQs, the company presented an analysis where patients would switch in 3 months rather than 1 year as the base case (CQ B12). The other considered that switching at around 1 year would be common. Both noted that practice in terms of the timing of switch and the frequency of dosing switched to was heterogeneous. The EAG's clinical advisors suggested the EAG consider a larger international study (Magerl et al. 2024[33]) in addition to the Dorr et. Al (2022) publication. This study

conducted a real-world evidence (RWE) analysis of 198 HAE patients in Germany, France, Greece, and Austria. The primary objective was to evaluate the effectiveness of lanadelumab on attack-free rates with Q2W (every two weeks) and Q4W dosing.(every four weeks) dosing. In the study, the first increase in the interval of administration from Q2W was to 15 or 16 days in eight patients (5.6%), 17 or 18 days in 38 patients (26.4%), Q3W (every three weeks) in 69 patients (47.9%), Q4W in 25 patients (17.4%), Q6W (every six weeks) in one patient (0.7%), and Q8W (every eight weeks) in three patients (2.1%). The main reasons for increasing the intervals were that the patients were stably attack-free (119 out of 144, 82.6%) or their condition had improved/sufficiently maintained (28 out of 144, 19.4%). The mean time to the first increase in interval was 8.2 months (SD=6.1; range=0.54 to 33.64 months). Most patients (75.7%) who had an interval increase did not return to the Q2W dosing regimen and attack frequency rates were reduced (rather than increased) following the switch, which the authors consider to be due to the effect of longer exposure. They cited three further small single-centre studies, which also concluded that increasing the interval between administrations does not compromise effectiveness.

The CS used lanadelumab Q4W effectiveness from the **HELP** trial to model stable patients switching to Q4W lanadelumab, even though patients in that study did not have the Q2W dosage before Q4W. However, based upon the HELP trial it is not possible to show the effectiveness of the population of interest to this submission: patients who were stable on Q2W and remained stable on the Q4W dosage after switching.[33] The EAG disagreed with the effectiveness assumptions from the company and in its base case assumed that the efficacy of lanadelumab Q4W is the same as Q2W and that that change occurs in the 12th cycle and that that switch occurs on month 12. This was based on the Magerl et al. (2024)[33] publication and that the EAG clinical experts considered that stable patients switched to Q4W would, in the majority of cases, maintain the effectiveness of Q2W. If this was not the case, they would be switched back to Q3W or Q2W in order to regain effectiveness.

In scenario analysis the EAG tested the impact of switching at month 6 rather than month 12, based on the lanadelumab submission (TA606), and the impact of switching at 8.2 months based on Magerl et al.[33]

4.2.6.8. Attack severity in the cost-effectiveness model

The severity distribution of HAE attacks was calculated using naïve data from individual studies (Table 33). These rates are applied to all HAE attacks and are constant throughout the model time horizon.

Table 33: Attack severity distribution by technology in company base case (reproduced from Table 22, CS)

Technology	Mild	Moderate	Severe (non-laryngeal)	Severe (laryngeal)	Source
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	VANGUARD
Lanadelumab (Q2W)	20%	67%	12%	2%	HELP
Lanadelumab (Q4W)	30%	50%	18%	2%	HELP
Berotralstat	37%	46%	15%	2%	Riedl (2016)*
Berinert	32%	52%	14%	2%	COMPACT**
Cinryze	59%	28%	12%	2%	Zuraw et al. (2010)***
On-demand	[redacted]	[redacted]	[redacted]	[redacted]	VANGUARD

Abbreviations: Q2W, every two weeks; Q4W, every four weeks

Notes

* Multicentre, observational registry was conducted at 30 U.S. and 7 European sites to collect both prospective and retrospective safety and usage data on subjects receiving pnfCI-INH. This registry aimed to gather comprehensive information on the safety and usage of pnfCI-INH for any reason

** Multicentre, double blinded study phase 3 trials comparing SC Berinert 0.08 mL/kg (40 IU/kg) twice weekly with SC Berinert 0.12 mL/kg (60 IU/kg) twice weekly.

*** Analysed two RCTs that evaluated nanofiltered C1 inhibitor concentrate for managing hereditary angioedema. The first trial assessed its effectiveness in treating acute attacks, while the second trial looked mainly at prophylactic use, focusing on the number of angioedema attacks per period. Participants in both studies were required to be at least 6 years of age and to have a confirmed diagnosis of hereditary angioedema

The company stated that naïve data was used as it was not possible to provide an ITC for severity because the definitions used for severity across the different trials were too heterogeneous (confirmed in clarification question response B5). The company explained that a similar approach was used in TA738. However, the TA738 submission used within trial data for berotralstat and placebo based upon attack location, as severity data was not considered to be robust enough for use in the Phase 3 trial, and in TA606, the same attack severities were assumed for lanadelumab and IV C1-INHs.

Following CQs from the EAG (CQ B5b), the company provided an analysis using the updated model, which assumes an equal split of severity across treatments with a similar mechanism of action with amends made as shown below:

- Garadacimab base – assumed by lanadelumab Q2W & Q4W
- Berinert base – assumed by Cinryze

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 (see Section 3.3.1.1). 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.

4.2.7. Mortality

Deaths due to HAE were not included in the company base case as no deaths were reported in the **VANGUARD** trial. The submitting company stated that this aligns with the previous NICE HAE submissions, which concluded that there is insufficient evidence to quantify an excess risk of death for HAE patients above that of the general population. The EAG's clinical experts agreed that deaths due to HAE are rare and predominantly occur where HAE is undiagnosed or untreated.

The company noted that although they assumed in the base case no disease-specific mortality, there is a study that assessed mortality due to laryngeal attacks: Zanichelli (2015).[73] This study analysed patients diagnosed in Italian centres between 1973 and 2013. However, the mortality seen in the study may be out of date because it pre-dates the availability of long-term prophylaxis treatments such as lanadelumab and berotralstat. The EAG did not believe that this study represented the current UK environment and therefore assumed a 0% mortality in its base case.

Background mortality for HAE patients was informed by life tables sourced from the Office of National Statistics for the years 2018–2020, This was not ideal as the 2017-2019 lifetables are preferred to avoid capturing the impact of COVID. However, this was not judged likely to have a major influence on model results. Mortality rates were matched for the age and gender of the patient population in the economic model.

4.2.8. Adverse events

Adverse event rates were reported as naïve comparisons utilising data from the relevant pivotal trials. A NMA was undertaken for Treatment-Emergent Adverse Events (TEAEs). However, it was not incorporated into the economic analysis as the number of TEAEs was limited and the NMA reported no significant differences in TEAEs across LTP treatments. The company noted that the use of naïve data is aligned with previous NICE appraisals and that AEs have limited impact on the cost-effectiveness conclusions. The EAG agreed with this conclusion, noting that AEs had limited impact on TA606 and TA738.

Adverse events were only included for HRQoL measures (see Section 4.2.9.8) as none of the AEs were considered severe enough to trigger resource use of any kind. The EAG accepted the company's position as clinical advisors to the EAG did not consider any of the adverse events to be likely to trigger substantial NHS resource use.

4.2.9. Health-related quality of life

4.2.9.1. Analysis of VANGUARD data

The **VANGUARD** study collected EQ-5D-5L domain scores, VAS and HSUV were scored for Visit Days 1, 91 and 182 (see Section 3.2.2.4). The company stated that the unpredictability of HAE attacks meant that EQ-5D is not a reliable measure of HRQoL. One of the reasons is that only a small number of relevant observations collected in **VANGUARD** [redacted] of the EQ-5D-5L responses occurred across any of the Visit Days 'during' an ongoing HAE attack, where 'during' is defined as the completion of the EQ-5D-5L response within seven days of a HAE attack. Similarly, in TA606, very few of the EQ-5D questionnaires coincided with an ongoing or recent attack. The company also considered the EQ-5D data in the trial to have low face validity, as garadacimab and placebo patients expressed mapped utility values higher than that of the general population (0.895 and [redacted] from Ara and Brazier 2010[74] and **VANGUARD** trial respectively).

Disease specific HRQoL tools, such as the AE-QoL, were used during the trials and measured more frequently than the EQ-5D in **VANGUARD**. However, the lack of a mapping algorithm to a measure of utilities prevented its use in the economic analysis (the company found that there was limited scope to perform a mapping exercise between AE-QoL and EQ-5D due to limited domain correlation).

The company explored the use of garadacimab and placebo trial responses as upper and lower baseline utility estimates and outputs from the mapping exercise as scenarios analysis. EQ-5D-5L data, collected in **VANGUARD**, was mapped to the EQ-5D-3L using the DSU Hernadez Alva et al. (2020)[75] algorithm.

4.2.9.2. Health-related quality-of-life studies

A SLR was conducted by the company to support the cost-effectiveness analysis. The following studies were chosen by the company as most relevant to consider for inclusion in the model.

- Nordenfelt et al. (2014)[52] – A retrospective study of HAE patients (n=103) from a Swedish registry captured by the Sweha-Reg census. The study captured patient EQ-5D-5L responses for both the attack-free state and the last HAE attack. The study pre-dates the use of lanadelumab and berotralstat and therefore may underestimate the HRQoL of patients treated with existing LTP options.

- Aygören-Pürsün et al. (2016)[49] – A cross-sectional study of HAE patients (n=111) from Spain, Germany and Denmark captured by the HAE European Burden of Illness survey. The study captured EQ-5D-3L responses for all respondents for the period of acute attacks and between attacks.

- Itzler et al. (2024)[50] – A panel study of HAE patients on long-term prophylaxis (n=159) from the United States, Australia, Canada, the United Kingdom, Germany and Japan conducted by MarketCast International. The study reported AE-QoL and Angioedema Control Tests results per attack-free durations of <1 month, 1-6< months and ≥6 months (n=67, 43 and 45, respectively).

- Lo et al. (2022)[51] – A vignette study of HAE patients and carers and clinical expert (n=15, 5 and 1, respectively) from England. The study reported the vignette development and time-trade off (TTO) results for attack-free, attack and care provision for HAE attack states.

Table 34 shows the full list of studies used in the model. Subsequent sections will detail how they were used.

Table 34: Sources of HRQoL data used in the model

Study	Baseline utility	Attack disutility	General population utility	Attack-free disutilities	AEs disutilities	Caregiver disutilities	Administration disutilities	Disutilities by severity	Number of tunnel states
Nordenfelt et al. (2014)[52]	✓	✓		✓				✓	
VANGUARD trial[25]	✓		✓						
Ara and Brazier 2010[74]			✓						
Hernández Alava et al 2022[76]			✓						
Aygoren-Pursun et al. (2016)[49]		✓						✓	
Matza 2013[77]							✓		
Beusterien 2010[78]					✓				
Sullivan 2006[79]					✓				
Stafford 2012[80]					✓				
Matza 2019[81]					✓				
Lo 2022[51]						✓			
Itzler 2024[50]									✓
Company clinical expert opinion									✓

Source: Economic model and CS; Abbreviations: AEs, adverse events

4.2.9.3. Baseline utility value

The Nordenfelt et al. (2014)[52] study was selected to derive the baseline utility values in the base-case cost-effectiveness analysis. The company justified choosing Nordenfelt et al. as it provides estimates of baseline utility data (sourced from responses of patients not experiencing an HAE attack) and provides consistency in decision making due to its use in previous HAE appraisals. The equation for the calculation of baseline utilities from Nordenfelt et al. (2014) study is described in Equation 3 of the CS (page 146). The equation implies that the baseline utility is a function of the age and the number of attacks in the previous cycles. The model allowed for the use of the **VANGUARD** utilities, and this option was explored in a scenario analysis.

Most utilities values are based on the baseline utilities. For example, the utility value in the attack health state is calculated by subtracting the disutility of HAE attacks (and other technology-specific disutilities) from the baseline utility value. Additionally, the value of each individual tunnel state is determined by the linear progression from the baseline utility value to the upper utility estimate value – general population utility.

4.2.9.4. General population utility

General population utilities based on the Ara and Brazier (2010)[74] study were chosen as the base case for the upper estimate of utility (i.e. the utility experienced in the sixth and final month without an attack). Equation 4 of the CS (page 147) shows the formula for the general population utility value as a function of age and gender. The alternative Hernández Alava et al. (2022)[76] general population utility was explored as a scenario to test the impact on the cost-effectiveness.

4.2.9.5. Attack-free utility values

Section 4.2.2 describes the Markov model in the economic analysis, which includes six tunnel states. These tunnel states house people who are attack-free only, and one of their functions is to estimate utility increases as people progress through the tunnel.

The utility within each individual tunnel state is a function of linear progression from the baseline utility value to the upper utility estimate value. This method is different from previous NICE appraisals in HAE. The concept of increasing quality of life according to time spent attack-free was supported by company clinical experts. It was also supported by a publication from Itzler et al. (2024)[50] that reported that longer attack-free durations are strongly associated with lower

fear or anxiety of having an attack, fewer psychological problems, fewer days missed from school or work, and fewer limitations on social and/or physical activity. The upper utility estimate (reached at the end of the tunnel) was assumed to be an equivalent quality of life to a member of the general population with the same age and sex.

The company, however, also noted in the CS (page 147) that clinical experts in England suggested that patients may never reach the general population HRQoL after an HAE attack – due to lingering fear or anxiety of the next attack. This was modelled in scenario analysis, with the possibility to introduce an auxiliary coefficient of a "not in perfect health state" from the UK EQ-5D-3L value set. This coefficient was adjusted by slightly lowering the upper utility estimate to account for lingering fear and anxiety, using a disutility of 0.071 which the company reference to Hernández Alava et al. (2022) but the EAG could not find a suitable value for this in that paper (which only concerns age adjustment of utilities).[76] Sensitivity analysis exploration of the uncertainty with other values (0.01, 0.02, and 0.03) was undertaken.

A summary of the utilities by health state in the tunnels are shown in Table 35.

Table 35: Summary of health state utility values in the tunnels (based from CS Table 27)

Cycle	Month 1 without an attack	Month 2 without an attack	Month 3 without an attack	Month 4 without an attack	Month 5 without an attack	Month 6 without an attack
Cycle 1	0.755					
Cycle 2	0.755	0.785				
Cycle 3	0.755	0.785	0.816			
Cycle 4	0.755	0.785	0.816	0.847		
Cycle 5	0.755	0.785	0.816	0.847	0.878	
Cycle 6	0.755	0.785	0.816	0.847	0.878	0.909
Cycle 7+	0.755	0.785	0.816	0.847	0.878	0.909

Notes: Grey cells indicate an infeasible quality-of-life outcome as, for example, one cannot have the utility benefit of being six cycles without an attack only two cycles into the modelling horizon. For illustrative purposes, the utility values presented are for a 40-year-old, male HAE patient.

4.2.9.6. HAE attack disutility values

HAE attack decrements to HRQoL were modelled according to the severity of each attack (Table 36). The Nordenfelt et al. (2014) study was used in the base case. This paper was used to calculate the impact of an attack based upon the difference in the baseline (EQ-5D today)

and HAE attack (EQ-5D attack) values reported in the paper. A similar approach was taken in previous TAs. The EAG notes that it is unclear whether all of the EQ-5D today values in the paper come from attack-free days. Scenario analysis uses Aygören-Pürsün et al. (2016),[49] which instead calculates HAE attack utilities by calculating the difference between the 'Between HAE attack' and 'By pain severity of last attack' utility values. The resulting HAE attack utilities can be seen in Table 37.

Based on clinical expert opinion that indicated that the HRQL consequences of HAE attacks last longer than the clinical duration (average length of [redacted]), the company assumed that the consequences of an attack would last for seven days. The EAG note that this does not align with the methodology used to calculate the attack decrement from the Nordenfelt (2014) paper. The EAG reviewed previous submissions to see whether or not the attack duration reported in VANGUARD aligned with what was reported from other clinical trials and how attack duration was applied. In both previous submissions attack disutilities were applied for the duration of an attack as reported in the trials. Unfortunately, attack duration data from the berotralstat and lanadelumab trials was redacted. The attack duration reported in the CHANGE trial used in TA606 was 2.1 days for C1-INH and 3.4 days for placebo.

Table 36: Company base case raw and scaled HAE attack disutility values

Source	Mild attack disutility value	Moderate attack disutility value	Severe (non-laryngeal) attack disutility value	Severe (laryngeal) attack disutility value
Nordenfelt et al. (2014)[52]	0.070 (0.0175)	0.369 (0.0923)	0.486 (0.1215)	0.486 (0.1215)
Aygören-Pürsün et al. (2016)[49]	0.109 (0.0273)	0.255 (0.0638)	0.642 (0.1605)	0.642 (0.1605)

Abbreviation: HAE, hereditary angioedema
Note: Scaled per-cycle disutility values in brackets adjusted to reflect the indirect duration of the HAE attack

The company provide an example of how the attack decrements stack up for patients experiencing multiple attacks per cycle.

Table 37: Utility inputs in the base case

Health state/ adverse event	Utility value: mean (standard error) *	Justification
Attack health state (three mild attacks)	0.667	
Attack health state (three moderate attacks)	0.443	

Health state/ adverse event	Utility value: mean (standard error) *	Justification
Attack health state (three severe attacks)	0.355	Baseline utility combined with HAE attack disutility sources.
Attack health state (three laryngeal attacks)	0.355	

Note: * Since the quoted values are a result of a composite formulas, the exact mathematical representations of their uncertainty statistics are not available. The composite outcomes are made up of - baseline utility value, Nordenfelt et al. (2014); upper utility estimate value, Ara and Brazier (2010); HAE attack disutility values, Nordenfelt et al. (2014).

4.2.9.7. EAG's position on the use of baseline, the general population, attack and attack-free utilities

The company assumed that patients can gradually reach a quality of life close to that of the general population by remaining attack-free. The EAG was skeptical that patients can achieve higher utilities than those implied by the regression conducted by Nordenfelt et al. (2014),[52] as it is aware that the utilities calculated from the Nordenfelt et al. equation already accounted for improvements in quality of life (QoL) that occur as the number of attacks reduces over time. The EAG also note that trial data showed that the main impact of treatment in improving HRQoL was seen within a month (Section 4.2.2).

The Nordenfelt equation (see Equation 1) used an intercept of 0.825 in the CS. However, the EAG considered that this might be a misinterpretation of the paper, as the intercept represents the mean EQ-5D score in that study, not a traditional intercept. Therefore, the EAG used 1 for that variable. The EAG also noted that the paper is unclear on whether the 0.0043 represents a decrement for attacks in the previous 28 days or the previous year, with the latter perhaps being a more natural interpretation of the paper. The EAG contacted the corresponding author to clarify but had not heard back at the time of production of this report.

Equation 1: Nordenfelt et al. (2014) company baseline utility equation

$$Baseline\ utility\ value = 0.825 - 0.02205 * age - 0.0043 * no.of\ attacks\ in\ previous\ cycle$$

The EAG therefore used the Nordenfelt et al. utilities as the only source of patient utilities in the model and tests scenario analysis:

- Assuming that the regression coefficient is based upon the number of attacks in the previous year, rather than previous cycle
- Replacing the calculation of the impact of age within the equation with the Hernández Alava decrement which assumes that return to general population utility is possible
- Using utility decrements during an attack calculated from Aygoren-Pursun et al. (2016)[49]

The company also assumed the duration of the impact on HRQoL of attacks to be seven days, supported by clinical assumptions that the impact extends beyond the [redacted] attack duration. The EAG noted that Longhurst (2018),[57] which used data from the Icatibant Outcome Survey to characterize the clinical profile, management, and outcomes of patients with HAE type I and II from three UK specialist centers between 2009 and 2016, reported a mean duration of attack of only 13.4 hours (SD 15.4). LTP use at entry was 75.3% and, during the follow-up period, it was 44.4%. The EAG also noted that the decrements calculated within the published literature appear only to apply to the utility impact during an attack. Given this the EAG base case used [redacted] as the duration of attack (defined as the time between start of attack and complete resolution of symptoms).

4.2.9.8. Adverse reactions

As described in section 4.2.8, the frequency of adverse events was drawn naively from individual studies (rather than a NMA) with disutilities then applied based upon a variety of literature sources and durations, based largely upon assumption and clinical advisor input. The EAG did not agree with this approach and noted that the assumptions appeared to largely favour garadacimab (Table 38). Given the NMA showed no significant difference in TEAEs across LTPs, and the differences the company estimated between treatments were small, these impacts were excluded in the EAG base case.

Table 38: Net disutilities from adverse events (per cycle)

Technology	Net effect
Garadacimab	[redacted]
Lanadelumab	-0.0039
Lanadelumab (Q4W)	-0.0019
Berotralstat	-0.0022
Berinert	-0.0006
Cinryze	-0.0024

Technology	Net effect
On-demand	[redacted]

4.2.9.9. Caregiver disutility

The company justified the inclusion of caregiver disutilities based on:

- Literature,[10,82] patient group feedback, and clinical expert opinion, which the company stated were consistent in reporting that the burden to caregivers of HAE patients is substantial
- Owing to the hereditary nature of the condition. In many cases the caregivers/parents themselves have HAE (see section 2.2)
- The reference case, which states that the perspective on outcomes should include all health effects, including carers where relevant
- Although not accepted in TA738, which the EAG interpreted to be due to the company base case applying decrements too broadly, the central point of discussion in that appraisal was the magnitude of the carer impact that should be modelled and the types of attacks it should be applied to.[21] The company base case disutility (0.145) falling within the range previous accepted based on NICE TSD 9[83] (0.01 and 0.173 per year for caregiver disutility).
- The impact of garadacimab on the number of HAE attacks avoided over a lifetime compared to IV C1-INHs; proportion of patients attack-free over 12-months, and the life years without attack health states were claimed to reduce caregiver burden if garadacimab is adopted.

The company base case inputs related to caregivers are described in Table 39.

Table 39: Summary of variables used to quantify caregiver outcomes in the cost-effectiveness analysis (company base case)

Variable	Value	Source
Caregiver state while caring for someone having an HAE attack	0.762	Lo et al. (2022)[51]
General population utility value for the median age of a carer	0.907	ONS Census 2021[84]

Variable	Value	Source
Unscaled caregiver disutility per HAE attack	0.145	0.907 minus 0.762
Average number of carers per household	1.46	Office of National Statistics (2021) - Dependent children Note the EAG could not find this number in the publication referenced and was not clear how it might relate to the number of carers
Percentage of HAE attacks requiring caregiver assistance (aged 12–18 years old)	52.4%	Aygören-Pürsün et al. (2014)
Percentage of HAE attacks requiring caregiver assistance (ages ≥18 years old)	All severe non-laryngeal and laryngeal attacks	Assumption, represents [redacted] of attacks in the company base case

Abbreviations: EAG, external assessment group; HAE, hereditary angioedema,

Despite the EAGs in TA606 and TA738 supporting the principle of including impacts on caregivers, the company for TA606 was unable to provide data on the utilities in this context, and in TA738 the committee considered that:

> *"…there was no clear evidence to suggest that the utility gains for carers associated with berotralstat use would be substantially greater than those with displaced treatments. It concluded that it was not appropriate to include health-related quality of life effects for carers in the base case."*

The main issue with including caregivers in economic cases in previous TAs were related to:

- the size of disutility
- the size of the population i.e. whether all patients and/or types of attacks would require a caregiver or not
- the consistency of its use in previous TAs
- the limited impact on the economic case

In the current submission, the company addressed some of these issues by allowing the selection of the age range eligible for a caregiver ("≤18 years old" and ">18 years old"). The model also addressed the size of the population by including the option to select the type of HAE attack that may require a caregiver: "all attacks", "some attacks" (52.4% of attacks as

reported by Aygören-Pürsün et al. 2014,[10] and "severe and laryngeal attacks" only. The proportion of attacks requiring a caregiver for patients ≤18 years old was also taken from Aygören-Pürsün et al. (2014),[10] a study conducted in Germany, Denmark, and Spain to estimate the number of attacks requiring a caregiver.

Regarding the size of the disutility, carer utilities reported by Lo et al. (2022)[51] were based on vignettes specifically designed to describe the HAE context. The EAG noted that this does not align with the NICE reference case and is uncertain whether these vignettes might be too sensitive to HAE, potentially leading to an overestimation of the disutility associated with the disease. The EAG further observed that the size of decrement is large compared to decrements used in previous submissions.

Therefore, the EAG identified a recent study by Pennington et al. (2024), which used the SF-6D to measure utilities from the UK Household Longitudinal Study (UKHLS), a survey of approximately 40,000 UK households. It found a carer disutility of 0.0123 for every 0.1 patient disutility. This figure was instead used in the EAG base case.

Finally, the EAG noted that the value of 1.46 carers per household could not be identified within the reference quoted by the company, and the EAG were unclear how the number of dependent children would dictate the number of caregivers. The EAG therefore preferred to apply disutility impacts to one caregiver per household.

In summary, the EAG included caregiver disutilities in its base case as follows:

Table 40: Summary of variables used to quantify caregiver outcomes in the cost-effectiveness analysis (EAG base case)

Variable	Value	Source
General population utility value for the median age carer	0.907	ONS Census 2021[84]
Unscaled caregiver disutility per HAE attack	Disutility of 0.0123 for every 0.1 patient disutility	Pennington et al 2024
Average number of carers per household	1	Assumption
Percentage of HAE attacks requiring caregiver assistance (aged 12–18 years old)	52.4%	Aygören-Pürsün et al. (2014)
Percentage of HAE attacks requiring caregiver assistance (ages ≥18 years old)	All severe non-laryngeal and laryngeal attacks	Company assumption

Abbreviations: EAG, External Assessment Group; HAE, hereditary angioedema; ONS, Office for National Statistics

The EAG also presented scenario analysis, consistent with prior submissions, excluding the impact of caregiver disutilities.

4.2.9.10. Administration disutility

Previous HAE appraisals included administration disutilities to differentiate the HRQoL associated with different routes of administration (TA606 used utilities from Holko et al. 2018[85] to differentiate SC and IV and TA738 included administration disutilities in scenario analysis again using Holko et al. 2018[85]). The company base case for this submission did not include administration disutilities. In a company scenario the Matza et al. (2013)[77] study was used to quantify the administrative disutility associated with LTP options in HAE (Table 41). The study enabled the application of disutilities per administration, allowing these values to be scaled to the appropriate number of administrations for all technologies. This approach is opposed to the previous appraisals, in which the dosing frequencies from the literature did not align with the administration frequencies considered in the health economic analysis.

Table 41: Administration disutility variables by technology

Technology	Administration route	Disutility per admin	Disutility per cycle	Source
Garadacimab	Autoinjector pen	0.004	0.0037*	Matza et al. (2013)[77]
Lanadelumab (Q2W)	Subcutaneous	0.004	0.008	
Lanadelumab (Q4W)	Subcutaneous	0.004	0.004	
Berotralstat	Oral	0	0	Assumption
Berinert	Intravenous	0.02**	0.16	Matza et al. (2013)[77]
Cinryze	Intravenous	0.02**	0.16	

Abbreviations: Q2W; Once every two weeks; Q4W, Once every four weeks.
Notes
* garadacimab follows a once monthly (QM) pattern.
** 30-minute infusion

The EAG agreed that the principle of more frequent administration incurring a greater disutility was reasonable but did not consider the magnitude of the impact calculated to have face validity for C1-INH. The EAG furthermore did not agree that the disutility for multiple administrations could be calculated by multiplying the disutility for one administration by the number of administrations. Hu et al. (2023)[86] showed that the incremental disutility of each additional infusion decreases compared to the previous one. The EAG calculated the disutility for each

treatment using the information from Hu et al. in its base case assuming that additional administrations beyond the 15th would result in a 0.001 disutility – therefore, IV administrations every three days (122 administrations yearly) would result in a per-cycle disutility of 0.012. If the administrations were every 4 days (90 administrations yearly), the per-cycle disutility would be 0.01. The EAG used the company's per-cycle utilities for garadacimab (autoinjector pen) and lanadelumab (subcutaneous) in its base case, as these treatments are administered less frequently and are therefore less prone to overestimation in QALY losses.

4.2.10. Resources and costs

Two studies were selected from the cost and resource use SLR to support the cost-utility analysis. These were:

- Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z et al. (2014) Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. Orphanet J Rare Dis 9 99.[10] - used in the model as a source of resource use for the management of acute attacks by severity

- Helbert M, Holbrook T, MacCulloch A and Mannan A. Understanding the cost of hereditary angioedema in England. The European Conference on Rare Diseases and Orphan Products. Berlin: Germany, 2013.Drug and administration costs[56] – used in the model as the source of the length of stay that supports the calculation of hospital stay

4.2.10.1. Dosage and drugs costs (1st line, subsequent treatment and acute therapies)

The recommended loading dose of garadacimab is 400 mg, administered as two 200 mg SC injections on the first day of treatment, followed by a monthly dose of 200 mg.[14] The price of garadacimab dropped from the list price of [redacted] after a simple PAS discount of [redacted] for garadacimab in a 200mg unit pre-filled pen to [redacted]. This confidential net price has been modelled in the cost-effectiveness analysis. List prices for lanadelumab, berotralstat, Cinryze and IV Berinert were taken from the BNF (analysis with comparator confidential prices will be shown separately in the cPAS document).[87]

Lanadelumab dosing is described in section 4.2.6.7.

A dose of 1,000 IU (in two 500 IU vials per administration) every 3-4 days (resulting in eight dosages per cycle) was assumed for Cinryze. This dosage is consistent with its license. Since the SmPC does not suggest any dosage of Berinert for prophylaxis, the company assumed a

dosage comparable to Cynrize's (1000IU), as both drugs are in effect the same protein. EAG clinical specialists suggested a dosage of 20 IU/Kg would be more appropriate, as 1,000 is lower than the dose used in practice for most patients. This alternative dose would result in a higher treatment cost and therefore the company costing of Berinert may be considered conservative.

Four acute therapies were considered in the model (Table 43), calculated with a flat cost of [redacted] per attack, for an 18-year-old. The EAG agreed with the dosages assumed for acute treatments in the company base case. The market shares assumed for each acute treatment are derived from the UK Adivo report Q1 2024[88] (a type of internal marketing document that the industry uses to provide market overviews and support decision-making). These were broadly in line with expectations from the EAG's clinical advisors.

Subsequent treatment costs were not considered in the company base case, but the following sequences were explored in the $\geq$ 2 attacks per week subgroup assuming that the effectiveness of subsequent treatment is not impacted by what is received in the prior line:

- Garadacimab → C1-INH (Berinert)
- Garadacimab → Lanadelumab (with progression to Q4W)
- Lanadelumab (with progression to Q4W) → C1-INH (Berinert)
- C1-INH (Berinert) → Lanadelumab (with progression to Q4W)

In section 4.2.3, the EAG proposed a similar treatment pathway scenario that excludes the garadacimab to lanadelumab progression only in scenario analysis to reflect expected practice.

Table 42: Long-term prophylaxis drug posology, form, administration, unit size, pack size and costs (list price)

Treatment	Posology			Unit strength	Pack size	Cost per pack	Cost per 28-day cycle	Loading dose
	Dose	Administration	Frequency					
Garadacimab	200mg	SC - Pen	Monthly	200mg	1	[redacted]	[redacted]	[redacted]
Lanadelumab	300mg	SC	Every 2 weeks or Every 4 weeks	300mg	1	£12,420	£24,840 or £12,420	N/A
Berotralstat	150mg	Oral	Once daily	150mg	28	£10,205	£10,205	N/A
Cinryze	1,000IU	IV	Every 3-4 days	500IU	1	£670	£10,688	N/A
IV Berinert	1,000IU	IV	Every 3-4 days	500IU	1	£670	£10,720	N/A

Abbreviations: IU, international units; IV, intravenous; N/A. not applicable; SC, subcutaneous

Table 43: Acute treatment costs

Treatment	Posology			Pack size	Cost per pack	Total cost per attack	Market shares (normalised)
	Dose	Administration	Units required per administration				
Berinert	20IU/kg	IV	0.04	500	£670	£26.80#	[redacted]
Cinryze	1000IU	IV	2	500	£688	£668	[redacted]
Ruconest	50IU/kg	IV	0.02	2100	£750	£17.86#	[redacted]
Firazyr	30mg	SC	1	30	£1,395	£1,395	[redacted]
Icatibant	30mg	SC	1	30	£837	£837	[redacted]
Basket	-						[redacted] flat price per attack, plus [redacted] extra per kg

Abbreviations: IU, international unit; IV, intravenous; kg, kilogram; mg, milligram; SC, subcutaneous
Note: # Refers to the cost per kilogram per attack as these are weight-based treatments.
Source: BNF,[87] Adivo Report Q1 2024[88]

4.2.10.2. Administration costs

A one-time, one-hour nurse time-cost was applied to non-oral treatment regimens to account for the training required for self-administration at home (£54 for one-hour of nurse time [District nurse, adult, face to face – code N02AF]). Patients on oral treatments were assumed to have no administration costs.

NHSE Commissioning Policy[23] states that *"training of eligible patients or their infusion partner would take on average two visits to a day-care unit experienced in training patients for self-administration of medication."* Two hours of nursing time was used in the EAG base case to replicate the average two visits specified in the policy.

4.2.10.3. Health state costs and resource use

Health state costs were divided according to attack status (i.e. "no attack" or "HAE attack"). The HAE attack health state included information about the severity of the attack (classified as 'mild', 'moderate', or 'severe'). The 'no attack' health states were further divided based on the number of cycles without an attack (e.g., month 1 without an attack, month 2 without an attack, and so on, until 6 months without an attack in the base case). These health states were based on TA606 and on TA738. The rationale for this method was the recognition that the heterogeneity of HAE imposes variations in resource use, dependent on attack severity, location of attack (not used in the model), and patient preference (not used in the model).

The SLR that supported resource use information did not identify suitable studies that could be generalized to the UK population. The only potentially relevant study to HAE patient management in the NHS, by Aygören-Pürsün et al. (2014),[10] took a European perspective – the company decided not to include it in the base case due to its limited generalisability to the UK. The EAG agrees with this approach because this population differs from the target population of this submission. Specifically, only 34% reported using long-term prophylaxis, and 71% of those used attenuated androgens, which is not a comparator in this submission.

Instead, the company consulted three clinical experts based in England to estimate the frequency and nature of resource utilization stratified by differing levels of attack severity. Clinical experts responses were subject to uncertainty as they found it difficult to estimate resource use and noted their responses were contingent on a case-by-case basis.[24,67] A mean value was assumed in case of conflicting estimates in the base case. Table 44 summarizes the

resource use inputs in the base case for HAE attack health state by severity and costs for acute attacks.

Accident and emergency visits and inpatient hospitalisations total costs were not only a function of the severity of the attack and unit costs but also a function of the length of time patients spent using these services. The average length of each hospital stay was estimated using data from Helbert et al. (2013),[56] in line with TA606.[22] The study compared HAE patients to a control group of non-HAE patients in the UK, analysing the mean number of hospital visits and bed days per patient per year. The company noted that the results showed that HAE patients had a significantly higher mean number of hospital visits (1.85 vs 0.33) and bed days (3.02 vs 0.95) per year compared to the control group. Hence, the average length of each hospital stay was calculated through the difference in bed days per patient per year between the two groups (2.07) divided by the difference in hospital visits (1.52). This resulted in an estimated average stay of 1.36 days. The length of stay of accident and emergency visit was assumed equal to the length of stay of each hospital – i.e. 1.36 days (which is similar to the 1.38 days from TA606).

One EAG clinical expert reported that HAE patients rarely see family physicians, because they manage attacks themselves, and that home nurses are not involved in the treatment of HAE attacks in the UK. They noted that patients with mild attacks very rarely go to A&E, except in cases involving children or untrained individuals, and that even patients with severe attacks rarely go to A&E (less than 5%) and are rarely admitted. This contrasts with another EAG clinical expert's view that severe and laryngeal patients have higher A&E attendance than the company suggests, noting that laryngeal patients should always go to the hospital. They also noted that Ear, Nose, and Throat consultations would be higher for severe and non-laryngeal severities.

Table 44 provides a summary of the company's base case, a company scenario derived from Aygoren-Pursun et al. (2014)[10] data, and the EAG base case derived from the EAG's clinical experts' opinion. A complete comparison of resource use costs with previous appraisals is provided in Table 45. Costs used broadly align to those from prior appraisals.

Table 44: Health care resource use consumption and costs for acute attacks

Variable	Prob. per mild			Prob. per moderate			Prob. per severe			Prob. per laryngeal			Cost	NHS Reference Cost Code
	Comp KOLs	Aygoren-Pursun et al. (2014)	EAG base case	Comp KOLs	Aygoren-Pursun et al. (2014)	EAG base case	Comp KOLs	Aygoren-Pursun et al. (2014)	EAG base case	Comp KOLs	Aygoren-Pursun et al. (2014)	EAG base case		
Family physician	[redacted]	4.0%	[redacted]	[redacted]	4.0%	[redacted]	[redacted]	4.0%	[redacted]	[redacted]	4.0%	0	£76.08	Follow-up, adult, Face to Face (code AS08)
Home nurse	[redacted]	1.0%	[redacted]	[redacted]	1.0%	[redacted]	[redacted]	1.0%	[redacted]	[redacted]	1.0%	0	£54.00	District nurse, adult, face to face (code N02AF)
Accident and emergency visit	[redacted]	2.0%	[redacted]	[redacted]	16.0%	[redacted]	[redacted]	19%	[redacted]	[redacted]	19%	[redacted]	£5.93	Emergency Medicine, No Investigation with No Significant Treatment (code VB11Z)
Inpatient hospitalisation	[redacted]	3%	[redacted]	[redacted]	3.0%	[redacted]	[redacted]	3.0%	[redacted]	[redacted]	3.0%	[redacted]	£19.08	Non-Elective Inpatient Short Stay for Abdominal Pain without Interventions (code FD05B)
Radiography	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	10%	[redacted]	[redacted]	15%	[redacted]	£90.11	Computerised Tomography Scan of One Area, without Contrast, 19 years and over (code RD20A)
Blood tests	[redacted]	0%	[redacted]	[redacted]	2.8%	[redacted]	[redacted]	10%	[redacted]	[redacted]	15%	[redacted]	£2.96	Haematology test (code DAPS05)
Electro cardiography	[redacted]	0%	[redacted]	[redacted]	5%	[redacted]	[redacted]	10%	[redacted]	[redacted]	20%	[redacted]	£159.36	Electrocardiogram Monitoring or Stress Testing (EY517Z)
Ear, Nose and Throat consultation	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	0%	[redacted]	[redacted]	10%	[redacted]	£247.30	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0 (CB02F)
Total resource use for treatment of acute attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Abbreviations: Comp, company; KOL, key opinion leader. Prob, probability.

Notes: Unit costs were derived from NHS reference costs 2021/22 and latest PSSRU publishedIn TA738, a different approach was taken that considered health resource use based on the location of the attack, rather than the severity of the disease. TA606 did not categorize attack resource use by severity and assumed that only 85% of attacks require treatment (based on pooled data from the HELP-03 trial). Unlike the garadacimab market share information for the UK, which was used to estimate the composition of the acute treatment basket, TA606 relied on the distribution of acute therapies data from the HELP-03 study CSR (redacted in the company papers).

Table 45: Resource use cost comparison with previous submissions

	Garadacimab submission		**TA738 (berotralstat)**		**TA606 (lanadelumab)**	
Variable	Cost/%	NHS Reference Cost Code	Cost/%	NHS Reference Cost Code	Cost/%	NHS Reference Cost Code
Accident and emergency visit	£194	Emergency Medicine, No Investigation with No Significant Treatment (code VB11Z)	£168	NHS reference costs 18/1973 – Service code 180	£139	WF01B - Non-Admitted Face-to-Face Attendance, First, Consultant Led and Non consultant led average
Inpatient hospitalisation	£623	Non-Elective Inpatient Short Stay for Abdominal Pain without Interventions (code FD05B)	£454	NHS reference costs 18/1973 – WJ11Z (non-elective short stay)	£2,961	KC04A Inborn Errors of Metabolism with CC 0-2 and 3+ average
Percentage of HAE attacks requiring hospitalisation	2-3%	Calculated based on attack severity data and KOL informed resource use rates	Redacted data from company clinical experts		11.9%	Source not available
Percentage of HAE attacks requiring A&E visit	6-8%	Calculated based on attack severity data and KOL informed resource use rates	Redacted data from company clinical experts		11.9%	The average annual attack rate estimated from the C1-INH arm in the economic model (12.6 attacks per year) was used as a proxy for the average number of attacks patients experience in practice per year.
Radiography	£90.11	Computerised Tomography Scan of One Area, without Contrast, 19 years and over (code RD20A)	£52	NHS reference costs 18/1973 – RD40Z		
Blood tests	£2.96	Haematology test (code DAPS05)	£3	NHS reference costs 18/1973 – DAPS08		
Intubation cost	N/A		£317	NHS reference costs 18/1973 – RN18A	N/A	
Ambulance transport cost	N/A		£258	PSSRU (2019)	N/A	
Family physician	£76.08	Follow-up, adult, Face to Face (code AS08)	N/A		£38	GP/per patient contact lasting 9.22 minutes

Abbreviations: A&E, Accident and Emergency; C1-INH, C1-inhibitor; GP, General Practitioner; HAE, hereditary angioedema; N/A, not applicable; NHS, National Health Service

4.2.10.4. Adverse event and monitoring costs

Adverse events were not considered as part of the economic analysis from the cost perspective. They were not deemed severe enough to trigger any type of resource use. The EAG agreed with this approach, with support from the EAG's clinical experts.

Unlike previous TAs, monitoring costs were included in the economic analysis. The SLR did not identify costs or resources associated with monitoring HAE patients and so information obtained from the three clinical experts was used in the model. Monitoring costs were divided into "attack-free" (e.g. stable patients defined as living six months without an attack) and "patients experiencing a HAE attack". A total rate per cycle of £75.67 and £35.58 was applied in the model for the attack state plus the first six attack-free health states, and for the subsequent attack-free health states respectively. Detailed monitoring costs of HAE patients can be found in Table 31 of the CS.

Since the company chose six tunnel states, monitoring costs never reach the lower cost (£35.58) in the company model, as this cost is only incurred from the 7th cycle onwards. Therefore, for monitoring cost purposes, the EAG in its base case chose to use 12 tunnel states in the economic model to capture patients who remain attack-free for longer than six months as this was considered to best reflect the company's original intention. It also aligned with clinical expert input to the EAG that monitoring would be less frequent for patients who had remained attack-free in the longer term.

4.3. Uncertainty

The company conducted extensive sensitivity and scenario analyses.

The company conducted a Probabilistic Sensitivity Analysis (PSA) on most variables. Following CQs, some variables were included or corrected. CODA samples have also been included in the analysis to address the uncertainty of the NMA after EAG request. For the clinical inputs and utilities in the initial submission, the company reviewed the uncertainty statistics from relevant sources. This review showed that the cost-effectiveness model for clinical, utility, and adverse event inputs lacked appropriate uncertainty statistics and therefore arbitrary assumptions had to be made.

Regarding the Deterministic Sensitivity Analysis (DSA), the company did not use credible intervals (CrI) from relevant studies for several variables. Instead, they applied ± 20% CrI's (for example, on baseline number of attacks). This approach estimates the model's sensitivity to the

variables rather than the uncertainty of the economic case at hand. Following CQs, the company made amendments to this approach.

A summary of scenario analysis conducted by the company can be found in Table 6 (page 5 of Appendix R). It is noteworthy that the company considered the ≥2 attacks per week as a scenario rather than a base case result for that subgroup. The company correctly depicted in Section B.1.3.2.2 that the ≥2 attacks per month population and the ≥2 attacks per week population have different comparators and assumptions. Including the ≥2 attacks per week population as a scenario may suggest that all comparators apply to all subgroups of patients. The EAG disagreed with this approach and has therefore included two base cases, one for each population subgroup.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results presented in this report incorporate a PAS discount for the garadacimab and list prices for all comparator treatments. This report is accompanied by a confidential appendix that reports the results of the analyses when confidential prices for comparator treatments are included. Results are presented based on the company model supplied at the clarification questions stage. The company did not update the results tables in the submissions following corrections.

5.1.1. Base case results

The results reported by the company are shown in Table 46. The deterministic and probabilistic results are presented in Table 46 and Table 47. Results are presented without the application of any severity modifier which the EAG agree is not relevant to this case.

In the ≥2 attacks per month population, garadacimab was compared to berotralstat. Garadacimab dominated berotralstat, with lower costs and higher QALYs. In the ≥2 attacks per week population, garadacimab was compared to Cinryze, Berinert and lanadelumab. Garadacimab was the most effective comparator and had the lowest costs, meaning that it dominated all other comparators. These results used list prices for all comparators. An analysis with comparators discounts will be presented in the cPAS document.

Table 46: Company base case results (≥2 attacks per month)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case					
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality adjusted life years

Table 47: Company base case results (≥2 attacks per week)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case					
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: QALYs, quality adjusted life years

5.2. Company's sensitivity analyses

5.2.1. Deterministic sensitivity analyses

5.2.1.1. ≥2 attacks per month population

A full list of variables, most with the option of being subject to sensitivity and scenario analysis, was reported in Table 6 (page 5) of Appendix R.

The DSA for berotralstat is shown in Table 48. These results, which used the berotralstat list price, indicate a positive INMB for the £20K NICE threshold, suggesting that garadacimab outperforms berotralstat in every variable presented. It should be noted that the variables tested did not reflect the uncertainty of the parameters as confidence intervals were not derived from the studies but rather assumed to be ±20% over the central value.

These results show that the INMB is insensitive to most variables, as they exhibit small relative changes from the base case in which garadacimab dominated. The sensitivity analysis Table 49 shows that the variables that caused the highest variations in the INMB, such as age, the assumption of no discontinuation, or the subgroup of patients, were not either considered unlikely to occur by the EAG or parameters for which DSA is inappropriate (patient characteristics).

Table 48: Deterministic sensitivity analysis results against berotralstat

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Attack rate requiring on-demand treatment - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
2	Rate ratio for the requirement of on-demand treatment - Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
3	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
4	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
6	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
7	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
8	Attack rate - ≥2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
9	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
10	Duration over the impact of an attack is felt (days)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: INMB, incremental net monetary benefit

Table 49: Scenario analyses against berotralstat

Scenario name	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
Undiscounted QALYs and costs	[redacted]	[redacted]	[redacted]	[redacted]
Males only	[redacted]	[redacted]	[redacted]	[redacted]
Female only	[redacted]	[redacted]	[redacted]	[redacted]
Ages 12-100	[redacted]	[redacted]	[redacted]	[redacted]
Ages 18-100	[redacted]	[redacted]	[redacted]	[redacted]
3 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]
9 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]
12 months in tunnel	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack rate: ≥ 2 attacks per month as subgroup*	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack rate: ≥ 8 attacks per month subgroup*	[redacted]	[redacted]	[redacted]	[redacted]
No discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Alternate HAE management source - A	[redacted]	[redacted]	[redacted]	[redacted]
Alternate upper utility - B	[redacted]	[redacted]	[redacted]	[redacted]
VANGUARD phase III utility	[redacted]	[redacted]	[redacted]	[redacted]
Alternate HAE disutility - C	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of administration disutility	[redacted]	[redacted]	[redacted]	[redacted]
HAE attack disutility duration informed by VANGUARD ([redacted] days)	[redacted]	[redacted]	[redacted]	[redacted]
Three-day HAE attack disutility	[redacted]	[redacted]	[redacted]	[redacted]

Scenario name	Incremental costs against berotralstat (£)	Incremental QALYs against berotralstat	INMB against berotralstat (£) at £30,000 threshold	Relative change of INMB from base case
0.01 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]
0.02 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]
0.03 decrement from general population utility to approximate patient's fear of attack	[redacted]	[redacted]	[redacted]	[redacted]
Adults (>18 years) requiring caregiver support for 52.40% of attacks	[redacted]	[redacted]	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]	[redacted]	[redacted]
Last observation carried forward (all cycles)	[redacted]	[redacted]	[redacted]	[redacted]
Poisson regression (all cycles)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema; INMB, incremental net monetary benefit; QALYs, quality adjusted life years

5.2.1.2. ≥2 attacks per week population

Since the ≥2 attacks per week population was considered a scenario rather than a base case, the DSA results were not provided in the CS. Only the fully incremental cost-effectiveness analysis of treatments with sequencing was available (see Table 50).

Due to the variety of treatments and prescribing options, the company included strategies involving treatment sequencing. The sequences were as follows:

- Garadacimab -> C1-INH (Berinert)
- Garadacimab -> Lanadelumab (with progression to Q4W)
- Lanadelumab (with progression to Q4W) -> C1-INH (Berinert)
- C1-INH (Berinert) -> Lanadelumab (with progression to Q4W)

The results show that garadacimab is [redacted].

Table 50: Fully incremental cost-effectiveness analysis with treatment sequencing, for the ≥2 attacks per week subgroup

Technology	Total costs (£)	Total LYG	Total QALYs	Inc Costs (£)	Inc LYG	Inc QALYs	ICER versus baseline (£/QALY)	ICER inc (£/QALY)
Garadacimab (C1-INH)	[redacted]	21.38	[redacted]	-	-	-	-	-
Garadacimab (lanadelumab)	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]
C1-INH (lanadelumab)	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]
Lanadelumab (C1-INH)	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: HAE, hereditary angioedema; inc, incremental; INMB, incremental net monetary benefit; QALYs, quality adjusted life years

5.2.2. Probabilistic sensitivity analysis

The company submitted a fully incremental probabilistic cost-effectiveness analysis for the base case which covered the ≥2 attacks per month subgroup of patients. The company stated that the analysis was conducted over 10,000 iterations, and the probabilistic outcomes closely converged with the deterministic outcomes (compared with Table 46). However, a few errors were detected in the model, and new PSA results were not presented following the CQs.

The EAG do, however, agree that the deterministic and PSA results are broadly consistent (Table 46 and Table 47). At list price for all comparators there was a [redacted]

5.3. Model validation and face validity check

According to the company, program's outputs, computations, data references, model interface, and VBA code were verified, and all input data were confirmed with original sources. Face validity, in terms of model structure, inputs, and assumptions, was insured by opinions of expert immunologists based in England.

The EAG noted various issues with face validity which do not appear to have been explored thoroughly within company clinical validation interviews. The following company assumptions lack face validity:

- The assumption that berotralstat responders have the same effectiveness as patients in the entire population (including non-responders) after the stopping rule is applied
- The assumption of linearity in adding IV administration disutilities. The study by Hu et al. (2023)[86] demonstrated that the increase is not linear, contrary to the company's base case.
- The caregiver disutility. Lo et al. (2022),[51] used by the company, reported much higher disutilities using vignettes weighted by TTO, compared to Pennington et al. 2024, who used EQ-5D to establish a correlation between patients' utility and caregiver utility.
- The assumption of a decrease in effectiveness for patients stable on lanadelumab switching from Q2W to Q4W commensurate to reducing effectiveness to that observed for patients initiated on Q4W in the **HELP-03** trial. Magerl et al. (2024)[33] showed 75.7% of patients who reduced their dosing frequency maintained effectiveness.

In response to CQs, the company explained that, due to redactions in NICE submissions, it was not possible to compare their outputs with those in the garadacimab model. However, the company provided a ranking of variables from the DSA, which serves as a reliable measure of validation since it reflects both the inputs and outputs of an economic analysis. The analysis compared the ranking of influential variables across TA738, Table 40 of the CS, Figure 24 of TA606, and the DSA results against lanadelumab. The results showed that parameters related to HAE attack rates are the most impactful across all three HAE submissions, as all cost-effectiveness models are based on HAE attack rates. The EAG agreed that this analysis showed consistency in the most important parameters across appraisals but noted that the size of QALY benefits assumed for each treatment could not be validated against prior models.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1. EAG corrections to the company's base case model

Several amendments were made to the implementation of sensitivity analysis. These changes did not impact the deterministic base case but did impact the centre and spread of the probabilistic results and the results of the deterministic sensitivity analysis.

- The data company did not consistently use credible intervals from relevant studies for included parameters, assuming instead that the credible intervals were 20% of the mean for most variables, even when relevant data were available. This was corrected for several variables where uncertainty estimates were available.
- The formula included for the variance associated with the log-normal distribution was incorrect, this was corrected: LOGNORM.INV($X747,LN($F747),(LN($F747*(1+PSA_var))-LN($F747*(1-PSA_var)))/(1.96*2)).
- Adverse events were excluded from the PSA. They have been included, following a lognormal distribution.
- Adverse event utility decrements were not functional, as they were included as negative values. They have been amended to positive values, and included in the PSA.
- Parameter T655 was not functional due to it not having been assigned a distribution. This has been amended to Beta.
- For the percentage reduction in time normalized HAE attack rates (row 724 to 748) the company used a log-normal distribution with a cap. The company provided some justification for this, however a Beta distribution was thought to be more appropriate.
- Attempts were made to amend the inclusion of caregiver utility parameters in the PSA. However, the level of uncertainty associated with this parameter meant that it wasn't possible to include it in the PSA and as it is not a key driver this was deemed acceptable. The company included this parameter in the PSA, but using an assumed standard error, rather than the standard error from the study.
- The company did not use CODA from their NMA in their PSA. This was amended.

In addition to the amendments made to the PSA, the EAG made corrections to the following errors:

- Several cell-referencing errors that only impacted the 'Calibrated attack rate' scenario and not the deterministic base case.
- Several cell-referencing errors to the way health state utility values were calculated in the model engines.
- The company indicated that they would implement six tunnel states. Monitoring costs were assumed to fall only after patients were attack-free for six months. Limiting the number of tunnels to six, therefore, made this assumption null and void, as no patients ever reached this definition of being attack-free in the long term. To ensure this assumption was applied, the EAG increased the number of tunnel states to 12 for healthcare resource use (although there is no difference whether there are 7 to 12 tunnels for resource use). This does not impact the tunnel states for utilities, which were handled separately.

The impact of the EAG corrected company base case results for both subgroups of patients is shown in Table 51 and Table 52. EAG corrections resulted in only minor changes to the total and incremental costs and QALYs.

Table 51: EAG-corrected company base case results: two or more attacks per month population

Correction	Comparator	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company base case	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calibrated attack rate error	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility implementation errors	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tunnel states	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Correction	Comparator	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
PSA fixes	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of corrections	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External assessment group; PSA, Probabilistic sensitivity analyses; QALYs, quality adjusted life years

Table 52: EAG-corrected company base case results: two or more attacks per week population

Preferred assumption	Comparator	Costs	QALYs	ICER
Company base case	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Calibrated attack rate error (no impact as not used in company base case)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Utility implementation errors	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Resource use tunnel states	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
PSA fixes	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	ICER
	Lanadelumab	[redacted]	[redacted]	[redacted]
Cumulative impact of corrections	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]

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

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG identified several limitations within the company's base case and explored the impact of parameter values, and assumptions, which the EAG believed were more plausible. These analyses were conducted within the company corrected base-case analysis.

Results are presented first for the ≥2 attacks per month population, then the ≥2 attacks per week population. A summary of the EAG changes and the corresponding sections in the report where they were discussed is provided in Table 53.

Table 53: EAG changes and corresponding sections

Change	Section
Addition of 2nd line treatments	4.2.3
Earlier time horizon for lanadelumab switching	4.2.6.5
Lanadelumab Q4W instantaneous switch	4.2.6.5
ML-NMR	3.5
Berotralstat responders increased effectiveness	4.2.6.5
Berotralstat discontinuation rate varied	4.2.6.6
Discontinuation aligned for non-oral treatments	4.2.6.6
Lanadelumab Q4W effectiveness = Q2W	4.2.6.7
Attack severity aligned with garadacimab	4.2.6.8
Attack rate extrapolation method aligned across treatments	4.2.6.5
NMA FE excl. ph 2	3.5
Attack rates from trial (cycle 0-24)	4.2.6.4
No utility tunnel states	4.2.2
Attack disutility source	4.2.9.7

Change	Section
Utility age adjustment source	4.2.9.7
AE utility decrements excluded	4.2.9.8
Amended application of Nordenfelt equation	4.2.9.3
Nordenfelt attack coefficient amended	4.2.9.7
Administration disutility included	4.2.9.10
Administration disutility for IV treatments source	4.2.9.10
Attack length (days)	4.2.10.3
Number of caregivers	4.2.9.9
Caregiver disutility source	4.2.9.9
Caregiver disutility excluded	4.2.9.9
Training costs	4.2.10.2
Resource use rates	4.2.10.3

Abbreviations: AEs, adverse events; FE, fixed effects; MLNMR, Multi-level network meta regression; NMA, network meta-analysis; Ph, phase; Q4W, administered every four weeks

6.2.1. ≥2 attacks per month population

6.2.1.1. EAG's preferred assumptions

At PAS price for garadacimab and list price for comparators, garadacimab [redacted] when compared to berotralstat. However, the incremental QALY gains predicted decreased substantially (from [redacted] in the EAG-corrected company base case to [redacted] in the deterministic EAG base case). Similarly incremental costs reduced from [redacted] to [redacted]. Key drivers of the results were:

- The duration for which the quality-of-life impacts of an attack apply
- Assumptions made in relation to the effectiveness of berotralstat responders after the stopping rule was applied
- Whether or not an assumption of return to general population quality of life was included and the method used to apply the Nordenfelt (2014) regression equation to calculate quality of life when an attack was not being experienced
- Assumptions made in relation to how attack rates were calculated in both the short and long-term

Table 54: EAG's preferred model in the ≥2 attacks per month population

Preferred assumption	Comparator	Costs	QALYs	Incremental costs	Incremental QALYs	Cost per QALY gained
EAG corrected ICER	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat responders increased effectiveness	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack severity aligned with garadacimab	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack rate extrapolation method aligned across treatments	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA FE excl. ph 2	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	Incremental costs	Incremental QALYs	Cost per QALY gained
Attack rates from trial (cycle 0-24)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No utility tunnel states	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amended application of Nordenfelt equation	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration disutility included	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration disutility for IV treatments source	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack length ([redacted] days)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One caregiver	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced caregiver disutility value	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased training costs	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amended resource use rates	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG base case	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; Ph, phase; Q2W, administered every two weeks; Q4W, administered every four weeks, QALY, quality-adjusted life year

6.2.1.2. Impact on the ICER of additional economic analyses undertaken by the EAG

EAG scenario analysis were run from the starting point of the EAG base case. Scenarios with the most substantial impact were:

- Assumptions made in relation to the proportion of patients who stop treatment with berotralstat and are classed as responders and the effectiveness of berotralstat responders after the stopping rule was applied
- What intercept is assumed when applying the Nordenfelt (2014) regression equation
- The duration for which the quality-of-life impacts of an attack apply

Table 55: EAG's exploratory analyses in the ≥2 attacks per month population

Scenario	Comparator	Costs	QALYs	Incremental costs	Incremental discounted QALYs	Cost per QALY gained
EAG base case ICER	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ML-NMR	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat maintenance effectiveness average with lanadelumab	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat maintenance effectiveness from Elbashir 2024	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat discontinuation (20%)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat discontinuation (60%)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat discontinuation (80%)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Comparator	Costs	QALYs	Incremental costs	Incremental discounted QALYs	Cost per QALY gained
Attack disutility source	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility age adjustment source	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE utility decrements excluded	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nordenfelt attack coefficient amended	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack length (2.1 days)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack length (3.4 days)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver disutility excluded	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality adjusted life year

6.2.1.3. Impact of altering position of garadacimab

To follow the NHSE Commissioning Policy for existing non-oral treatments for patients with ≥2 attacks per month, a comparison was made between berotralstat as the first-line treatment followed by no prophylaxis (original comparison) and berotralstat followed by garadacimab (Table 56). This change in positioning resulted in a change from berotralstat at 1st line being dominated by garadacimab at 1st line using the EAG-corrected ICER to an ICER of [redacted] for berotralstat followed by garadacimab versus berotralstat followed by no prophylaxis.

Table 56: Altered positioning of garadacimab (corrected ICER)

	Treatment	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Treatment	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected ICER	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Altered positioning	Berotralstat then no prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat then gara	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: gara, garadacimab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.2.2. ≥2 attacks per week population

6.2.2.1. EAG's preferred assumptions

At list price for comparators and PAS price for garadacimab [redacted] when compared to lanadelumab and C1-INH. However, the incremental QALY gains predicted decreased substantially (from [redacted] in the EAG-corrected company base case to [redacted] in the EAG base case in comparison to lanadelumab). Similarly incremental costs reduced from [redacted] to [redacted] Key drivers of the results were:

- The duration for which the quality-of-life impacts of an attack apply
- Assumptions made in relation to the effectiveness of stably attack free patients switching from lanadelumab Q2W to Q4W
- Assumptions made in relation to how attack rates were calculated in both the short and long-term
- Assumptions made in relation to attack severity, particularly in comparison to lanadelumab and Berinert
- The inclusion of administration-related disutilities in comparison to C1-INH

Table 57: EAG's preferred model assumptions in the ≥2 attacks per week population

Preferred assumption	Comparator	Costs	QALYs	ICER
	Garadacimab	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	ICER
Cumulative impact of corrections	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W instantaneous switch	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Lanadelumab Q4W effectiveness = Q2W	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack severity aligned with garadacimab	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack rate extrapolation method aligned across treatments	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
NMA FE excl. ph 2	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack rates from trial (cycle 0-24)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
No utility tunnel states	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Amended application of Nordenfelt equation	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	ICER
	Lanadelumab	[redacted]	[redacted]	[redacted]
Administration disutility included	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Administration disutility for IV treatments source	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack length ([redacted] days)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
One caregiver	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Reduced caregiver disutility value	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Increased training costs	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Amended resource use rates	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG base case	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Probabilistic	Garadacimab	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	ICER
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; Ph, phase; Q2W, administered every two weeks; Q4W, administered every four weeks, QALY, quality-adjusted life year

6.2.2.2. Impact on the ICER of additional economic analyses undertaken by the EAG

The results of the EAG's exploratory analyses are provided in Table 58. Scenarios with the most substantial impact were:

- The timing of the switch between Q2W and Q4W lanadelumab
- What intercept is assumed when applying the Nordenfelt (2014) regression equation
- The duration for which the quality-of-life impacts of an attack apply

Table 58: EAG scenarios in the ≥2 attacks per week population

Preferred assumption	Comparator	Costs	QALYs	ICER
Cumulative impact of EAG base case	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Addition of 2nd line treatments	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Timing of lanadelumab switching (8.2 months)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Timing of lanadelumab switching (6 months)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	ICER
	Lanadelumab	[redacted]	[redacted]	[redacted]
ML-NMR	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Discontinuation aligned for non-oral treatments	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack disutility source	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Utility age adjustment source	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
AE utility decrements excluded	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Nordenfelt attack coefficient amended	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack length (2.1 days)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
Attack length (3.4 days)	Garadacimab	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]
	Garadacimab	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	ICER
Caregiver disutility excluded	Cinryze	[redacted]	[redacted]	[redacted]
	Berinert	[redacted]	[redacted]	[redacted]
	Lanadelumab	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; EAG, External Assessment Group; ICER, incremental cost-effective ratio; NMA, network meta-analysis; QALY, quality-adjusted life year

6.3. Conclusions of the cost-effectiveness section

The company submitted a de novo economic model and ICER estimates for garadacimab in comparison to berotralstat, lanadelumab and C1-INH. However, the EAG identified several limitations with the company's base case model.

Key issues were:

- The presentation of comparison to all comparators in the ≥2 attack per month population, even though the only comparator available in this population is berotralstat. Also, the lack of exploration of uncertainty in the ≥2 attack per week population and the lack of any analyses addressing cost-effectiveness in the ≥2 attack per month population following berotralstat (Key Issue 1)

- The methods and data used to estimate treatment effectiveness. In particular, the use of a constant attack rate within the model where trial data was available, despite said trial data demonstrating a reduction in rates over time. Also, the use of biased assumptions following the end of trial data, wherein the attack rate for garadacimab was reduced using the AARRCF methodology but comparator attack rates were kept the same using LOCF methodology (Key Issue 3)

- The way effectiveness was modelled following application of the stopping rule for berotralstat (Key Issue 4)

- The way effectiveness was modelled for "stably attack free" patients who switch from Q2W to Q4W lanadelumab (Key Issue 5)

- The way patient quality of life was modelled. In particular, the application of decrements for attacks beyond the duration of the attack, and the application of utilities for patients who were not experiencing an attack that cycle (Key Issue 6)

To address these issues and clarify uncertainties, the EAG made the necessary corrections and conducted a range of scenario analysis. Errors identified in the company model were minimal and had only a minor impact. However, several of the EAG's preferred assumptions led to substantial shifts in incremental costs and QALYs from the company's base case.

The assumptions with the largest impact on the cost-effectiveness case based upon EAG analysis were:

- The duration for which the quality of life impacts of an attack apply
- The effectiveness of berotralstat responders after the stopping rule was applied
- The effectiveness of "stably attack free" patients switching from lanadelumab Q2W to Q4W
- The inclusion of a return to general population quality of life, and the method used to apply the Nordenfelt (2014) regression equation to calculate quality of life when an attack was not being experienced
- How attack rates were calculated in both the short and long-term
- Attack severity, particularly in comparison to lanadelumab and Berinert
- The inclusion of administration-related disutilities in comparison to C1-INH

The EAG's exploratory analysis tested several assumptions and parameters on top of its base-case, especially where cost effectiveness results were likely to show the greatest sensitivity.

The most impactful of these was the scenario comparing first-line berotralstat + second-line garadacimab vs first-line berotralstat + no prophylaxis (after EAG corrections). This resulted in an ICER of [redacted] (using list prices for all treatments except garadacimab). The timing of the switch to lanadelumab and the proportion of patients who respond to berotralstat, and therefore stop treatment, were also found to be important parameters.

In conclusion, some important uncertainties remain. The EAG's adjustments and analysis aimed to reflect more realistic assumptions. However, redacting of prior submissions made it difficult for the EAG to provide more robust scenario analyses to account for uncertainties, particularly in the comparison to berotralstat.

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Appendix A: Assessment of the homogeneity within the NMA

The EAG has presented head-to-head meta-analyses for the gardacimab versus placebo comparison using **VANGUARD** and **SL312_2001** and the berotralstat versus placebo comparison using **APeX-2** and **APeX-J**.

Garadacimab versus placebo

Figure 17: Time-normalized number of HAE attacks during treatment NMA (FE)

Figure 18: Time-normalized number of HAE attacks during treatment NMA (RE)

Figure 19: Time-normalized number of HAE attacks requiring on-demand treatment (FE)

Figure 20: Time-normalized number of HAE attacks requiring on-demand treatment (RE)

Figure 21: Time-normalized number of moderate and/or severe HAE attacks during treatment (FE)

Figure 22: Time-normalized number of moderate and/or severe HAE attacks during treatment (RE)

Figure 23: Proportion of attack-free patients (FE)

Figure 24: Proportion of attack-free patients (RE)

Figure 25: Attack-free days (FE)

Figure 26: Attack-free days (RE)

Figure 27: Treatment-emergent adverse events (FE)

Figure 28: Treatment-emergent adverse events (RE)

Berotralstat versus placebo

Figure 29: Time-normalized number of HAE attacks during treatment NMA (FE)

Figure 30: Time-normalized number of HAE attacks during treatment NMA (RE)

Figure 31: Time-normalized number of HAE attacks requiring on-demand treatment (FE)

Figure 32: Time-normalized number of HAE attacks requiring on-demand treatment (RE)

Figure 33: Time-normalized number of moderate and/or severe HAE attacks during treatment (FE)

Figure 34: Time-normalized number of moderate and/or severe HAE attacks during treatment (RE)

Figure 35: AE-QoL total score (FE)

Figure 36: AE-QoL total score (RE)

Appendix B: Network meta-analysis model fit

Table 59: Network meta-analysis model fit (adapted from Tables C.1 to C.7 in the NMA report)

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Time-normalized number of HAE attacks during treatment				
Base Case	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Removal of phase 2 trials	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Including Cinryze	Fixed effect	[redacted]	[redacted]	-
Time-normalized number of HAE attacks requiring on-demand/acute treatment				
Consistency	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Removal of phase 2 trial	Fixed effect	[redacted]	[redacted]	-
Time-normalized number of moderate and/or severe HAE attacks during treatment				
Base Case	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Removal of phase 2 trial	Fixed effect	[redacted]	[redacted]	-
Proportion of attack-free patients				
Consistency	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Removal of phase 2 trial	Fixed effect	[redacted]	[redacted]	-
Sensitivity: without cloglog function	Fixed effect	[redacted]	[redacted]	-
Attack-free days				
Consistency	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]

Model		DIC[a]	Total residual deviance	SD (95% CrI)
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Removal of phase 2 trial	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Addition of APeX-2	Fixed effect	[redacted]	[redacted]	-
Treatment emergent adverse events				
Consistency	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-
Sensitivity: Removal of phase 2 trial	Fixed effect	[redacted]	[redacted]	-
Sensitivity: without cloglog function	Fixed effect	[redacted]	[redacted]	-
Change from baseline in AE-QoL total score				
Consistency	Fixed effect	[redacted]	[redacted]	-
	Random effects	[redacted]	[redacted]	[redacted]
Sensitivity: All doses	Fixed effect	[redacted]	[redacted]	-

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; cloglog, Complimentary Log-Log; CrI, credible interval; DIC, Deviance information criterion; HAE, hereditary Angioedema; SD, standard deviation

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 12 February** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Uncertainty around the treatment pathway for people with HAE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 2.3.4, page 31, the EAG report states that "the [treatment] pathway does not specify that C1-INHs and lanadelumab are only given after failure of oral prophylaxis (i.e. berotralstat), which clinical advice to the EAG said was current commissioning policy in England". This is incorrect since the LTP option pathway provided by the company in Figure 7 of the CS clearly states that C1-INHs or lanadelumab are used for those experiencing ≥2 attacks per week, **despite oral treatment.**	Please reword this section to remove mention that the treatment pathway provided by the company does not specify that C1-INHs and lanadelumab are only given after failure of oral prophylaxis, in line with the NHSE clinical commissioning policy.	Figure 7 of the Company Submission clearly states that C1-INHs and lanadelumab are only eligible for those experiencing ≥2 attacks per week, despite oral treatments, as is described in the top right box in the flow chart.	Thank you for the correction. The EAG has edited the report to reflect this.
In Section 2.4, page 32, the EAG states that "lack of evidence of the efficacy and tolerability of current LTP options formed the central argument of the company's rationale for unmet need.	Please redraft the first sentences of Section 2.4 to accurately reflect the unmet need and treatment limitations set out in Section 1.3.3 of the Company submission.	In Section 1.3.3 of the Company Submission, the company indicates that efficacy and tolerability of currently available LTP options form a key unmet need. Additionally, the company outlines specific limitations for	Thank you for the advice. The EAG have edited this section to draw attention to the unmet need in populations of people with HAE. Specifically, the treatments available

Clinical advice to the EAG questioned this rationale, given that lanadelumab has been demonstrated to have high efficacy. The unmet need is instead that the most effective treatment is currently restricted to those with ≥2 attacks per week due to its high cost." This statement does not fully or accurately capture the company's argument for the unmet need.		each LTP options, which includes: • The proportion of patients that experience a sufficient number of attacks (≥2 per week) to be eligible for IV C1-INHs or lanadelumab is very small (~8%). • A substantial proportion of patients treated with berotralstat may discontinue treatment due to established tolerability concerns and/or failure to meet the continuation rule (20% to 50%), as estimated by clinical experts (consultant immunologists) in England.[2,9,17,63] This can leave patients with no effective, licensed treatment options if ineligible for C1-INHs or lanadelumab.[8-10] It is important that these aspects are captured, to accurately show the unmet need in the England associated with HAE LTP options. Particularly when	to people with < 2 attacks per month, people with ≥2 attacks per month, and people with ≥2 attacks per week. The EAG has detailed where there is an unmet need and where the company's proposed positioning to garadacimab meets that need. The EAG have specifically noted the unmet need in people with ≥2 attacks per month for whom berotralstat fails. LTP in that population is limited to off-label oral generics. The company did not position garadacimab as a subsequent treatment to berotralstat in the CS and this has been rectified by the EAG.

		discussing the effectiveness of lanadelumab, it is essential to put into perspective how few patients are eligible for this treatment, and that a substantial proportion of patients are left without any effective, licensed treatment options when failing to meet berotralstat's continuation rule but not experiencing sufficient attacks to be eligible for C1-INHs or lanadelumab.	
In Section 2.4, page 33, the EAG states that it was unclear to the EAG whether the positioning of garadacimab, as presented by the company, was fully reflective of the current care pathway. Instead, they offer the following proposed positioning of garadacimab: • In people with ≥2 attacks per month, garadacimab could either be offered first-line as an alternative to berotralstat, or second-line in people for whom berotralstat failed.	The company would like to request the EAG to amend the second paragraph on page 33, where it states that the EAG are unclear whether the positioning presented by the company is fully reflective of the current care pathway. The company does not deem it necessary to provide a newly drafted positioning pathway.	The positioning proposed by the company in Figure 8 of the Company Submission is identical to the proposed positioning by the EAG on page 33. As per Figure 8 of the CS: • People experiencing ≥2 attacks per month may be treated with either berotralstat or garadacimab. Patients will be eligible for garadacimab treatment regardless of prior therapy use.	The EAG does not consider this to be a matter of factual inaccuracy. The EAG maintains that the company's positioning was not fully reflective of the current care pathway. No changes have been made to the report.

• In people with ≥2 attacks per week, garadacimab could be offered to people for whom oral treatment (predominantly berotralstat) had failed and compete with lanadelumab to be the main treatment for this population. The company would like to clarify that the positioning proposed by the EAG is identical to the positioning proposed by the company in Figure 8 of the CS, the only difference is the addition of detail to reflect an EAG scenario analysis which considers treatment sequencing in the ≥2 attacks per month setting. As such, describing it as not fully reflective of the current pathway is inaccurate.		• People experiencing ≥2 attacks per week despite oral treatment (i.e., for whom oral treatment has failed) may be treated with lanadelumab, garadacimab or C1-INHs. Taking into account that decision-making of treatment choice is informed by clinical judgement of suitability, clinical effectiveness, contraindications, ability of patient/carer to use the required administration technique, regional network approval and patient choice, company believes this positioning to be identical to the one laid out by the EAG.	

Issue 2 Methods and trials used in the indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 1.4, page 19, the EAG has identified Key Issue 2 as important, because ITC results impact the cost-effectiveness estimates.	Please reword all mentions of cost-effectiveness around Key Issue 2, to avoid emphasising the magnitude of the issue.	In the section expected effect on the cost-effectiveness estimates, the EAG detail that the incremental cost and QALYs increased by [redacted] and [redacted] respectively for the ≥2 attacks per month subgroup because of removing the phase 2 trial. For the ≥2 attacks per week subgroup, removing the phase 2 trial was described as "minimal in terms of costs or QALYs in the garadacimab arm". The reported results are inconsistent in magnitude relative to the language used to describe the importance of the issue.	Thank you for your comment. It is true that inclusion or exclusion of the Phase 2 trials had a small impact. Whether or not the ML-NMR model is used, does have an impact on the results. The impact is modest, and this is reflected in the language used by the EAG.
In Section 1.4, page 19, the EAG states that "This (a ML-NMR without phase 2 studies)	Please amend this to	As the EAG acknowledges the evidence provided by the company in Section 3.4.2.6, the	The EAG does not consider this to be a matter of factual

would have addressed a key concern of the EAG".	"This **may have** addressed a key concern of the EAG"	statement should reflect potential uncertainty. i.e. there is **no guarantee** that such analysis would certainly address the key concern, given that the existing analysis of larger sample size is exposed to significant variation and uncertainty.	inaccuracy. The phase 2 trial introduced substantial heterogeneity into the network, and this was a key concern for the EAG. Removing the phase 2 trial from the network in the ML-NMR would have addressed this concern. The company did not carry out this analysis and it was unclear what effect this change would have had on model fit. No changes have been made to the report.
In Section 3.4.2.6, page 92, the EAG states that, "As noted in Section 3.4.2.4, the EAG requested a ML-NMR excluding the phase 2 trial (CSL312_2001). The company reasoned that this would lead to convergence issues and unreliable estimates".	Please amend this using the text below: "As noted in Section 3.4.2.4, the EAG requested a ML-NMR excluding the phase 2 trial (CSL312_2001). The company reasoned that this would further exacerbate the convergence issues that already existed within the model even with phase 2 trial being included and	As explained on the clarification call and detailed in a response to clarification question A21, the company did provide a clear rationale to not conduct a ML-NMR excluding phase 2 trial (CSL312_2001). This was mainly because existing ML-NMR of larger sample size already experienced divergent transition issues related to the underlying negative binomial	Thank you for the feedback. The EAG has not used the text proposed by the company but has edited the report in line with the company's suggestion.

	so results from such an analyses will only produce more unreliable estimates".	regressions for the count (time-normalised) outcomes which already generated less reliable estimates. Hence, this needs to be accurately reflected in the reasoning provided by the company.	

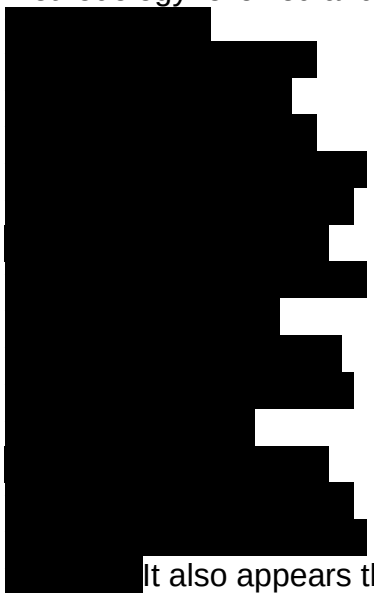
Issue 3 Methods and data used to estimate treatment effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.2.1, page 44, the EAG report states that "The EAG's clinical experts agreed that the trial eligibility criteria were appropriate. They indicated that the criteria were **similar** to the lanadelumab trials and that this was reassuring as lanadelumab is the treatment most commonly offered to the subgroup of people with severe HAE". However, this is in contradiction to a statement made by the EAG in Section 4.2.6.4, page 112 which says "The company	Please clarify whether the study designs and populations of the VANGUARD and HELP studies are similar or not and amend throughout the document.	To ensure consistency throughout the document. Furthermore, Table 15 of the EAG report also states all the clinical trial features of VANGUARD and HELP are similar.	Thank you for your comment. The EAG does not consider this to be a factual inaccuracy. Trial designs and populations being relatively similar is an indication that a network meta-analysis is feasible. It is not an indication that a naïve comparison is appropriate, as these can be sensitive to even small differences between trials.

considered the lognormal curve to be the most externally valid based on naïve comparison to data from the HELP-03 trial for lanadelumab Q2W (44.4% remained attack-free at 6 months vs 55.0% with the gamma curve and 50.8% with the lognormal). The EAG considered this type of naïve comparison of external validity to be **problematic**, given the differences in study designs and populations". The statements are contradictory with respect to the similarity or difference between VANGUARD and HELP studies.			

Issue 4 The handling of berotralstat stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 1.5, page 21, to remedy Key Issue 4, the EAG assumed that the efficacy of	Utilising the Elbashir et al (2024) study to model the efficacy of berotralstat	The assumption made by the EAG of equal efficacy among berotralstat and lanadelumab	Thank you for your comment. This is not considered to be a factual inaccuracy as this source

berotralstat responders is the same as that of lanadelumab administered every two weeks (Q2W).	responders would be an accurate and objective way to resolve Key Issue 4 and the associated factual inaccuracies.	Q2W is substantiated by no clinical evidence, except for clinical experts contacted by the EAG. Although clinical experts contacted by the company have provided differing opinions and are not in agreement. Importantly, the EAG stated that “Data on the effectiveness of berotralstat following application of the stopping rule at 3 months” would suffice as additional evidence that might resolve this key issue. To this end, CSL Behring did provide EAG with Elbashir et al. (2024) study during the clarification question stage, which reports data on the effectiveness of berotralstat following the application of the stopping rule in UK clinical practice This study includes Table 2 that presents the mixed regression model for HAE	has a number of major limitations. The fact that it is a poster, means there is limited information presented on the methodology followed and  It also appears that the study includes patients who would not have been subject to the stopping rule applied following NICE recommendation in TA738, as data collection started in November 2020 whereas TA738 was published

		attacks which shows the associated attack rate regression outputs for berotralstat patients at different time intervals. Results from this study show that berotralstat responders at time interval (3-6 months after) have around a 50% decrease in their number of predicted mean HAE attacks from baseline. Hence, this further demonstrates that berotralstat responders do not have the same efficacy as lanadelumab Q2W patients. These real-world published attack rates are in line with a scenario presented by CSL Behring as a response to the clarification question B7. Furthermore, from a mathematical viewpoint as well, the same efficacy effect between berotralstat and lanadelumab Q2W is implausible. Examining FIG E2 of Zuraw et al. (2021),	in October 2021. [redacted] compared to 54 patients who discontinued. However, the timing of the discontinuation is not known. Nevertheless, we have added a scenario analysis. [redacted]. After 24 months we calculated the attack rate as the average of months 12 – 24. The discontinuation rate from this paper was also implemented in this scenario, in the absence of any other data it is assumed all disco

		shows the percentage reduction in attack rate per patient taking berotralstat 150mg during the APeX trial, and there the treatment responders (who experience a ≥50% reduction in attack rates since baseline) do not express the same efficacy magnitude as reported for lanadelumab Q2W patients.	tinuation took place at the 3 month stopping rule. The results are presented in Table 55 and are more favourable to garadacimab (with incremental costs for berotralstat vs garadacimab rising from [redacted] to [redacted] and incremental QALYs falling from [redacted] to [redacted]).

Issue 5 The handling of lanadelumab switch between Q2W and Q4W

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 1.5, page 22, the polarity of the results described in Key Issue 5 is incorrect. "≥2 attacks per week subgroup – lanadelumab arm cost **increased**" The same table also reports "which found that switching from Q2W to Q4W did not impact effectiveness"	Please change to "≥2 attacks per week subgroup – lanadelumab arm cost **decreased**" Please also amend to "cost-effectiveness is impacted from switching of Q2W to Q4W".	Increasing the effectiveness of a comparator would reduce the need for resources such as the number of acute attacks treatment, which would decrease cost, not increase. Generally, switching from lanadelumab Q2W to Q4W impacts efficacy, costs, etc. although the user needs to adjust both the rate ratios for the time-normalised number of	Thank you for your comment. This has highlighted an error in the way we implemented this scenario. The Company is correct that this relates to failing to account for on-demand attacks. This has been amended in E50, of Inputs - Efficacy. The EAG report has now been amended to include

		HAE attacks and time-normalised number of HAE attacks requiring on-demand.	corrected results in the relevant population. When investigating this issue, an additional issue was found relating to the scenarios regarding carer utilities. The scenario for amending the implementation of carer utilities and excluding the impact of carer disutilities were overlapping. The change impacts column DH in the engine switch which calculates the HSUV for the attack state, it was linking to the wrong switch. Amending these issues had a minor impact (0.01 QALYs). In relation to the EAG statement about the impact on effectiveness we have added some extra detail on the conclusions of the Magerl et al. (2024) study to clarify the point made.

In Section 5.3, page 156, the EAG claim that the Magerl et al. (2024) study “showed that stable patients who reduced their dosing frequency maintained effectiveness.”, page 151. This is an incorrect conclusion of the paper as the results are overgeneralised.	Please justify the claim by adding further detail. “showed that stable patients who averaged 2.98 attacks per month, who reduced their dosing frequency (which includes reductions to more frequent dosing than Q4W) and did not thereafter return to the original dosing frequency, maintained effectiveness.”	On page 386 of the study, it is reported “Most patients (75.7%) who had an interval increase did not return to Q2W-dosing regimen”. Therefore, 24.3% of patients who had an interval increase (reduced dosing frequency), did return to the original Q2W dosing regimen because of changes in treatment effectiveness. Generally, if an outcome (maintained effectiveness) is not true for a quarter of the population, it cannot be said that the outcome is true for the entire population. Furthermore, the generalisability of the findings from the study are limited in relation to clinical practice in the NHS. This is because Table II in the study reports that the mean Preindex annualised [monthly] HAE attacks per patient was 35.8 [2.98]. Therefore, the outcomes from the study may not apply to the	Thank you for the correction. The EAG has edited the report to reflect that 75.7% of patients with increased dosing interval did not return to the original Q2W. Magerl et al. (2024) was originally suggested by one of the clinical experts consulted by the EAG, who considered this study to be generalisable to the NHS. Furthermore, 59.6% of patients in that study used LTP before starting lanadelumab. Therefore, it can be assumed that the yearly number of attacks would be higher than 35.8 if these patients were not previously receiving LTPs. Finally, we note that the company themselves argue that a patient’s prior attack frequency does not impact on the effectiveness of LTPs.

		NHS clinical practice where lanadelumab is restricted to the ≥2 attacks per week subgroup.	This was in order to justify the use of VANGUARD trial data to assess expected effectiveness in the ≥2 attacks per week subgroup.
In Section 4.2.6.7, page 124, the wording contains a polarity error, “They cited three further small single-centre studies, which also concluded that **increasing** the interval of administration does not compromise effectiveness”.	Please amend the wording of the following text to: “They cited three further small single-centre studies, which also concluded that **decreasing** the interval of administration does not compromise effectiveness”.	Should be decreasing rather than increasing from the context of the section.	This is not a factual inaccuracy. The argument is that increasing the interval, moving from Q2W to Q3W or Q4W or even longer, does not compromise the effectiveness. The EAG will clarify in the report.
In Section 4.2.6.7, page 124, the wording implies error made on the company’s behalf. “The CS used lanadelumab Q4W effectiveness from HELP trial to model stable patients switching to Q4W lanadelumab, even though patients in that study did not have the Q2W dosage before Q4W. **Therefore,** it is not possible to show the	Please amend the wording of the following text to: “The CS used lanadelumab Q4W effectiveness from HELP trial to model stable patients switching to Q4W lanadelumab, even though patients in that study did not have the Q2W dosage before Q4W. **Due to the lack of data on the population of interest,** it is not	In the EAG report, the connective “Therefore” implies that something was not possible because of the CS rather than general data availability. Hence, this should be amended.	Thank you for the correction. The EAG has edited the report to reflect that the issue is that the HELP trial does not contain data on patients starting on Q2W and switching to Q4W if stable.

effectiveness of the population of interest to this submission: patients who were stable to Q2W and had remained stable in Q4W dosage afterwards".	possible to show the effectiveness of the population of interest to this submission: patients who were stable to Q2W and had remained stable in Q4W dosage afterwards".		

Issue 6 The calculation of patient utilities

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In Section 1.5, page 22, in Key Issue 6, the EAG claims that "AE-QoL results from VANGUARD showed improvement within the first month of treatment **followed by stabilization**". This is incorrect because the AE-QoL did not stabilise and continued to improve for garadacimab patients.	Please amend as follows: "AE-QoL results from VANGUARD showed substantial improvement within the first month of treatment, which was followed by further improvements thereafter."	Accounting for the values found in Figure 11, the EAG claim that the improvement from baseline to Month 1 is significant is true. (There is an improvement of 60.31%) The values cannot be said to be stabilised thereafter. This is because the mean AE-QoL questionnaire total scores continue to improve (decrease) by a margin of 24.06% from Month 1 to Month 6.	This is not a factual inaccuracy. Placebo AE-QoL scores follow a similar decrease beyond month 1 to the garadacimab arm. In both arms, mean scores post month 1 fluctuate from month to month with no clear pattern of a month on month decrease observed in either arm.
In Section 4.2.9.7, the EAG's view that patients cannot achieve higher utilities than	Please consider the findings reported by Nordenfelt et al. (2014), which highlight the	The Nordenfelt et al. (2014) study states "**Days since last attack** has a positive	This is not a factual inaccuracy.

those implied by the regression conducted by Nordenfelt et al. (2014) is inaccurate.	difference between quality-of-life impacts from the number of attacks reduced over time **and** time since last attack.	correlation with EQ5D today scores, which suggests an improvement in QoL as the time since last attack increases", page 188 of the study. The study does not report the coefficient for the 'Days since last attack' variable but does highlight that higher utilities than those specified in Equation 1 are possible due to this omission.	The Nordenfelt paper does include that line "Days since last attack has a positive correlation with EQ5D today scores" but does not present a coefficient for this variable and it is unclear what that statement is referring to. It may refer to a separate regression/correlation analysis to the regression analysis used in the model, which is reported separately in the paper. In any case, 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.
In Section 4.2.9.7, the EAG's interpretation of the attack frequency coefficient from Nordenfelt et al. (2014) is inaccurate.	Please refer to the attack frequency coefficient from Nordenfelt et al. (2014) as "per attack".	The Nordenfelt et al. (2014) study states "Attack frequency and age have a negative correlation with EQ5D today scores with more attacks (-**0.0043 per attack**; p < 0.0001)", page 187 of the study.	This is not a factual inaccuracy. The EAG has interpreted this co-efficient as being per-attack, the ambiguity is over what time period. The EAG has assumed it is per attack per month in the base case, with a scenario where it is assumed to be per attack per year. The EAG attempted to contact the authors to clarify but has not heard back. It is unfortunate it is not clearer in the paper and that, despite this being the third appraisal to be conducted in HAE data, it has not yet been generated from a more contemporary source.

General

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report, the EAG names SC Berinert or SC C1-INHs as ‘Haegarda’.	Please amend all mentions of Haegarda to say SC Berinert.	Haegarda is a branded name of SC Berinert but this name is not used in the UK. As such, it is inaccurate to call SC Berinert or SC C1-INHs ‘Haegarda’ in this report. This is in line with email communications on the 23rd of January.	As stated in the report, the EAG did this to differentiate CS C1-INHs (out of scope) from IV C1-INHs (in scope), and to differentiate SC Berinert (out of scope) from IV Berinert (in scope). Also, the company used the term Haegarda in their NMA report. However, we have altered all uses of “Haegarda” to “SC Berinert” in the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report, the EAG inconsistently refers to the original company submission (provided on 7 November 2024) or the shortened company submission (provided on 14 November 2024, requested by NICE [updated confidential markings provided on 18 December 2024]). Example: The EAG mostly seems to mean the original submission when referring to the company submission. However, on page 111 of the EAG report (Figure 15), the EAG states that Figure 15 is taken from Figure 19 in the CS, but this would refer to the shortened submission rather than the original submission.	Please make amendments to clearly reference which submission is being cited. The request to utilise a constant version of the CS to draft the EAG report was previously requested by the company (22 Jan 2024). Ideally, all references to the Company Submission should be made to the **shortened** submission, since that is latest updated submission requested by NICE.	It is key that all documents (CQs, EAG report) all utilise the same Company Submission, to ensure clarity for all stakeholders.	Thank you for the correction. The EAG has edited the report to refer to the shortened submission.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 1.1, table 2, the EAG states that “All comparators presented regardless of whether available for the ≥2 per month population or not” This is misleading and not fully accurate.	Please amend this as follows: “To maintain brevity and present a fully incremental analysis from the health economic perspective, all comparators were presented regardless of whether available for the ≥2 per month population or not”	The company was requested to cut down the length of the report and the only difference presenting the comparators separately for ≥2 attacks per month population and then ≥2 attacks per week population would have made is to increase the baseline number of attacks and showcase the improved results for garadacimab. Instead the company chose to be conservative and present the ≥2 attacks per week population under scenarios to maintain brevity and provide a fully incremental analyses.	This is not a factual inaccuracy. The relevant comparisons were not presented in the CS. It is up to the company to decide what to keep and what to cut to provide a report within the word limits.
In Section 1.2, page 17 (sixth bullet point) EAG’s claim of garadacimab being not cost-effective against no prophylaxis is unsubstantiated since no results have been presented for this comparison.	We request EAG to either remove this sentence “garadacimab is not-cost effective when compared to no prophylaxis (which was also the case for lanadelumab in TA606);”	Neither the CS nor the EAG report present a cost-effectiveness analysis of garadacimab against no prophylaxis, therefore there is no evidence currently produced to make this claim.	This is not a factual inaccuracy but we have clarified that the statement is based on scenario analysis in the ≥2 attacks per month population following berotralstat.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Or if included, qualify the claim by presenting the detailed results for cost-effectiveness analyses of garadacimab versus no prophylaxis in the ≥2 attacks per month population and ≥2 attacks per week population.	This claim is also misleading because it suggests that garadacimab would never be cost-effective against no prophylaxis under any circumstances.	
In Section 1.2, page 17 (sixth bullet point), the EAG stated that, “cost-effectiveness also varies between the ≥2 attacks per month population, w[h]ere berotralstat is the only available treatment” This is inaccurate since there are other treatments available.	Reword the sentence using the words ‘licensed and approved’- “cost-effectiveness also varies between the ≥2 attacks per month population, were berotralstat is the only available **licensed and approved** treatment” before the word treatment in the sentence so that it becomes factually accurate.	TA738 recommends berotralstat for ≥2 attacks per month population as the only licensed option. In several instances the EAG also discusses other treatments (not licensed or approved) available for ≥2 attacks per month population, so then not qualifying berotralstat as licensed and approved in this instance makes it inaccurate and so should be amended.	Thank you for this correction. The report has been altered to reflect that berotralstat is the only treatment recommended by NICE in this population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 2.2, page 27, (first two bullet points), when discussing C1-esterase inhibitors, the EAG report sometimes describes these as 'IV C1-INHs' rather than C1-INH.	Please correct 'IV C1-INHs' to say 'C1-INH' or 'C1-esterase inhibitor' in the first two bullet points in Section 2.2 (p27).	C1-INH (C1-esterase inhibitor) is a protein in the body, while IV C1-INHs is the treatment of supplying C1-INHs intravenously. In this case, the description of the disease includes the protein C1-INH, not the treatment IV C1-INHs. This is a key distinction and should be corrected to avoid confusion.	Thank you for this correction. The report has been altered in line with the proposed amendment.
In Section 1.2, page 16 – under the table it states 'IV C1-INHs' means C1-inhibitor.	Please correct the definition of 'IV C1-INHs' to be 'intravenous C1-esterase inhibitors' Please also include this abbreviation and definition below the table outlining key issue 6, on page 24	Incorrect definition of the abbreviation, which would suggest that all C1-INHs are intravenous, which is not correct.	Thank you for this correction. The report has been altered in line with the proposed amendment.

In Section 3.2.2.4, page 49, the EAG states that the clinical experts indicated that reducing the number of moderate or severe attacks is more important than reducing the overall number of attacks and again in Section 3.2.3.6, page 53 it states that a reduction in moderate or severe attacks is the most important outcome of treatment for many people with HAE. This is contradictory to what is mentioned in Section 2.6, page 36, Table 5, where the EAG states that clinical advice to the EAG was that all these outcomes were of clinical value and that there was not one outcome that is necessarily more important than the others.	Could the EAG please clarify which of the statements are accurate and ensure alignment on this throughout the report.	Statements regarding the relative importance of outcomes contradict each other throughout the EAG report. It is key for all stakeholders that a consistent and aligned narrative can be understood.	The EAG's statements did not contradict each other. In Section 3.2.2.4, the EAG noted advice from a clinical expert that for *many people with HAE*, reducing the number of moderate or severe attacks is more important than reducing the overall number of attacks. However, this was not a statement that it is the most important outcome for all people with HAE. The objective of the expert's comment was to emphasise the importance of looking at the totality of a person's experience of HAE, which includes attack rate but also includes attack severity. No changes have been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.1, page 41, Table 7 of the EAG report, the population of CSL312_2001 is described as: "People aged 18-65 years old with HAE-1 or HAE-2 who either: • experienced ≥4 HAE attacks over 2 months during the 3 months prior to screening • had previously initiated prophylaxis for HAE" This is not accurate.	Please amend the table cell describing the population of CSL312_2001 to state: 'People aged 18–65 years old with HAE who either: • HAE-1/HAE-2: experienced ≥4 HAE attacks over 2 months during the 3 months prior to screening • HAE-3: experienced ≥1 HAE attack during the 3 months prior to screening"	As is described in the CSL312_3002 CSR (provided alongside the clarification question responses), the OLE eligibility criteria state that patients with HAE-1 or HAE-2 as well as those with HAE-3 are eligible to enrol in the clinical study. Moreover, the eligibility criteria state: • For subjects with C1-INH HAE (i.e., HAE-1 or HAE-2): ≥ 4 HAE attacks over a consecutive 2-month period during the 3 months before Screening, as documented in the subject's medical record. Note: For subjects taking any prophylactic HAE therapy during the 3 months before Screening, ≥ 4 HAE attacks were documented over any consecutive 2-month period during the 3	Thank you for the amendment. The report has been edited as suggested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		months before commencing the prophylactic therapy. • For subjects with normal C1-INH HAE (i.e. HAE-3): ≥ 1 HAE attack during the 3 months before Screening, as documented in the subject's medical record. Note: For subjects who took any prophylactic HAE therapy during the 3 months before Screening, 1 HAE attack was documented during the 3 months before commencing the prophylactic therapy. Moreover, there are no eligibility criteria requiring previous prophylactic treatment prior to Run-In. As such, the described population/eligibility criteria in Table 7 of the EAG report is inaccurate and should be amended.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.1, page 41, Table 7 of the EAG report, the intervention in CSL312_2001 is described as: "Garadacimab SC injection (pre-filled syringe), once per 28 days: • 75 mg (n=9) • 200 mg (n=8) • 600 mg (n=7)" This is not accurate	Please amend the table cell describing the intervention used in CSL312_2001 to incorporate the information provided in the column to the right.	The phase 2 study comprised of a randomised, placebo-controlled, double-blind treatment phase (12 weeks) and OLE phase (117 weeks). The double-blind treatment phase included 32 patients who were randomly assigned to receive once monthly placebo or garadacimab, including n=8 randomised to 200 mg garadacimab. Additionally, a further six patients were assigned to open-label garadacimab 400 mg every 2 weeks. After this, all 38 patients enrolled in the open-label extension (OLE) phase. Based on the information outlined in Section 9.4.1 of the	Thank you for noting this inaccuracy. The company presented a more concise summary of the interventions in CSL312_2001 at the clarification stage. The EAG has edited the interventions to match Table 7 in the clarification response.

		CSL_2001 CSR, the treatment schedule is as follows: Garadacimab SC every 4 weeks (q4wk), following an intravenous (IV) loading dose. **Treatment Period 1:** *Blinded patients with HAE-1/2* • A loading dose of 40 mg garadacimab IV followed by 75 mg garadacimab SC q4wk (n=9) • A loading dose of 100 mg garadacimab IV followed by 200 mg garadacimab SC q4wk (n=8) • A loading dose of 300 mg garadacimab IV followed by 600 mg garadacimab SC q4wk (n=7) *Patients with HAE-1/2 assigned to open-label treatment* • 400 mg garadacimab SC administered every 2 weeks (q2wk) SC with no loading dose (n=6) *Patients with HAE-3 assigned to open-label treatment*	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		• A loading dose of 300 mg garadacimab IV followed by 600 mg garadacimab SC q4wk (n=6) **Treatment Period 2 (all open-label):** *Patients with HAE-1/2* • 200 mg or 600 mg garadacimab SC q4wk (n=38) *Patients with HAE-3* 600 mg garadacimab SC q4wk (n=2)	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.2.1, page 43, the EAG states: "The eligibility criteria for **VANGUARD** and **CSL312_3002**, the OLE trial, were identical:" This is not fully accurate.	Please amend to "The eligibility criteria for **VANGUARD** and *the garadacimab-naïve patients in* **CSL312_3002**, the OLE trial, were identical:"	As per the CSL312_3002 CSR, the eligibility criteria listed are for the garadacimab-naïve patients. This is a key difference since patients in CSL312_3002 may have rolled over from CSL312_2001 and this contains slightly different eligibility criteria (i.e., inclusion of HAE-3 patients)	Thank you for this correction. The report has been altered in line with the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.2.1, pages 44–45, the EAG states the numbers of patients receiving LTPs prior to study enrolment. These numbers are not quite correct, nor are they appropriately marked up (see 'confidential markings' section below).	Please amend the last two sentences of page 44, running over into page 45, into the following, and ensure the appropriate markings: [redacted] people in the garadacimab arm received either C1-INHs ([redacted] people), berotralstat ([redacted]people), tranexamic acid ([redacted] people), danazol ([redacted] person), or lanadelumab ([redacted]*people*) [redacted] people in the placebo arm received either berotralstat ([redacted] people), C1-INHs ([redacted] people), tranexamic acid [redacted] person), or danazol [redacted] person).	The number of patients previously receiving berotralstat and lanadelumab in the garadacimab arm are incorrect. Moreover, the numbers should be marked CIC. These numbers were provided in the CQ response to question A2.	Thank you for pointing out this inaccuracy. The EAG have edited the report to match that reported in question A2 in the clarification response. However, the EAG note that this is different to the company's proposed amendment. These data have been marked up appropriately.

In Section 3.2.2.1, page 47, the EAG states the number of discontinuers. These numbers are not all correct, nor are they appropriately marked up (see 'confidential markings' section below).	Please amend the following on page 47 and ensure the appropriate markings: At that point, [redacted] people had discontinued treatment: • [redacted] people discontinued due to study site being terminated by the sponsor • [redacted] people discontinued due to physician decision • [redacted] people withdrew from the study • [redacted] person discontinued due to adverse event (AE) • [redacted] person discontinued due to pregnancy • [redacted] person was lost to follow-up • [redacted] person due to lack of efficacy Please also amend the paragraph directly below that,	As per pages 61 and 94 of the company submission, and the CSL312_3002 TFLs (data on file). Incorrect numbers include the total number of discontinuers and the number of people who had discontinued due to: • Withdrawal from the study • An adverse event • Lack of efficacy Moreover, data should be marked up CIC as indicated	Thank you. The report has been edited in line with the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	where the EAG draws conclusions based on the above, as this was based on incorrect data.		
In Section 3.2.2.2, page 47, the EAG states that a loading dose is administered to participants in both VANGUARD and CSL312_3002. This is not correct.	Please amend to the following in the final paragraph of page 47: In **VANGUARD** and *in CSL-study-naïve patients* in **CSL312_3002**, participants received a 400 mg loading dose of garadacimab SC as two 200 mg injections, followed by additional self-administered (or caregiver-administered) monthly doses of 200-mg garadacimab SC.	In CSL312_3002, the loading dose is only provided for the CSL312-study-naïve patients (i.e., those who have not rolled over from CSL312_2001 or VANGUARD). This should be clarified in the EAG report.	Thank you. The report has been edited in line with the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.2.3.8, page 57 the EAG states: "The patient-reported outcomes (PROs) collected in **VANGUARD** were EQ-5D-5L, the Angioedema QoL (AE-QoL) questionnaire, and the Subject's Global Assessment of Response to Therapy (SGART)." This is not accurate, since additional PROs were collected during VANGUARD and reported in the company submission.	Please amend this statement to the following: The patient-reported outcomes (PROs) collected in **VANGUARD** were EQ-5D-5L, the Angioedema QoL (AE-QoL) questionnaire, the Subject's Global Assessment of Response to Therapy (SGART), the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire and Investigator's Global Assessment of Response to Therapy (IGART)."	As per Company Submission Section 2.6.8, HRQoL was measured via the EQ-5D-5L questionnaire as an exploratory outcome. Additionally, Patient-reported outcome (PRO) data were also obtained using the Subject's Global Assessment of Response to Therapy (SGART), AE-QoL questionnaire, Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire and Investigator's Global Assessment of Response to Therapy (IGART). A summary of the results of IGART and WPAI are provided in Appendix Q of the Company Submission, while the others are described directly in the Company Submission. This is clarified in Section 2.6.8 of the Company Submission.	Thank you. The report has been edited in line with the proposed amendment, with the exception of the Investigator's Global Assessment of Response to Therapy (IGART), which is not a patient-reported outcome.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.3, page 65, the EAG report states an unsubstantiated claim. "However, people who are stable on lanadelumab every two weeks may have their dose reduced to lanadelumab every four weeks, where they may experience fewer adverse events **but retain similar efficacy**".	Please remove the phrase "but retain similar efficacy"	Figure 4.3 of the company NMA reports that the fixed effect NMA estimates of time-normalized number of HAE attacks [redacted] (The inclusion or exclusion of phase 2 studies does not impact this conclusion) We are also aware of no such clinical trial data for this patient population (switching from lanadelumab Q2W to lanadelumab Q4W) that has been made available since this appraisal.	Thank you. This paragraph has been edited to explain the protocol for dose reduction of lanadelumab used in the NHS.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 3.4.2.5, page 90 the EAG makes a claim that is contrary to the conclusions made in the ML-NMR report. "The ML-NMR **demonstrated**…" which connotes reliability to the subsequent results which is not supported by the uncertainty of the approach.	Please reword to "The ML-NMR indicates … [the results]. These results should be interpreted with caution due to issues of non-convergent transitions."	As detailed in Section 5.2 of the ML-NMR report, the time-normalised HAE attack family of outcomes did not converge, and therefore the ML-NMR could not have reliably demonstrated the results that the EAG go on to report in the following sub-sections.	Thank you. The report has been edited in line with the proposed amendment
In Section 3.4.1.6, page 80, use of Proportion of attack-free patients in the economic analysis is inaccurately described. "This outcome was used to calculate calibrated attack rates in company sensitivity analysis in the economic analysis"	Please remove the sentence	Tables 43 and 44 of the shortened CS, specify all scenario analyses. Calibrated attack rates, which indeed depend on the proportion of attack-free patients, were not presented in the economic analysis. Neither was such scenario presented in the clarification questions.	The report has been amended to clarify this data was used in the model

In Section 3.4.2, page 86, the EAG's claims relating to why the company undertook a ML-NMR are not consistent with the arguments laid out by the company, "The company performed an ML-NMR because, despite efforts to minimise bias by excluding insufficiently similar study data, residual heterogeneity between studies included in the NMA reduced the validity of some analyses",.	Please refer to the company's justification for the rationale behind the ML-NMR: "This addendum provides a ML-NMR analysis of efficacy data comparing garadacimab to berotralstat, lanadelumab and HAEGARDA (a subcutaneous C1-esterase inhibitor named Berinert SC in the NHS). **This analysis is to supplement the existing NMA used in the company's cost-effectiveness model by further exploring the base case assumption that there is no evidence of treatment effect modification that would necessitate adjustment**, be it for garadacimab or the comparator technologies. Such an assumption has been made for previous NICE TA606 and TA738"	Currently, the EAG claim does not accurately reflect the rationale behind the ML-NMR.	The EAG used the explanation in Appendix T to characterise the reasoning behind the company's decision to conduct the ML-NMR. Page 9, Appendix T: "*However, despite best efforts made to minimise bias by excluding insufficiently similar study data residual heterogeneity between studies included in the NMA may have reduced the validity of some analyses. Hence to further support the conclusions derived from the NMA, a ML-NMR was undertaken as it offers distinct methodological benefits in capturing and adjusting for heterogeneity and contextual factors that a standard NMA may*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			overlook" The EAG accepted the company's reasoning as presented in Appendix T, and as such, no changes have been made to the report.
In Section 4.1, page 98, the EAG states that "The company selected four HRQoL studies to support the cost-utility analysis. No rationale was provided for the prioritisation of these four articles". This is inaccurate.	Please amend as follows: "The company selected four HRQoL studies to support the cost-utility analysis. Rationale and relevance for each study was provided".	The rationale and relevance for each study was provided in CS B.3.4.3 and then again as a response to clarification question B17.	This is not a factual inaccuracy. The company only provided a short description of the studies but did not justify why they were chosen above other studies identified in the SLR.

In Section 3.4.2.3, page 88, the EAG claimed that the company did not clarify the reason for the choice of covariates i.e. the text states “Given the lack of transparent reasoning for the choice of covariates, it was unclear to the EAG whether all of the relevant covariates were tested in the ML-NMR”,	Please remove this sentence.	The subsequent paragraph goes on to describe how the main effects and their interactions were fitted for each of these covariates, and covariates were removed one-by-one as per the priority order. Hence, the company has been transparent in providing their reasoning of the process undertaken.	The EAG was referring to the choice of covariates rather than the methods of how they were used in the analysis. As stated in the report the covariates should be the treatment effect modifiers for people with HAE. However, there was little discussion of what might be a treatment modifier. The only discussion was a statement in Section B.2.2.2.1 of the CS where the company stated that baseline attack rate was not a treatment effect modifier for garadacimab. This was a cause for concern to the EAG as many of the ML-NMR outcomes adjusted only for baseline HAE attack

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			rate. No changes have been made to the report.

In Section 3.4.2.4, page 90, the EAG states “It was not clear from Appendix T which studies were used in the ML-NMR. However, Figures 31 to 33 in Appendix T indicated that VANGUARD and CSL312_2001 were used alongside HELP (landadelumab once per 2 weeks and once per 4 weeks), APeX-2 (berotralstat), APeX-J (berotralstat), and COMPACT (Haegarda)”. This is misleading and inaccurate.	Please amend as follows: “It was clear from Appendix T which studies were used in the ML-NMR. Figures 31 to 33 in Appendix T indicated that VANGUARD and CSL312_2001 were used alongside HELP (landadelumab once per 2 weeks and once per 4 weeks), APeX-2 (berotralstat), APeX-J (berotralstat), and COMPACT (Haegarda)”.	The first sentence by EAG suggests that Appendix T does not provide clarity around which studies were included in ML-NMR, but then the next sentence contradicts this by discussing how figures 31 to 33 in Appendix T shows all studies included in ML-NMR.	It would have been appropriate to state the studies included in the ML-NMR prior to figure 31 in the appendix of the report. A table of included studies should have been presented with the key characteristics of each study included in the analysis. This could have included factors like study design, participant population, intervention details, measured outcomes, and key findings. In this case it would have been appropriate to include details of the covariates relevant to the ML-NMR. Therefore, the EAG consider their critique was appropriate and no changes have been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 4.2.3, page 104, Figure 12 is incorrectly labelled. It is titled “EAG analyses of population subgroups” and the figure presents the <2 attacks per month subgroup within the diagram.	Please amend the figure to exclude the <2 attacks per month part of the visual.	The EAG did not analyse the <2 attacks per month subgroup in their economic analyses therefore, this subgroup should not be present in a figure which describes the analyses that the EAG did undertake. The figure could also be interpreted as garadacimab being considered as a second line treatment in the <2 attacks per month subgroup, in a scenario analysis. This is also not a subgroup that CSL Behring are seeking a recommendation in, as noted in the EAG report.	Thank you for the correction. The EAG has edited the report to reflect that the company are not positioning garadacimab in the <2 attacks per month subgroup.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 4.2.2, page 102, caution is needed when referring to QALYs versus utility. "For example, in the 6-cycle tunnel, for each cycle patients remain attack-free, they accrue an additional 0.031 QALYs compared to the previous attack-free cycle, until reaching the maximum general population utility".	Please amend to "For example, in the 6-cycle tunnel, for each cycle patients remain attack-free, they experience an additional 0.031 utility gain compared to the previous attack-free cycle, until reaching the maximum general population utility"	QALY calculations are subject to other factors such as effects discounting. Therefore, the QALY value gained as the patient progresses throughout the tunnel states would vary with time. It is more accurate to report the effects of the tunnels through utility rather than QALYs.	Thank you for the correction. The EAG has edited the report to reflect this.
In Section 4.2.6.4, page 111, the EAG report states "The company did not fit a curve to placebo participants".	Please refer to the response for question B1b of the clarification questions.	The company did fit curves to placebo patients as requested by the EAG in clarification question B1b. Please see Figure 7 of the clarification questions.	Thank you for the correction. The EAG has edited the report to reflect this.
In Section 4.2.6.4, page 117, the EAG report states "Interestingly, this methodology was used in the model to extrapolate attack rates beyond the 24th cycle but not for the first 24 cycles."	Please update to "The AARRCF methodology was used in the model to extrapolate attack rates beyond the 24th cycle but not for the first 24 cycles.	To ensure clarity on what methodology is being referred to. Otherwise, it may seem the parametric curves were used to extrapolated attack rates beyond cycle 24 which is not true.	Thank you for the correction. The EAG has edited the report to reflect this.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 4.2.6.4, page 115, Figure 15 is outdated.	Please use Figure 13 provided as a response to clarification question B9c.	The figure was updated. This is an important thing to adjust because Figure 13 of the clarification questions shows a good fit of observed and predicted HAE attack rates for garadacimab.	Thank you for the correction. The EAG has edited the report to reflect this.
In Section 4.2.6.4, page 117, Table 30 of the EAG report inaccurately describes the company base case.	Please update Table 30 to quote both the company base case and EAG base case in terms of "% reduction in time-normalised HAE attacks" and "Garadacimab attack rate (placebo value of [redacted])"	The current company base case is portrayed as using the calibrated attack rates (also known as cumulative time to first attack method). This is incorrect, as the company base used constant attack rates (also known as last observation carried forward), and AARRCF for cycles 1-24, and 25 beyond respectively. The company base case has been accurately described in the EAG report at the beginning of section 4.2.6.3.	Thank you for the correction. The EAG has edited the report to reflect this.

Section 4.2.6.6, page 121: Incorrect description of differences in discontinuation rates: “The source of C1-INHs discontinuation rates was unclear in the CS. The company state that they took this from a multi-centre review of LTP which showed that only one out of 47 C1-INH patients discontinued treatment due to ineffectiveness over 15 months. In response to clarification questions they mention a publication by Mendivil (2023).The EAG could not identify the source of the one in 47 from this paper. This was modelled through the linear extrapolation of the 15 months discontinuation rate, resulting in a 40-year discontinuation of 50.25%. This translated into a per cycle discontinuation rate of 0.10% per cycle. **Berinert IV and SC forms of administration were assumed to have no difference in discontinuation rates**.”	Please remove the bolded sentence.	The bolded sentence is incorrect from two perspectives. Firstly, Berinert IV and SC forms of administration have different discontinuation rates, as garadacimab (SC – [redacted] per cycle) and lanadelumab (SC – 0.087% per cycle) have different discontinuation rates described in the preceding paragraphs. Secondly, if the sentence is relating to the discontinuation rate differences between the IV and SC forms of Berinert, then the sentence itself would not provide value since SC Berinert is not included in the cost-effectiveness analysis and is not available in the model.	Thank you for the correction. The EAG has edited the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.8, page 125: Incorrect description of company's overview of attack severity modelling "The company stated that naïve data was used as it was not possible to provide an ITC for severity because the definitions used for severity across the different trials were too heterogeneous (confirmed in clarification question response B5)."	Please restructure the sentence as follows: "The company stated that naïve data was used and it was also possible to provide an time-normalised number of HAE attacks by moderate/severe and mild severities separately, from the NMA."	During the clarification questions (question B5a), the company stated that it was possible to provide attack rates stratified by mild, moderate/severe attacks using the NMA. Possible heterogeneity of attack severity definitions across trials do not impact the feasibility of such an analysis, instead what it may impact is the uncertainty of the estimates.	This is not a factual inaccuracy. In CQ B5a the company stated the following: *"This is because although the NMA does report the outcomes of time-normalised number of HAE attacks and those of the moderate/severe severities separately, it is still unable to adjust for the different definitions of attack severities across trials"* The EAG's comment was prompted by the statement above.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.9.1, page 127: The EAG claims that a mapping exercise between AE-QoL and EQ-5D was attempted by the company and failed. "(the company unsuccessfully attempted to conduct a mapping exercise between AE-QoL and EQ-5D, which failed due to the limited domain correlation)", page 123	Please use language consistent with the CS as found in B.3.4.1, in line with "there is limited scope to perform a mapping exercise between AE-QoL and EQ-5D due to the limited domain correlation". Furthermore, amend the associated section accordingly to align with the above.	The company conducted a feasibility assessment to explore if a mapping exercise is feasible. The feasibility assessment was successful as it showed that a mapping exercise was not feasible due to limited domain correlation. Hence, the company never undertook a mapping exercise and failed which makes the claim from EAG inaccurate.	Thank you for the correction. The EAG has edited the report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.10.1, page 140: The EAG claims that “Subsequent treatment costs were not considered in the company base case”	Please amend the text to say, “Treatment sequences (apart from the switch from lanadelumab Q2W to Q4W), were not considered in the company base case.”	The current sentence gives the impression that costs for patients who discontinued the primary treatment were not captured. This is not true, as for example, the costs of the subsequent lanadelumab Q4W treatment are accurately accounted for. The amendment clarifies the distinction between subsequent treatments costs, and subsequent treatment sequences (which also involve a cost aspect).	This is not a factual inaccuracy. The EAG does not consider the possibility of dose optimization for lanadelumab as a subsequent treatment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.10.3, page 142: The following paragraph of the EAG report contains multiple factual inaccuracies. “Health state costs were divided according to attack status (i.e. “no attack” or “HAE attack”). The latter was further subdivided according to the severity of the HAE attack (“mild”, “moderate” or “severe”). These health states were based on TA738, in which the approach was to introduce granularity into the estimation of resource use for HAE attacks, rather than simply calculating an average and applying it to all attacks. The rationale for this method was the recognition that the heterogeneity of HAE imposes variations in resource use, dependent on attack severity, location of attack, and patient preference.”	Please amend to the following text: “Health state costs were divided according to health state (i.e., “Attack health state”, “Month 1 without attack health state”, etc.) Although the number of attacks by severity were reported, all costs associated with attacks were reported under the “attack health state”. The base health states were based on TA606 and TA738 submission models.”	The amended text accurately names the health states used in the company model, accurately details how attack costs were reported, and accurately describes the origin of the health states. Location of attack and patient preference are not described in the company CS.	Thank you for the correction. The EAG has edited the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 5.2.1.2, page 153: The EAG inaccurately describes the results for ≥2 attacks per week. “The results show that garadacimab is [redacted]	Please reword this as follows: “The results show that garadacimab is [redacted]	As per Table 45 of the shortened CS.	Thank you for the correction. The EAG has edited the report.

Section 5.3, page 155: The following claim in the report is incorrect, “If the clinical outcomes were implemented correctly, the model should show no patients beyond the third month, rather than the opposite. This issue arises from the incorrect assumption of no change to berotralstat effectiveness beyond the third month (see Section 4.2.6.5). ”	Please remove this point as it is factually inaccurate.	The cost-effectiveness model handles the attack rates and the continuation rule of berotralstat separately. Therefore, the EAG’s claim that the company’s assumption relating to effectiveness of berotralstat responders causing issues in relation to the number of berotralstat responders beyond three months is incorrect. This inaccuracy stems from the EAG applying aggregate outcomes to an individual patient level. This is commonly known as **Aggregation Bias** when data is aggregated in a way that obscures or distorts underlying patterns in individual data points. The APeX-2 publication by Zuraw et al. (2021) does report a cohort average attack rate ratio relative to placebo of 0.56. This is equivalent to a 44% reduction in attack rates from baseline, so on the surface it appears that ‘on average’ no	Thank you for the correction. The EAG has edited the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		berotralstat patients should meet the continuation rule, i.e., do not continue treatment beyond three months. However, CSL Behring has been careful not to overgeneralise this fact due to being aware of the aggregation bias, where aggregate data findings do not translate well to the patient level. In fact, CSL Behring specifically reached out to clinical experts to confirm proportion of patients who meet the continuation rule in clinical practice, as elaborated in the clarification question response B14d.	

Section 6.1, page 157: Incorrect description of company's approach to modelling the PSA (first, sixth and seventh bullet point) "• The data company did not use credible intervals from relevant studies for included parameters, assuming instead that the credible intervals were 20% of the mean for all variables. This was corrected for several variables where uncertainty estimates were not available in the trials. …. • For the percentage reduction in time normalized HAE attack rates (row 724 to 748) the company used a log-normal distribution with a cap. The rationale for this was unclear, so Beta was implemented instead • Attempts were made to amend the inclusion of caregiver utility parameters in the PSA. However, the level of uncertainty associated with this parameter meant that it wasn't	Please amend the comment to acknowledge that CSL Behring accurately modelled credible intervals where data was available for the CS (for example, NMA credible intervals). Please acknowledge that further checks of available data were made as a response to clarification question. Please amend the comment to acknowledge that CSL Behring provided rationale as to the use of the log-normal distribution for the AARRCF variables as explained in the response to clarification question B23a. Please amend the comment to acknowledge that CSL Behring was able to include the caregiver utility in the PSA as explained in the response to clarification question B23a.	To accurately reflect the company's base case model developments	Thank you for these comments. We agree with them for the most part and have amended the text accordingly. We would like to note that for a number of variables, standard error inputs were added, but the formulas were coded in such a way that assumed standard errors were used, instead of inputs added.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
possible to include it in the PSA and as it is not a key driver this was deemed acceptable.", page 153			
Section 6.1, page 158: Incorrect description of company's approach to modelling monitoring costs (third bullet point). "The company indicated that they would implement six tunnel states. Monitoring costs were assumed to fall only after patients were attack-free for six months. Limiting the number of tunnels to six, therefore, made this assumption null and void, as no patients ever reached this definition of being attack-free in the long term"	Please amend the comment to acknowledge that CSL Behring accurately modelled monitoring costs in line with the description found in the CS and as explained in the clarification question process B29a.	Monitoring costs have been clearly explained that it is *different* for months 6 and beyond of the tunnels, and not *absent* as claimed by the EAG.	Thank you for your comment. This is not a factual inaccuracy. It is the case that the company modelled six tunnel states but only implemented different monitoring costs after six tunnel states. This made the modelling of different monitoring costs redundant. The EAG has amended this in our base case. The EAG would like to note that this change favours garadacimab and the impact is modest.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1, pages 158-159: Table 51 and Table 52 are incorrect	The only change in QALY outcomes made from the row 'Utility implementation errors', does not align to the row 'Cumulative impact of corrections.	Given this is the only change that impacts QALYs, the 'Cumulative impact of corrections' should have the same value as the 'Utility implementation errors' row.	Thank you for your comment. This highlighted an error in the way that the tunnel states and utility corrections were interacting. This has now been amended. The change Impacts column DI onwards in the engines, which is the section in which health state utility values are calculated. Amending this change had a minor impact on results.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1, Tables 51 and 52 (pages 158-159), and Section 6.2.1.1, Table 54 (pages 161-162): Inconsistent and incorrect labelling of preferred assumptions For example, there is inconsistency with respect to calling the Nordenfelt et al. (2014) equation change as a “utility implementation error”, and whether “Several cell-referencing errors to the way health state utility values were calculated in the model engines” influenced the deterministic results.	Please ensure consistency with respect to the naming of the equation change as “Amended application of Nordenfelt equation” and clarify the supposed utility errors and their relation to the health state utility values.	The EAG's preferred amendment to the Nordenfelt et al (2014) paper follows a preference and not an error correction, insofar as the EAG's interpretation is unconfirmed and not validated by the study author. CSL Behring’s approach is consistent with the application of the equation as used in previous HAE appraisals and is therefore not an error. Furthermore, if there were errors in the way health state utilities were calculated then this should affect the deterministic base case which the EAG has constructed. This is not the case in the report.	To clarify, the utility implementation errors are entirely separate from Nordenfelt. They relate to the way in which health state utility values have been calculated. This impacts column DI onwards in the engine. The errors relate to incorrect weighting of the health state utility values, according to the three treatment lines, in each engine. As can be seen in response to a different comment, an error was identified in the way in which these fixes were implemented. This has now been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.2, Table 53 (page 159), Section 6.2.1.2, Table 55 (page 163) and Section 6.2.2.2, Table 58 (page 168-169): Incorrect labelling	Row ‘NMA MLNMR’ contains a typographical error as it should read ‘ML-NMR’, but also it is not clear what this proposed change is doing since the NMA and ML-NMR are alternative sources of relative efficacy. Please clarify.	Clarity on labelling	Thank you for your comment. This has been corrected.

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, Key Issue 5 (page 21): Column heading states “4.2.6.74.2.6.6”	Please amend to “4.2.6.7, 4.2.6.6”	Typographical error	Thank you for your comment. This has been corrected.

Section 2.3.4, pages 30–31 (last bullet point on page 30 and first two bullet points on page 31): Formatting issue with reference number not being in superscript.	Please correct the formatting of these references in line with the referencing throughout the document (superscript).	Impact on clarity may reduce readability.	Thank you for your comment. This has been corrected.
Section 2.3.4, Figure 1 (page 32): Typographical error – The table legend states “Nptes:”	Please amend to “Notes:”	Typographical error	Thank you for your comment. This has been corrected.
Section 3.2.2.4, page 48: Cross-referencing error	Please correct the following cross-referencing error, since two tables are linked: “However, as noted in Table7Table9,”	Cross-referencing error, needs fixing for clarity	Thank you for your comment. This has been corrected.
Section 3.2.3.3, page 52: Typographical error	Please amend “45.9,%” to “45.9%”	Typographical error	Thank you for your comment. This has been corrected.
Section 3.4.1.4, page 77, Section 3.4.1.4, page 78, Section 3.4.1.7, page 83, Section 3.4.1.8, page 85: Typographical errors	Please amend “SL312_2001” to “CSL312_2001”	Typographical error	Thank you for your comment. This has been corrected.

Section 3.4.1.6, page 82 (heading attack-free days per month): Typographical error	Please amend “Haegarda were” to “Haegarda was”	Typographical error	Thank you for your comment. This has been corrected.
Section 3.4.1.8, page 85: Repetition of sentences	Remove the duplicate of the sentence beginning “The clinical outcome where garadacimab…”	Repetition	Thank you for your comment. This has been corrected.
Section 6.2.1.3, page 164: Typographical error	“…a comparison was made between berotralstat as the first-line treatment followed by **no** prophylaxis”	Routine correction	Thank you for your comment. This has been corrected.

NICE 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]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **7 April 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Comments received during engagement 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.

Technical engagement response form

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	CSL Behring
Disclosure 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.] Please state: • 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.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Uncertainty around the treatment pathway for people with HAE	Yes	The newly published National Health Service England (NHSE) HAE treatment algorithm[1] is in line with CSL Behring's outlined treatment pathway and supports CSL Behring's positioning of garadacimab as an alternative prophylactic treatment to berotralstat in patients with ≥2 attacks per month and as an alternative prophylactic treatment to lanadelumab and C1-INHs in patients with ≥2 attacks per week. Moreover, the positioning laid out in the Company Submission (CS) (and further explained in the factual accuracy response form) states that decision-making of treatment choice is informed by several factors, such as clinical judgement of suitability, clinical effectiveness, contraindications, ability of patient/carer to use the required administration technique, regional network approval and patient choice, which is further in line with the new treatment algorithm.

		On the other hand, the positioning proposed by the EAG in the EAG report reads as follows: "*In people with HAE who have ≥2 attacks per month, the EAG understood first-line treatment to be berotralstat. Garadacimab could be positioned as an alternative at first-line or at second-line as an alternative to no LTP.* *In people with HAE who have ≥2 attacks per week, oral treatment (predominantly berotralstat) is first-line. Garadacimab could be positioned at second-line as an alternative to lanadelumab or IV C1-INHs. Selection of second-line treatment is based on efficacy, tolerability, and safety, with most people initiating treatment currently receiving lanadelumab rather than IV C1-INHs. People for whom garadacimab is not effective may be treated with lanadelumab; if lanadelumab is also ineffective, patients may be treated with IV C1-INHs."* For those experiencing ≥2 attacks per month, the EAG-proposed positioning would place berotralstat as a comparator in the first line and on-demand treatment as a comparator in the second line. However, this proposed positioning would introduce several issues: • On-demand treatment is not in the NICE scope as a comparator against garadacimab, and as such, this comparison will not be made.[2] • 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.

		• Finally, the EAG's proposed positioning of garadacimab at ≥2 attacks per month is discordant with the approach taken of the proposed positioning of garadacimab at ≥2 attacks per week – in the latter population, garadacimab is solely positioned as an alternative to the currently available LTP options lanadelumab and C1-INHs. CSL Behring does not believe it is appropriate to introduce further treatment sequencing in the ≥2 attacks per month population, but not in the ≥2 attacks per week population. This position is furthered when it is known that no such sequencing was introduced into the company or EAG base case in TA606, where multiple treatment options were available.[3] Taken together, CSL Behring disagrees with the EAG-proposed positioning of garadacimab, particularly since garadacimab can simply be placed as an alternative to berotralstat, as per the NHSE HAE treatment algorithm. Garadacimab's positioning as an alternative to berotralstat, rather than limiting by first- or second-line treatment at ≥2 attacks per month, would provide healthcare providers (HCPs) and people with HAE with improved treatment choices. Both a UK Delphi panel (n=59 HCPs [30 consultants, 1 immunology nurse, 26 immunology clinical nurse specialists and 2 advanced nurse practitioners]) reported by Yong et al. (2024)[4] and recent engagement with HAE clinical experts in England (Appendix A) underscore the importance of improved patient choices, as outlined below. As per Yong et al:[4] • The current access criteria for LTP medication in the UK are solely determined by numerical attack frequency. There was an agreement between UK HCPs that this

		is too simplistic and that these criteria disadvantage a cohort of patients who would significantly benefit from LTP but currently are unable to access it. • UK HCPs confirmed that the current NICE assessments and commissioning policies in the UK mean that the recommendations in the WAO/EAACI HAE guidelines cannot be fully recognised in all patients. • HCPs also agreed that the prophylaxis policy in the UK is far more stringent and restrictive compared to other countries, putting patients in the UK at a comparative disadvantage. Moreover, after receiving the report drafted by the external assessment group (EAG), [redacted] clinical experts in England were contacted by CSL Behring to confirm the assumptions used in the base case. A report on the engagement is available in Appendix A. Overall, the clinical experts indicated their support of a broadly placed product, highlighting their desire for offering choices to patients and making the management of their patients easier. [redacted]. Taken together, the UK Delphi panel consensus statements and England clinical expert engagement highlight the need for improved choice in the UK and less stringent policies surrounding number of attacks. CSL Behring's proposed positioning would increase the treatment option choice for the patients and HCPs. Finally, the EAG noted that CSL Behring's base case included lanadelumab and IV C1-INHs as comparators in the ≥2 attacks per months population. In order to align with the approach of two base cases, CSL Behring has provided additional analyses in Table 4, showing the two base cases covering ≥2 attacks per month and ≥2 attacks per week

		subgroup as two distinct health economic analyses. In all cases, these analyses demonstrate improve cost-effectiveness results for garadacimab vs comparators and reinforce the conservative nature of the company base case analyses.
Issue 2: Methods and trials used in the indirect treatment comparison	No	CSL Behring has resolved Key Issue 2, as it has accepted the EAG preferences regarding the exclusion of Phase II studies from the ITC network and revised the base case accordingly.
Issue 3: Methods and data used to estimate treatment effectiveness	Yes	CSL Behring has resolved key issue 3 and revised its TE base case to align with the EAG approach, that is: • Include garadacimab attack rates from the VANGUARD trial (cycle 0-24) • Apply partial average attack rate reduction carried forward (PAARRCF) • Anchor relative efficacy estimates to garadacimab rather than placebo While CSL Behring have aligned with the EAG approach, it would like to note that the EAG approach to modelling attack rates introduces methods that deviate from established precedent as seen in TA606 for lanadelumab without clear justification. Whilst CSL agree with the EAG that transitivity of the NMA allows for the above changes to the company base case to be made, the company strongly objects to the efficacy assumed for berotralstat responders to which these extrapolation methods are being applied. The long-term efficacy attributed to berotralstat responders by the EAG is supported by limited evidence from EAG clinical expert feedback. The combination of EAG preferred assumptions for Key Issues 3 and 4 that is, berotralstat responder efficacy is the same

		as lanadelumab Q2W efficacy, which leads to overestimation of the responder efficacy for berotralstat when compared with efficacy demonstrated by APeX-2[5] and Elbashir et al. (2024) real-world evidence. The EAGs assumptions lead to all patients on berotralstat after month 3 having the long-term attack free outcomes of lanadelumab Q2W for their lifetime. Feedback from three clinical experts (Appendix A) indicates that the clinical experts all understand the products to not be equally effective, with lanadelumab being more effective than berotralstat. One clinical expert added that not one of their HAE patients who are receiving berotralstat was attack free (Appendix A). As such, CSL Behring believe it is not appropriate to assume that the efficacy of berotralstat is the same as lanadelumab. To resolve this, CSL Behring have provided an alternative approach to the modelling of attack rates for berotralstat patients, where the use of the UK based Elbashir et al. (2024) study leads to an estimate that more accurately reflects the relative clinical efficacy of berotralstat compared with garadacimab (see Key Issue 4).
Issue 4: The handling of berotralstat stopping rule	Yes	**Alignment in position between the EAG Report and amended company technical engagement base case** In the amended technical engagement base case, the company is aligning with the EAG's post-FAC model which uses a continuation rate of 67% from Elbashir et al. (2024)[6]. This is the responder proportion value chosen when 'Elbashir' is selected as the source of responder efficacy. This responder proportion value may be more reflective of clinical practice than earlier company estimates based on clinical expert feedback and from APeX studies[5].

		Whilst the company strongly disagree with the source of berotralstat efficacy used by the EAG in its base case, the company is more aligned to the approach taken in the scenario analysis using the Elbashir et al (2024)[6] study. The company this approach is more aligned with UK clinical practice and more appropriate for informing Committee decision making than an assumption alone. **<u>Outline and critical appraisal of the EAG base case approach to attributing efficacy to berotralstat responder patients</u>** The EAG has assumed in its base case that the efficacy of berotralstat responders, that is, those who remain on treatment following the continuation rule at month 3, is equal to that experienced by lanadelumab Q2W patients based on limited feedback from clinical experts. This has limited evidential basis and applies to patients for the remainder of their lives in the cost-effectiveness model. The EAG have extrapolated broad feedback that "responders to berotralstat generally have a high level of response" and attributed a specific and unsubstantiated claim to it. For example, no feedback was provided regarding the time period over which this feedback might apply, the percentage of responder patients to which the feedback might differentially apply, and "high level of response" is not defined or benchmarked in any way. On the available evidence in the EAG report, it is very unclear how the EAG arrived at this conclusion from the limited clinical feedback they received. The current EAG base case assumes that "a high level of response" (for some patients) is sufficient to equate efficacy of two treatments which have been statistically proven to be different. Furthermore, according to Zuraw et al. (2021)[5], only 10% (n=4) of all berotralstat patients in APeX were attack free over a 168-day treatment period, compared to 44.4% (n~12) of all lanadelumab Q2W patients at Day 182 visit reported in TA606[3].

Comparison of these values suggests that the efficacy of the two treatments is different, as also indicated by clinical expert opinion mentioned in Key Issue 3.

Elbashir et al (2024) remains the best source to obtain responder efficacy for berotralstat patients, after acknowledging EAG limitations

To best address this lack of responder efficacy, the company provided the EAG with the Elbashir et al. (2024)[6] poster and Ahuja et al. (2023)[7] publication. These publications report on the Clinical Immunology Trainee Research Network (CITRN) national audit of real-world evidence of clinical effectiveness, and patient-reported outcomes of long-term use of berotralstat as a long-term prophylaxis in individuals with HAE across 18 United Kingdom immunology centres. The studies covered a large number of patients on berotralstat totalling n=164, more than four times the number of berotralstat patients in its pivotal Phase III trial.

This is the best source on the matter of berotralstat responder efficacy identified by any stakeholders, as it contains a large sample size and is specific to NHS clinical practice. The EAG now include this as a scenario to their base case in the EAG report.

The EAG noted some limitations of the study during the response to the FAC, which are presented below, with the company view of the limitations and their expected impact to inform decision making.

Limitation raised by the EAG	Company view of the limitation
Values need to be digitised from figures	Not detrimental to the use of the study as the EAG themselves were able to obtain efficacy estimates from the study to present a scenario

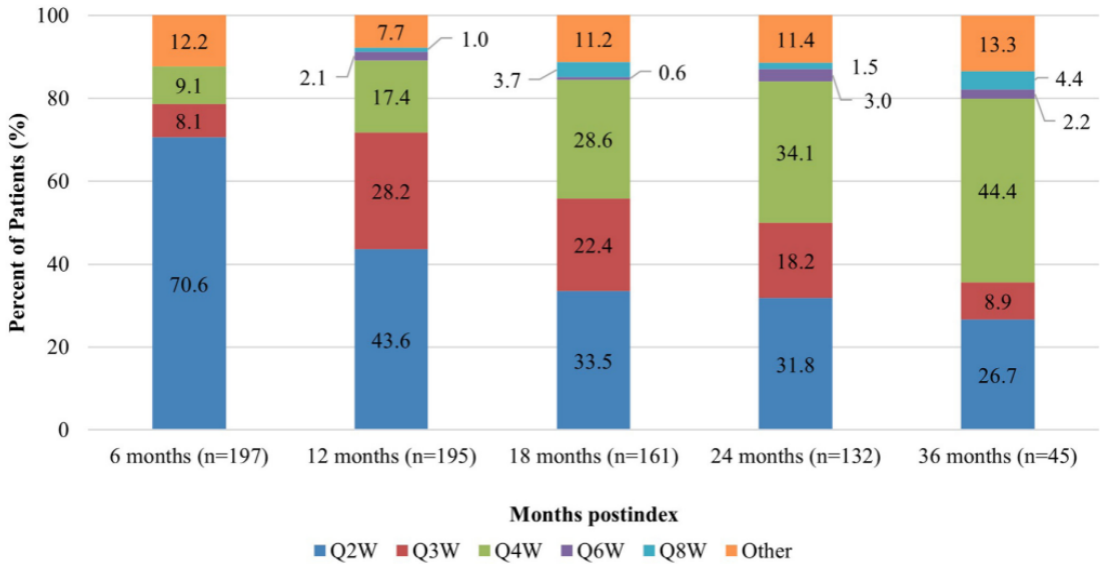
Unclear how well the Poisson regressions matched the observed data	If the Poisson regressions did not match the observed data, the analysis would not be presented at the BSI-CIPN 2024 conference or published by the European Journal of Allergy and Clinical Immunology.
The poster does not separate discontinuers from patients who remained in the study with less than 24-months of observation	The 'Other' patients in Figure 3. include discontinuers whereas Figure 2. excludes discontinuers providing good contrast
Study includes some patients who have not been subject to the continuation rule applied following TA738 from October 2021	As per the Appendix C, the majority of patients (Estimate ~67-76%) in the study were subject to the continuation rule, solidifying the value of the study

The company and the EAG have jointly reached out to the authors of the study to gain further clarity on the study and its findings. At the time of submitting the technical engagement response form, the authors have not formally responded to requests and questions raised.

Overall, the view of the company is that the limitations identified by the EAG are not detrimental to using it to inform the issue at hand and resolve uncertainty. The study serves as an NHS specific data source with a large sample size (relative to the rarity of the disease) and covers a significant period of time. When considering the hierarchy of evidence, CSL Behring firmly believe the utilisation of efficacy estimates from Elbashir et al (2024)[6] to be the best source of long-term efficacy estimates for the responder population for berotralstat. The APeX-2 ad hoc subgroup data utilised in TA738[8] was

		sufficiently low in sample size as to be considered a key issue. It is likewise a source of evidence that neither the EAG nor the company have access to. Elbashir et al (2024), for the most part, resolves this uncertainty, with the largest population of responder efficacy available forming most of its aggregate population (aggregate n=164). Whilst limited, this is a superior source of evidence than that the assumption utilised in the EAG base case which inflates berotralstat responder's efficacy to unrealistic level not observed in clinical practice. **Estimates from the company amended technical engagement base case utilising Elbashir et al (2024)** In light of the above, the company has revised their TE base case to include estimates from Elbashir et al. (2024) to inform the efficacy of berotralstat responders. The company NMA still serves as the basis for the relative efficacy estimates of berotralstat patients for the first three months of treatment, since this concerns the aggregated cohort of both would be responders and non-responders. Please refer to Appendix B for company's derivation of berotralstat responder efficacy estimates from Elbashir et al. (2024). As per the findings of Elbashir et al. (2024), the 24-month completers do not express attack rates that are significantly different that the combined cohort of berotralstat patients as the credible intervals of attack rates in Figures 2 and 3 overlap to a significant degree. Accounting specifically for the outcomes for 24-month responders, the company derivations of responder efficacy come to the range of 50.18% to 65.45%. The wider berotralstat cohort's efficacy from Elbashir et al. (2024) is broadly generalisable to responders because as outlined in Appendix B, the majority of these patients were subject to the continuation rule.

		CSL Behring believes that of Elbashir et al. (2024) represents the best available source of data to model the efficacy of berotralstat responders, as opposed to the EAG's approach which is based on limited feedback from clinical experts.
Issue 5: The handling of lanadelumab switch between Q2W and Q4W	Yes	Key Issue 5 has minimal impact on the overall cost-effectiveness results. The handling of lanadelumab switch between Q2W and Q4W is broken down into four key components and the below points summarise CSL Behring's stance: • EAG accepted company's proportion value • CSL Behring accepts EAG's duration of the switch • CSL Behring disagrees with EAG's assumption: o of an instantaneous switch, and o that lanadelumab Q2W efficacy values are the same as Q4W values CSL Behring has provided a scenario analysis using the EAG preferred assumptions (patients switch instantaneously and efficacy of lanadelumab Q2W is the same as Q4W) to explore the impact of this Issue. The impact on the cost-effectiveness results of the EAG approach change the INMB by [redacted] and do not change the cost-effectiveness conclusions. The limitations of the EAG approach this Key Issue is explored in further detail below. The EAG assumes that lanadelumab Q2W efficacy values are the same as Q4W values, however feedback gathered from three consultant immunologists found that one clinician had not yet been able to extend a patient from Q2W to Q4W, stating that: *'In patients who are stably attack-free on treatment moving to Q4W may be considered, especially in patients with low weight. We have not managed to do this in our centre ie reduced to Q4W.'* (Appendix A)

		This supports CSL Behring's position that there is a difference in efficacy between lanadelumab Q2W and Q4W. The EAG prefers to assume that patients switch dosing regimens instantaneously, however Figure 1 of Magerl et al. (2024)[9] shows that patients switch dosing regimens gradually and over time. This is directly contrary to the instant switch assumption the EAG prefers. **Figure 1. Lanadelumab dosing intervals at 6, 12, 18, 24 and 36 months postindex**  Abbreviations: Q7W, every 7 weeks; Q8W, every 8 weeks. Note: Intervals of administration Q2W, Q3W, Q4W, Q6W, Q8W (±2 days) were grouped to the appropriate interval. "Other" includes frequency: Q5W, Q7W, >Q8W, intervals every 17, 18, 24, 25, 31, 32, 53, 59, 60 days.

		The Magerl et al. (2024)[9] study does not support the EAG assumption that all lanadelumab Q4W patients have the same efficacy as on the Q2W dosing. As per primary outcome 2, 76.2% of patients experience attack freedom with lanadelumab Q4W. Primary outcome 2 did not include 24.3% of patients who did increase their dosing interval needed to decrease it because of attack rate increases. Both findings suggest the efficacy among the two dosing regimens is not equal. Furthermore, lanadelumab is available in the NHS in the ≥8 attack per month subgroup compared to the indication-based access experienced in the countries covered by the study. This means patients eligible for lanadelumab in the NHS have a lower likelihood of achieving stable attack freedom, compared to the patients in the study, meaning conclusions of efficacy from Magerl et al. (2024)[9] are of limited validity to the decision problem. Of note is that the submitting company of lanadelumab did not assume equal efficacy among the Q2W and Q4W dosing regimens in NICE TA606[3]. Given the limitations in the EAG's approach and the additional evidence provided, CSL Behring believes our base case remains the most reasonable and appropriate for informing decision-making. The inclusion of the alternative scenario including the EAG's preferred assumptions ensures the committee has a full view of the impact of this Key Issue. Importantly, the impact of this scenario on the cost-effectiveness results is small, indicating that it has limited influence on overall decision-making.
Issue 6: The calculation of patient utilities	Yes	The calculation of patient utilities is broken down into four key components and the below points summarise CSL Behring's stance: • New evidence strongly supports CSL Behring's stance on tunnel states • Some of the EAG views on Nordenfelt et al. (2014)[10] are valid but the study does not preclude the use of tunnels states

		• Nordenfelt et al. (2014)[10] and other sources point to a substantial burden for patients who are recovering from a HAE attack • Lo et al. (2022)[11] is the most robust study on caregiver outcomes in HAE **New evidence supporting the tunnel states in the cost-effectiveness model** The EAG critiqued the use of tunnel states in CSL Behring's economic model however, they are important to include as they capture a key impact on patient HrQoL. Tunnel states are used to capture history of attacks, i.e., how long it has been since a patient had an HAE attack and attack freedom is a key concern for HAE patients given the spontaneous, unpredictable and debilitating nature of HAE attacks. There are four key sources of evidence that support the inclusion of tunnel states in the economic model: 1. EQ-5D data from VANGUARD[12] confirms the relationship between quality of life and the history of attacks. The regression analysis consisted of a mixed model with repeated measures analysis of EQ-5D-3L (Hernandez value set) scores (post-baseline at visit days 91 and 182) with treatment, visits, interaction of treatment and visits as fixed factors; baseline scores and cumulative attack free days as covariates. For example, if a patient went the entire Phase III period without attacks, then they would record 91 days attack free at visit day 91, and respectively 182 days attack free at visit day 182. Despite the limitations outlined in the company submission and TA606[3] for the use of the EQ-5D in measuring quality of life outcomes in HAE, the p-value for cumulative attack free days amounted to 0.0413. Therefore, this evidence is supportive of the company stance that time since last attack is a statistically

meaningful outcome for quality of life in patients with HAE, which also supports the tunnel states approach.

2. AE-QoL data from VANGUARD[3] and 3002[13] confirms the relationship between quality of life and time since last attack. The regression analysis centred on capturing time to first attack and the neighbouring AE-QoL mean scores. The coefficient of time (in days) since last attack was valued at [redacted] with a p-value of <0.001. For contrast, the coefficient of baseline number of HAE attacks was valued at [redacted] with a p-value of 0.0736. Jointly, these results are strongly indicative that time since the last attack is positively associated with quality of life outcomes. Please find remaining regression outcomes in Appendix C. Table 1 below disaggregates the AE-QoL outcomes by attack-free period using the ANCOVA framework in a separate but related analysis, and the results are strongly indicative that the quality of life benefits from time since last are experienced within the first six months, further solidifying the tunnel states approach.

   (Please note the stratification is relative to the [redacted] patients who have not had an attack for more than 36-months)

Table 1. ANCOVA AE-QoL and period categorical time since last HAE attack outcomes

Parameter	Coefficient	Standard error	t-value	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]

		0-<1 month since last attack (n=18)	[redacted]	[redacted]	[redacted]	[redacted]	
		1-<6 months since last attack (n=27)	[redacted]	[redacted]	[redacted]	[redacted]	
		6-<12 months since last attack (n=8)	[redacted]	[redacted]	[redacted]	[redacted]	
		12-<18 months since last attack (n=4)	[redacted]	[redacted]	[redacted]	[redacted]	
		18-<24 months since last attack (n=5)	[redacted]	[redacted]	[redacted]	[redacted]	
		24-<30 months since last attack (n=21)	[redacted]	[redacted]	[redacted]	[redacted]	

		30-<36 months since last attack (n=23) [redacted]
		Baseline attack rate [redacted]

3. Itzler et al. (2024)[14], an international, cross-sectional survey of 159 patients with HAE who were receiving LTP, supports the use of tunnel states in the economic model. The study assessed the impact of the duration of the attack-free period on HRQoL and found that patients who were attack-free for longer periods reported significantly improved HRQoL. The mean Angioedema Quality of Life (AE-QoL) score was lower (indicating less impairment) in patients who had been attack-free for ≥6 months compared to those who were attack-free for 1 to <6 months and less than one month (mean scores of 19.9, 33.2 and 51.8, respectively). These results are closely matched to the trial based 3001 and 3002 AE-QoL findings presented in point 2 above.

4. Banerji et al. (2020)[15], a burden of illness study reports the physical and mental summary scores of the SF-12 per number of attacks, ranging from zero to more than 13 over a 6 month-period. The SF-12 physical component score (PCS) and mental component score (MCS) reported in the study show that these scores were substantially lower for those with no attacks over a six-month period compared to those who had more than 13 attacks. See the Appendix E for a detailed breakdown of these values, along with sensitivity

analysis through mapping to EQ-5D. The four mapping algorithms explored[16] showed that six-months of attack freedom compared to a baseline of roughly two attacks per month are in the range of a utility gain of 0.102 – 0.155. These values directly support the magnitude of the tunnel states used in the cost-effectiveness analysis. Please see Table 2 for the utility gains discussed.

Table 2. Time since last attack EQ-5D outcomes from Banerji et al. (2020)

Number of attacks (over six months)	EQ-5D – Lawerence et al. (2004)[17], 3-variable model	EQ-5D – Franks et al. (2004)[18], SF-12 items only	EQ-5D – Sullivan and Ghuschchyan (2006)[19], SF-12 items only	EQ-5D – Le (2013)[20], CLAD US D1 model
0	0.890	0.900	0.937	0.962
1-3	0.834	0.850	0.899	0.926
4-6	0.768	0.788	0.856	0.882
7-12	0.735	0.756	0.835	0.860
≥13	0.638	0.659	0.776	0.790

Abbreviations: CLAD, censored least absolute deviations; US, United States.

In summary, the disease specific AE-QoL and generic EQ-5D and SF-12 instruments all strongly indicate and quantify the relationship between attack freedom and quality of life for HAE patients. In summary, the disease specific AE-QoL and generic EQ-5D and SF-12 instruments all strongly indicate and quantify the relationship between attack freedom and quality of life for HAE patients. Such a diverse and robust evidence base serves as a good basis for CSL Behring's modelling approach. Although the exact

		coefficient is not provided, the Nordenfelt et al. (2014)[10] study does also confirm that utility increases as days since last attack increase. **<u>The tunnel state approach remains valid, despite some concerns raised about Nordenfelt et al. (2014)</u>** The EAG put forward that tunnel states may not be appropriate and that it was "*skeptical that patients can achieve higher utilities than those implied by the regression conducted by Nordenfelt et al. (2014), as it is aware that the utilities calculated from the Nordenfelt et al. equation already accounted for improvements in quality of life (QoL) that occur as the number of attacks reduces over time.*" There two limitations to this line of reasoning: • Firstly, it is important to recognise that patients can achieve utilities higher than those suggested by the regression in Nordenfelt et al. (2014)[10]. The reported mean utility of 0.825 is simply the outcome when the regression is evaluated at average covariate values, yet there is a wide range of covariate combinations that can yield greater utilities than the mean. Figure 1 of Nordenfelt et al. (2014)[10] clearly shows that the confidence intervals include values above this mean, underscoring the potential for higher utility gains. This observation is crucial in highlighting the opportunity for improved patient outcomes through innovative treatments. • Secondly, the number of attacks a patient experiences is included as a covariate to examine the impact of life with HAE attacks as a possibility and the associated pains and anxieties, rather than capturing the impact of attack rate reductions over time. This is evident as Nordenfelt et al. (2014) mentions a separate variable that captures the impact of time since last attack. In fact, including the variable that captures the number of HAE attacks in the preceding

		period would accurately distinguish quality of life for patients whose disease was well controlled or not, a factor considered important by Itzler et al. (2024)[14]. CSL Behring agrees with the EAG and their clinical experts that there will always be a degree of outstanding fear/anxiety as patients experience periods with or without attacks. However, this fact is accounted for in the cost-effectiveness model as it used the 'General Population' estimates of utility from Ara and Brazier (2010)[21], rather than the healthy population utilities implied by the 'No CVD' estimates. Therefore, there is a degree of disease burden already incorporated into the general population utility used in the cost-effectiveness model, further solidifying CSL Behring's approach of modelling utility. Two out of three UK clinical immunologists providing feedback to CSL agreed that people with HAE would experience their quality of life would returning to the level observed in the general population, provided their attacks are controlled. Sensitivity analysis showed that stepwise decrements from this upper value have marginally small to no impacts on the cost-effectiveness results, likely because, a degree of disease burden already accounted for. CSL Behring agrees with the EAG that there are aspects of Nordenfelt et al. (2014)[10] that are difficult to interpret, due to incompleteness or other factors. However, in line with precedence established in two prior NICE appraisals in HAE, CSL Behring wishes to re-iterate that without confirmatory interpretation of particular findings from the corresponding author, it is the same *use* of the study and associated regression analyses that should apply in this appraisal. This includes the use of the same utility regressions as TA606[3] and TA738[8], which use number of attacks in the previous cycle and not in the previous year for modelling. To follow any other course of action is to allow hypothesis/suspicion drive deviation from established precedence, as opposed to

		new evidence. Until such point as this new evidence is received, there is no strong rationale to deviate from the same approaches seen in TA606[3] and TA738[8]. **New evidence supports that the EAG base case does not adequately reflect the quality of life impact attacks have, after their clinical duration** One aspect where the Nordenfelt et al. (2014)[10] study reports clear outcomes is in relation to the temporal relationship between HAE attacks and their impact on quality of life. Page 189 of the study reports that EQ-5D attack utilities at month three or more (i.e., more than three months since the attack) corresponded to 0.577 (n=25). Consider this as the illustrative baseline. Attack utilities at one month since the last attack are valued at 0.587 (n=41). These two values are similar which contrasts with the attack utility reported when the last attack was within one week, with a utility value of 0.382 (n=27). This demonstrates that the there is a significant drop in quality of life for patients who have had an attack within the last week. Thereby, given that HAE attacks clinically do not last a week, but the study reports that quality of life for patients is impacted over a period of one week, this notion strongly supports CSL Behring 's stance that the impact of attacks is felt beyond the clinical duration of an attack. This finding is further supported by the evidence from the 2020 Hereditary Angioedema Survey of 100 patients and 150 licensed Allergists/Immunologists who have treated/managed at least two HAE patients in the past 12 months in the US. [redacted] of patients stated that recovering from a HAE attack is disruptive, and another [redacted] of patients reported **recovering** from a HAE is very disruptive. In contrast, only [redacted] and [redacted] reported that **managing** a HAE attack is disruptive. These large sample size-based insights clearly communicate that patient's lives are greatly affected not only during

		attacks, but also for a foremost period following the clinical attack. This evidence supports CSL Behring's claim that the quality-of-life impact from HAE attacks last more than the clinical duration of the attack. A proxy that can be used to determine the duration over which the impact of an attack affects quality of life can be productivity loss. For example, if a HAE patient misses out on three working days and one leisure day because of an acute attack, it can be assumed that the patients needed to manage the attack/recover from the attack over the collective four days and therefore their quality of life would also be determinately affected over the course of the four days. To this effect, CSL Behring proposes the use the values reported in Lumry et al. (2010) which reports the mean number of days missed of work and leisure. The new value that the company utilise in their amended technical engagement base case quantifies the duration of impact from HAE attacks is 3.13 days, which is in-line with a scenario considered by the EAG. This finding is supported by the HAE patient and carer survey (2024)[22] which also indicates that recovering from HAE attacks can take multiple days. **The EAG base case underestimates the impact of HAE attacks on carers and the Lo et al (2022)[11] study is the best available source of evidence to quantify this impact.** Caregiver outcomes are an important aspect of HAE care, with many of those delivering care themselves having HAE. This introduces perverse spillover effects whereby the management of the condition of the carer and the dependent are interwoven and impact each other during and in anticipation of periods of attack. The use of this source, given the latter conclusion, does not align with the claim from the EAG that the utility decrements utilised by the company are large by reference to the range reported in DSU TSD 9 (0.01 - 0.173). Of note is that the real impact of caregiver disutility is scaled by the duration of the attack and subsequent recovery,

		meaning the modelled utility is towards the bottom range of the reference range, unlike EAG claims that centre on the unscaled value. As suggested by the EAG in the technical engagement meeting, CSL Behring conducted an appraisal of the Lo et al. (2022)[11] vignette study according the DSU guidance[23] . The results confirm that the Lo et al. (2022)[11] was evaluated to match "Yes" to 11 of the DSU recommendations, with one DSU recommendation begin evaluated at "Maybe" and "No" respectively. Please see Appendix F for more details. This solidifies the use of the study as the source of caregiver disutility in the cost-effectiveness model. Furthermore, Lo et al (2022) is more suitable for the task compared to the study proposed by the EAG in Pennington et al. (2023), which itself states that it should not be used to quantify caregiver outcomes in acute conditions. Whereas most of the burden in HAE is in supporting the patient during acute attacks. Similarly, the Pennington et al (2023) study is not disease specific, focusing on the burden that carers of people with HAE face. Instead, it is disease agnostic focusing on care delivered across the board using data from the UK household longitudinal survey. The study finds no association between particular diseases and worsened carer HrQoL. Whilst this is unlikely at first principle, it also does not align with the benchmarking of the inclusion of carer utilities in this appraisal to the range presented in DSU TSD 9 which demonstrates a varying burden on carers accepted in NICE appraisals in different disease areas. It is also of note that the appraisals constituting the range in TSD 9 all appear to have gained recommendation using a disease specific source to quantify carer burden.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Discontinuers from Elbashir et al. (2024)	Inputs – Switching F20	Yes	54 discontinuers from 164 patients in Elbashir et al. (2024) results in a rounded continuation value of 67% and not 66%. The company is modelling accordingly.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 3. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key Issue 5: Earlier time horizon for lanadelumab	1-year	6-months	Incremental costs / Incremental QALYs / ICER vs. lanadelumab TE: [redacted] / [redacted] / Dominating Original: [redacted] / [redacted] / Dominating Difference: [redacted] / [redacted] / Dominating
Key Issue 4: Berotralstat responder efficacy source	Company network meta-analysis	Company Elbashir et al. (2024) values	Incremental costs / Incremental QALYs / ICER vs. berotralstat TE: [redacted] / [redacted] / Dominating Original: [redacted] / [redacted] / Dominating Difference: [redacted] / [redacted] / Dominating
Key Issue 4: Berotralstat responder proportion source	APeX-2 and Clinical experts	Company Elbashir et al. (2024) values	Incremental costs / Incremental QALYs / ICER vs. berotralstat TE: [redacted] / [redacted] / Dominating Original: [redacted] / [redacted] / Dominating Difference: [redacted] / [redacted] / Dominating

Key Issue 2: Indirect treatment comparison	Company NMA including Phase II studies	Company NMA excluding Phase II studies	Incremental costs / Incremental QALYs / ICER vs. berotralstat TE [redacted] Dominating Original [redacted] Dominating Difference [redacted] Dominating Incremental costs / Incremental QALYs / ICER vs. lanadelumab TE [redacted] Dominating Original [redacted] Dominating Difference [redacted] Dominating
Key Issue 3: Modelling assumptions	First 24 cycles: Last observation carried forward Cycle 25 and beyond: AARRCF Anchoring of comparators: to placebo	First 24 cycles: VANGUARD attack rates Cycle 25 and beyond: PAARRCF Anchoring of comparators: to garadacimab	Incremental costs / Incremental QALYs / ICER vs. lanadelumab TE [redacted] Dominating Original [redacted] Dominating Difference [redacted] Dominating Outcomes against berotralstat not presented since modelling of berotralstat attack rates is covered by Key Issue 4 exclusively
Administration disutility	Scenario and Matza et al. (2013)	Base case and Hu et al. (2023)	Incremental costs / Incremental QALYs / ICER vs. berotralstat TE [redacted] Dominating Original [redacted] Dominating Difference [redacted] Dominating Incremental costs / Incremental QALYs / ICER vs. lanadelumab TE [redacted] Dominating

			Original	[redacted]	[redacted]	Dominating
			Difference	[redacted]	[redacted]	Dominating
Key Issue 6: Quality of life impact from HAE attacks	Attack and recovery duration equal to seven days	Attack and recovery duration equal to 3.13 days		Incremental costs	Incremental QALYs	ICER vs. berotralstat
			TE	[redacted]	[redacted]	Dominating
			Original	[redacted]	[redacted]	Dominating
			Difference	[redacted]	[redacted]	Dominating
				Incremental costs	Incremental QALYs	ICER vs. lanadelumab
			TE	[redacted]	[redacted]	Dominating
			Original	[redacted]	[redacted]	Dominating
			Difference	[redacted]	[redacted]	Dominating
Key Issue 6: Caregivers	Number of caregivers per household: 1.46	Number of caregivers per household: 1		Incremental costs	Incremental QALYs	ICER vs. berotralstat
			TE	[redacted]	[redacted]	Dominating
			Original	[redacted]	[redacted]	Dominating
			Difference	[redacted]	[redacted]	Dominating
				Incremental costs	Incremental QALYs	ICER vs. lanadelumab
			TE	[redacted]	[redacted]	Dominating
			Original	[redacted]	[redacted]	Dominating
			Difference	[redacted]	[redacted]	Dominating
Training costs and resource use rates	No training costs and clinical expert-based resource use rates	Training costs and EAG adjusted resource use rates		Incremental costs	Incremental QALYs	ICER vs. berotralstat
			TE	[redacted]	[redacted]	Dominating
			Original	[redacted]	[redacted]	Dominating
			Difference	[redacted]	[redacted]	Dominating

			Incremental costs / Incremental QALYs / ICER vs. lanadelumab TE: [redacted] / [redacted] / Dominating Original: [redacted] / [redacted] / Dominating Difference: [redacted] / [redacted] / Dominating
Company's base case following technical engagement (or revised base case)	N/A	All company TE assumptions cumulatively	Incremental costs / Incremental QALYs / ICER vs. berotralstat TE: [redacted] / [redacted] / Dominating Original: [redacted] / [redacted] / Dominating Difference: [redacted] / [redacted] / Dominating Incremental costs / Incremental QALYs / ICER vs. lanadelumab TE: [redacted] / [redacted] / Dominating Original: [redacted] / [redacted] / Dominating Difference: [redacted] / [redacted] / Dominating

Abbreviations: HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; (P)AARRCF, (Partial) average attack rate reduction carried forward; QALY, quality-adjusted life-year; TE, technical engagement

Sensitivity analyses around revised base case

All sensitivity analyses have been conducted at the updated PAS discount and at all company technical engagement base case assumptions.

More than two attacks per month

Table 4. Deterministic sensitivity analysis results against berotralstat (TE)

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Attack rate - >=2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
2	Attack rate requiring on-demand treatment - >=2 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
3	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
4	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
5	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
6	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
7	Rate ratio for the requirement of on-demand treatment - Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
8	Rate ratio - Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
9	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
10	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 5. Fully incremental probabilistic sensitivity analysis in the more than two per month attack subgroup (TE)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Probability of cost effectiveness at £20,000/QALY WTP threshold
Garadacimab	[redacted]	21.37	[redacted]	-	-	-	-	100%
Berotralstat	[redacted]	21.37	[redacted]	[redacted]	0.00	[redacted]	Dominated	-

Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life-years gains; QALYs, quality-adjusted life-years; WTP, willingness to pay

More than two attacks per week

Table 6. Deterministic sensitivity analysis results against lanadelumab (TE)

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Rate ratio for the requirement of on-demand treatment - Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
2	Rate ratio - Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
3	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
4	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
5	Proportion of males	[redacted]	[redacted]	[redacted]	[redacted]
6	Rate ratio for the requirement of on-demand treatment - Lanadelumab (Q4W)	[redacted]	[redacted]	[redacted]	[redacted]
7	Rate ratio - Lanadelumab (Q4W)	[redacted]	[redacted]	[redacted]	[redacted]
8	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
9	Attack rate requiring on-demand treatment - >=8 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
10	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 7. Deterministic sensitivity analysis results against Berinert (TE)

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Rate ratio - Berinert	[redacted]	[redacted]	[redacted]	[redacted]
2	Rate ratio for the requirement of on-demand treatment - Berinert	[redacted]	[redacted]	[redacted]	[redacted]
3	Attack rate requiring on-demand treatment - >=8 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
4	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
6	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
7	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
8	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
9	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
10	Attack rate - >=8 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 8. Deterministic sensitivity analysis results against Cinryze (TE)

Rank	Parameter	Lower INMB (£)	Upper INMB (£)	Absolute difference	Relative difference
1	Rate ratio - Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
2	Rate ratio for the requirement of on-demand treatment - Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
3	Attack rate requiring on-demand treatment - >=8 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]
4	Number of on-demand administration per mild attack	[redacted]	[redacted]	[redacted]	[redacted]
5	Rate ratio for the requirement of on-demand treatment - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
6	Rate ratio - Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
7	Number of on-demand administration per moderate attack	[redacted]	[redacted]	[redacted]	[redacted]
8	Nordenfelt et al. (2014) intercept	[redacted]	[redacted]	[redacted]	[redacted]
9	Number of on-demand administration per severe attack	[redacted]	[redacted]	[redacted]	[redacted]
10	Attack rate - >=8 attacks per month	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit

Table 9. Fully incremental probabilistic sensitivity analysis in the more than two attacks per week subgroup (TE)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Probability of cost effectiveness at £20,000/QALY WTP threshold
Garadacimab	[redacted]	21.38	[redacted]	-	-	-	-	100%
Cinryze	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	-
Berinert	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	-
Lanadelumab	[redacted]	21.38	[redacted]	[redacted]	0.00	[redacted]	Dominated	-

Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life-years gains; QALYs, quality-adjusted life-years; WTP, willingness to pay

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NICE 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]

Appendix to the technical engagement response form

Appendix B: Responder efficacy derivations - number of patients that were subject to the continuation rule

Key Issue 4: Handling of the berotralstat stopping rule

In the interim period whilst CSL Behring, the EAG and other stakeholders are awaiting responses from the authors of the Elbashir et al. (2024)[1], CSL Behring presents below the derivations of responder efficacy that are needed to inform the cost-effectiveness model.

Transcription error of sample sizes from the Elbashir study in the EAG report scenario

On the 26th March 2025, CSL Behring notified the NICE technical team of factual errors concerning the EAG estimates of berotralstat responder efficacy used in the post-FAC model and scenario. The sample sizes were incorrect in the calculations that were utilised in the EAG report scenario that utilises the Elabshir study[1] for the efficacy of berotralstat responder patients. For full transparency please see the text from the email below.

“Dear team,

As part of our conversations with the EAG during the technical engagement meeting, we mentioned an error of implementation of the data from the Elbashir study in the post FAC model. As promised in the call, please pass on the below detail regarding the nature of the error.

Cells S12 and U12 of Inputs - Transitions have incorrect values since the total number of patients in the Elbashir study are 164 (instead of 162 inputted in the

model) and the number of patients who completed 24 months of treatment are 32 (instead of 108 inputted in the model).

The company will present its derivation of berotralstat responder efficacy values with the technical engagement response form.

Best wishes,

Alex Evans
Market Access, Value and Pricing Manager
UK & Ireland"

In line with the discussions that were had in the technical engagement call, and the above email communication, we have outlined in greater detail below how the Elbashir study would best be utilised as a source of evidence and why it is the best available source of evidence for berotralstat responder patients.

Relevant figures from the Elbashir et al. (2024) [1] study

Explanation of the company approach refers to Figure 2 and Figure 3 from the Elbashir et al (2024)[1] study. For ease of reference, we have copied these figures below along with explanation of the figures that is based on the poster itself.

Figure 2 presents the marginal predicted mean number of HAE attacks for the entire cohort of berotralstat patients. These averages are presented with their associated 95% confidence intervals and are presented for 6-month time intervals. These time intervals begin 3 months prior to the initiation of berotralstat and end 24 months after initiation. This mixed model showed a statistically significant decrease in the number of HAE attacks across each time interval compared to baseline (3 months prior to commencing berotralstat (Figure 2 and Table 2)).

Figure 2. Average number of HAE attacks

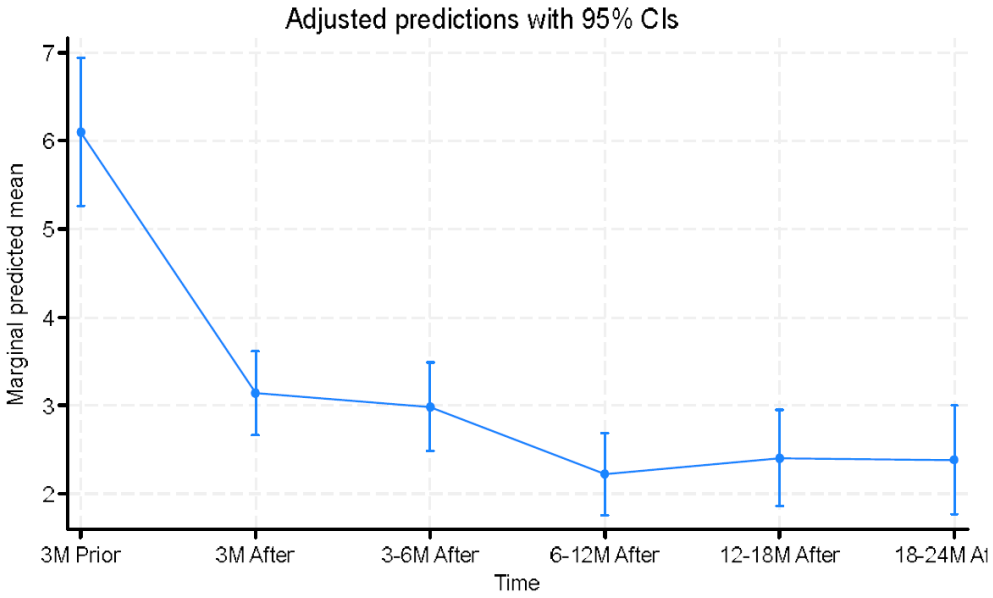

Table 2. The mixed regression model for HAE attacks

Output for Number of Attacks using Mixed Models			
Time Intervals	Regression Coefficient	Std. Error	P-value for Time
3 Months After	-0.664	0.0557	<0.0005
3-6 Months After	-0.714	0.0655	<0.0005
6-12 Months After	-1.008	0.0916	<0.0005
12-18 Months After	-0.931	0.102	<0.0005
18-24 Months After	-0.938	0.121	<0.0005
Constant	1.554	0.0665	<0.0005

Figure 3 presents the marginal predicted mean number of HAE attacks for an identified cohort of 32 patients who completed 24 months of treatment. These averages are presented with their associated 95% confidence intervals and are

presented for 6-month time intervals. These time intervals begin 3 months prior to the initiation of berotralstat and end 24 months after initiation. This mixed Poisson regression chart compares the marginal predicted mean number of HAE attacks for this cohort to the entire cohort and finds that their results align.

The study authors note that this mixed Poisson regression shows that 24-month completers started with higher baseline attack rates but demonstrated higher reductions over time.

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

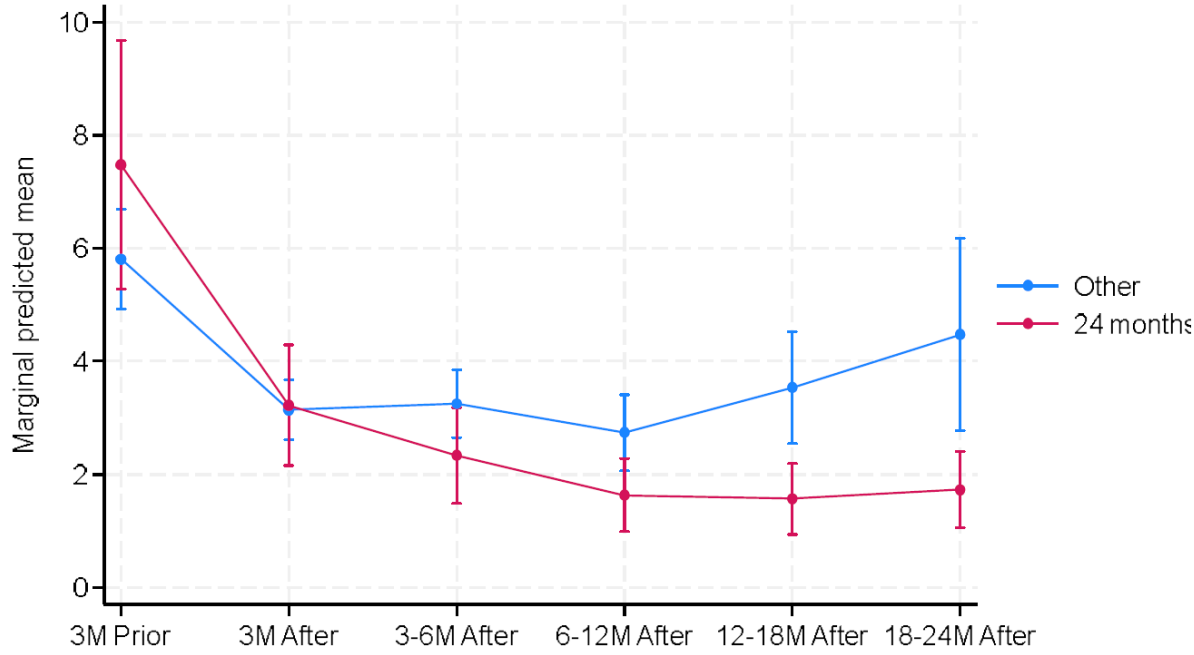

Table 1**Company estimates of berotralstat responder efficacy from Elbashir et al (2024)**

In the EAG scenario utilising Elbashir et al. (2024)[1], the efficacy of the 'Other' population that is reported in Figure 3 is utilised. The company do not consider this to be appropriate, insofar as, this group are likely to include patients who are no longer taking berotralstat as their prophylaxis treatment. If the reader observes the trends seen in Figure 2 and Figure 3, this may be the reason why the 'Other' attack rates increase over time in Figure 3 whereas the curve in Figure 2 is stable towards

the tail end. The latter would be the case with Figure 2 only accounting for berotralstat observations.

CSL Behring estimated berotralstat responder efficacy by comparing 24-month responders to the average number of HAE attacks reported in Figure 2. Please see Table 1 for the outline of the approach where the values used have been obtained from the relevant figures.

Table 1. Company estimates of berotralstat responder efficacy from Elbashir et al. (2024)

Month	24-month responder (n=32) – HAE attack rate - Figure 3	Average number of HAE attacks (n=110*) – HAE attack rate - Figure 2	24-month responder (n=32) – percentage reduction from baseline - Figure 3	Average number of HAE attacks (n=110) – percentage reduction from baseline - Figure 2	Weighted cohort – percentage reduction from baseline
3	3.4	3.1	55%	48.3%	50.18%
6	2.6	3	65%	50.0%	54.46%
9	2.6	3	65%	50.0%	54.46%
12	1.9	2.3	75%	61.7%	65.45 %
15	1.9	2.3	75%	61.7%	65.45%
18	1.75	2.5	77%	58.3%	63.67%
21	1.75	2.5	77%	58.3%	63.67%
24	1.9	2.45	75%	59.2%	63.68%

Abbreviations: HAE, hereditary angioedema, *This value excludes discontinuers (n=54) from the aggregate population (n=164) from figure 2

Figure 2 is reported for the whole cohort of berotralstat patients and, as such, it is reasonable to assume that 24-month responders contributed to the data presented in Figure 2. Accordingly, the average number of HAE attacks reported in Figure 2 were adjusted by the 24-month responder values specifically found in Figure 3. Assuming discontinuers (n=54) did not contribute to the 24-month responder values, this left n=110 patients contributing to Figure 2, and the weighted efficacy estimates Appendix to the technical engagement response form

presented in Table 1 are weighted on a 32 to 78 basis resulting in the values shown. The baseline number of attacks from which point the relative reductions are calculated is 7.5 attacks, and 6 attacks for the patients examined in Figure 2.[1,2]

Estimating the proportion of patients subject to the berotralstat continuation rule

A critique of the study by the EAG in relation to the use of the Elbashir et al. (2024) study for the purposes of the decision problem is that it contains patients who have initiated berotralstat prior to October 20th 2021, where the continuation rule was formally introduced as part of NICE TA738[3].

However, CSL Behring object to this limitation because most of the patients considered in the study are understood to have been subject to the continuation rule, making the efficacy values presented above robust for the purposes of the decision-making process.

Consider some of the known facts below:

1. Berotralstat was approved in the United Kingdom in November 2020
2. Berotralstat's continuation rule was introduced in October 2021
3. Ahuja et al. (2023)[4] was first published 7 January 2023
4. Ahuja et al. (2023)[4] reports on n=54 patients
5. Elbashir et al. (2024)[1] was first presented in December 2024
6. Elbashir et al. (2024)[1] reports on n=164 patients

Utilising the above information, the company propose two alternative methodologies to estimate the proportion of patients who were subject to the October 2021 continuation rule.

Approach 1: Determining an average monthly recruitment of patients based on data from Elbashir et al. (2024) and Auhja et al. (2023)

The first step is to introduce some assumptions to define a framework to work with the known information in points 1-6 above:

a) First patient began treatment with berotralstat that was included in the audit started in November 2020

b) Patients' uptake berotralstat in a linear fashion across the published period covered by the two studies
c) All n=54 patients reported on by Ahuja et al. (2023)[4] began treatment with berotralstat prior to October 2021
d) The last observation that was reported on in the published studies occurred in September 2024, since this is three months prior to the date mentioned in 5. Three months is the lower range of the duration of treatment reported in Elbashir et al. (2024)[1].

Combining points number 1, 6, a., b., and d. it can be deducted that on average the number of patients joining the audit per month is 3.56 ~ 164/46. This is calculated as the total number of patients audited by Elbashir et al. (2024)[1], which also includes all Ahuja's patients, over the relevant period from November 2020 to September 2024. If this rate of joining is assumed to hold true, then for the period from November 2020 to October 2021 there would be around 39 patients who commenced treatment prior to the introduction of the continuation rule. This means that 76.1% of patients considered in the audit would have been subject to the continuation rule.

Approach 2: Conservatively excluding all patients from Ahuja et al (2023)

Another potential solution is to work with assumption c. If all of Ahuja's patients were not subject to the continuation rule, and the additional Elbashir patients all began treatment after October 2021, then there would 67.1% of patients who were subjected to the continuation rule. This assumption would remove patients who were recruited as part of the EAMS designation that berotralstat received and that was no longer actively recruiting new patients as of the NICE recommendation in October 2021. However, this assumption may be overly conservative because it implies that Ahuja et al. (2023) did not audit any patients from October 2021 to October 2022, where October 2022 is a potential data cut off point prior to the study being first published in January 2023 as per fact 3. If Ahuja did consider patients after October 2021 in their study, this means the proportion of patients subject to the continuation rule would be more than 67.1% and closer to the estimate of approach 1.

Concluding remarks:

Overall, the approaches presented above demonstrate that it is plausible that around two-thirds to three-quarters of patients audited in the Elbahsir et al. (2024)[1] study were subject to the berotralstat continuation rule. Even when shifting date

assumptions within reasonable ranges, the overall conclusions remain unchanged, reinforcing the robustness of the findings.

It is unfortunate that no data for the APeX-2 subpopulation[5] of responders can be utilised in this appraisal from TA738. Whilst that is true, and in the absence of analyses requested together with the EAG from Elbashir et al. co-authors the company believe this appendix demonstrates that this study remains the best source of available evidence.
This is true, insofar as, this appendix has shown:

1) Elbashir et al allows for more evidence-based assumptions regarding the efficacy of the responder population to be made, utilising the largest known population of UK-based observational evidence
2) In the absence of the poster being re-analysed for known responders recruited after October 2021, it is reasonable to assume that over two thirds to three quarters of the aggregate population satisfy this criterion.

Point 2 has since (7th April 2025) been externally validated by the Elbashir study co-authors who confirm that there are [redacted] patients from the poster who commenced berotralstat prior to October 2021 on the EAMS scheme. This would mean [redacted] of patients were recruited after the introduction of the continuation rule, a value in line within the range of company estimates in this appendix. This confirmation has been forwarded to the EAG, via the TA Team on the 7th April 2025. The line of reasoning presented in this appendix strongly suggests that the efficacy values presented in Elbahsir et al. (2024) are the most robust source for modelling the efficacy of berotralstat responders.

Appendix C: Garadacimab 3002 OLE[6] based AE-QoL and VANGUARD based EQ-5D regression outcomes

Table 2. AE-QoL GLM regression using duration of attack free time, baseline attack rate

Parameter	Estimate	Standard error	t-value	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Duration of attack-free	[redacted]	[redacted]	[redacted]	[redacted]
Baseline attack rate	[redacted]	[redacted]	[redacted]	[redacted]

The above analysis excludes subjects who rolled over into 3002 from the 2001 phase 2 study for garadacimab. It also excludes patients without available AE-QoL measurements. The population size supporting table two is [redacted] patients.

The regression in Table 2 is associated with an R^2 of [redacted], root MSE of [redacted] and degrees of freedom totalling [redacted].

Table 3 shows the repeated mixed model results for VANGUARD based EQ-5D-5L observations mapped onto the EQ-5D-3L value set using the Hernandez mapping function[7]. Notably, the covariate of cumulative attack free (days) shows a positive and statistically significant association with EQ-5D utility. This finding strongly supports the use of the tunnel states to model improvements in quality of life for HAE patients the longer they remain attack free.

Table 3. Repeated Mixed Model Results for EQ-5D-3L (Hernandez[7]) – cumulative attack free days

Repeated Mixed Model Results	CSL312-200mg	Placebo
Visit Day 91		
LS Mean Estimate (Standard Error)	[redacted]	[redacted]
LS Mean Difference (Standard Error)		[redacted]
95% Confidence Interval		[redacted]
p-value		[redacted]
Visit Day 182		
LS Mean Estimate (Standard Error)	[redacted]	[redacted]
LS Mean Difference (Standard Error)		[redacted]
95% Confidence Interval		[redacted]
p-value		[redacted]
	Coefficient (p-value Pr>|t|)	p-value for Fixed Effects (Pr>F)
Visit	[redacted]	[redacted]
Treatment	[redacted]	[redacted]
Cumulative Attack Free (days)	[redacted]	[redacted]
Baseline EQ-5D-3L score	[redacted]	[redacted]
Visit*Treatment	[redacted]	[redacted]

Abbreviations: LS, least-squares, mg, milligram

Please see Figure 1 for the residual plots and associated statistics of the regression presented in Table 3. Notably, the mean residual value is very close to zero at a value of [redacted] indicating good fit as the residuals appear to follow a $\varepsilon \sim N(0, \sigma^2)$ distribution. The R^2 numbered [redacted], with the root mean squared error numbering [redacted].

Figure 1. Residual plots and statistics for the EQ-5D-3L Repeated Mixed Model regression using cumulative attack free (days)

Patients experiencing an attack on the day of the EQ-5D questionnaire were not included, that is those patients who experienced an attack:

- on the visit day, or
- before the visit day and continued throughout the visit day.

Table 4 presents the number of patients who have been excluded by visit per treatment for the EQ-5D analyses.

Table 4. Number of subjects excluded by visit per treatment

Visit day	Placebo	CSL312-200mg	Total
Visit day 91	[redacted]	[redacted]	[redacted]
Visit day 182	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: mg, milligram

Supplementary analyses requested by the EAG

Following the submission of the company technical engagement response, the EAG requested analyses that would supplement the results presented in Appendix B. The requests have been addressed and included:

- Could we please request the R2, RMSE and residual plot for the utility analysis - there's currently nothing in the document looking at goodness of fit (see Table 3 and Figure 1).
- Could we please ask the company to confirm that patients experiencing an attack on the day of the questionnaire were not included (see Table 4).
- Could we please also request a version of this analysis with treatment excluded and attack freedom grouped in bands of months (see below).

The EAG request of attack freedom being grouped in bands of months has been presented using two different methods:

1. Continuous attack freedom, and
2. Treating attack freedom as separate categorical dummy variables.

Appendix to the technical engagement response form

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

CSL Behring's preferred approach is continuous attack freedom, mainly due to the low number of patients informing certain bands in the categorical dummy variables approach with no patients falling into the month one and three bands at visit day 182.

Table 5 presents the repeated mixed model results for the relationship between EQ-5D and attack freedom, with the treatment covariate excluded and attack freedom expressed in months. In effect, this regression provides very similar outcomes to the repeated mixed model with attack freedom expressed in days, because during optimisation the linear predictors are scaled by the relevant factors. Generally, the coefficient of the day variable multiplied by the mean of attack free days is equal to coefficient of the month variable multiplied by the mean of the attack free months. The only difference is the exclusion of the treatment covariate. Please refer to Figure 2 which presents the residual plots and associated statistics of the regression presented in Table 5. This regression also presents good fit characteristics with a R^2 of [redacted], with the root mean squared error numbering [redacted].

Table 5. Repeated Mixed Model Results for EQ-5D-3L (Hernandez) – cumulative attack months free without the treatment covariate

Repeated Mixed Model Results	**Visit Day 91**	**Visit Day 182**
LS Mean Estimate (Standard Error)	[redacted]	[redacted]
	Estimate	**(p-value: Pr>|t|)**
Visit	[redacted]	[redacted]
Cumulative Attack Free (months)	[redacted]	[redacted]
Baseline EQ-5D-3L score	[redacted]	[redacted]

Abbreviations: LS, least-squares

Figure 2. Residual plots and statistics for the EQ-5D-3L Repeated Mixed Model regression using cumulative attack free (months)

Table 6 presents the predicted estimates of EQ-5D-3L at each visit under maximum cumulative attack free periods of one through six months, based on the regression specified in Table 5. The estimates, based on a model with good fit, clearly indicate improved EQ-5D-3L outcomes with longer cumulative attack free duration as expressed by both visit days (Day 91/182).

Table 6. Least squares mean EQ-5D-3L estimates based on Repeated Mixed Model regression by month from Visit Day 91/182 observations

Least squares mean EQ-5D-3L estimate (Pr > |t|)	Visit Day 91	Visit Day 182
Month 1	[redacted]	[redacted]
Month 2	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
Month 4	[redacted]	[redacted]
Month 5	[redacted]	[redacted]
Month 6	[redacted]	[redacted]

Table 7 presents the repeated mixed model results for the relationship between EQ-5D and attack freedom, with the treatment covariate excluded and attack freedom expressed in months as categorical variables. Whilst the general trend that attack freedom improves quality of life holds true across this regression as determined by F-tests of joint significance, the categorical approach of defining attack freedom is less reliable than the continuous, with the latter being CSL Behring's preferred analysis approach. Overall, this appendix strongly supports the use of the tunnel states in the cost-effectiveness model.

Table 7. Repeated Mixed Model Results for EQ-5D-3L (Hernandez) – cumulative attack months free as categorical without the treatment covariate

Repeated Mixed Model Results	**Visit Day 91**	**Visit Day 182**
LS Mean Estimate (Standard Error)	[redacted]	[redacted]
	Estimate	**(p-value: Pr>|t|)**
Visit	[redacted]	[redacted]
Maximum cumulative attack freedom in months (categorical)		
Month 2 (reference month)	[redacted]	[redacted]
Month 4 (n=[redacted])	[redacted]	[redacted]
Month 5 (n=[redacted])	[redacted]	[redacted]
Month 6 (n=[redacted])	[redacted]	[redacted]
Baseline EQ-5D-3L score	[redacted]	[redacted]
Type 3 Tests of Fixed Effects	**F-value**	
Visit	[redacted]	
Maximum cumulative attack freedom in month (categorical)	[redacted]	
Baseline EQ-5D-3L score	[redacted]	

Abbreviations: LS, least-squares. Italics represent a group of variables

Appendix D: Mapping Banerji SF-12 outcomes to EQ-5D

Key Issue 6: Mapping Banerji SF-12 outcomes to EQ-5D, to further establish the link between attack freedom (time since last attack) and quality of life.

Whilst Banerji et al. (2020)[8] provides a strong justification as to the relationship between attack freedom (time since last attack) and quality of life, it reports outcomes using the generic SF-12 instrument. This is valuable evidence as it shows that another generic HRQoL instrument shows consistent results and a consistent narrative to other sources, however, this appendix presents the SF-12 outcomes mapped to the EQ-5D. According to the NICE methods and guidance[9], EQ-5D is the preferred method of valuing health for health technology assessments.

The only SF-12 to EQ-5D mapping study that expresses EQ-5D through a UK value set is the Gray et al. (2006) algorithm, as per the Oxford database of mapping studies[10]. Unfortunately, this is a direct mapping algorithm which relies on individual responses, making it unsuitable for mapping outcomes from Banerji et al. (2020)[8] since only SF-12 summary scores are reported.

Nevertheless, the purpose of this exercise is not to replace utility values in the cost-effectiveness model but rather to express SF-12 outcomes to the EQ-5D as a means of a sensitivity analysis. Table 8 presents the relevant SF-12 outcomes from Figure 4B of the study.

Table 8. Banerji et al. (2020) SF-12 outcomes

Number of attacks (over six months)	PCS Mean	PCS SD	MCS Mean	MSC SD
0	54.5	8.7	51.0	8.1
1-3	52.6	7.8	47.6	10.6
4-6	50.2	9.4	44.2	10.9
7-12	48.2	8.8	43.8	10.2
≥13	42.3	10.4	42.8	11.6

Higher scores represent better outcomes. Abbreviations: MCS, mental component summary; PCS, physical component summary; SD, standard deviation

Table 9 presents the associated EQ-5D values expressed by the mapping studies listed. The trend of greater periods of without attack are clearly associated with higher EQ-5D utility values, supporting CSL Behring's assumption for tunnel states. While other specification of mapping algorithms from these studies are available, the broad vertical agreement across the studies suggests the results are not sensitive to the choice of algorithm.

Six months of attack freedom compared to a baseline of roughly two attacks per month (≥13 attacks over 6-months) are in the range of a utility gain of 0.102 - 0.155, which are consistent with those modelled in the company's cost-effectiveness model.

Table 9. EQ-5D outcomes from Banerji et al. (2020)

Number of attacks (over six months)	EQ-5D – Lawerence and Fleishman (2004)[11], 3-variable model	EQ-5D – Franks et al. (2004)[12], SF-12 items only	EQ-5D – Sullivan and Ghuschchyan (2006)[13], SF-12 items only	EQ-5D – Le (2013)[14], CLAD US D1 model
0	0.890	0.900	0.937	0.962
1-3	0.834	0.850	0.899	0.926
4-6	0.768	0.788	0.856	0.882
7-12	0.735	0.756	0.835	0.860
≥13	0.638	0.659	0.776	0.790

Abbreviations: CLAD, censored least absolute deviations; US, United States.

Appendix E – Appraisal of Lo et al. (2022) relative to DSU Guidance

Table 10. Appraisal of Lo et al. (2022)

Figure 2: Proposed recommendations of best practice for vignette development	**Lo et al. 2022 findings[15]**	**Matches recommendation Yes/No/Maybe**
Obtain high quality appropriate, reliable and informative evidence to inform vignette development. This could consist of, and be strengthened by the use of, multiple different types of evidence: "· Published literature, for example reviews or original studies including qualitative studies around the HRQoL of patients with the condition. · Qualitative studies (for example interviews or focus groups) with patients, and if relevant carers. · Qualitative studies (for example interviews) with clinical experts. · Qualitative analysis of social media data (for example online patient discussion forums) though care should be taken with interpretation and representativeness since patients may not be representative and formal diagnosis is not ensured. · Quantitative data (for example patient-reported outcome measures of HRQoL in clinical trials or observational studies)."	<u>Part I: Qualitative Interviews on Patient and Caregiver Burden</u> Qualitative interviews with 15 patients, five caregivers and one clinical expert. Qualitative interviews were supported by a semi-structured guide (Online Resource 1) developed based on previous studies of the burden of HAE in people with the disease and caregivers [8, 20, 26, 27]. <u>Part II: Vignette Development</u> Vignettes were refined through interviews with two people with HAE and two caregivers who had participated in Part I of the study and had agreed to be recontacted and one clinician with experience of HAE. <u>Part III: Time Trade-Off (TTO) Valuation of Vignettes</u> TTO interviews using the vignettes developed in Part II and participants from the general public to estimate utility weights.	Yes – high quality evidence gained from qualitative interviews
Vignette development including content and format		
The number of vignettes and the required severity/disease state of each of these vignettes should be selected to meet the requirements of the economic model structure for the TA and HST evaluation. Considerations include the requirement that vignettes meaningfully differ, as subtle differences in descriptions may not be captured in the valuation stage, but these differences should not be exaggerated.	<u>Vignettes for five HAE health states and one caregiver health state:</u> • HAE adult patient: attack-free (i.e. currently not experiencing any swelling) • HAE adult patient: abdominal attack (i.e. currently experiencing swelling in the abdomen) • HAE adult patient: facial attack (i.e. currently experiencing swelling in the face) • HAE adult patient: hand attack (i.e. currently experiencing swelling in a hand)	Yes – appropriate health state vignette for the economic model structure including 'HAE attacks'

	• HAE adult patient: laryngeal attack (i.e. currently experiencing swelling in the throat) **• HAE caregiver: person they care for is experiencing an attack.**	
Vignettes should be presented and formatted to enable easy reading and comprehension e.g. simple language where possible if presented to members of the general public, appropriate font size, use of boldening/underlining to highlight different levels of severity.	See supplementary materials, Online Resource 7 – Final vignettes. https://link.springer.com/article/10.1007/s41669-021-00302-6 Clear table of each of the six states, including use of bold for key points.	Yes – clearly presented and formatted table for each of the six states
Vignettes should be presented and formatted to enable ease of understanding of the target audience of the differences between the different vignettes. For example, the aspects of health described in the vignette should always be presented in the same format and order for a given participant. This is important since it can impact on the utility values that are elicited as some participants may provide relative values for the vignettes whilst considering all vignettes.	Online Resource 7 – Final vignettes. Each state has slightly different descriptions and orders, for example ability to wash and dress is the fourth bullet point of abdominal attack and fifth of facial attack. However, presumably all participants would be given the same final vignette table, so would get the descriptions in the same order. Part III: Time Trade-Off (TTO) Valuation of Vignettes Interviews were conducted according to a script (see Online Resource 4 for interview script). Each participant was assigned to one of four versions of the vignettes, with versions counterbalancing order effects.	Yes – clearly presented and formatted table with order effects considered
Vignettes should include descriptions of the generic dimensions of HRQoL, for example using the EQ-5D dimensions and descriptions. This can reduce focussing effects where respondents may focus on the symptoms or treatment effects described rather than considering these in a wider context of HRQoL.	In both the final vignettes (Online Resource 7) and qualitative interviews, each of the five EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) have one or more questions/statements relating to them, however not specific separate sections on each.	Maybe – each of the five EQ-5D dimensions have one or more questions/statements relating to them, however not specific separate sections on each.
Vignettes should include all important and relevant aspects of HRQoL to ensure accuracy and minimise bias. Important and relevant aspects should be identified using good quality evidence.	As above; in both the final vignettes (Online Resource 7) and qualitative interviews, each of the five EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) have one or more questions/statements relating to them,	Yes – each of the five EQ-5D dimensions have one or more questions/statements relating to them

	however not specific separate sections on each.	
Vignettes should be easy to understand with minimal potential for ambiguity and misinterpretation by the target audience. Clinical experts, for example, may interpret clinical stages differently in terms of their impact on HRQoL, so care should be taken to describe the aspects of HRQoL rather than clinical stages, since this is the focus of utility values.	Multiple points to clearly describe each state given, for example, "You are able to wash and dress normally."	Yes – points to clearly describe each state given
Each vignette should reflect the typical patient experience for the disease state in question, rather than extremes, though some vignettes may present plausible ranges, for example 5 to 8 events per month.	Typical patient experience included, for example in the abdominal attack state, "You currently have swelling in your tummy causing you to experience cramps and severe pain. Symptoms may also include diarrhoea, nausea and vomiting."	Yes – typical patient experience included
Vignette descriptions should provide clarity and certainty where possible and avoid probabilistic statements, to reduce the variability in the interpretations made by the target audience. Where there is a probability of different outcomes, separate vignettes can be valued for the different outcomes and combined using probabilities to generate the state required in the economic model.	Patient health state descriptions are generally clear and certain (you have/you find it/you are unable to/you feel etc.) Caregiver health state more open to interpretation for example "**You might need** to take them to hospital if their swelling is not controlled….Your normal daily activities, such as work, housework, childcare and social activities, **may be interrupted**. You **may need to** take on more household tasks (e.g. cooking)."	No – while the health state descriptions are generally clear and certain, for the caregiver health state it includes some probabilistic statements

Carefully consider whether to include the disease label and/or the treatment in the health state. Where possible it is recommended to avoid the condition or treatment because there is a chance that this could lead to biased estimates. If aspects of treatment are unavoidable, for example mode of administration, these should be clearly explained to target populations who may be unfamiliar with these.	"You have a lifelong incurable condition that sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers." Injections mentioned for treating swelling – but no specific drug names.	Yes – specific disease and treatment names not given
Ensure wording is not leading or outside of the context of what should be reasonably considered, for example avoiding descriptive phrases such as 'devastating', 'debilitating' or 'difficult to treat', naming the patient, or issues around burden of illness or disease history unrelated to the current state.	No leading descriptive phrases (could be fatal and "severe" pain are factual descriptions).	Yes – no leading descriptive phrases
Vignette refinement, validation and interpretation		
Input from clinical experts and/or patients via interviews, focus groups or patient involvement meetings should be undertaken to ensure that the vignettes are a clear and accurate description of the health state or adverse event that they are intended to represent. Vignette descriptions before and after this stage should be presented to identify the changes, and the rationale behind the changes should be transparent and explicit.	Online Resource 5 – Revisions to patient vignettes Vignettes were refined through interviews with two people with HAE and two caregivers who had participated in Part I of the study and had agreed to be recontacted. 'Online Resource 5 – Revisions to patient vignettes' gives a clear table of the original text and final text.	Yes – vignettes were refined through interviews with two people with HAE and two caregivers, and changes clearly reported
Prior to the main valuation study it is recommended to ensure that the descriptions are able to be understood and are clear for the target audience. For example, the general population may need explanations of some aspects such as seizures, and this could be examined using a pilot study.	Clear language used in vignettes.	Yes – clear language used

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Appendix to the technical engagement response form

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

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NICE 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]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

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The deadline for comments is **5pm** on **Monday 7 April.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Technical engagement response form

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHSE Specialised Immunology and Allergy Clinical Reference Group ([redacted])
Disclosure 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.] Please state: • 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.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Nil**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty around the treatment pathway for people with HAE. This is about what treatments are available currently for HAE in the NHS. EAR section 2.3.4 and 2.4. Following the recent publication of the NHS England HAE Algorithm please confirm the company's proposed positioning of garadacimab in the treatment pathway (see the final row of this table with 'Other information from the NICE technical team' for further information).	No	Please provide your response to this key issue, including any new evidence, data or analyses The company's response appears to be in keeping with the existing NHSE clinical commissioning algorithm for HAE patient management and accurately summarises the current treatment landscape and exclusions for anti-fibrinolytics and attenuated androgens as non-licensed therapies, which are not included as routine standard of care in the algorithm for the same reasons outlined in the submission.
Key issue 2: Methods and trials used in the indirect treatment comparison.	No	Please provide your response to this key issue, including any new evidence, data or analyses

The company preferred the fixed effect NMA where the phase 2 garadacimab trial CSL312_2001 was included in the model. However, based on the model fit and heterogeneity between garadacimab trials, the EAG preferred the FE NMA where CSL312_2001 was removed. EAR section 3.4.1.4-5 and 3.4.2.3-4.		Due to the redactions in the EAG document it is not possible to conclusively comment. The essential statements equivalence or not are redacted, so the veracity of the conclusions or indeed the conclusions cannot be confirmed or refuted. It is not possible therefore to comment on how the efficacy or safety compares under these 2 models.
Key Issue 3: Methods and data used to estimate treatment effectiveness. Long-term effectiveness is uncertain for all treatments due to a lack of long-term data. The company and EAG used different methods and data used to estimate the treatment effect of garadacimab works versus comparators, including when making predictions in the longer terms. EAR section 4.2.6.3.	No	Please provide your response to this key issue, including any new evidence, data or analyses The conclusion that long term efficacy over decades is unclear for all novel LTP is correct due to the duration of availability as routinely commissioned medicines. It is not possible to comment on the company and EAG comparison because the data is redacted. The basis of the Cycle 25 onwards approach by the company appears sound and the difference with the EAG model is not clear (due to lack of data presented in the redacted document)
Key Issue 4: The handling of berotralstat stopping rule. Berotralstat efficacy data includes responders and non-responders (based on a response rate of 50%), which underestimates berotralstat effectiveness. This	No	Please provide your response to this key issue, including any new evidence, data or analyses Within the EAG report they comment that the TA738 data is redacted re: Berotralstat stopping rule and that data has not been made available to the EAG. A selection of data was provided, but the treatment of the comparison with responders as an intention to treat would be a more robust comparison of the

issue is about the methods used to estimate what proportion of people taking berotralstat stop treatment due to it not working well enough. EAR section 4.2.6.5.		overall efficacy of the 2 medicines and in the view of this review it would prejudice unfairly against the new TA if a comparison cannot be made due to selective data presentation from TA738 that itself cannot be verified.
Key Issue 5: The handling of lanadelumab switch between Q2W and Q4W. Lanadelumab effectiveness was based on the HELP-03 trial, which does not include switching from Q2W to Q4W in patients with low body mass who are stably attack free on treatment, which is recommended in the SmPC (especially in patients with low weight). This underestimates the effectiveness of lanadelumab. This is about the methods used to estimate what proportion of people move from taking lanadelumab once every 2 weeks to once every 4 weeks. EAR section 4.2.6.6.	No	Please provide your response to this key issue, including any new evidence, data or analyses The efficacy of lanadelumab and switching from Q2W to Q4W is likely overestimated in the original TA and the data offered from real world analysis from other regions (Germany, France, Greece and Austria) does not appear to be more valid than the real-world data from the UK which was previously independently published by Dorr et al. An assumption of lanadelumab switching in non-UK regions is biased by the entry criteria to therapy, the threshold for commissioning of medicines in other EU countries is based on the licence by the EMA and not a starting threshold of >2 attacks per week. This skews the ability to reduce to Q4W due to inheterogeneity of comparators and the assumptions in the view of this review re: earlier switching and ability to remain at Q4W do not appear to be clinically or biologically valid based on the efficacy data in real life or from the HELP studies when starting at high attack frequency. Efficacy at Q4W in those with low attack frequency is similar to Q2W but this group are excluded from treatment in the UK and therefore this is a questionable comparison.
Key Issue 6: The calculation of patient utilities. The EAG preferred alternative assumptions in their base case (EAR section 4.2.2.):	No	Please provide your response to this key issue, including any new evidence, data or analyses Real life QoL benefit from clinically reported outcomes are a continuing and changing outcome that are hard to capture in QoL studies. The outcome tools score current experience based on the last 3 months and from the time that patients become attack free there is a distinct improvement in QoL. That does not

• that the impact of an attack lasted only for the duration of the attack • that if there was a benefit of being 'attack free', this would be incurred after the first month through the application of the Nordenfelt (2014) equation • that an intercept of 1 rather than the mean EQ-5D today is used when applying the Nordenfelt (2014) paper.		negate the impact on lived experience, the effect of continued good attendance at school or the workplace that result in security rather than loss of employment or educational attainment that cannot be assessed by QoL scoring alone. Patients report ongoing "relief" the longer they are attack free. The gradual reduction in anxiety not assessed in these QoL scores and other benefits such as loss of fear of termination of employment due to sickness absence and improved life chances due to improved performance at school/college/university. The alternative case as presented is a valid consideration based on patient experience.
Other information from the NICE technical team	N/A	Please note that some important information relevant to the evaluation has been confirmed since the company submission and EAG report were received by NICE: 1. In January 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) approved garadacimab, as being indicated for 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older'. The following are links to the Summary of Product Characteristics for garadacimab as a pre-filled pen SmPC or pre-filled syringe SmPC. 2. In February 2025, NHS England published a new clinical commissioning algorithm for commissioned treatment options for hereditary angioedema. This can be found online at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE 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]

Technical engagement response form

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Technical engagement response form

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	BioCryst Pharmaceuticals
Disclosure 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.] Please state: • 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.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty around the treatment pathway for people with HAE. This is about what treatments are available currently for HAE in the NHS. EAR section 2.3.4 and 2.4. Following the recent publication of the NHS England HAE Algorithm please confirm the company's proposed positioning of garadacimab in the treatment pathway (see the final row of this table with 'Other information from the NICE technical team' for further information).	No	Since the EAG report for garadacimab was generated, the NHSE HAE Algorithm has been published[1]. In the updated treatment algorithm, berotralstat is positioned as a first-line LTP treatment for patients ≥12 years old who have ≥2 attacks per month. Lanadelumab and C1-esterase inhibitors are recommended as LTP treatment for patients who have ≥2 attacks per week despite oral prophylaxis. Patients treated with berotralstat who experience a reduction of at least 50% in attack frequency after 3 months are eligible to continue treatment with berotralstat. As noted by the EAG, there is substantial uncertainty regarding the relative clinical efficacy of garadacimab. Whether garadacimab might be suitable as a second-line treatment option would depend on whether garadacimab is cost-effective in that position in the treatment algorithm. Whether garadacimab is a cost-effective alternative to the existing LTP treatments depends on the comparative clinical efficacy and cost of garadacimab. While we are not in a position to comment on the cost of garadacimab, we wish to emphasize that the clinical efficacy of garadacimab, particularly relative to other LTPs, remains highly uncertain. There are no clinical studies in which garadacimab has been compared directly to other LTPs such as berotralstat and lanadelumab; therefore, the comparative efficacy of garadacimab and other LTPs is unknown. While an indirect treatment comparison

		was provided by the company to address the lack of comparative efficacy data, this approach is not a substitute for direct comparative data and is associated with substantial limitations (see Key Issue 2), such that the clinical efficacy of garadacimab remains highly uncertain. REFERENCES: 1. NHS England algorithm for commissioned treatment options for hereditary angioedema (February 2025) hereditary-amd-acquired-angioedema-algorithms-v2.pdf.
Key issue 2: Methods and trials used in the indirect treatment comparison. The company preferred the fixed effect NMA where the phase 2 garadacimab trial CSL312_2001 was included in the model. However, based on the model fit and heterogeneity between garadacimab trials, the EAG preferred the FE NMA where CSL312_2001 was removed. EAR section 3.4.1.4-5 and 3.4.2.3-4.	Yes	We agree with the EAG that the substantial uncertainty regarding comparative clinical effectiveness is a major issue. The EAG has noted several methodological limitations in the company's comparative clinical analyses (ITC), including the pooling of data from heterogenous garadacimab trials, testing of covariates, and the inclusion of only a single covariate in the final model for the principal efficacy outcomes. We note that there are several additional relevant limitations and biases associated with the company's ITC, including heterogeneity among the included studies, which leads to substantial uncertainty regarding comparative efficacy. Specifically, the studies included in the company's ITC exhibit heterogeneity with respect to trial design (e.g., crossover versus parallel) and duration; demographics and baseline characteristics of the study populations; background (SOC) treatments; and outcome definitions. While the company's multi-level network meta regression (ML-NMR) offers some limited methodological benefits in terms of adjusting for heterogeneity, it does not address the fundamental sources of heterogeneity and bias that have been noted by the EAG. With regards to heterogeneity in the company's ITC, the EAG has correctly noted the limitations with respect to difference in the age of study participants; differences in baseline attack rates; differences in the classification of attack severity; differences in the manner in which attacks were confirmed; differences in the use of on-demand treatments; and the absence of measures of uncertainty for

		clinical outcomes reported in the included studies. We wish to note additional limitations of the company's ITC that result in substantial heterogeneity, such as the necessity to limit the comparison to the duration of the shortest study, and excluding relevant long-term outcome data and data from real-world settings. The latter, in particular, could be a source of bias against berotralstat, as there are long-term data that demonstrate that berotralstat is highly efficacious in long-term studies that were not included in the ITC[2]. Indeed, results of the long-term extension of the APeX-2 RCT[2] demonstrated that berotralstat was generally well tolerated, provided rapid and sustained reductions in HAE attacks, and improved quality of life over 96 weeks. Specifically, patients who completed 96 weeks of berotralstat treatment exhibited an average percentage reduction in attack rate from baseline of 90.8%[2]. REFERENCE: 2. Kiani-Alikhan S, et al. Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial. J Allergy Clin Immunol Pract. 2024 Mar;12(3):733-743.e10. doi: 10.1016/j.jaip.2023.12.019. Epub 2023 Dec 18. PMID: 38122865.
Key Issue 3: Methods and data used to estimate treatment effectiveness. Long-term effectiveness is uncertain for all treatments due to a lack of long-term data. The company and EAG used different methods and data used to estimate the treatment effect of garadacimab works versus comparators, including when	No	We agree with the EAG that the methods used for extrapolation >24 cycles in the model are consistent with previous assessment of HAE treatments.

making predictions in the longer terms. EAR section 4.2.6.3.		
Key Issue 4: The handling of berotralstat stopping rule. Berotralstat efficacy data includes responders and non-responders (based on a response rate of 50%), which underestimates berotralstat effectiveness. This issue is about the methods used to estimate what proportion of people taking berotralstat stop treatment due to it not working well enough. EAR section 4.2.6.5.	No	We agree with EAG that the company has made an assumption regarding the application of a stopping rule for berotralstat that underestimates the effectiveness of berotralstat. We agree with the EAG that it is appropriate to assume that the efficacy of berotralstat beyond month 3 in patients who respond to berotralstat (defined as a ≥50% reduction in attack frequency) is comparable to lanadelumab Q2W.
Key Issue 5: The handling of lanadelumab switch between Q2W and Q4W. Lanadelumab effectiveness was based on the HELP-03 trial, which does not include switching from Q2W to Q4W in patients with low body mass who are stably attack free on treatment, which is recommended in the SmPC (especially in patients with low weight). This underestimates the effectiveness of lanadelumab. This is about the methods used to estimate what proportion of people move from taking lanadelumab	No	

once every 2 weeks to once every 4 weeks. EAR section 4.2.6.6.		
Key Issue 6: The calculation of patient utilities. The EAG preferred alternative assumptions in their base case (EAR section 4.2.2.): • that the impact of an attack lasted only for the duration of the attack • that if there was a benefit of being 'attack free', this would be incurred after the first month through the application of the Nordenfelt (2014) equation • that an intercept of 1 rather than the mean EQ-5D today is used when applying the Nordenfelt (2014) paper.	No	We support the view of the EAG that the impacts of HAE attacks be limited to the duration of the attack, as well as the temporal constraint of the potential benefits of being attack-free.
Other information from the NICE technical team	N/A	Please note that some important information relevant to the evaluation has been confirmed since the company submission and EAG report were received by NICE: 1. In January 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) approved garadacimab, as being indicated for 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older'. The following are

		links to the Summary of Product Characteristics for garadacimab as a pre-filled pen SmPC or pre-filled syringe SmPC. 2. In February 2025, NHS England published a new algorithm for commissioned treatment options for hereditary angioedema. This can be found online at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf.

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

The unresolved issues regarding the cost-effectiveness and long-term impact of Garadacimab for hereditary angioedema include concerns about the sustainability of its benefits over extended periods and its financial implications for healthcare systems. Questions remain about the comparative effectiveness of Garadacimab versus other treatment options available, and how it may affect the overall quality of life for patients in the long run. Additionally, the economic burden posed by the treatment, including its affordability and accessibility, continues to be a major area of debate among stakeholders.

Overview of Single Technology Appraisal

Impact, Stakeholders, and Unresolved Issues

Impact of the Document

The document "Single Technology Appraisal: Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]" serves as a technical engagement response form. Its primary impact lies in inviting stakeholders to provide feedback on the External Assessment Report (EAR) for the evaluation of Garadacimab. The feedback gathered will assist the committee in making informed decisions about the treatment's cost-effectiveness during the committee meeting.

Key Stakeholders

- Healthcare professionals specializing in hereditary angioedema
- Patient advocacy groups
- Pharmaceutical companies
- Health economists
- Regulatory authorities

Main Unresolved Issues

The unresolved issues affecting the cost-effectiveness of Garadacimab, which are likely to be discussed by the committee, include:

- Areas of uncertainty in the evidence presented in the EAR
- Concerns regarding the clinical efficacy of Garadacimab
- Questions about the long-term safety and side effects
- Economic implications and budget impact

These key issues are summarized in the executive summary at the beginning of the EAR and are crucial for the stakeholders' feedback to shape the committee's decision-making process.

Technical Engagement Response

Stakeholders are encouraged to focus their comments on the key issues highlighted in the EAR, emphasizing areas of uncertainty and evidence gaps that may impact the cost-effectiveness evaluation. This collaborative approach aims to address unresolved questions and provide a comprehensive understanding of Garadacimab's potential benefits and drawbacks.

Summary of Single Technology Appraisal

This document, "Single Technology Appraisal: Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394]," is a technical engagement response form. Stakeholders are invited to comment on the External Assessment Report (EAR) for this evaluation. Your feedback on the key issues is highly valued, as it will assist the committee in making decisions at the committee meeting. Typically, only unresolved or uncertain key issues will be discussed in the meeting.
The form seeks stakeholders' views on the key issues in the EAR that are likely to be discussed by the committee. These issues reflect areas where there is uncertainty in the evidence, which consequently affects the cost-effectiveness of the treatment. The key issues are summarized in the executive summary at the beginning of the EAR.

NICE National Institute for Health and Care Excellence

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

Technical engagement response form

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Thank you for your time.

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

Comments received during engagement 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.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Takeda UK
Disclosure 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.] Please state: • 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.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty around the treatment pathway for people with HAE. This is about what treatments are available currently for HAE in the NHS. EAR section 2.3.4 and 2.4. Following the recent publication of the NHS England HAE Algorithm please confirm the company's proposed positioning of garadacimab in the treatment pathway (see the final row of this table with 'Other information from the NICE technical team' for further information).	~~Yes~~**/No**	In line with our response to the draft remit and scope for garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394], attenuated androgens continue to be a routinely used long-term prophylactic agent in the UK and should be considered as a comparator. The newly published HAE treatment algorithm published by the NHS England, despite not recommending androgens as a first line prophylactic treatment, still acknowledges that some patients are still receiving androgens and may continue to do so if clinically appropriate: '*Some adult patients are treated with androgens as oral prophylactic treatment…Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate.*'[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 androgens and 26.3% (10/38) were taking tranexamic acid, making androgens the most widely used long-term prophylactic agent in the UK in this dataset (n = 85).[2] Further, 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.[3] Given the provided

		supportive evidence demonstrating that patients with HAE are still receiving androgens as long term prophylaxis, we feel it is important to re-highlight to the EAG that attenuated androgens should be considered as an appropriate comparator. 1. NHS England algorithm for commissioned treatment options for hereditary angioedema, February 2025. Available at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf. 2. BSACI 2024 Yong et al, Patient Characteristics, Treatment Patterns and Clinical Outcomes of Hereditary Angioedema Patients Self-administering Icatibant using Homecare in the UK: An Interim Analysis of a Real-World Study. Poster presentation Poster A014 3. 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.
Key issue 2: Methods and trials used in the indirect treatment comparison. The company preferred the fixed effect NMA where the phase 2 garadacimab trial CSL312_2001 was included in the model. However, based on the model fit and heterogeneity between garadacimab trials, the EAG preferred the FE NMA where CSL312_2001 was removed. EAR section 3.4.1.4-5 and 3.4.2.3-4.	~~Yes~~**/No**	N/A

Key Issue 3: Methods and data used to estimate treatment effectiveness. Long-term effectiveness is uncertain for all treatments due to a lack of long-term data. The company and EAG used different methods and data used to estimate the treatment effect of garadacimab works versus comparators, including when making predictions in the longer terms. EAR section 4.2.6.3.	~~Yes~~/**No**	N/A
Key Issue 4: The handling of berotralstat stopping rule. Berotralstat efficacy data includes responders and non-responders (based on a response rate of 50%), which underestimates berotralstat effectiveness. This issue is about the methods used to estimate what proportion of people taking berotralstat stop treatment due to it not working well enough. EAR section 4.2.6.5.	~~Yes~~/**No**	We agree with the EAG that the effectiveness of berotralstat has been underestimated through the inclusion of efficacy data for both responders and non-responders (based on a response rate of 50%). While we appreciate there is an absence of head-to-head trials, the results from a Takeda sponsored network meta-analysis (NMA) for indirect comparison of lanadelumab and berotralstat for treatment in HAE, reported in Watt et al[1], demonstrated statistically significant higher effectiveness for lanadelumab 300 mg administered every 2 weeks (Q2W) and every 4 weeks (Q4W) compared to berotralstat 150 mg once daily (q.d.) or 110 mg q.d. This NMA compared efficacy in terms of HAE attack rate per 28 days and ≥90% reduction in monthly HAE attacks using phase III clinical trial data from HELP (lanadelumab vs placebo) and APeX-3 (berotralstat vs placebo) and CHANGE (C1-INH vs placebo). Therefore, despite limitations, the results of the NMA demonstrating statistically superior efficacy across both outcomes for lanadelumab[1], make it challenging for us to confirm the EAG's assumption in its base case that the efficacy of patients on

		berotralstat beyond month 3 is the same as lanadelumab administered Q2W. Due to an absence of head-to-head trials, responder-only subgroup analyses and heterogeneity across patient populations in publicly available publications, we are unable to provide the EAG with any alternative approaches at this time. 1. Watt M,et al, Network meta-analysis for indirect comparison of lanadelumab and berotralstat for the treatment of hereditary angioedema. *J Comp Eff Res*. 2023;12(6):e220188. doi:10.57264/cer-2022-0188
Key Issue 5: The handling of lanadelumab switch between Q2W and Q4W. Lanadelumab effectiveness was based on the HELP-03 trial, which does not include switching from Q2W to Q4W in patients with low body mass who are stably attack free on treatment, which is recommended in the SmPC (especially in patients with low weight). This underestimates the effectiveness of lanadelumab. This is about the methods used to estimate what proportion of people move from taking lanadelumab once every 2 weeks to once every 4 weeks. EAR section 4.2.6.6.	~~Yes~~**/No**	We agree with the issues raised by the EAG on the handling of lanadelumab switching between Q2W and Q4W. The data used in the CS potentially leads to an underestimation of lanadelumab's effectiveness by not considering the effect of Q2W dosing prior to Q4W switching. The alternative approach suggested by the EAG, which assumes patients who switch to Q4W dosing have the same efficacy as when on Q2W dosing, is reasonable and is aligned with the assumptions used in the lanadelumab NICE single technology appraisal for preventing recurrent attacks of hereditary angioedema (TA606, October 2019), which we believe are still the most reasonable and suitable for application within this appraisal (ID6394).
Key Issue 6: The calculation of patient utilities.	~~Yes~~**/No**	N/A

The EAG preferred alternative assumptions in their base case (EAR section 4.2.2.): • that the impact of an attack lasted only for the duration of the attack • that if there was a benefit of being 'attack free', this would be incurred after the first month through the application of the Nordenfelt (2014) equation • that an intercept of 1 rather than the mean EQ-5D today is used when applying the Nordenfelt (2014) paper.		
Other information from the NICE technical team	N/A	Please note that some important information relevant to the evaluation has been confirmed since the company submission and EAG report were received by NICE: 1. In January 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) approved garadacimab, as being indicated for 'routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older'. The following are links to the Summary of Product Characteristics for garadacimab as a pre-filled pen SmPC or pre-filled syringe SmPC. 2. In February 2025, NHS England published a new algorithm for commissioned treatment options for hereditary angioedema. This can

		be found online at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

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

EAG Review of Company's Response to Technical Engagement Response

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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1. INTRODUCTION

The purpose of this addendum is to respond to points raised by stakeholders as part of the technical engagement (TE) process. The sections of the report are split according to each of the key issues raised in the original EAG report and address stakeholder comments in response to each issue. Updated economic analyses are then presented based upon the company's updated PAS.

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 TO COMPANY'S TECHNICAL ENGAGEMENT RESPONSE FORM

2.1. Key issue 1: Uncertainty around the treatment pathway for people with HAE

The EAG described in Key issue 1 the uncertainty regarding the current treatment pathway for people with hereditary angioedema (HAE), that then led to uncertainty in the positioning of garadacimab. The EAG understood that the NHS England (NHSE) treatment algorithm for HAE would help resolve this uncertainty. The NHSE HAE treatment algorithm[1] was published in February 2025 and was in line with the treatment pathway the EAG outlined in Section 2.3.4 of the EAR. Therefore, as stated in Section 2.4 of the EAR, if adopted in routine clinical practice, garadacimab would most likely be used in the following cases:

- In people with ≥2 attacks per month, garadacimab could either be offered first-line as an alternative to berotralstat, or second-line in people for whom berotralstat failed.
- In people with ≥2 attacks per week, garadacimab could be offered to people for whom oral treatment (predominantly berotralstat) had failed and compete with lanadelumab to be the main treatment for this population.

The company noted that positioning garadacimab as second-line in people with ≥2 attacks per month for whom berotralstat failed makes on-demand treatment (i.e. best supportive care; BSC) the comparator. The company explained that because BSC (on-demand treatment) of HAE attacks was not a comparator in the final scope issued by NICE,[2] they would not be making this comparison. However, for garadacimab to be positioned second-line to berotralstat for people ≥2 attacks per month, given the treatment pathway, the appropriate comparator was BSC.

In addition, the company noted that the EAG's proposed positioning of garadacimab as a second-line treatment in people with ≥2 attacks per month was "discordant" with the approach taken of the proposed positioning of garadacimab in people with HAE who have ≥2 attacks per week. Berotralstat is the first-line treatment in the current treatment pathways for people with ≥2 attacks per month and people with ≥2 attacks per week. Second-line treatment is BSC for people with ≥2 attacks per month, and Lanadelumab or C1-INHs for people with people with ≥2 attacks per week. The EAG's options for the positioning of garadacimab sit within this pathway and do not add any further treatment sequencing, outside of the addition of garadacimab.

The company go on to reference analysis undertaken in TA606 (the appraisal of Lanadelumab).[3] In TA606, lanadelumab and C1-INHs did not have to prove cost-effectiveness versus BSC as there was already an NHS commissioning policy in place for C1-INHs. In the appraisal, the EAG did present a comparison to BSC, however, as the company chose to request an optimised recommendation only within the population eligible for C1-INH. This was not taken further. No such optimised recommendation has been made for garadacimab, and as such, the relevant comparator for the second-line position in the treatment pathway is BSC.

The EAG also noted that analysis versus BSC could support the first-line comparison of garadacimab versus berotralstat where there is uncertainty regarding the stopping rule (Key issue 4). It could be used for triangulation of results versus berotralstat, given that berotralstat demonstrated cost-effectiveness versus BSC (no prophylaxis) in TA738.[4]

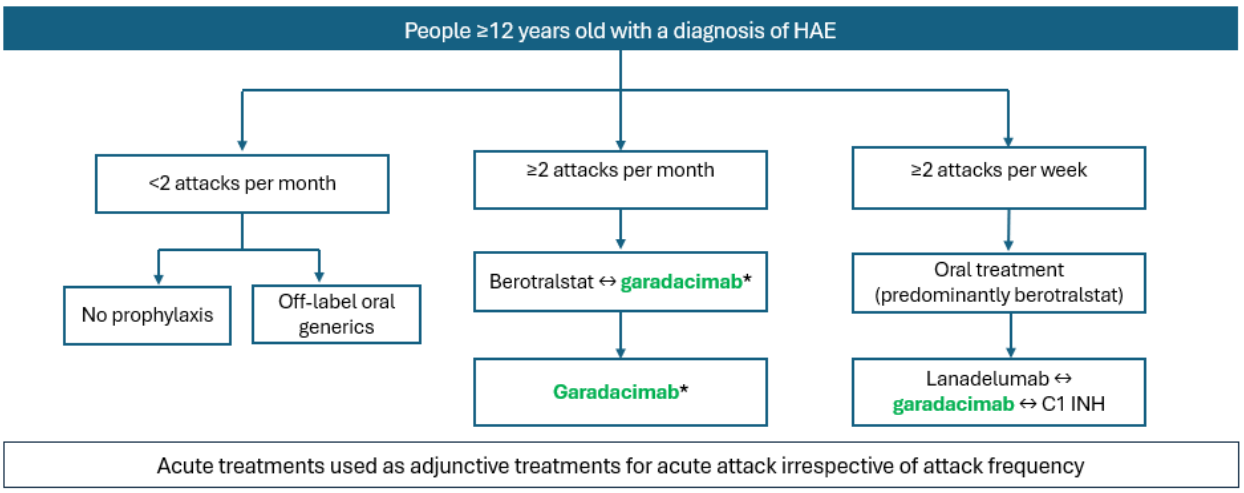
In sum, the EAG considered that, as in prior appraisals, uncertainty remained around the effectiveness of different sequences of treatments in HAE. No prophylaxis has been included as a comparator in the company base case and EAG base case as it enables triangulation and provides contextual information to inform the committee. This is of interest because berotralstat has already been found to be cost-effective compared to BSC (no prophylaxis) in a previous appraisal. It is also of interest because it can be used to inform a comparison of garadacimab with no prophylaxis, amongst people for whom berotralstat failed.

The company also raised a concern that:

> *"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".*

However, the EAG's clinical experts explained that people might decide to switch their first-line treatment, whether that was berotralstat or garadacimab, due to toxicity or lack of efficacy. The EAG have updated the treatment pathway (Figure 1), initially presented in Section 2.4 of the EAR, to remove any ambiguity related to treatment switching.

Figure 1: The EAG's positioning of garadacimab based on the NHSE treatment algorithm and advice from clinical experts



Abbreviations: C1-INH, C1-Inhibitor; HAE, hereditary angioedema.

Notes:
* Garadacimab has been placed in two possible treatment pathway locations for people with ≥2 attacks per month. It could be as a first-line alternative to berotralstat or second-line as a treatment in people for whom berotralstat fails.

↔ Treatment switching permitted

The company, in their TE document, also responded to the EAG's critique of the company's comparators in their base case. In the company's base case, lanadelumab, Cinryze and Berinert were included as comparators for the ≥2 attacks per month population, but this did not reflect the EAG's understanding of the treatment pathway. In order to align with the approach of two base cases, the company provided additional analyses, showing the two base cases covering ≥2 attacks per month and ≥2 attacks per week subgroup as two distinct health economic analyses. The EAG would like to thank the company for this and consider this part of Key Issue 1 is resolved.

Summary of the EAG response to the company's TE in relation to Key issue 1:

- The EAG's positioning of garadacimab in the treatment pathway remained the same after the publication of the NHSE treatment algorithm. However, the EAG made it more explicit in the treatment pathway that treatment switching was permitted.
- The EAG maintained that BSC (no prophylaxis/on-demand treatment) was the relevant comparator when garadacimab was positioned second-line in people with ≥2 attacks per

month (after berotralstat has failed). Analysis versus BSC could also support the first-line comparison of garadacimab versus berotralstat where there is uncertainty regarding the efficacy of berotralstat (Key issue 4).

- In the company's base case, lanadelumab, Cinryze and Berinert were included as comparators for the ≥2 attacks per month population, but this did not reflect the EAG's understanding of the treatment pathway. The company has resolved this part of Key issue 1.

2.2. Key issue 2: Methods and trials used in the indirect treatment comparison

The EAG agreed that the company has resolved Key Issue 2, as it accepted the EAG preferences regarding the exclusion of Phase II studies from the ITC network and revised the base case accordingly.

2.3. Key issue 3: Methods and data used to estimate treatment effectiveness

The EAG was pleased that the company had for the most part resolved Key issue 3. Some of the discussion in this section in the company's response form appeared to relate to Key issue 4 and has consequently been handled in that section.

Regarding Key issue 3, the first point made by the company was in relation to the anchoring for the NMA. The company argued that the efficacy of comparators should not be anchored to garadacimab because this is not in line with the precedent set by previous appraisals.

However, the EAG noted that the NICE manual states that precedent is not sufficient grounds to justify modelling assumptions.

> *'It is not enough to state that the chosen model structure has previously been used in published model reports or accepted in submissions to NICE. The chosen type of model (for example, Markov cohort model, individual patient simulation) and model structure should be justified for each new decision problem.'*[5]

Rather, the strengths and weaknesses of the different methods were discussed extensively in the EAG report.

The use of constant attack rates was not considered appropriate as it did not fit the data well. The same applied to the Poisson regression. The calibrated attack rate method in the company model used the proportion of attack-free patients that came from an NMA not considered robust.

This was due to low event numbers for some treatments and the use of Average Attack Rate Ratio Carried Forward (AARRCF) only for garadacimab and not for comparators, which instead used Last Observation Carried Forward (LOCF), and which biased the comparisons.

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.

2.4. Key issue 4: The handling of berotralstat stopping rule

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. No data are available on attack rates among patients who achieve 50% attack rate reduction by month 3 – in part, because they are redacted in TA738.

NHSE made the following point as part of the consultation.

> *'It would prejudice unfairly against the new TA if a comparison cannot be made due to selective data presentation from TA738 that itself cannot be verified' (NHSE)*

The EAG was required to make the assumptions it believed to be the most appropriate, given the information it had access to. The EAG does not have the ability to insist upon access to redacted data from previous appraisals.

The EAG would like to reiterate that the Elbashir poster was not provided as part of the original submission. Rather, it was provided in response to clarification questions to support claims regarding discontinuation. It was only during the factual accuracy check that the company suggested using it to inform efficacy. The EAG noted some limitations with the source, but nonetheless agreed to include it within scenario analysis. The company and EAG shared several questions with the authors to better understand the data and assumptions, and to request a supplementary analysis that would be better aligned with the research question within this appraisal. The authors did not respond to most questions, but did provide the proportion of patients in their study who received berotralstat prior to the introduction of the stopping rule in October 2021 ([redacted]).

The company made some corrections to the way in which the EAG interpreted and extracted the values from the poster. These were valid corrections and the EAG has accepted them. Specifically, the EAG had conflated the number of patients who discontinued treatment (n = 54), with the number who discontinued or were not in the study for 24 months (n = 132).

The company also attempted a different method to implement the Elbashir values within the model. The Company and EAG's methods are summarised in Figure 2. The EAG did not agree with the assumptions underlying the company's new implementation. The company assumed that Figure 2 contains patients who had not discontinued berotralstat at the time of the analysis, with a sample size of 110. However, this sample size is uncertain, given the figure is not labeled in the poster. It was equally possible that that figure contained all 164 patients (in line with a standard intention to treat analysis). This is further supported by the fact that the average of the baseline attack rate in each arm in Figure 3 (7.5 and 5.8) was approximately 6.1, which appears to align with Figure 2. This suggested Figure 2 may contain all patients.

The company further attempted to calculate the proportionate reduction in the attack rate for different subgroups presented in the paper compared to baseline (patients who received 24 months of treatment and, what they assumed to be, patients who did not discontinue treatment during the study). This seemed appropriate, although it required an additional assumption that the baseline values were the same for both groups. The company calculated a weighted average of the change in attack rate from baseline, using the 32 patients who continued treatment to month 24 and the total number of berotralstat only patients based on their assumptions regarding Figure 2 in the poster (n=110) (See red box in Figure 2 below).

This meant the company assumed that:

- 29% of patients (32/110) achieved the attack rate reduction for patients who continued to month 24 (e.g. -55% in month 3), and
- 71% (1-32/110) achieved the attack reduction from Figure 2 in the poster (assumed to be patients who did not discontinue berotralstat during the study) (e.g. -48.3% at month 3).
- The company then combined these totals to get an attack rate reduction of 50.18% in month 3.

However, this did not appear appropriate, as the 110 patients who did not discontinue berotralstat during the study already included the 32 patients who continued treatment to month

24. The EAG were therefore unclear what the company was trying to demonstrate with this approach.

The EAG also noted that, in attempting to use the Elbashir data to directly calculate the attack rate ratio, the company were disregarding the attack rate ratio NMA. This effectively constituted a naïve comparison, which is not in line with NICE guidance.

Figure 2: Comparison of methods for using data from the Elbashir paper to model berotralstat maintenance response

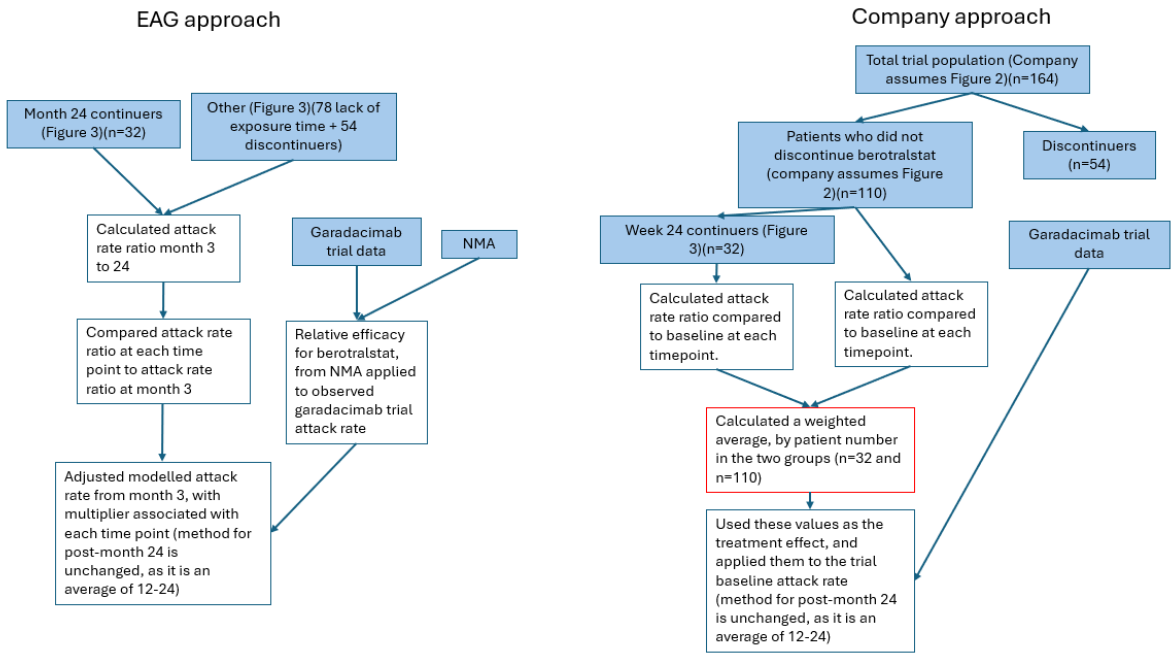


Table 1 provides a comparison of the modelled attack rate in the berotralstat arm when using three different methods. The EAG's original method applied the attack rate reduction associated with lanadelumab, to berotralstat, to account for the stopping rule. This yielded the lowest attack rate. There are then the two different implementations of the Elbashir paper. The EAG implementation was relatively more favourable to berotralstat than the company's implementation. The two EAG methods both used the NMA data for the attack rate in month 3, then used different assumptions to make adjustments to the attack rates in subsequent months. As noted above, however, the company abandoned the NMA, hence the higher attack rate – including in month 3 – before the stopping rule takes effect. The EAG also believed the company's implementation to be erroneous, for the reasons set out in the previous paragraph.

Table 1: Comparison of modelled attack rate using the different methods

Month	EAG original method	EAG amended implementation of Elbashir	Company implementation of Elbashir
3	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25+	[redacted]	[redacted]	[redacted]

Notes: All methods run in the EAG base case, in the ≥2 attacks per month population.

The EAG considered that the most fundamental issue was that the data presented in the poster were not well aligned with the decision problem. The poster presented attack reduction for a subgroup of patients who continued treatment to month 24, which could potentially be used as a proxy for attack reduction amongst patients who responded to treatment after 3 months. However, there were several challenges and limitations to this approach.

One issue was that the subgroup of 32 patients who continued treatment for 24 months, was likely to be mostly, or entirely, made up of the [redacted] patients who entered the study before the stopping rule was introduced. This meant that this group was a poor proxy for the level of maintenance response, factoring in the 3-month stopping rule (attack rate ratio among patients who achieve a 50% reduction). There was no information in the poster on whether these were patients who responded for 24 months, or merely continued treatment for 24 months. The EAG had originally compared this to the attack rate in 'Other patients'. Unfortunately, the 'Other patients' group was a poor proxy for patients who discontinued due to lack of response, because many of the patients in that group were merely patients who had not been in the study long enough to achieve 24 months on treatment.

Nevertheless, comparing the patients who continued on the treatment to month 24 to those who did not, did give some weak information about the way response varies for patients who maintain response, with patients who did not, because the patient group with 24 months of drug survival will likely be skewed towards those who maintain response.

Another issue was from the results of the open label extension for berotralstat, presented in Kiani-Alikhan (2024).[6] The results showed high levels of disease control late in the trial. For patients who completed 96 weeks of treatment, the average attack rate was 0.2 attacks per month, with a mean change of -2.21 (92% reduction). In the EAG base case at week 96 (which is month 22), these patients were modelled to experience [redacted] attacks per month, with [redacted] in the long term. This compares to [redacted] at week 96, when using the EAG's implementation of Elbashir, and [redacted] when using the company's implementation of Elbashir. This study did not include a stopping rule, which would contribute to making the results conservative (although it is an open label extension, so may be subject to confounding and other methodological limitations). Overall, this study suggested that berotralstat is effective over the long term and supported the plausibility of the EAG's base case.

Based on the above reasoning, the EAG did not believe the Elbashir poster was an adequate source to inform this reimbursement decision in the base case. The EAG has included a new scenario with the original EAG approach for implementing Elbashir (Figure 2), but using amended values suggested by the company.

The EAG have also modelled a scenario in which the ITT berotralstat effectiveness was used from the company's indirect treatment comparison, with no adjustment for the stopping rule. This was the assumption used in the company base case (Table 6 and Table 7). This was viewed by the EAG as an unrealistically favourable scenario.

2.5. Key issue 5: The handling of lanadelumab switch between Q2W and Q4W

The company raised two relevant issues:

- Whether the switch to Q4W is instantaneous in the model or split across cycles.
- Whether patients who switch to Q4W are assumed to achieve the same attack rate reduction as patients who remain on Q2W.

2.5.1. Instantaneous switching to Q4W

In relation to the timing of regimen switching, the EAG assumed that patients switched to Q4W at 12 months. This was discussed extensively in the EAG report and was informed by input from the EAG's clinical experts.

The EAG also noted that the economic model is a cohort model, so the percentage of patients on Q4W at any given time represents the net effect of some patients moving onto Q4W and some patients moving off Q4W dosing back to Q2W dosing.

Assuming that the switching is gradual, and starting earlier, will only benefit garadacimab if it is implemented in combination with assuming that patients on Q4W are not able to achieve the same level of response that they achieved on Q2W.

Switching at different timepoints was tested in scenario analysis by EAG and the company. This change alone had only a minor impact on the results.

2.5.2. Assumption of comparative effectiveness

The company argued against assuming that Q2W and Q4W have equal effectiveness. NHSE also commented on this in their submission to the consultation:

> *'The efficacy of lanadelumab and switching from Q2W to Q4W is likely overestimated in the original TA and the data offered from real world analysis from other regions (Germany, France, Greece and Austria) does not appear to be more valid than the real-world data from the UK which was previously independently published by Dorr et al. An assumption of lanadelumab switching in non-UK regions is biased by the entry criteria to therapy, the threshold for commissioning of medicines in other EU countries is based on the licence by the EMA and not a starting threshold of >2 attacks per week. This skews the ability to reduce to Q4W due to inheterogeneity of comparators and the assumptions in the view of this review re: earlier switching and ability to remain at Q4W do not appear to be clinically or biologically valid based on the efficacy data in real life or from the HELP studies when starting at high attack frequency. Efficacy at Q4W in those with low attack frequency is similar to Q2W but this group are excluded from treatment in the UK and therefore this is a questionable comparison.' (NHSE Consultation response)*

The Dorr study does not appear to present disaggregated data for the Q4W dose compared with the Q2W dose, so it was not clear how this could be used to make inferences about their relative effectiveness. The study reported, however, that around half of patients reduced their dose frequency below Q2W, supporting the EAG's assumption that 45% of patients switch to Q4W. Patients in this trial achieved 93.5% attack reduction at month 12. Considering that half of these patients may have been taking Q4W, this provided some support for the assumption that

Q4W is effective. This compares to a [redacted] when using the time normalised NMA at month 12.

The EAG were not aware of data from the HELP study that could be used to inform these assumptions.

Takeda (the manufacturer of lanadelumab) supported the EAG's assumption and stated that it is in line with the assumptions made in the lanadelumab appraisal.

> *'The alternative approach suggested by the EAG, which assumes patients who switch to Q4W dosing have the same efficacy as when on Q2W dosing, is reasonable and is aligned with the assumptions used in the lanadelumab NICE single technology appraisal for preventing recurrent attacks of hereditary angioedema (TA606, October 2019), which we believe are still the most reasonable and suitable for application within this appraisal (ID6394).' (Takeda consultation response)*

It was not entirely clear from reviewing TA606 whether patients who switched to Q4W accrued the absolute efficacy of Q4W or the efficacy of Q2W adjusted by the relative efficacy of Q4W, compared to its efficacy at the point of switch. The latter would be substantially more favourable to lanadelumab. The consultation response from Takeda appears to indicate that it was the latter.

The EAG did not assume that Q2W and Q4W have the same effectiveness, all else being equal. Rather, the EAG assumed that only stably attack free patients are transferred to Q4W, and that if they do not maintain attack freedom, they then switch back to Q2W. This was informed by input from the EAG's clinical experts.

The EAG report references Magerl et al. (2024),[7] a large real-world study of lanadelumab use. It found that:

> *'Most patients (75.7%) who had an interval increase did not return to the Q2W dosing regimen and attack frequency rates were reduced (rather than increased) following the switch, which the authors consider to be due to the effect of longer exposure. They cited three further small single-centre studies, which also concluded that increasing the interval between administrations does not compromise effectiveness.' (EAG Report)*

The company reported that, of the three clinicians they consulted, one had not chosen to switch any patients to Q4W. This does not present evidence as to the relative effectiveness of Q4W

and Q2W. The company further stated that a limitation of the Magerl (2024) study was that it included different countries with different patient populations, some of whom may be expected to have lower baseline attack frequency – so may be more likely to achieve attack control – compared with the UK population. Whilst this is true, the EAG was not aware of a better alternative source of evidence and the company did not provide one. The EAG also noted that the company assumed that attack frequency at baseline does not impact on the effectiveness of treatments in their submission. Further, the EAG's clinical expert suggested this study and believed it to be generalisable to the NHS. Finally, as the EAG previously stated:

> *'Furthermore, 59.6% of patients in that study used LTP before starting lanadelumab. Therefore, it can be assumed that the yearly number of attacks would be higher than 35.8 if these patients were not previously receiving LTPs. Finally, we note that the company themselves argue that a patient's prior attack frequency does not impact on the effectiveness of LTPs. This was in order to justify the use of VANGUARD trial data to assess expected effectiveness in the ≥2 attacks per week subgroup.' (FAC response)*

2.6. Key issue 6: The calculation of patient utilities

The company raised four issues related to patient utilities:

- The company sought to defend the use of tunnel states for utilities
- The company argued that use of Nordenfelt (2014)[8] is compatible with use of utility tunnel states
- The company argued that the assumed length of utility decrement associated with attacks should be increased
- The company argued that the Lo (2022)[9] study was the most appropriate source for carer utilities

Table 2 provides a summary of the approach implemented by the EAG and the company.

Table 2: Comparison of health state utility modelling approaches

Feature	EAG base case approach	Company base case approach
How were health state utilities calculated?	Nordenfelt utility regression with attack disutilities added, also using Nordenfelt. Assumed that coefficient 'attacks in past cycle' in the Nordenfelt paper meant attacks in the past year.	Nordenfelt utility regression with attack disutilities added, also using Nordenfelt. Assumed that coefficient 'attacks in past cycle' in the Nordenfelt paper meant attacks in the past month.
How does attack rate impact patient utility over the long term?	Patient utility is a function of the number of previous attacks. This means patients that are 6 months attack free, have a higher utility than patients who are 1 month attack free, because all else being equal, a patient with 6 months of attack freedom, will have a lower previous attack rate.	The company added tunnel states, in which patients gradually converge on the general population utility over 6 months if they remain attack free.
How is general population utility calculated	Used the age coefficient from Nordenfelt, applied to an intercept of 1, to estimate general population utility.	Used the standard formula from Ara and Brazier (2010)[10] to estimate general population utility.
What is the maximum utility that patients experience in the garadacimab arm?	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 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.

2.6.1. Tunnel states for utilities and combining use of Nordenfelt with tunnel states (point 1 and 2)

The company presented several analyses to justify the use of tunnel states. These are discussed in turn below.

The first piece of evidence presented was that days since last attack was a statistically significant covariate in an EQ-5D regression using the Vanguard trial data, with a p value of [redacted]. The coefficient was [redacted] per day attack free. This implied that patients with 365 days attack freedom would have a utility value [redacted] above those who had not. Such a very

large differential suggested that a linear regression may not be an appropriate approach. It was also unclear how patients currently experiencing an attack were handled within this regression. The fact the baseline was (a very low) [redacted] suggested that this was not a regression of attack free patients alone; rather, it included patients experiencing attacks. Upon request, the company provided additional information on the specification and fit of the regression. The fit statistics were reasonable, given the data, with some evidence of a ceiling effect in the residual plot. The company presented a different regression, with a dummy variable for each month of attack freedom. The sample sizes within this regression made clear that at each visit, most patients were in the six month of attack freedom state. In using a linear regression, the company assumed that relationship between length of attack freedom and patient utility was linear. The fact that the data were clustered in two categories (less than 2 months attack freedom and 5-6 months attack freedom) meant it was not possible to determine whether the underlying relationship was linear. Logically, it is unlikely that the relationship between length of time attack free and utility is linear, given that the maximum utility a patient can achieve is a value of 1.

Again, upon EAG request, the company provided an additional regression with dummy variables for each month of attack freedom. The reference was 0 to 2 months of attack freedom, with dummy variables for 4, 5 and 6 months of attack freedom (see Table 3). The vast majority of patients were in the six months of attack freedom category ([redacted]). The EAG noted that patients with four months attack freedom had a higher modelled utility than patients with five months attack freedom, which the EAG considered lacked internal consistency (coefficient of [redacted], compared to [redacted]). This probably related to the fact that the sample sizes were small for both categories ([redacted] and [redacted] respectively). Statistical significance was presented relative to the reference category of 0 to 2 months of attack freedom, but not comparing 4, 5 and 6 months of attack freedom.

The regression was therefore predominately a binary comparison between patients with 0 to 2 months attack freedom (so including patients who experienced an attack in that cycle) and patients with six months attack freedom (as discussed in the previous paragraph). Whilst the company clarified that patients were not included if they were experiencing an attack on the day of the questionnaire, there may still have been patients included who had attacks in the last 1-2 days, which could have had a residual impact on their utility.

It has already been established that patients with 0-1 months of attack freedom have a lower utility value than patients with one or more months attack freedom, and this was accounted for in the EAG base case. The company's justification for tunnel states was based on assuming that patients' utility improves gradually as they progress from 1 to 2 months' attack freedom to over 6 months attack freedom. The analysis presented provided some evidence that patients with 0 to 2 months attack freedom have lower utility than patients with 6 months attack freedom. However, this was not sufficient to support the use of tunnel states.

An analysis was presented of AE-QoL, a disease specific measure. This measure appeared to be more sensitive to days since last attack, based on the evidence submitted by the company. The fact these results did not align with the results from the analysis using EQ-5D suggested that this disease specific measure could not be used to make inferences about how EQ-5D correlates with time since last attack. The AE-QOL regression results could not be used to make inferences about the magnitude of the effect in relation to EQ-5D as these were different scales. The ANCOVA results were also confusing because 36-months of attack freedom was being used as a reference, so it appeared that the 0-1 month of attack freedom category include patients currently experiencing an attack. This meant that the fact that patients with 0-1 months of attack freedom had statistically significantly [redacted] utility, could not be used to make inferences about the utility impact of the length of time a patient had been attack free, independent of the impact of the attack itself.

The Itzler (2024)[11] study was presented, which included similar analyses to those in Point 2. The limitations were also similar, namely that it was not clear the extent to which AE-QoL could be used to make inferences about EQ-5D. It was noted that the company attempted to map AE-QoL to EQ-5D and found it was not feasible due to lack of domain correlation, as was discussed in the EAG report: *'the company found that there was limited scope to perform a mapping exercise between AE-QoL and EQ-5D due to limited domain correlation'* (EAG report).

Banerji et al. (2020)[12] was presented, which analysed the relationship between attack frequency and SF-12 questionnaire responses. The EAG believed this study was not relevant to the point the company was making because it was analysing the impact of attack rate (comparing patients experiencing 'no attacks', 'some attacks' or 'lots of attacks'), not the impact of remaining attack free for different lengths of time. Table 2 makes this misunderstanding clear, because the title says 'time since last attack', then the first column says 'number of attacks over six months'. In fact, Banerji employed a similar approach to Nordenfelt.

The company raised the point that Nordenfelt et al presented data that patients who had not experienced an attack in the last three months achieved a utility value of 0.577 (n=25), whereas patient utilities one month since attack were 0.587 (n=41). This small change in utilities refutes the claim of convergence on the general population over a 6-month period. The company stated in relation to the EAG's implementation of Nordenfelt that:

> *'To follow any other course of action is to allow hypothesis/suspicion drive deviation from established precedence, as opposed to new evidence. Until such point as this new evidence is received, there is no strong rationale to deviate from the same approaches seen in TA6063 and TA7388.'* (Company TE form)

The EAG reiterated that the NICE manual states that precedent is not sufficient justification for modelling assumptions. Also, the company, in proposing using tunnel states, was equally attempting to deviate from precedent.

Table 3: Company regression: Repeated Mixed Model Results for EQ-5D-3L (Hernandez) – cumulative attack months free as categorical without the treatment covariate

Maximum cumulative attack freedom in months (categorical)	Estimate	(p-value: Pr>|t|)
Baseline EQ-5D-3L score	[redacted]	[redacted]
Month 2 (reference month)	[redacted]	[redacted]
Month 4 (n=[redacted])	[redacted]	[redacted]
Month 5 (n=[redacted])	[redacted]	[redacted]
Month 6 (n=[redacted])	[redacted]	[redacted]

2.6.2. Implementation of Nordenfelt equation

The EAG believed there was no reason to think that the exclusion of length of time attack free, from the regressions in the Nordenfelt paper, biased the results. Therefore, the EAG suggested that introducing tunnel states would represent double counting.

In the EAG's base case model, patients in the garadacimab arm not currently experiencing an attack, achieved utility values that were the same as the general population, excluding adverse events (See Table 2). Therefore, tunnel states were only relevant if additional changes were made to the way in which utilities were calculated.

It was not clear from the Nordenfelt paper whether the attack covariate referred to annual or monthly attacks. The EAG contacted the authors to clarify this but did not receive a response. On the basis of the information available, the EAG believed that annual attacks was the most plausible interpretation of the covariate. Assuming that the covariate represented monthly attacks was tested in sensitivity analysis.

To support validation, the EAG ran a scenario analysis in which the Nordenfelt covariate was assumed to be monthly attack rate, in the ≥2 attacks per week population, with no prophylaxis included. In this scenario, the QALYs were negative in the no prophylaxis arm in the company base case. This provided further evidence that this was not a plausible interpretation of this covariate.

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 raised some issues with the implementation of Nordenfelt. The company stated that the mean value of 0.825 was *'simply the outcome when the regression is evaluated at average covariate values'*. However, the EAG noted that this was not accurate. It was, in fact, the mean observed value for the patients included in the analysis. Either way, this was consistent with the EAG's implementation of Nordenfelt's regression. Within the model, it was possible for patients to achieve utility values higher than this, before adjusting for general population quality of life. The company cited the wide spread of modelled utilities as an argument for making an adjustment using tunnel states. However, the EAG believed that this was in fact an argument for the regression being appropriate, and that providing additional adjustments was unnecessary.

The company states the following:

> *'Secondly, the number of attacks a patient experiences is included as a covariate to examine the impact of life with HAE attacks as a possibility and the associated pains and anxieties, rather than capturing the impact of attack rate reductions over time. This is evident as Nordenfelt et al. (2014) mentions a separate variable that captures the impact of*

> *time since last attack. In fact, including the variable that captures the number of HAE attacks in the preceding period would accurately distinguish quality of life for patients whose disease was well controlled or not, a factor considered important by Itzler et al. (2024)[14] '(Company TE form)*

The first half of this statement was not very clear to the EAG, as the motivation for specifying a regression is not what's important, rather, it is what it actually examines. In the second half of the statement, the company referred to a different line in the Nordenfelt paper which stated that:

> *"Days since last attack has a positive correlation with EQ5D today scores, which suggests an improvement in QoL as the time since last attack Increases" (Nordenfelt 2014)*

The EAG believed that this line was referring to a separate regression that Nordenfelt conducted, in which they ran a regression comparing days since last attack with EQ-5D scores. The outputs from this regression were not included in the paper. The fact that the company did not include days since last attack as a separate covariate in their regression suggested they also believed this. As is explained above, the statement within the paper was consistent with the EAG's approach, as days since last attack would be correlated with attacks in the last year.

Whilst the EAG believed the Banerji paper was not relevant to considering the impact of the length of time a patient has been attack free, it could be used as an alternative source to Nordenfelt to model quality of life. The paper presents the relationship between attack rate and SF-12, which the company had mapped onto EQ-5D using mapping algorithms from four different papers, which presented mappings using aggregate mental and physical component scores rather than requiring individual level data. These papers are summarised in Table 4. They have several limitations, which are summarised in Le 2013.[13] All studies were in a US population and two studies used a US tariff. Le 2013 states that: *"prediction is less precise in poor health states and when the EQ-5D utility score is below 0.50"*. Also, changes occurring in certain health dimensions from the SF-12 (particularly energy) may not be captured and predicted EQ-5D values might fall outside the valid or possible range of the EQ-5D utility scale.

There was a reasonable spread in the utilities the company estimated using the mapping algorithms, with patients experiencing 13 or more attacks, accruing modelled health state utilities of 0.638 to 0.790 dependent on the algorithm used (Table 5). All four sets of utility estimates were tested as part of EAG scenario analysis. All four scenarios yielded results that were substantially more favourable for garadacimab. This was due to the paper yielding very

low utility estimates for patients with ≥2 attacks per month (0.638 to 0.79). This seemed low, considering that this is the less severe population, and would likely yield unrealistically low utility values if applied to the population with ≥2 attacks per week.

Table 4: Summary of mapping studies presented by the company

	Lawrence 2004[14] 3 variable model	**Franks 2004[15] SF12 items only**	**Sullivan 2006[16] SF12 items only**	**Le 2014[13] CLAD US D1 model**
Sample size	14,580	12,998*	37,933	19,678
Population	US general population (MEPS 2000)	US general population (MEPS 2000)	US general population (MEPS 2000 - 2002)	US general population (MEPS 2003)
Health state distribution	Mean 0.818 SD 0.225, majority of observations >0.5	Mean 0.83, noted that included sample had higher EQ-5D than other eligible respondents	Mean 0.868	Mean 0.863, range (-0.109, 1)
Type of model	Linear regression	Linear regression	CLAD minimized prediction error	CLAD
Tariff	UK	UK	US	US
Goodness of fit	R^2 0.616 Mean within 0.035 of actual for conditions tested Good fit to validation sample	R^2 0.626 MAE increases the lower the EQ-5D score (from 0.07 in range 0.9 – 1.0 to 0.381 for scores <0.1)	R^2 0.405 MAE 0.0744 CLAD model does not predict utilities lower than 0.42	R^2 0.645 MAE 0.073 MAE in range decreases as EQ-5D reduces from 0.034 in band 0.9-1 to 0.416 in band <0

Abbreviations: CLAD, Censored Least Absolute Deviations; MAE, mean absolute error; MEPs, Medical Expenditure Panel Survey.

Notes:* Franks 2004 uses complete responses to both questionnaires, Lawrence 2004 imputes; additionally Lawrence 2004 fits to half the sample and validates with the other half whereas Franks 2004 fits to the entire sample

Table 5: EQ-5D estimates mapped using Banerji et al. 2020

Number of attacks (over six months)	EQ-5D – Lawerence and Fleishman (2004),[14] 3-variable model	EQ-5D – Franks et al. (2004),[15] SF-12 items only	EQ-5D – Sullivan and Ghuschchyan (2006),[17] SF-12 items only	EQ-5D – Le (2013),[13] CLAD US D1 model
0	0.890	0.900	0.937	0.962
1-3	0.834	0.850	0.899	0.926
4-6	0.768	0.788	0.856	0.882
7-12	0.735	0.756	0.835	0.860
≥13	0.638	0.659	0.776	0.790

Abbreviations: CLAD, censored least absolute deviations; US, United States.

The EAG believed that implementing Nordenfelt alone was the most appropriate approach (Table 2). The EAG was sceptical that patients could achieve higher utilities than those implied by the regression conducted by Nordenfelt et al. (2014),[8] as it was aware that the utilities calculated from the Nordenfelt et al. equation already accounted for improvements in quality of life (QoL) that occurred as the number of attacks reduces over time. Patients who achieved 6-12 months attack freedom in the EAG model accrued a utility value close to the general population (Table 2) and the company's clinicians and EAG's clinicians did not support attack free patients fully converging on general population utility.

2.6.3. Length of utility decrement associated with attacks

The company argued that recovering from attacks has important impacts on quality of life. This is equivalent to arguing that the length of the impact of attacks on quality of life is longer. The EAG used attack length from the trial in the base case ([redacted]). It tested 2.1 days and 3.4 days in scenario analysis, which was based on attack duration in the two arms of the CHANGE trial. This had a substantial impact on the results within this population.

The company pointed to the fact that Nordenfelt et al demonstrated a substantial drop in utility among patients who have had an attack in the last week. They suggested this is evidence that the utility decrement associated with an attack lasts for a week. The EAG argued that this was not the case, as some of these patients may have had an attack in the last one or two days.

Also, the Nordenfelt paper implemented a decrement based on the number of attacks experienced in the last year. This should therefore capture all short-term effects of recovering from an attack.

The company argued in favour of using the Lumry 2010 paper, which included a survey of the average number of days of work or leisure missed per attack. The paper reported that people with the condition missed an average of 3.13 days. Whilst the EAG does not believe that this paper presents sufficient evidence to deviate from using attack rates from the company's trial data, it does have merit and is accounted for by testing longer attack lengths in sensitivity analysis.

2.6.4. Use of Lo (2022) to inform carer disutilites

The company argued that the EAG should have used the Lo (2022)[9] paper, instead of the Pennington (2025)[18] paper, to inform caregiver disutilites. The company conducted a critical appraisal of the Lo (2022) paper, which the EAG welcomed.

The company claimed that the Pennington paper says it should not be used for acute conditions. The paper actually says the reverse. It says that it uses a fixed effects regression approach. An alternative approach would be to use difference in difference, which may be more robust in some contexts, but could not be used in relation to acute/intermittent conditions.

The company reported the fact that TSD 9[19] cites examples of appraisals that used disease specific measures of carer burden. The EAG believed they may be referring to a DSU report with a systematic literature review of carer disutility modelling in appraisals, published in 2020.[20] The EAG would like to clarify that this report, and hence all appraisals it references, was published before the Pennington (2025) paper.

The company stated that because the carer burden in the model only applies during an attack, it is low compared to estimates used in appraisals referenced in TSD 9 (likely the report mentioned above). However, the EAG argued that the company is not comparing like with like, as these are appraisals for chronic conditions in which carers are constantly burdened. As the company states, this condition is acute, so it is not expected that carers will be substantially burdened due specifically to HAE, when attacks are not taking place.

A DSU report[21] on the use of vignettes says that vignettes should only be used when preference-based measures are deemed inappropriate, in which case this needs to be justified.

The report provides extensive discussion on the limitations of vignettes and examples of where EAG's have identified face validity issues within health state utility values calculated using vignettes. Of relevance here are issues related to the small sample sizes used in these studies and uncertainty as to how representative they are. The Lo (2022) study included five carers without HAE and six carers who have HAE. It is uncertain how representative they are of the carer population as a whole.

The EAG therefore maintained its position on caregiver utilities and noted that this makes a very minor difference to cost-effectiveness results.

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

The company accepted a number of the EAG's assumptions and provided an updated base case with a new PAS. The PAS for garadacimab has gone from [redacted] to [redacted] The tables below compare the new company base case, with the original EAG base case (with the old and new PAS). Results for all other comparators are presented using their list price. There are also a number of relevant scenarios 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.

No prophylaxis has been included as a comparator in the company base case and EAG base case, as additional to enable triangulation.

3.1. ≥2 attacks per month

Table 6: Exploratory analyses undertaken by the ERG

Preferred assumption	Comparator	Costs	QALYs	Incremental costs	Incremental QALYs	Cost per QALY gained
New company base case (new PAS)	No Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (old PAS)	No Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (new PAS)	No Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG probabilistic base case (new PAS)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nordenfelt scenario (annual to monthly)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attack length (3.4 days)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	Incremental costs	Incremental QALYs	Cost per QALY gained
Berotralstat maintenance based on Elbashir (new implementation)	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company implementation of Elbashir	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT berotralstat data (no stopping rule adjustment)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Lawrence (2004)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Franks (2004)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Sullivan (2006)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Lawrence (2013)	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lo paper carer utilities	Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ITT, intention-to-treat; QALY, quality-adjusted life year.

3.2. ≥2 attacks per week

Table 7: Exploratory analyses undertaken by the ERG

Preferred assumption	Comparator	Costs	QALYs	Cost per QALY gained
New company base case (new PAS)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	Cost per QALY gained
EAG base case (old PAS)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (new PAS)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Nordenfelt scenario (annual to monthly)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Attack length (3.4 days)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Lawrence (2004)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Franks (2004)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Sullivan (2006)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Utility from Banerji (2020), mapped using Lawrence (2013)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Lo paper carer utilities	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Costs	QALYs	Cost per QALY gained
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ITT, intention-to-treat; QALY, quality-adjusted life year.

4. EAG RESPONSE TO ISSUES RAISED BY STAKEHOLDERS.

No separate issues were raised by stakeholders that require a response. Some issues were raised by stakeholders that were relevant to the key issues in Section 2 and these have been responded to in Section 2.

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