Medicinrådet

Bilag til direkte indplacering af garadacimab i Medicinrådets evidens-gennemgang vedrørende lægemidler til arveligt angioødem

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. garadacimab
2. Forhandlingsnotat fra Amgros vedr. garadacimab
3. Ansøgers endelige ansøgning vedr. garadacimab

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CSL Behring

CSL comments on the Summary and addendum (garadacimab) to the Danish Medicines Council's evidence review for the treatment guideline on severe hereditary angioedema

Comments on the conclusion regarding Andembry's relative efficacy compared to the relevant comparator.

CSL notices that DMC have confined the evidence base in the assessment of the relative efficacy and safety of garadacimab vs lanadelumab to the VANGUARD and HELP trials, omitting to include a phase II trial (NCT03712228) for garadacimab.

CSL deems it critical to consider enriching the evidence base with this phase II trial, namely for the following reasons:

- After a careful assessment of potential sources of bias due to between-study heterogeneity, *Walsh et al. 2025* concluded that, on balance, the eligibility criteria among the three trials – covering aspects such as trial design characteristics, eligibility criteria, baseline patient characteristics and outcome assessments – were similar enough to allow for a robust and reliable indirect treatment comparison. As a result, the pooled phase II/VANGUARD trials, alongside HELP, formed the evidentiary basis in their primary analysis.
- As HAE is a rare disease, every patient meeting the eligibility criteria for the indirect treatment comparison should be included in the analysis. The 16 phase II trial participants account for 20% of all garadacimab patients, improving the chance of observing an effect.
- Differences in study treatment periods (12 vs 26 weeks) were adjusted for in the rate and binary outcomes as described in *Walsh et al. 2025*.

The trials analyzed were designed to compare active treatments against placebo, which introduces methodological challenges when comparing active treatments indirectly. Because of smaller effective sample sizes and smaller relative effects, statistically significant differences between interventions are less likely to be detected. Thus, it is not surprising that some comparisons do not achieve statistical significance at a strict level.

The data consistently shows that garadacimab demonstrates superior clinical efficacy compared to lanadelumab Q2W, with effect sizes increasing as more data (i.e the Phase II trial) is added. Importantly, all primary analyses by *Walsh et al 2025*. comparing garadacimab to lanadelumab Q4W reached statistical significance, consistently favoring garadacimab. Taken together, these results provide strong evidence for garadacimab's overall therapeutic advantage over both lanadelumab Q2W and Q4W and underscore the importance of including Phase II data in the total evidence base.

The addendum refers to the Angioedema Quality of Life Questionnaire (AE-QoL) as of moderate quality. CSL would like to emphasize that AE-QoL is a validated, disease-specific tool to assess health-related quality of life (HRQoL) (*Weller et al. 2016*).

Importantly, it is tailored to the distinct and multifaceted burden of HAE. Unlike generic QoL instruments, AE-QoL effectively captures the psychosocial and functional impairments that are characteristic of HAE. Additionally, its relevance and utility have been further used as a critical outcome measure in recent phase III clinical trials. According the *Baroni et al. 2025*, no other QoL tool received a higher rating than the AEQoL, indicating that it is the best option for measuring HRQoL in HAE patients.

Comments on the calculation of treatment costs for long-term prophylactic therapies (LTPs)

Table 2. *Basis for clinical comparison…* in the updated summary of evidence, inaccurately describes the estimated drug utilization of different LTPs:

- Andembry is administered once monthly, not every four weeks as stated by the DMC.
- The drug utilization of Takhzyro is underestimated, as the current model does not account for the fact that all patients initiate treatment with biweekly dosing.

According to DMC (page 8, Summary of evidence), dose adjustment of Takhzyro occur over 9-12 months in Danish clinical practice. By extending the time horizon to 12 months, which aligns Andembry's dosing with the approved SmPC, allows for the gradual transition from Takhzyro Q2W to Q4W, and better reflects the typical duration of a national tender period in Denmark and the economic impact of switching in between therapies, CSL has modeled the following revised estimates for drug utilization:

Basis for clinical comparison for medicinal products used in the prophylactic treatment of hereditary angioedema (≥12 years) over a 12-month period

Medicinal Product	Comparison Dose	Quantity
s.c. C1-inhibitor (berinert 2000 IE og 3000 IE)[1]	60 IE/kg body weight, twice weekly	218,4 packs of 2000 IE or 145,6 packs of 3000 IE[2]
s.c. lanadelumab	100% Q2W as starting dose until month 3, then gradually switching[3] to Q4W until reaching 50%/50% Q2W/Q4W at month 12	23.4 doses (7,020 mg)
s.c. garadacimab	Initial loading dose of 400 mg, followed by followed by a monthly dose of 200 mg.	13 doses (2,600 mg)

[1] Only these presentations/strengths are approved for routine prophylactic treatment.
[2] Calculated based on an average body weight of 70 kg.
[3] A linear switch from Q2W to Q4W over a 9-month period was modeled in accordance with the DMC description of dose adjustment in Danish clinical practice.

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03.10.2025

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.10.2025
Leverandør	CSL Bering
Lægemiddel	Andembry (garadacimab)
Ansøgt indikation	Garadacimab er indiceret til rutinemæssig forebyggelse af tilbagevendende anfald af hereditært angioødem (HAE) hos voksne og unge patienter i alderen 12 år og derover.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (direkte indplacering)

Prisinformation

Amgros har forhandlet følgende pris på Andembry (garadacimab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Andembry	200 mg x 1 stk.	179.182,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Andembry, indkøbes lægemidlet til AIP.

Aftaleforhold

[redacted]

Konkurrencesituationen

Medicinrådet har en gældende behandlingsvejledning vedr. lægemidler til arveligt angioødem, hvor lægemidlerne Takhzyro (lanadelumab) og Berinert (C1-esteraseinhibitor) er klinisk ligeværdige som 1. valg til forebyggende behandling af patienter med arveligt angioødem. Medicinrådet vurderer, om Andembry kan ligestilles med Takhzyro og Berinert som 1. valg til disse patienter. Dawnzera (donidalorsen) er også under vurdering til arveligt angioødem i Medicinrådet.

Tabel 2 viser lægemiddeludgifter til Andembry i relation til Takhzyro og Berinert baseret på Medicinrådets kliniske sammenligningsgrundlag. I det kliniske sammenligningsgrundlag benyttes en sammenligningsperiode på 8 uger, der betragtes som et udsnit af et livslangt behandlingsforløb.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for 8 ugers behandling

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Mængde	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 8 ugers behandling (SAIP, DKK)
Andembry	200 mg x 1 sprøjte	200 mg (s.c.) 1 gang månedligt	1,84 stk. 200 mg sprøjter *I alt 368 mg*	[redacted]	[redacted]
Takhzyro	300 mg x 1 sprøjte	50%: 300 mg (s.c.) hver 2. uge 50%: 300 mg (s.c.) hver 4. uge	3 stk. 300 mg sprøjter *I alt 900 mg*	[redacted]	[redacted]
Berinert	2000 IE x 1 sprøjte	60 IE/kg legemsvægt (s.c.), 2 gange ugentligt	33,6 pakker á 2000 IE eller 22,4 pakker á 3000 IE *I alt 67.200 IE**	[redacted]	[redacted]

*Beregnet for en gennemsnitsvægt på 70 kg, jf. opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til arveligt angioødem

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
England	Under vurdering	Link til status
Sverige	Under vurdering	Link ikke tilgængeligt

Opsummering

[redacted]

Application for the assessment of ANDEMBRY® (garadacimab) for routine prevention of recurrent attacks of hereditary angioedema (HAE)

29 August 2025

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

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Abbreviations

AAS	Angioedema activity score	**LS**	Least squares
ACE	Angiotensin-converting enzyme	**LTP**	Long-term prophylaxis
AE	Adverse event	**MAIC**	Matching-adjusted indirect comparison
AECT	Angioedema Control Test	**MCID**	Minimal clinically important difference
AESI	Adverse event of special interest	**MD**	Mean difference
AE-QoL	Angioedema Quality of Life questionnaire	**MedDRA**	Medical Dictionary for Regulatory Activities
ALT	Alanine transaminase	**N**	Number of scores or individuals
AST	Aspartate aminotransferase	**n**	Number of observations
BK	Bradykinin	**NA**	Not applicable
BMI	Body mass index	**NCT**	National clinical trial
C1-INH	C1 esterase inhibitor	**NICE**	National Institute for Health and Care Excellence
CADTH	Canadian Agency for Drugs and Technologies in Health	**NR**	Not reported
CI	Confidence interval	**OLE**	Open-label extension

CSL312	Garadacimab	**PBO**	Placebo
CTCAE	Common Terminology Criteria for Adverse Events	**PD**	Pharmacodynamic
CSR	Clinical study protocol	**pdC1-INH**	Plasma-derived C1 esterase inhibitor
DKK	Danish krona	**PICO**	Population, Intervention, Comparator, Outcome
DMC	Danish Medicines Council	**PK**	Pharmacokinetic/plasma kallikrein
DRG	Diagnosis-related group	**PLG**	Plasminogen gene
eCOA	electronic Clinical Outcome Assessment	**PO**	Oral(ly)
EAACI	European Academy of Allergy and Clinical Immunology	**PRO**	Patient-reported outcome
eCRF	Electronic case report form	**Q2W**	Every two weeks
EMA	European Medicines Agency	**Q4W**	Every four weeks
EQ-5D-5L/3L	EuroQoL Five-Dimension-Five-Level/Three-Level questionnaire	**Q1M/QM**	Once a month
ESS	Effective sample size	**QALY**	Quality-adjusted life year
FXIIa	Activated Factor XII	**QoL**	Quality of life
Gara	Garadacimab	**RCT**	Randomized controlled trial
GMS	General medical services	**RR**	Rate ratio
HAE	Hereditary angioedema	**RWE**	Real-world evidence
HAE-AS	Hereditary angioedema activity score	**SAE**	Serious adverse event
HAE-BOIS	Hereditary Angioedema Burden of Illness Study	**SC**	Subcutaneous
HAE-nC1-INH	HAE with normal C1-INH	**SD**	Standard deviation
HAE-QoL	Hereditary angioedema quality of life questionnaire	**SE**	Standard error

HILA	The Finnish pharmaceuticals pricing board	**SGART**	Subject's Global Assessment of Response to Therapy
HK/HMWK	High molecular weight kininogen	**SLD**	Summary-level data
HR	Hazard ratio	**SLR**	Systematic literature review
HRQoL	Health-related quality of life	**SMD**	Standardized mean difference
HS	Health state	**SOC**	Standard of care
HSUV	Health state utility value	**t-Pa**	Tissue plasminogen activator
HTA	Health technology assessment	**TEAE**	Treatment-emergent adverse event
ICER	Incremental cost effectiveness ratio	**TP2**	Treatment period 2
IGART	Investigator's Global Assessment of Response to Therapy	**UK**	United Kingdom
IPD	Individual patient data	**ULN**	Upper limit of normal
IQR	Interquartile range	**US**	United States
IRT	Interactive response technology	**VAS**	Visual analogue score
ISR	Injection site reaction	**WAO**	World Allergy Organization
ITT	Intention-to-treat	**WPAI:GH**	Work Productivity and Activity Impairment: General Health questionnaire
IU	International unit		
IV	Intravenous		
LANA	Lanadelumab		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	ANDEMBRY®

Overview of the medicine	
Generic name	Garadacimab
Therapeutic indication as defined by the European Medicines Agency (EMA)	Garadacimab is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Marketing authorization holder in Denmark	CSL Behring GmbH
ATC code	B06AC07
Combination therapy and/or co-medication	No
Date of EC approval	10 February 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	No Nordic countries essentially follow the same international treatment guidelines, but available treatments vary due to different reimbursement landscapes. Hence, the use of different treatments in clinical practice varies significantly between Nordic markets. In addition, as HILA in Finland is not part of the JNHB collaboration garadacimab would not be assessed in Finland and therefore not a suitable candidate for the JNHB process.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	1 pre-filled pen / 3 pre-filled pen

Abbreviations: BEGR = Medicines only to be distributed to hospitals; HILA = The Finnish pharmaceuticals pricing board; JNHB = Joint Nordic HTA bodies

2. Summary table

Summary	
Indication relevant for the assessment	For routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Dosage regiment and administration	Once monthly, subcutaneous (SC) injections.
Choice of comparator	Takhzyro (lanadelumab), 300 mg every 2-4 weeks.
Prognosis with current treatment (comparator)	The current treatment guideline concludes, based on pivotal studies and a COCHRANE review, that first line treatments (lanadelumab and Berinert SC) reduce the number of attacks, improves quality of life (QoL) and that approx. 40% of treated patients achieve an attack-free life with lanadelumab.
Type of evidence for the clinical evaluation	Matching-adjusted indirect comparison (MAIC).
Most important efficacy endpoints (Difference/gain compared to comparator)	**Critical endpoints** • **Percentage of patients experiencing a 100% reduction in attack frequency (freedom from symptoms) from baseline** Garadacimab: 61.5% (45.9% to 75.1%). Lanadelumab (Q2W): 0% (0.1% to 13.8%). Unadjusted comparison of proportion of attack-free patients (GARA 200 QM versus LANA 300 Q2W) (HR: 1.93 [95% CI: 1.00, 3.93; P = 0.051]) in favor of GARA 20 QM (not statistically significant). In the primary MAIC scenario, the result was favorable for GARA 200 QM (HR: 1.93 [95% CI: 0.92, 4.03; P = 0.080]) (not statistically significant). • **Proportion of Patients with ≥90% Attack Rate Reduction** Garadacimab: 74% (28.9% to 85.4%). Lanadelumab: 66.7% (NR). Unadjusted comparison of proportion of patients with ≥90% attack rate reduction (GARA 200 QM versus LANA 300 Q2W), the result was favorable for GARA 200 QM HR: 1.51 (95% CI: 0.83, 2.77; P = 0.181) (not statistically significant). In the primary MAIC scenario, the result was favorable for GARA 200 QM (HR: 1.50 [95% CI: 0.77, 2.90; P = 0.230]) (not statistically significant). • **Mean change in total score from baseline to minimum week 12 measured with Angioedema Quality of life Questionnaire (AE-QoL)** Garadacimab: -26.47 (-32.8 to -20.1). Lanadelumab: –21.29 (−28.21 to −14.37). Unadjusted comparison of mean change in total score from baseline to minimum week 12 measured with Angioedema Quality of life Questionnaire (AE-QoL) (GARA 200 QM versus LANA 300 Q2W) (MD: 7.69 [95% CI: -23.41 to 8.02]),

Summary	
	in favor of GARA 20 QM (not statistically significant). In the primary MAIC scenario, the result was favorable for GARA 200 QM (MD: -17.38 [95% CI: -33.67, -1.08; P = 0.037]) (statistically significant).
Most important serious adverse events for the intervention and comparator	**Garadacimab**: Laryngeal attack: 1 (3%) (not related to study drug). **Lanadelumab**: Catheter site infection: 1 (1.2%) (not related to study drug). Pyelonephritis: 1 (1.2%) (not related to study drug). Meniscus injury: 1 (1.2%) (not related to study drug). Bipolar II disorder: 1 (1.2%) (not related to study drug).
Impact on health-related quality of life (HRQoL)	Clinical documentation: MAIC results of garadacimab vs. lanadelumab indicate a statistically significant improvement in AE-QoL change from baseline to day 182: -17.38 (95% CI: -33.67, -1.08).
Type of economic analysis that is submitted	NA
Data sources used to model the clinical effects	NA
Data sources used to model the HRQoL	NA
Life years gained	**NA**
QALYs gained	NA
Incremental costs	NA
ICER (DKK/QALY)	NA
Uncertainty associated with the ICER estimate	NA
Number of eligible patients in Denmark	NA
Budget impact (in year 5)	NA

Abbreviations: AE = Adverse event; DKK = Danish krona; DMC = the Danish medicines council; AE-QoL = Angioedema Quality of Life questionnaire; EQ-5D-5L/3L = EuroQol-5 Dimensions-5 level/3 level; GARA = Garadacimab; HAE = Hereditary angioedema; HTA = Health technology assessment; HSUV = Health state utility value; ICER = Incremental cost effectiveness ratio; IPD = Individual patient data; LTP = Long-term prophylaxis; MAIC = Matching-adjusted indirect comparison; NA = not applicable; Q2W = Every two weeks; QM = Once a month; QALY = Quality-adjusted life year; QoL = Quality of Life; RR =Risk ratio; SC = Subcutaneous; SLD = Summary-level data; SMD = Standardized mean difference

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

The normal biological role of C1 esterase inhibitor (C1-INH) in the immune response is to regulate activation of blood-based systems involved in inflammation and coagulation (Zuraw and Christiansen 2011). The bradykinin (BK)-forming cascade, also called the plasma contact system, plays a crucial role in vasodilation, blood coagulation, and fibrinolysis (Busse and Kaplan 2022). The plasma contact system is initiated when factor XII (FXII) is activated to factor XIIa (FXIIa) via autoactivation, which may be idiopathic or triggered by trauma, microbial infections, or oestrogen-containing medications (Busse and Kaplan 2022, Lopez Lera 2021). FXIIa converts prekallikrein to plasma kallikrein, which then cleaves high molecular weight kininogen (HK) into BK (Busse and Kaplan 2022). BK binds to the B2 receptor on endothelial cells, resulting in smooth muscle cell relaxation, vasodilation, and increased vascular permeability (Lopez Lera 2021). At normal functional physiologic levels, C1-INH inhibits plasma kallikrein and FXIIa, thus regulating BK production (Sinnathamby et al. 2023). In patients with HAE, the C1-INH protein is deficient or defective, which ultimately leads to the uncontrolled activation of the contact system and continuous production of kallikrein, which can lead to vascular leakage and oedema in the submucosal space (i.e., an HAE attack) (Figure 1) (Lopez Lera 2021, Sinnathamby et al. 2023).

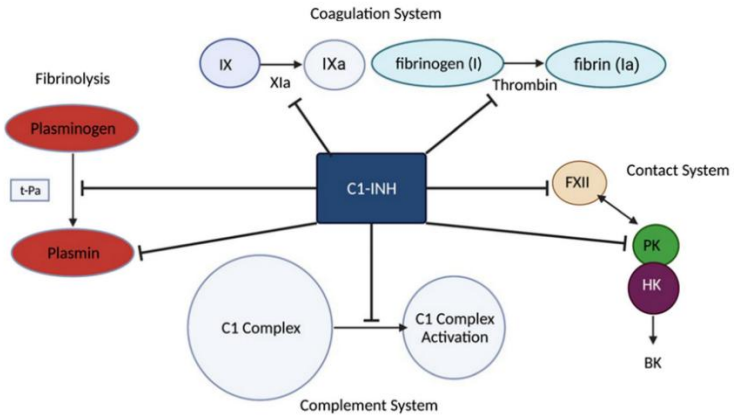


Figure 1 Pathophysiology of HAE

Abbreviations: t-Pa = Tissue plasminogen activator; C1-INH = C1 esterase inhibitor; PK = Plasma kallikrein; HK = High molecular weight kininogen; BK = Bradykinin
Source: (Sinnathamby et al. 2023)

Symptoms of the condition

HAE is characterized by recurrent swelling of the skin (e.g., extremities, face, and genitals) and gastrointestinal attacks (e.g., painful abdominal cramps) and/or laryngeal oedema. Episodes of HAE are unpredictable, painful, and, if not treated, potentially life-threatening, which causes stress for both patients and caregivers (Maurer et al. 2022).

A noninterventional, cross-sectional, global, web-based survey described real-world attack characteristics and burden of illness from the perspective of patients with self-reported HAE type I/type II (N=242). HAE attacks most frequently affected the trunk (75.6%), extremities (43.0%), face (12.4%), and throat/mouth (10.3%); half of the respondents indicated that >1 location was affected in their most recent attack. HAE attacks were frequently accompanied by additional symptoms, which varied in severity (when thinking of their most recent HAE attack at its worst) (Mendivil et al. 2021).

Symptoms are generally specific to the site of the attack (Longhurst and Cicardi 2012, Lumry 2013). HAE attacks are often preceded by prodromal symptoms, such as erythema marginatum, tingling, fatigue, or local discomfort (Busse and Christiansen 2020).

Patient prognosis

Some of the greatest challenges in HAE are its variability and unpredictability, both between patients and within an individual patient over time. Neither previous history nor family history of attacks, nor C1-INH levels can predict the site or nature of the next attack (Busse et al. 2021, Zuraw et al. 2013). It is not possible to predict when and which patients will have a laryngeal attack, the most severe presentation. Laryngeal oedema, which accounts for approximately 0.9% of all attacks, is a potentially life-threatening clinical manifestation of HAE that occurs in >50% of HAE patients at some point in their lives (Busse and Christiansen 2020); laryngeal swelling can cause upper airway obstruction, which can rapidly progress to asphyxiation (Maurer et al. 2022). However, the reported percentage of patients experiencing laryngeal oedema may have been impacted by the introduction and adoption of long-term prophylaxis (LTP).

The frequency of HAE attacks is highly variable among patients and over time. Studies have shown that on average, untreated patients experience an attack every 2 weeks (i.e., 26 attacks per year), with frequencies ranging from very rare to every 3 days. Length of attack is also variable, especially among untreated patients, where HAE attacks can gradually worsen over the first 12 to 36 hours and subside over 2 to 5 days. Individual attack severity is difficult to clinically quantify, as attacks are episodic, can be highly variable, and can occur simultaneously across multiple anatomical sites; attack severity is comprised of the location of the attack, need for rescue medication, need for retreatment, and patient perception of the attack's disruption on daily living. Attack frequency and severity should be evaluated within the context of the patient's QoL and ability to conduct activities of daily living (Bork et al. 2021).

Quality of Life (QoL) and impact on daily life

HAE attacks themselves have a substantial impact on patient functioning and QoL. During an HAE attack, patients are impacted by the location of the attack, symptom

severity and duration, need for hospitalisation, and disruption of life. As HAE is a chronic condition, however, QoL is not only impacted during, but between attacks as well (Bork et al. 2021). The burden of HAE continues to be substantial between attacks, as patients experience persistent fear, anxiety, and depression, while also restricting their lifestyles to avoid potential triggers. The unpredictable nature of HAE attacks leads to the reduced ability to perform activities of daily living, such as driving, exercising, working, or socialising.

A global survey of 242 patients with HAE (62.4% on LTP) found that the unpredictability and frequency of HAE attacks negatively impacted QoL. Patients reported “much” or “very much” impairment in QoL due to angioedema (26.9%) and were “much” or “very much” bothered by the unpredictability of their angioedema (44.3%) over the past 3 months (Mendivil et al. 2021).

A targeted literature review (n=22 studies; 2009−2019) found that symptoms related to HAE were reported to occur before, during, after, and between attacks, thereby disrupting QoL on a continuous basis. Emotional symptoms, such as sadness, depression, worry, fear, and anxiety were reported throughout the patient experience; feelings of anxiety were experienced in between attacks (focus on when another attack would begin) and during attacks (focus on severity of swelling) (Jean-Baptiste et al. 2022).

Data from Hereditary Angioedema Burden of Illness Study (HAE-BOIS) showed that HAE limited patients’ ability to perform daily activities, both during and between attacks. The impact of HAE on the ability to perform daily activities increased with attack pain severity. Items of anxiety included passing HAE to their children, future attacks, traveling, having sudden feelings of panic, and being distressed about HAE attacks; anxiety levels generally increased with attack pain severity ($p<0.05$ for each item) (Caballero et al. 2014).

In a burden of disease study conducted in Sweden, 64 patients with HAE completed various QoL questionnaires. On the RAND-36 (range: 1 to 100, where 100 is most favourable), women with HAE reported significantly lower QoL than men in both general health (50 vs 75; $p<0.05$) and energy/fatigue (50 vs 70; $p<0.05$) dimensions. Additionally, patients with sick leave reported having more impaired QoL, as reported on the EuroQol-5 Dimensions-5 level (EQ-5D-5L) and Angioedema Quality of Life questionnaire (AE-QoL), compared to patients with HAE who took no sick leave (EQ-5D-5L: 0.71 vs 0.88; AE-QoL: 53.7 vs 25.7, respectively). Patients who reported any Angioedema Activity Score had significantly more impaired QoL on all dimensions (Nordenfelt et al. 2017).

A global online survey of 159 patients with HAE type I/II found a positive relationship between attack-free duration and overall QoL. Among those who were attack-free, AE-QoL scores continued to improve as patients remained attack-free for longer. The mean total AE-QoL score (where higher scores are indicative of greater negative impact on QoL) was 51.8 among patients who were attack-free for <1 month, compared to 33.2 and 19.9 among patients who were attack-free for 1 to <6 months and ≥6 months, respectively. A similar pattern was observed for individual AE-QoL domains (Itzler et al. 2024a, Itzler et al. 2024b).

3.2 Patient population

Bygum *et al.* employed a nationwide survey in Denmark to identify all patients with HAE with C1-INH deficiency (Bygum 2009). The survey was initiated in 2001–2002 and repeated in 2007–2008. In the study, patients were recruited from all departments of dermatology, pulmonary medicine and allergy, ears, nose and throat, paediatrics and the two national centres for rare diseases. The number of patients registered by January 2009 was 76 which corresponds to 1.41 per 100,000 individuals.

In a later study by the same authors, a survey of patients with HAE type I or II between November 2001 and December 2012 was used. Bygum (2014) estimates the prevalence of HAE in Denmark at 95 individuals (1.70 per 100,000 individuals) (Bygum 2014). The study also showed that attack frequency varied from 1 – 84 attacks per year, and there were also patients who were asymptomatic. The average attack frequency was 17 per year (Bygum 2014).

In the protocol for the treatment guidelines on medicinal products for routine preventive treatment of HAE attacks, the Danish Medicines Council (DMC) concludes that 107 Danish patients with HAE types I and II were currently registered and regularly monitored at the National Competence Center for HAE at Odense University Hospital (Table 1) (The Danish Medicines Council 2024, Bygum 2014).

Table 1 Incidence and prevalence in the past 5 years (Denmark)

Year	2020	2021	2022	2023	2024
Incidence in Denmark	1	1	1	1	1
Prevalence in Denmark	104	105	106	107	108
Global prevalence	1.7 per 100,000 individuals				

Sources: (Statistics Denmark 2024, The Danish Medicines Council 2024)

In the DMC treatment guideline for preventive treatment of HAE from 2024, it is assumed that around 45 patients receive prophylactic treatment for HAE in Denmark, and there will be approximately one new patient per year (incidence) who will be a candidate for LTP (The Danish Medicines Council 2024) The current treatment guidelines stipulate that at least 80% of patients are eligible for first-line options. Hence, it is estimated that 37-45 individuals will be eligible for treatment with garadacimab in 2025 and one additional patient each year (Table 2).

Table 2 Estimated number of patients eligible for treatment

Year	2025	2026	2027	2028	2029
Number of patients in Denmark who are eligible for treatment in the coming years	37	38	39	40	41

3.3 Current treatment options

3.3.1 On-demand therapies for treatment of HAE attacks

HAE attacks of the upper airways can result in asphyxiation. Abdominal attacks are painful and debilitating. Peripheral attacks such as those of hands or feet result in impaired function. All these consequences of HAE attacks can be minimized by on-demand treatment and on-demand treatment should, therefore, be considered to be used to treat all attacks (Maurer et al. 2022). Current on-demand therapies utilize the following mechanisms to treat HAE attacks as early as possible:

- Increasing C1-INH plasma levels – HAE attacks have traditionally been treated with intravenous (IV) infusion of replacement plasma-derived C1-INH (pdC1-INH) isolated from pooled human plasma. C1-INH products are a natural replacement therapy, as opposed to other drug treatments, which utilize various other mechanisms to decrease attack frequency and severity. Ruconest, which has an identical mechanism of action to pdC1-INH, is the only authorised recombinant human C1-INH (Maurer et al. 2022). Current available C1-INH treatments in Danish clinical practice are Berinert IV and Cinryze.
- Blockade of BK signalling – BK inhibition blocks the binding of this molecule to the BL B2 receptor, thereby interrupting and inhibiting oedema formation. Icatibant (Firazyr) was the first BK receptor antagonist to be approved for treatment for HAE (Maurer et al. 2022).

HAE is unpredictable, and any attack may be followed by another one in short succession. It is essential that patients have on-demand medication to treat all attacks. It is therefore recommended that all patients have and carry on-demand medication for the treatment of at least two attacks (Maurer et al. 2022).

3.3.2 Long-term prophylactic treatment for HAE control

In the International WAO/EAACI guideline for the management of HAE, it is stated that the goals of HAE treatment are to achieve complete control of the disease and normalise patients' lives. It is also stated that this currently only can be achieved by long-term prophylactic treatment. Moreover, it is suggested that patients on LTP should be routinely monitored using appropriate tools to assess the effectiveness of treatments (Maurer et al. 2022).

The goals for long-term prophylactic treatment of HAE according to the WAO/EAACI guideline are the following (Maurer et al. 2022):

- Achieve complete disease control and normalise patients' lives
- Patients should be evaluated for LTP at every visit, taking disease activity, burden, and control as well as patient preference into consideration
- First-line treatment options include plasma-derived C1 inhibitor, lanadelumab (SC) and berotralstat (oral)
- Androgens are recommended only as second-line treatment
- Antifibrinolytics such as tranexamic acid are not recommended for LTP
- All patients on LTP should be routinely monitored for disease activity, impact, and control to inform optimisation of treatment dosages and outcomes
- Validated patient-reported outcome (PRO) measures
    - angioedema activity score (AAS)
    - hereditary angioedema activity score (HAE-AS)
    - angioedema quality of life questionnaire (AE-QoL)
    - hereditary angioedema quality of life questionnaire (HAE-QoL)
    - angioedema control test (AECT)

LTP should be individualized and considered in all HAE-I/II patients taking into consideration the disease activity, patient's QoL, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy. It is, therefore recommended to evaluate patients with HAE for LTP at every visit, taking disease activity, burden, and control as well as patient preference into consideration. As all of these factors can vary over time, all patients should be evaluated for LTP at least once a year. The goal of LTP is to achieve full control of disease burden while attempting to minimize treatment burden and side effects. Successful LTP requires a high degree of compliance; therefore, the patient's preferences should be taken into consideration.

The DMC published a summary of an evidence review regarding drugs for preventive treatment of HAE in 2024. Overall, patients older than 12 years of age with significant reduced QoL and ≥4 attacks/month should receive preventive treatment. As summarized in Table 3, it is recommended to use lanadelumab or Berinert SC as a first choice first-line options to at least 80% of patients. In case of insufficient efficacy (less than 50% reduction attack frequence) of the economically preferred option, the prescriber may consider a switch of treatment (The Danish Medicines Council 2024).

After starting treatment, the patient should be monitored every three months within the first year and thereafter once yearly for potential treatment adjustments. When treated with lanadelumab, the treatment interval should get extended by 3 days if patients are attack-free for three months. This should be continued until the patient is no longer attack-free. In this scenario, the patient should return to the previous attack-free dosing regimen (The Danish Medicines Council 2024).

Switching to oral berotralstat may be considered if the patient experiences local injection site reactions or systemic side effects of subcutaneous (SC) drugs.

IV Cinryze may be considered in special situations, where it is not possible to use a SC or orally administered drug.

Only C1-INH can be used during pregnancy.

Table 3 The Medicines Council's clinical sequence for medicines for the preventive treatment of HAE

	Medicinal product
Apply to at least 80% of the population*	SC lanadelumab (C1-INH)
	SC Berinert 2000 IU and 3000 IU (C1-INH)
Consider	Oral berotralstat
Use only in special cases	IV Cinryze (C1-INH)

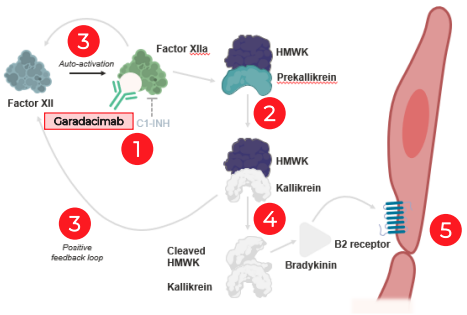
* The Note: Percentage indicates the proportion of the population expected to be treated with the drug that becomes the first choice in the drug recommendation.

Abbreviations: C1-INH = C1 esterase inhibitor; IU = International unit; IV = Intravenous; SC = Subcutaneous

Source: (The Danish Medicines Council 2024)

3.4 The intervention

Garadacimab is a specific FXIIa inhibitor intended for self- or caregiver-administration by SC injection. It is indicated for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older (European Medicines Agency 2025). A brief description of garadacimab is provided in Table 4. Garadacimab is a specific inhibitor of FXIIa, which prevents the initiation of the internal processes which cause an HAE attack and subsequently blocks this chain of events, as illustrated in Figure 2. Garadacimab is a novel fully human IgG4 recombinant monoclonal antibody which binds to the catalytic domain of FXIIa and potently inhibits its catalytic activity. FXII is the first factor activated in the contact activation pathway and initiates the BK-producing plasma contact system. The inhibition of FXIIa prevents the activation of prekallikrein to kallikrein and the generation of BK, which is associated with inflammation and swelling in HAE attacks; thus, inhibition of FXIIa blocks the cascade of events leading to an HAE attack (McKenzie et al. 2022, Cao et al. 2018, Pawaskar et al. 2022).



1. Garadacimab binds to the catalytic domain of Factor XIIa, inhibiting its catalytic activity
2. thereby blocking activation of the kallikrein-kinin pathway
3. And blocking the activation of the positive feedback loop
4. preventing bradykinin production
5. and the occurrence of HAE attacks

Figure 2 Garadacimab mechanism of action

Abbreviations: C1-INH = C1 esterase inhibitor; HAE = Hereditary angioedema; HMWK = High-molecular-weight kininogen
Sources: (Craig et al. 2023, McKenzie et al. 2022, Pawaskar et al. 2022)

Table 4 Overview of intervention | ANDEMBRY (garadacimab)

Overview of intervention	ANDEMBRY (garadacimab)
Indication relevant for the assessment	Routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older
ATMP	Not applicable
Method of administration	Subcutaneous administration
Dosing	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
Dosing in the health economic model (including relative dose intensity)	One 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
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Continuous treatment
Necessary monitoring, both during administration and during the treatment period	Routine monitoring and HAE attack management, varying by attack severity
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No

Overview of intervention	ANDEMBRY (garadacimab)
Package size(s)	Pre-filled pen for single use (contains 200 mg of garadacimab in 1.2 mL solution).

Abbreviations: HAE = Hereditary angioedema; SC = Subcutaneous

3.4.1 The intervention in relation to Danish clinical practice

Garadacimab is expected to be used as a prophylactic treatment in patients aged 12 years or older diagnosed with HAE. As detailed in Section 3.3.2, the treatment algorithm for HAE is based on the number of attacks, Health-related quality of life (HRQoL), the severity of the attack, and other factors influencing drug administration. Lanadelumab is currently recommended by the DMC as first choice of the first-line treatments for at least 80% of patients (Maurer et al. 2022, Betschel et al. 2019, Busse et al. 2021, Okuno 2023). Garadacimab is expected to be the first-line treatment option due to superior efficacy compared with lanadelumab as presented in the indirect treatment comparison (ITC) (see Section 0). In addition to superior efficacy, garadacimab demonstrate the advantage of a reduced treatment interval in all patients by a fixed once monthly dosing regimen with immediate onset of attack reduction without the need for initial dose titration.

3.5 Choice of comparator(s)

3.5.1 Takhzyro (lanadelumab)

Lanadelumab is chosen as the relevant comparator as it is the first choice of two first-line treatments in the current DMC treatment guideline (The Danish Medicines Council 2024). Lanadelumab was approved based on clinical data from pivotal clinical trials with similar population, intervention, comparison, and outcomes (PICO) as garadacimab pivotal studies and is approved for the same indication as garadacimab. Also, both lanadelumab and garadacimab are administered SC. Today, in agreement with the DMC guidelines, lanadelumab is the most prescribed LTP in Denmark.

SC C1-esterase inhibitors are considered equipotent with lanadelumab, whereas IV C1-esterase inhibitors and berotralstat are considered less effective.

Lanadelumab, is indicated for routine prevention of recurrent attacks of HAE and is administered SC. Lanadelumab is used either every 2 weeks, or every 4 weeks if the patient is attack-free. Numerous guidelines recommend lanadelumab as a first-line treatment option for LTP (Betschel et al. 2019, Busse et al. 2021, Maurer et al. 2022, Okuno 2023).

In Denmark, lanadelumab is recommended as standard treatment since January 2022 for patients with significant reduced QoL and at least four attacks per month (The Danish Medicines Council 2020b). According to current Danish treatment guidelines, lanadelumab is the first choice of two first-line treatments and should be used for at

least 80% of patients who start prophylactic treatment of HAE (The Danish Medicines Council 2024).

In Denmark, 50% of patients are assumed to manage the every four week (Q4W) dosing regimen, as per the DMC evidence summary (The Danish Medicines Council 2024). This assumption resonates with real-world evidence (RWE) from the United States (US) market, indicating that only half (46%) of patients in a retrospective observational study had evidence of down titration of lanadelumab during a 18 months follow-up period (Shah et al. 2023).

The EMPOWER study, a phase 4 prospective noninterventional observational study evaluating the real-world effectiveness of lanadelumab, indicated only 19,2 % of patients achieve to down titrate to the Q4W dosing regimen (Goodyear et al. 2022).

Table 5 Overview of lanadelumab

Overview of comparator	
Generic name	Lanadelumab
ATC code	B06AC05
Mechanism of action	Lanadelumab is a fully human, monoclonal antibody. Lanadelumab inhibits active plasma kallikrein proteolytic activity. Increased plasma kallikrein activity leads to angioedema attacks in patients with HAE through the proteolysis of high-molecular-weight-kininogen to generate cleaved HMWK and BK. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits BK generation in patients with HAE.
Method of administration	Subcutaneous
Dosing	The recommended starting dose in adults is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight. The recommended dose of lanadelumab for children aged 2 to < 12 years is based on body weight.
Dosing in the health economic model (including relative dose intensity)	SC – 300 mg every 2 weeks (Q2W); 44% of Q2W-initiated may reduce dosing intervals to every 4 weeks
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Continuous treatment

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	150 mg and 300 mg in pre-filled pen. The 150 mg dose is intended for paediatric population only.

Abbreviations: BK = Bradykinin; HAE = Hereditary Angioedema; HMWK = High-molecular-weight kininogen; SC = Subcutaneous; Q2W = Every 2 weeks
Source: (The European Medicines Agency 2024)

3.6 Cost-effectiveness of the comparator(s)

On January 22, 2020, the DMC recommended lanadelumab as a possible standard treatment for the preventive treatment of HAE. The recommendation applies to patients with a minimum of four attacks per month. For patients with significantly reduced QoL who do not meet the criterion of four monthly attacks, treatment can only be started after a single application to the Regional Medicines Committee (The Danish Medicines Council 2020b).

In February 2024, the DMC published a treatment guideline after comparing clinical evidence on efficacy and safety of LTP options in HAE (The Danish Medicines Council 2024).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Relevant outcome measures for this application (Table 6) are aligned with what is previously considered critical or important by DMC (please see validity of outcomes).

Table 6 Efficacy outcome measures relevant for the application

Essential efficacy outcomes in the MAIC	Time point*	Definition	How was the measure investigated/method of data collection
Time-Normalized Number of HAE Attacks VANGUARD (NCT04656418)	Day 1- day 182, outcome measured every 2 weeks	Time-normalized number of HAE attacks for garadacimab treatment is defined as the number of investigator-confirmed HAE attacks per month during treatment period.	Measured by the investigator at every study visit or via phone call by reviewing the patients' electronic diary.
CSL312A_2001 (NCT03712228)	12 weeks, outcome measured every 4 weeks		

Rate of Investigator Confirmed HAE Attacks HELP (NCT02586805)	Day 1- day 182, outcome reported latest within 72 hours to study site	HAE attack was defined as a discrete episode during which the participant progressed from no angioedema to symptoms of angioedema.	Patient reported to the study site within 72 hours of the onset of an attack and were investigator confirmed.
Time-Normalized Number of Moderate and/or Severe HAE Attacks *VANGUARD (NCT04656418)* *CSL312A_2001 (NCT03712228)*	Day 1- day 182, outcome measured every 2 weeks 12 weeks, outcome measured every 4 weeks	Time-normalized number of moderate or severe HAE attacks is defined as the number of investigator-confirmed HAE attacks per month during treatment period.	Measured by the investigator at every study visit or via phone call by reviewing the patients' electronic diary.
Rate of Moderate or Severe Investigator Confirmed HAE Attacks *HELP (NCT02586805)*	Day 1- day 182, outcome reported latest within 72 hours to study site	HAE attack was defined as a discrete episode during which the participant progressed from no angioedema to symptoms of angioedema. Moderate and severe investigator-confirmed HAE attacks were the attacks that were moderate or severe as per the HAE attack assessment and reporting procedures (HAARP) defined severity.	Patient reported to the study site within 72 hours of the onset of an attack and were investigator confirmed.
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction *VANGUARD (NCT04656418)* *CSL312A_2001 (NCT03712228)*	Day 1- day 182, outcome measured every 2 weeks 12 weeks, outcome measured every 4 weeks	Proportion of Subjects who Achieved ≥90% Attack Rate Reduction is defined as the proportion of patients who achieved at least a 90% attack rate reduction at 6-months compared to the run-in period.	Measured by the investigator at every study visit or via phone call by reviewing the patients' electronic diary with subsequential statistical analysis.
Proportion of Subjects who Achieved ≥90%	Day 1- day 182, outcome reported latest	Proportion of Subjects who Achieved ≥90% Attack Rate Reduction is defined as the	Patient reported to the study site within 72 hours of the onset of an attack and were investigator

Attack Rate Reduction *HELP (NCT02586805)*	within 72 hours to study site	proportion of patients who achieved at least a 90% attack rate reduction at 6-months compared to the run-in period.	confirmed with subsequential statistical analysis.
Proportion of Attack-Free Patients *VANGUARD (NCT04656418)* *CSL312A_2001 (NCT03712228)*	Day 1- day 182, outcome measured every 2 weeks 12 weeks, outcome measured every 4 weeks	Proportion of attack-free patients is defined as the percentage of subjects with a percentage reduction of 100%.	Measured by the investigator at every study visit or via phone call by reviewing the patients' electronic diary with subsequential statistical analysis.
Proportion of Attack-Free Patients *HELP (NCT02586805)*	Day 1- day 182, outcome reported latest within 72 hours to study site	Proportion of attack-free patients is defined as the percentage of subjects with a percentage reduction of 100%.	Patient reported to the study site within 72 hours of the onset of an attack and were investigator confirmed with subsequential statistical analysis.
AE-QoL Change *VANGUARD (NCT04656418)* **AE-QoL Change** *HELP (NCT02586805)*	Day 1 to day 182, assessed at day 31 and after day 182 Day 1 to day 182, assessed after day 182	AE-QoL was assessed from a questionnaire consisting of four domains (functioning, fatigue and mood, fears and shame, and nutrition).	The questionnaire responses were provided via electronic case report form (eCRF) data, and this outcome was reported for patients of age ≥18 years. In HELP, the questionnaire was administered pre-dose.
Proportion of patients achieving an MCID ≥6 points in total score *VANGUARD (NCT04656418)* *HELP (NCT02586805)*	Day 1 to day 82	The proportion of patients with MCID change (≥6 points) in AE-QoL total score from day 1 to day 182	In the VANGUARD trial, this outcome was reported for patients of age ≥18 years.

* Time point for data collection used in analysis (follow up time for time-to-event measures)
Abbreviations: AE-QoL = Angioedema quality of life questionnaire; eCRF = Electronic case report form; HAE = Hereditary angioedema; MCID = Minimal clinically important difference
Sources: (Craig et al. 2023, Craig et al. 2024, Banerji et al. 2018)

3.7.1.1 Validity of outcomes

In recent years, a number of LTPs has been approved by European Medicines Agency (EMA) based on clinical studies on similar efficacy outcomes related to attack reduction, reduced need for on-demand treatment, proportion of study population being attack free and HRQOL measures (Longhurst et al. 2017, Kiani et al. 2021, Banerji et al. 2018).

These endpoints are recognized as clinically meaningful to patients, clinicians and regulatory agencies.

Regarding the MCID for these efficacy endpoints and their outcomes, there are no established or validated MCIDs, except for AE-QoL (Weller et al. 2016).

In the evaluation of new LTPs as possible standard treatment in Denmark, DMC has consequently acknowledged the same outcome measures as clinically critical or important (The Danish Medicines Council 2023).

Table 7 Outcome measures to assess routine preventive care

Efficacy outcome	Importance	Outcome measure	Minimal clinically important difference
Attack freedom	Critical	Percentage of patients experiencing a 100% reduction in attack frequency (freedom from symptoms) from baseline	10 %-points
		(alternatively 90% reduction if there is no data for 100%)	(15 %-points)
Health-related quality of life	Critical	Mean change in total score from baseline to minimum week 12 measured with Angioedema Quality of life Questionnaire (AE-QoL)	6 %-points
		Percentage of patients experiencing a 6-point improvement from baseline	20 %-points
Attack frequency	Important	Percentage reduction in the number of HAE attacks per month	15 %-points
		Review of the severity of the remaining seizures (breakthrough seizures)[1]	-
Adverse events	Important	Treatment discontinuation due to side effects	10 %-points
		Qualitative review of the side effect profile of drugs	

For all endpoints, the Council uses data with the longest possible follow-up time unless otherwise stated.

1 In addition to the calculation of the average reduction in seizure frequency, the expert committee will also review the severity of the remaining attacks (breakthrough attacks).

Abbreviations: AE-QOL = Angioedema quality of life questionnaire; HAE = Hereditary angioedema

Source: (The Danish Medicines Council 2023)

The DMC rationale for critical and important outcome measure is described in the protocol for the HAE treatment guideline (The Danish Medicines Council 2023).

3.7.1.1.1 Attack freedom, frequency and severity

The ultimate desire for patients is to become symptom-free (Maurer et al. 2022). By achieving freedom from symptoms, the fear of laryngeal edema can be eliminated, which has a significant impact on patients' QoL. Hence, this attack freedom is categorized as critical efficacy outcome (The Danish Medicines Council 2023). In addition to reducing the number of attacks, LTP may also impact the severity of the remaining attacks (breakthrough attacks). Hence, this attack frequency and severity of breakthrough attacks are categorized as important efficacy outcomes.

3.7.1.1.2 Health-related quality of life

Even between seizures, when patients are symptom-free, many patients still experience anxiety and limitations in daily activities (Caballero et al. 2014). Anxiety may relate to uncertainty about the next attack, availability of rescue medication and self-administer the rescue medication. Living with the unpredictable and potentially life-threatening disease, HAE therefore has a significant impact on QoL. Hence, improvement in HRQoL is categorized as a critical efficacy outcome.

AE-QoL
The DMC prefer the use of AE-QoL as a validated, questionnaire to determine HRQoL in patients with recurrent angioedema (The Danish Medicines Council 2023).

The AE-QoL questionnaire is an instrument to assess QoL impairment in subjects with recurrent angioedema attacks (Weller et al. 2012). It covers 4 domains (functioning, fatigue / mood, fear / shame, and nutrition), and consists of 17 questions with 5 levels of response (never, rarely, occasionally, often, and very often). A linear transformation of raw scores results in a range of possible total scores from 0 (minimum) to 100 (maximum). The AE-QoL was completed using a provisioned electronic Clinical Outcome Assessment (eCOA) solution.

The clinical meaningfulness of the improvement in scores for the Angioedema QoL was assessed by calculating the proportion of subjects who achieved a minimal clinically important difference (MCID) (defined as a 6-point change) in domain and total scores (Weller et al. 2016).

EQ-5D-5L
In addition, EQ-5D-5L was used in the pivotal study (Craig et al. 2023). The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The questionnaire, which is designed for self completion by respondents, is applicable to a wide range of health conditions and treatments (EuroQol 2025).

The EQ-5D-5L consists of 2 parts:

- A descriptive profile, comprising the following 5 domains: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Respondents rate

each domain based on 5 levels of severity (ie, no problems, slight problems, moderate problems, severe problems, extreme problems).

- A vertical, visual analog scale, on which the respondent rates their overall health from 'Best imaginable health state' to 'Worst imaginable health state.'

Subjects completed the EQ-5D-5L using a provisioned eCOA solution.

4. Health economic analysis

4.1 Model structure

Not applicable.

4.2 Model features

Not applicable.

Table 8 Settings of the economic model

Model features	Description	Justification
Patient population		
Perspective		
Time horizon		
Cycle length		
Half-cycle correction		
Discount rate		
Intervention		
Comparator(s)		
Outcomes		

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted on April 8, 2024, and subsequently updated on August 5, 2024. Three studies were included in the Matching-adjusted indirect comparison (MAIC) (Table 9). The SLR is summarized in Appendix H.

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Craig, T. et al. (2023). Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 401(10382), 1079-1090. (Craig et al. 2023)	VANGUARD	NCT04656418	Start: 27/01/21 Completion: 07/06/22	Garadacimab vs. lanadelumab
Craig T et al. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2022;10328(399):945-955. (Craig et al. 2022)	CSL312_2001	NCT03712228	Start: 29/10/18 Completion: 15/10/21	Garadacimab vs. lanadelumab
Banerji, A. et al. HELP Investigators (2018). Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA, 320(20), 2108–2121. https://doi.org/10.1001/jama.2018.16773 (Banerji et al. 2018)	HELP	NCT02586805	Start: 3/3/16 Completion: 13/4/17	Garadacimab vs. lanadelumab

Abbreviations: NCT = national clinical trial; HAE = hereditary angioedema
Source: (National Library of Medicine 2023, National Library of Medicine 2024, National Library of Medicine 2022, Craig et al. 2023, Craig et al. 2022, Banerji et al. 2018)

5.2 Literature used for the assessment of HRQoL

Table 10 Relevant literature included for (documentation of) HRQoL (Section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Craig, T. J., Reshef, A., Li, H. H., Jacobs, J. S., Bernstein, J. A., Farkas, H., ... & Magerl, M. (2023). Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 401(10382), 1079-1090.	Health state utility values after conversion to Danish tariff	Section 10.1
Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Björkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc. 2014 Mar-Apr;35(2):185-90.	Utility values for attack severity	Section 10.3

5.3 Literature used for inputs for the health economic model

Not applicable.

Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied

6. Efficacy

6.1 Efficacy of garadacimab compared to lanadelumab for prevention of recurrent hereditary angioedema attacks in adolescent and adult patients

6.1.1 Relevant studies

6.1.1.1 VANGUARD (NCT04656418)

This was a Phase 3, randomized, double-blind, placebo-controlled, multinational, multicentre study, conducted at 28 sites in 7 countries (Canada, Germany, Hungary, Israel, Japan, the Netherlands, and the US) from January 2021 to June 2022 (Craig et al. 2023).

The study design is illustrated in Figure 3. 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 confirm eligibility. During screening, patients were to discontinue HAE prophylaxis (eg, C1-INH replacement therapy, androgens, antifibrinolytics, or other small molecule medications) for ≥2 weeks before the run-in period. Eligible patients entered a treatment period (6 months) and were randomized 3:2 to garadacimab 200 mg or placebo (Craig et al. 2023) It was determined 40 patients would be needed to achieve a power of 90% for a two-sided Wilcoxon test, and a ratio of 3:2 would be appropriate assuming an attack rate per month of 0.3125 with garadacimab 200 mg and 1.3 with placebo (CSL Behring GmbH 2022b).

Randomization was stratified by patient age (≤17 years and >17 years) and, for adults, baseline attack rate (1 to <3 per month and ≥3 per month) observed during the run-in period. On the first day of the treatment period (day 1), patients in both arms 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 (Craig et al. 2023).

At the end of the treatment period, patients either entered a 2-month follow-up period or entered the Open-label extension (OLE) (Craig et al. 2023).

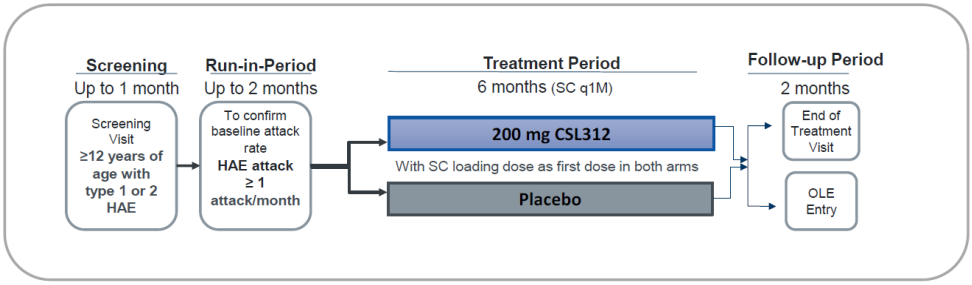


Figure 3 VANGUARD Phase 3 study design

Abbreviations: CSL312 = Garadacimab; HAE = Hereditary angioedema; OLE = Open-label extension; q1M = Once a month; SC = Subcutaneous
Source: (CSL Behring GmbH 2022b)

6.1.1.2 CSL312_2001 (NCT03712228)

This was a Phase 2, randomized, double-blind, placebo-controlled, multinational, multicentre, dose-finding study, conducted at 12 sites in 4 countries (Canada, Germany, Israel, and the US) from October 2018 to August 2019. The full study included patients with HAE type 1 or 2 or HAE with normal C1-INH, with either a FXII or plasminogen mutation; reported here are analyses for patients with HAE type 1 or 2 only (Craig et al. 2022).

Potentially eligible patients entered into a run-in period (4–8 weeks) to assess underlying disease status, confirm baseline HAE attack rate and confirm eligibility for the study. Patients deemed eligible entered an administration period (12 weeks) in which patients were randomized 1:1:1:1 to garadacimab 600 mg, garadacimab 200 mg, garadacimab 75 mg, or placebo. On the first day of the administration period (day 1), patients were treated with an initial IV loading dose of garadacimab 300 mg, garadacimab 100 mg, garadacimab 40 mg, or placebo; this was followed up with SC doses of garadacimab 600 mg, garadacimab 200 mg, garadacimab 75 mg, and placebo, respectively, on day 6 and every 4 weeks thereafter. All patients entered an extension period of 44 weeks (and were followed up for an additional 14 weeks) (Craig et al. 2022).

6.1.1.3 HELP (NCT02586805)

HELP was a double-blind, parallel arm, phase III clinical trial conducted to characterize safety and efficacy of lanadelumab in patients with HAE (Banerji et al. 2018). A total of 125 patients were included in the intention-to-treat (ITT) population and were randomized to receive 150 mg lanadelumab Q4W (n = 29), 300 mg lanadelumab Q4W (n = 29), 300 mg lanadelumab Q2W (n = 27), or placebo (n = 41). Randomization was carried out using an interactive web-based randomization system and stratified by normal number of attacks during the run-in period. All randomized patients were included in the ITT population, regardless of the treatment received.

A summary of the eligibility criteria is presented in Table 48. Patients in the lanadelumab arms received either a 300 mg SC injection Q2W for 26 weeks, a 300 mg SC injection Q4W for 26 weeks, or a 150 mg SC injection Q4W for 26 weeks, whereas patients in the placebo arm received an SC injection Q4W for 26 weeks.

The primary endpoint the number of investigation-confirmed attacks of HAE over the treatment period. Secondary endpoints included the number of attacks requiring acute treatment during the treatment period, the number of moderate or severe attacks during the treatment period, and the number of attacks from days 14 to 182 of the treatment period (Banerji et al. 2018).

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
VANGUARD, NCT04656418 (Craig et al. 2023)	Phase 3, randomized, double-blind, placebo-controlled, multinational, multicentre, dose-finding study	27/01/21-07/06/22	Patients (≥12 years) with type 1 or 2 HAE recruited from 28 sites in 7 countries (N=65)	On the first day of the treatment period (day 1), patients in both arms 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 garadacimab SC injections over the remaining treatment period.	Placebo	**Primary endpoints** The primary endpoint was the investigator-assessed time-normalized number of HAE attacks with garadacimab 200 mg vs placebo during the 6-month treatment period (day 1 to day 182). **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 through to day 91 • Percentage of patients rating therapy as “good” or better with the subject's global assessment of response to therapy (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) and 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. **Exploratory efficacy analyses**

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Prespecified exploratory endpoints included the time to first attack after days 1 and 14, and garadacimab concentrations at scheduled timepoints during the treatment period (days 1 [start of treatment period], 31, 61, 91, 121, 151, and 182 [end of treatment period]) and at follow-up visit (day 242) **Investigator-reported outcomes and PROs** PROs analysed as exploratory endpoints at day 31 and day 182 included the AE-QoL questionnaire, Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire, and EQ-5D-5L. An additional investigator-reported outcome (Investigator's Global Assessment of Response to Therapy [IGART]) was also reported. **Safety** Safety endpoints were AEs (including AESIs comprising anaphylaxis, thromboembolic, or abnormal bleeding events), AEs by severity, concentrations of anti-garadacimab antibodies, and clinically significant abnormalities in laboratory assessments. **PK/PD** 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 schedules timepoints

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
CSL312_2001, NCT03712228 (Craig et al. 2022)	Phase 2, randomized, double-blind, placebo-controlled, multinational, multicentre, dose-finding study	29/10/18-15/10/21	Patients (18-65 years) with type 1 or 2 HAE recruited from 12 sites in 4 countries (N=32)	Garadacimab 600 mg, garadacimab 200 mg or garadacimab 75 mg. On the first day of the administration period (day 1), patients were treated with an initial IV loading dose of garadacimab 300 mg, garadacimab 100 mg, garadacimab 40 mg, or placebo; this was followed up with SC doses of garadacimab 600 mg, garadacimab 200 mg, and garadacimab 75 mg respectively, on day 6 and	Placebo	**Primary efficacy endpoints** The primary endpoint was the time-normalized number of HAE attacks per month with garadacimab (75 mg, 200 mg, or 600 mg) vs placebo during the treatment period. **Secondary efficacy endpoints** Secondary efficacy endpoints comparing garadacimab (75 mg, 200 mg, or 600 mg) vs placebo over the treatment period were: • Proportion of patients who responded to garadacimab (75 mg, 200 mg, or 600 mg) or placebo (defined as ≥50% relative reduction in the number of HAE attacks vs the run-in period) • Proportion of patients who were attack-free • Proportion of mild, moderate, or severe HAE attacks • Overall number of HAE attacks • Proportion of patients requiring rescue medication **Exploratory efficacy analyses** • Number of days per month patients experienced attacks • Number of rescue medication uses per month **Investigator-reported outcomes and PROs** Investigator-reported outcomes and PROs were analysed as exploratory endpoints. These included AE-QoL, WPAI:GH, SGART, and IGART. **Safety**

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
				every 4 weeks thereafter.		Safety endpoints were AEs, serious AEs, AESIs (e.g., anaphylaxis, thromboembolic, and bleeding events), injection-site reactions, abnormalities in laboratory assessments, vital signs, and inhibitory antibodies to garadacimab. **PK/PD** The PK of garadacimab were assessed as a secondary endpoint. Further exploratory analyses were conducted on PD biomarkers (i.e., activated partial thromboplastin time and FXIIa-mediated kallikrein activity).
HELP, NCT02586805 (Banerji et al. 2018)	Phase 3, double-blind, parallel arm study	03/03/16-13/04/17	Patients (≥12 years) with type 1 or 2 HAE recruited from 41 locations in 7 countries (N=125)	Patients were randomized to receive 150 mg lanadelumab Q4W (n = 29), 300 mg lanadelumab Q4W (n = 29), or 300 mg lanadelumab Q2W (n = 27)	Placebo	**Primary endpoint** Rate of investigator confirmed HAE attacks during treatment period **Secondary endpoints** Rate of investigator confirmed HAE attack requiring acute treatment Rate of moderate or severe investigator confirmed HAE attacks Rate of investigator confirmed HAE attacks during day 14 through day 182

Abbreviations: AE = Adverse event; AESI = Adverse event of special interest; AE-QoL = Angioedema quality of life questionnaire; FXIIa = Activated Factor XII; HAE = Hereditary angioedema; IGART = Investigator's global assessment of response to therapy ; N = Number of scores or individuals; NCT = National clinical trial; PK/PD = Pharmacokinetics/Pharmacodynamics; PRO = Patient-reported outcome; Q2W = Every two weeks; Q4W = Every four weeks; QoL = Quality of life; SC = Subcutaneous; SGART = Subject's global assessment of response to therapy; WPAI:GH = Work productivity and activity impairment - general health questionnaire

6.1.2 Comparability of studies

As no comparative clinical trial data are available for garadacimab vs. lanadelumab, a MAIC based on VANGUARD, CSL312_2001 and HELP was conducted (Section 0).

Inclusion and exclusion criteria for these studies were compared for implication on the MAIC and summarized in Appendix C3. In summary, the differences were small and acceptable.

6.1.2.1 Comparability of patients across studies

Before weighting, there were considerable differences in several patient characteristics at baseline, e.g. the gender distribution (Table 49 in Appendix C). In Table 50, the distributions of baseline characteristics after the adjustment process are presented.

The patient weight, gender distribution and age at baseline used in the health economic model are derived from the ITT population at baseline in VANGUARD (Table 13) (Craig et al. 2023). [redacted]. We therefore assumed that the values are similar to the VANGUARD trial. In the Danish Medicines Council's assessment of lanadelumab, a patient age at start of treatment of 41 years was used (The Danish Medicines Council 2020a).

Table 13 Characteristics in the relevant Danish population and in the health economic model

pre	Value in Danish population	Value used in health economic model (Craig et al. 2023)
Age	N/A	41.2 years
Gender	N/A	59.4% females
Patient weight	N/A	80.4 kg

Abbreviations: N/A = Not available

6.1.3 Efficacy – results per VANGUARD (NCT04656418)

A summary of the outcomes from the VANGUARD trial is shown in

Table 14. More details about respective outcome can be found in Appendix B.

Table 14 Summary of outcomes from the VANGUARD trial (ITT population)

Outcome	Garadacimab (200 mg) (ITT population; n=39)	Placebo (ITT population; n=25)	p-value

Time-normalized number of HAE attacks (mean rate [95% CI], attacks per month)	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)	<0.001
Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment	0.23 (0.02, 0.45)	1.86 (1.26, 2,46)	<0.001
Time-Normalized Number of Moderate and/or Severe HAE Attacks	0.13 (0.03, 0.22)	1.35 (0.86, 1,84)	<0.001
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	29/39 (74%; 58.9, 85.4)	2/24 (8.3%; 2.3, 25.9)	<0.001
Proportion of Attack-Free Patients	24/39 (61.5%; 45.9, 75.1)	0/24 (0%; 0.1, 13.8)	<0.001
Attack-Free Days per Month	NR	NR	NR
AE-QoL Change from baseline	-26.47 (-32.8, -20.1)	-2.21 (-11.1, 6.7)	
Proportion of patients achieving an MCID ≥6 points in AE-QoL total score	29/33 (87.9%; 71.8, 96.6)	11/25 (55.0%; 31.5, 76.9)	

Abbreviations: AE-QoL = Angioedema Quality of Life questionnaire; CI = Confidence interval; HAE = Hereditary angioedema; ITT = Intention-to-treat; MCID = Minimal clinically important difference; n = Number of observations; NR = Not reported.

Source: (Craig et al. 2023)

6.1.4 Efficacy – results per CSL312_2001 (NCT03712228)

A summary of the outcomes from the CSL312_2001 trial is shown in Table 15. More details about respective outcome can be found in Appendix B.

Table 15 Summary of outcomes from the CSL312_2001 trial (ITT population)

Outcome	Garadacimab (200 mg) (ITT population; n=8)	Placebo (ITT population; n=8)	p-value
Time-normalized number of HAE attacks (mean rate [95% CI], attacks per month)	0.05 (-0.06, 0.15)	4.24 (2.74, 5.75)	<0.001
Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment	0.045 (-0.06,0.15)	3.98 (2.5,5.45)	NA

Time-Normalized Number of Moderate HAE Attacks	0.05 (-0.06,0.15)	1.93 (0.76,3.11)	NA
Time-Normalized Number of Severe HAE Attacks	0.00 (0.00,0.00)	0.89 (-0.25,2.03)	NA
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	8/8 (100%, 67.6%,100%)	0/8 (0%, 0%,32.44%)	NA
Proportion of Attack-Free Patients	7/8 (88%, 52.91%, 97.76%)	0/8 (0%, 0%, 32.44%)	NA
Attack-Free Days per Month	NR	NR	
AE-QoL Change from baseline (total score; mean(SD))	-20.04 (11.971)	0.37 (7.851)	NA
Proportion of patients achieving an MCID ≥6 points in AE-QoL total score	NR	NR	

Abbreviations: AE-QoL = Angioedema Quality of Life questionnaire; CI = Confidence interval; HAE = Hereditary angioedema; ITT = Intention-to-treat; MCID = Minimal clinically important difference; n = Number of observations; NR = Not reported

Source: (Craig et al. 2022, CSL Behring GmbH 2022a)

6.1.5 Efficacy – results per HELP (NCT02586805)

A summary of the outcomes from the HELP trial is shown in Table 16. More details about respective outcome can be found in Appendix B.

Table 16 Summary of outcomes from the HELP trial (ITT population)

Outcome	Lanadelumab Q2W (300 mg) (ITT population; n=27)	Placebo (ITT population; n=41)	p-value
Time-normalized number of HAE attacks (mean rate [95% CI], attacks per month)	0.26 (0.14 to 0.46)	1.97 (1.64 to 2.36)	<0.001
Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment	0.21 (0.11 to 0.40)	1.64 (1.34 to 2.00)	<0.001

Time-Normalized Number of Moderate and/or Severe HAE Attacks	0.20 (0.11 to 0.39)	1.22 (0.97 to 1.52)	<0.001
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	18 (66.7%)	2 (4.9%)	<0.001
Proportion of Attack-Free Patients	12 (44.4%)	1 (2.4%)	<0.001
Attack-Free Days per Month	27.3 (SD 1.3)	22.6 (SD 4.4)	<0.001
AE-QoL Change from baseline	–21.29 (−28.21 to −14.37)	–4.72 (−10.46 to 1.02)	N/A
Proportion of patients achieving an MCID ≥6 points in AE-QoL total score	21/26 (80.8%)	14/38 (36.8%)	0.001

Abbreviations: AE-QoL = Angioedema Quality of Life questionnaire; CI = Confidence interval; HAE = Hereditary angioedema; ITT = Intention-to-treat; MCID = Minimal clinically important difference; n = Number of observations

Source: (Banerji et al. 2018)

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

A number of clinically relevant outcome measures from clinical trials of prophylactic treatment of HAE attacks were considered in Appendix C.

Based on data availability as detailed above, the following outcomes were chosen for MAIC analysis:

- Time-normalized number of HAE attacks
- Time-normalized number of HAE attacks requiring on-demand treatment
- Time-normalized number of moderate and/or severe HAE attacks
- Proportion of attack-free patients
- Proportion of patients who achieved ≥90% attack rate reduction
- Attack-free days per month
- AE-Qol change from baseline to day 182
- Proportion of patients achieving a MCID ≥6 points in total score from baseline to day 182

Below, in Table 17, the definitions and differences in definitions between the studies are presented.

Table 17 Differences in definitions of outcomes between studies

Outcome	Outcome definitions
Time-Normalized Number of HAE Attacks	Time-normalized number of HAE attacks for garadacimab treatment is defined as the number of investigator-confirmed HAE attacks per month during treatment period from day 1 (first study drug administration) through day 182 (6-month). The outcome definition is similar in the HELP trial. However, CSL312_2001 has a shorter treatment period of 12 weeks for this outcome.
Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment	Time-normalized number of HAE attacks requiring on-demand treatment for garadacimab treatment is defined as the number of investigator-confirmed HAE attacks during the 6-month treatment period where an HAE attack required an on-demand treatment. The outcome definition is similar in the HELP trial. However, CSL312_2001 measures the number of attacks requiring acute treatment and has a shorter treatment period of 12 weeks for this outcome.
Time-Normalized Number of Moderate and/or Severe HAE Attacks	Time-normalized number of moderate or severe HAE attacks for garadacimab treatment is defined as the number of investigator-confirmed HAE attacks per month during treatment period from day 1 (first study drug administration) through day 182 (6-month). The outcome definition is similar in the HELP trial. However, CSL312_2001 has a shorter treatment period of 12 weeks for this outcome.
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	This outcome is defined as the proportion of patients who achieved at least a 90% attack rate reduction at 6-months compared to the run-in period. The outcome definition is similar in the HELP trial, with a treatment period of 26 weeks. However, CSL312_2001 has a shorter treatment period of 12 weeks for this outcome.
Proportion of Attack-Free Patients	Proportion of attack-free patients for the garadacimab population is defined as the percentage of subjects with a percentage reduction of 100% (i.e., who do not experience an HAE attack and so are attack-free for the 6-month treatment period. The outcome definition is similar in the HELP trial. However, CSL312_2001 has a shorter treatment period of 12 weeks for this outcome.
Attack-Free Days per Month	Across all trials, attack-free days per month is defined as the number of attack-free days per month during the 6-month treatment period. An attack-free day for the garadacimab population is defined as a calendar day with no investigator-confirmed HAE attack. The attack-free day definition is similar in the HELP trial. However, CSL312_2001 has a shorter treatment period of 12 weeks for this outcome.
AE-QoL Change from Baseline to Day 182	For both the garadacimab and lanadelumab populations, AE-QoL change from baseline (day 1 for garadacimab and day 0 for lanadelumab) to day 182 was assessed from a questionnaire consisting of four domains (functioning, fatigue and mood, fears and shame, and nutrition). In the VANGUARD trial, the questionnaire responses were provided via eCRF data, and this outcome was reported for patients of age ≥18 years. In the HELP trial, the questionnaire was administered pre-dose. CSL312_2001 did not report this outcome.
Proportion of Patients	This outcome is defined as the proportion of patients with MCID change (≥6 points) in AE-QoL total score from day 1 to day 182 (garadacimab) through

Achieving an MCID ≥6 Points in Total AE-QoL Score from Baseline to Day 182	day 182 (lanadelumab). In the VANGUARD trial, this outcome was reported for patients of age ≥18 years. CSL312_2001 did not report this outcome.

Abbreviations: AE-QoL = Angioedema Quality of Life questionnaire; CSL312 = Garadacimab; HAE = Hereditary angioedema; eCRF = Electronic case report form; MCID = Minimal clinically important difference

7.1.2 Method of synthesis

A protocol and statistical analysis plan were developed prior to conducting the MAIC analyses. The methodology and considerations used to conduct the analyses are summarised below.

The MAIC uses pooled data from the Phase II (CSL312_2001) and Phase III (CSL312_3001) trials of garadacimab. Pooling data from the Phase II (CSL312_2001) and Phase III (CSL312_3001) trials of garadacimab is methodologically justified and enhances the robustness of the matching-adjusted indirect comparison (MAIC) against lanadelumab.

First, combining data from both trials increases the overall sample size, which directly improves the statistical power of the analysis. This allows for more precise estimates of treatment effects and narrower confidence intervals. In rare diseases like hereditary angioedema (HAE), where patient populations are inherently limited, maximizing the use of all available data is critical. The pooled dataset enabled more stable weighting in the MAIC and supported the inclusion of key covariates without excessive loss of effective sample size (ESS), which remained within acceptable thresholds as per NICE guidelines (Phillippo et al. 2016).

Second, despite being conducted in different phases, the two trials share substantial methodological and clinical alignment. Both were randomized, double-blind, placebo-controlled studies evaluating the same dose of garadacimab (200 mg monthly) in similar patient populations with type I or II HAE. While some differences exist, such as trial duration and certain eligibility criteria, these were either minor or addressed through statistical adjustment. The MAIC methodology effectively reweighted the pooled population to match the comparator trial (HELP), mitigating potential biases from cross-trial differences.

Third, pooling represents the optimal use of current evidence. The Phase II trial contributes valuable data on the same treatment regimen and expands the evidence base, particularly for outcomes with low event rates. This is especially important for binary endpoints like attack-free status or ≥90% attack rate reduction, where small sample sizes can limit interpretability. To address differences in trial durations for these binary outcomes, the analysis employed a robust methodological approach: pseudo individual patient data (IPD) were generated for the HELP trial, standardizing follow-up to 182 days (26 weeks) for each pseudo patient. These were combined with the pooled IPD from the garadacimab trials in a weighted generalized linear model. The model used a binomial likelihood with a complementary log-log (cloglog) link function and included the logarithm of each patient's follow-up time as an offset variable. This allowed for

accurate estimation of hazard ratios (HRs) while accounting for differing follow-up durations, with variance estimated using a robust sandwich estimator.

In summary, pooling data from CSL312_2001 and CSL312_3001 is a methodologically sound. It enhances statistical power, leverages consistent trial designs, and ensures optimal use of available evidence. The MAIC analysis, supported rigorous adjustment for effect modifiers and trial duration, demonstrates that this pooled approach yields robust and credible comparative efficacy estimates for garadacimab versus lanadelumab in the prophylactic treatment of HAE.

In addition, a sensitivity analysis was conducted using Bucher methodology, based only on the VANGUARD and HELP trials (Appendix 0). Notably, unlike the MAIC analysis reported below, the Bucher analysis does not account for between study-heterogeneity (i.e. baseline HAE attack rate during run-in, weight, age, and sex).

7.1.3 Identification and Ranking of Covariates

Imbalances in baseline patient characteristics (e.g., average age) between the VANGUARD, CSL312_2001, and HELP trials can lead to biased comparative efficacy estimates if not adjusted for, due to confounding driven by baseline patient or disease characteristics that differ across patient populations and are treatment effect modifying. The steps undertaken for identifying and rank-ordering treatment effect modifiers are outlined below.

- Prior to conducting the analyses, a list of potential treatment effect modifiers consisting of baseline characteristics reported across the VANGUARD, CSL312_2001 and HELP trials were identified.
- The list of treatment effect modifiers was shared with internal clinical experts for their review. The internal clinical experts were asked to confirm which factors are clinically important and should be included in the list, and whether any additional factors should be included.
- After all relevant factors were identified, the list of treatment effect modifiers were ranked by internal clinical experts in order of importance based on how likely a specific covariate is to be treatment effect modifying of the outcomes of interest. A consensus among all internal clinical experts was reached.
- A pooled rank-ordered list of treatment effect modifiers was generated and was shared with an external clinical expert for objective validation. After validation, the final ranked list incorporated feedback from all clinical experts. A single list of ranked treatment effect modifiers was applied to all outcomes of interest.

The list of treatment effect modifiers, their availability in VANGUARD and CSL312_2001 and HELP trials, and their individual and final rankings are presented in Appendix C**.**

7.1.3.1 Matching-adjusted indirect comparison method

Given the availability of a common comparator, an anchored MAIC was used to estimate the relative effect of garadacimab versus lanadelumab by leveraging Individual patient

data (IPD) from VANGUARD and CSL312_2001 and published summary-level data (SLD) from HELP for most outcomes. Due to zero or low event rates in the placebo arms of CSL312_2001, VANGUARD, and HELP, unanchored MAICs were conducted for the proportion of attack-free patients over the trial period outcome, and the proportion of subjects who achieved ≥90% attack rate reduction compared to run-in outcome.

To assess between-study heterogeneity prior to conducting the MAIC, the eligibility criteria reported by VANGUARD, CSL312_2001 and HELP were compared (see Appendix A). Moreover, descriptive statistics for the treatment effect modifiers were assessed. For continuous variables, the mean and standard deviation (SD) were reported if available for lanadelumab. For categorical variables, the number of patients and proportions were reported. Each treatment effect modifier being adjusted for in the analysis was compared between the IPD and SLD using standardized mean differences (SMDs) before and after adjustment (where an SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference) (Austin 2009).

To reduce between-study heterogeneity, the pooled VANGUARD and CSL312_2001 trial population was reweighted so that the distribution of the identified baseline characteristics matched those reported in HELP. A logistic propensity score model was estimated that includes the identified covariates (i.e., treatment effect modifiers), which is equivalent to the model on the log of the individual weights: $\log(w_i) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X}_i$, where X_i was the covariate vector for the ith individual; and where the regression parameters, α_1, was estimated by a method-of-moments. The use of method-of-moments guaranteed a close balancing of covariates between the garadacimab trials and HELP populations (Phillippo et al. 2018, Signorovitch et al. 2010). That is, after reweighting patients, the means (or proportions/percentages) and SDs of covariates from the garadacimab trials were almost exactly equal to those published in HELP.

The method applied is further discussed in Appendix C.

7.1.4 Results from the comparative analysis

7.1.4.1 MAIC Analyses

When adjusting for all available factors, the primary analyses showed at most a 55% reduction in Effective sample size (ESS) compared to the original sample size which was considered an appropriate reduction based on a NICE review of the literature which showed reductions of at least 57% (Phillippo et al. 2016). Therefore, the "primary scenario" adjusted for all available factors, which were baseline HAE attack rate during run-in, weight, age, and sex.

7.1.4.2 Summary of MAIC results

A summary of results of the analyses for garadacimab 200 QM versus lanadelumab 300 Q2W is presented in Table 18.

MAIC results were numerically favourable for garadacimab (GARA) 200 QM across most primary analyses. GARA 200 QM was statistically superior to lanadelumab (LANA) 300 Q2W for time-normalized number of moderate and/or severe HAE attacks, and AE-QoL change from baseline to day 182. However, LANA 300 Q2W was numerically favourable compared to GARA 200 QM for proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182.

Table 18 Results from the comparative analysis of garadacimab vs. lanadelumab for patients with HAE

Outcome measure	GARA 200 QM vs PBO (ESS=61; 27 for PROs)	LANA 300 Q2W vs PBO (N=68; 64 for PROs)	Anchored MAIC Result for GARA 200 QM vs LANA Q2W
Time-normalized number of HAE attacks	RR (95% CI) 0.072 (0.037, 0.140)	RR (95% CI) 0.13 (0.07, 0.24)	0.55 (0.22, 1.37)*
Time-normalized number of HAE attacks requiring on-demand treatment	RR (95% CI) 0.068 (0.034, 0.137)	RR (95% CI) 0.13 (0.07, 0.25)	0.52 (0.20, 1.35)*
Time-normalized number of moderate and/or severe HAE attacks	RR (95% CI) 0.043 (0.016, 0.114)	RR (95% CI) 0.17 (0.08, 0.33)	0.25 (0.07, 0.84)*
Proportion of patients with ≥90% attack rate reduction compared to run-in[1]	Weighted proportion*** 0.782	Proportion*** 0.667	1.50 (0.77, 2.90)¤
Proportion of attack-free patients over the trial period[2]	Weighted proportion*** 0.650	Proportion*** 0.444	1.93 (0.92, 4.03)¤
Number of attack-free days per month	MD (95% CI) 5.138 (3.535, 6.741)	MD (95% CI) 4.7 (3.2, 6.2)	0.44 (-1.76, 2.63)#
AE-QoL change from baseline to day 182[3]	MD (95% CI) -33.949 (-45.020, -22.877)	MD (95% CI) -16.57 (-28.53, -4.62)	-17.38 (-33.67, -1.08)4#
Proportion of patients achieving an MCID ≥6 points in total score from	Weighted proportion** 0.803	Proportion** 0.547	0.97 (0.31, 3.05)¤

baseline to day 182[3]	

Notes: *: RR (95% CI); ¤: HR (95% CI); #: MD (95% CI)
[1] Unanchored MAICs were considered the primary analysis for proportion of patients with ≥90% attack rate reduction compared to run-in.
[3] Only GARA 200 QM patient data from VANGUARD was used as CSL312_2001 did not report change from baseline in AE-QoL or the proportion of patients achieving an MCID ≥6 points in total score over the trial period.
[4] The corresponding SE = 8.31, derived as per the NICE Decision Support Unit Technical Support Document 18 (Phillippo et al. 2016).
** Proportions are for the pooled active treatment and placebo arms.
*** Proportions are for the active treatment arms.
Abbreviations: AE-QoL = Angioedema quality of life questionnaire; CI = Confidence interval; HAE = Hereditary angioedema; HR = Hazard ratio; MAIC = Matching-adjusted indirect comparison; MCID = Minimal clinically important difference; MD = Mean difference; NICE = National institute for health and care excellence; RR = Rate ratio; SE = Standard error; GARA 200 QM = Garadacimab 200 mg once monthly; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Efficacy – results per [outcome measure]

Not applicable.

8.1.2 Extrapolation of efficacy data

Not applicable.

8.1.2.1 Extrapolation of [effect measure 1]

Not applicable.

Table 19 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	[Name of registrational study, name of studies from indirect comparison]
Model	[Describe which/how many models have been applied in extrapolating efficacy e.g. full parametrization vs. piecewise]
Assumption of proportional hazards between intervention and comparator	[Yes/No/Not applicable]

Method/approach	Description/assumption
Function with best AIC fit	[Intervention: X function] [Comparator: X function]
Function with best BIC fit	[Intervention: X function] [Comparator: X function]
Function with best visual fit	[Intervention: X function] [Comparator: X function]
Function with best fit according to evaluation of smoothed hazard assumptions	[Intervention: X function] [Comparator: X function]
Validation of selected extrapolated curves (external evidence)	[E.g. studies, databases, RWE, clinical experts' opinions on clinical plausibility]
Function with the best fit according to external evidence	[Intervention: X function] [Comparator: X function]
Selected parametric function in base case analysis	[Intervention: X function] [Comparator: X function]
Adjustment of background mortality with data from Statistics Denmark	[Yes/No] If 'No': briefly describe why the data has not been adjusted for background mortality
Adjustment for treatment switching/cross-over	[Yes/No] If 'Yes': briefly describe the assumption/method
Assumptions of waning effect	[Yes/No] If 'Yes': briefly describe the assumption/method
Assumptions of cure point	[Yes/No] If 'Yes': briefly describe the assumption/method

8.1.2.2 Extrapolation of [effect measure 2]

8.1.3 Calculation of transition probabilities

Not applicable.Table 20 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		
	Death		

Recurrence	Death
Health state/Transition	

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Not applicable.

Table 21 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	[X months/years]	[X months/years]	[X months/years]

Table 22 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Prone to attack [months]	Full attack freedom [months]
Garadacimab	[xx]	[xx]	[xx]
Lanadelumab	[xx]	[xx]	[xx]

9. Safety

9.1 Safety data from the clinical documentation

Table 23 below describes the overview of safety events across VANGUARD, CSL312_2001, and HELP.

9.1.1 VANGUARD

Safety data from the VANGUARD study safety population, included 64 patients with HAE randomised to receive either 200 mg garadacimab (n=39) or placebo (n=25) SC once monthly. The analyses summarise data collected during the 6-month treatment period across multiple safety parameters.

9.1.1.1 Overview of adverse events

During the 6-month treatment period, 75 AEs occurred in 25 (64%) of 39 patients in the garadacimab group and 54 AEs occurred in 15 (60%) of 25 patients in the placebo group (Table 87 in Appendix E).

The most common treatment-emergent adverse events (TEAEs) were upper-respiratory tract infections, nasopharyngitis, and headaches. One SAE (a severe laryngeal attack) occurred in the garadacimab group but was assessed as unrelated to treatment. No adverse events of special interest (AESI) (anaphylaxis, thromboembolic events, or abnormal bleeding) occurred. There were no deaths or treatment discontinuations due to AEs.

Injection-site reactions occurred in 5% of garadacimab patients and 12% of placebo patients. One garadacimab patient had increased prothrombin fragment 1+2 An overview of AEs is summarised inTable 87. Overall, the safety profile of garadacimab was similar to placebo, with no major safety signals identified during the study period (Craig et al. 2023).

9.1.1.2 Common treatment-emergent adverse events

In the garadacimab 200 mg group (N=39), 25 patients (64.1%) experienced a total of 75 TEAEs (CSL Behring GmbH 2022b). The most common TEAEs by System Organ Class (incidence of ≥10%) in both garadacimab 200 mg and placebo arms were infections and infestations (33.3% of patients, 28.0% of events), followed by gastrointestinal disorders (20.5% of patients, 13.3% of events). By preferred term (incidence of ≥3%), the most frequently reported TEAEs in both garadacimab 200 mg and placebo arms were upper respiratory tract infection (10.3% of patients, 5.3% of events) and headache (7.7% of patients, 12.0% of events). Injection site reactions occurred in 2 patients (5.1%), accounting for 3 events (4.0%), all of which were of mild severity, transient and resolved within 1–4 days (Craig et al. 2023).

9.1.1.3 Treatment-related TEAEs

Overall, treatment-related TEAEs were infrequent and mostly mild (Table 88 in Appendix E) (CSL Behring GmbH 2022b). In the garadacimab 200 mg group (N=39), 4 patients (10.3%) experienced 9 treatment-related TEAEs. These were primarily injection site reactions (2 patients, 3 events) and headaches (1 patient, 5 events). One patient had increased prothrombin fragment 1+2. In the placebo arm, three events of fatigue that were related to study treatment were reported in one patient; all events were of mild severity, occurred within 24 hours after SC dose, and all resolved within three days (Craig et al. 2023).

9.1.1.4 Deaths, serious adverse events and adverse events of special interest

No deaths occurred in the during the VANGUARD study.

One patient (2.6%) in the garadacimab 200mg group experienced one SAE of HAE (reported term: overnight stay in hospital for observation after laryngeal attack). This event was severe in intensity but was assessed as not related to the study treatment and had an outcome of recovered/resolved. No events were assessed as AESIs by the investigator during the study as per protocol (CSL Behring GmbH 2022b).

9.1.1.5 Clinical laboratory evaluation and immunogenicity

There were no clinically relevant trends or imbalances across treatment arms for haematology, biochemistry, urinalysis, or coagulation parameters in the VANGUARD study. Three patients in the garadacimab 200 mg arm had transient aPTT prolongation (59.4-126 seconds) without associated bleeding events (Craig et al. 2023).

Two patients (5.1%) in the garadacimab 200 mg arm had very low-level anti-garadacimab antibody responses (titre value 10) (one at baseline and one at Day 182), without any observed impact on pharmacokinetics, pharmacodynamics, safety, or efficacy (Craig et al. 2023, CSL Behring GmbH 2022b)

9.1.2 CSL312_2001

In CSL312_2001, across all treatment groups, no SAEs or AESIs (i.e., anaphylaxis, thromboembolic events, or bleeding) were observed, showing that SC treatment with garadacimab was well tolerated for up to 12 weeks (Craig et al. 2022).

9.1.3 HELP

The most frequently reported TEAEs (excluding HAE attacks) among patients treated with lanadelumab throughout the treatment period were injection site pain (42.9%), viral upper respiratory tract infection (23.8%), headache (20.2%), injection site erythema (9.5%), injection site bruising (7.1%), and dizziness (6.0%). The majority of TEAEs (98.5%) were mild to moderate in severity. AEs considered related to lanadelumab treatment most commonly included injection site pain (41.7%), injection site erythema (9.5%), injection site bruising (6.0%), and headache (7.1%) (Banerji et al. 2018).

There were no deaths or related serious TEAEs during the HELP study (Banerji et al. 2018).

9.1.4 Comparison of safety data

An overview of safety events during the respective study's treatment periods is provided in Table 23.

Table 23 Overview of safety events during the respective treatment periods

	VANGUARD		CSL312_2001		HELP		
	Garadacimab 200 mg (N=39) ((Craig et al. 2023))	Placebo (N=25) ((Craig et al. 2023))	Garadacimab 200 mg (N=18) (Craig et al. 2022)	Placebo (N=8) (Craig et al. 2022)	Lanadelumab 300 mg Q2W (N=27) ((Banerji et al. 2018))	Placebo (N=41) ((Banerji et al. 2018))	Difference, % (95 % CI)
Number of adverse events, n	75	54	18	12	NR	NR	NR
Number and proportion of patients with ≥1 adverse events, n (%)	25 (64.1)	15 (60.0)	7 (88)	6 (75)	26 (96.3)	31 (75.6)	NR
Number of serious adverse events*, n	1	0	0	0	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	1 (2.6)	0 (0)	0	0	1 (3.7)	0	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[s], n (%)	NR	NR	NR	NR	NR	NR	NR
Number of adverse reactions, n	3	3	NR	NR	NR	NR	NR

Number and proportion of patients with ≥ 1 adverse reactions, n (%)	2 (5.1)	3 (12.0)	NR	NR	NR	NR	NR
Number and proportion of patients who had a dose reduction, n (%)	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	0	3	0	0	NR	NR	NR
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	NR	NR	0	0	0	1 (2.4)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.
Abbreviations: CTCAE = common terminology criteria for adverse events; NR = not reported; N = number of scores or individuals; Q2W = every 2 weeks

Table 24 Adverse events used in the health economic model

Adverse events	Garadacimab	Lanadelumab		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justi-fication**

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 25 Adverse events that appear in more than X % of patients

Adverse events		Intervention (N=x)		Comparator (N=x)		Difference, % (95 % CI)	
Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events

10. Documentation of health-related quality of life (HRQoL)

Not applicable.

Table 26 Overview of included HRQoL instruments for HSUV

Measuring instrument	Source	Utilization

10.1 Presentation of the health-related quality of life

Not applicable.

10.1.1 Study design and measuring instrument

10.1.2 Data collection

Table 27 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)

10.1.3 HRQoL results

Table 28 HRQoL [instrument] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value

10.2 Health state utility values (HSUVs) used in the health economic model

Not applicable.

10.2.1 HSUV calculation

10.2.1.1 Mapping

10.2.2 Disutility calculation

10.2.3 HSUV results

Table 29 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

10.3.2 Data collection

10.3.3 HRQoL Results

10.3.4 HSUV and disutility results

Table 30 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				

Table 31 Overview of literature-based utility values

	Comments

11. Resource use and associated costs

Not applicable.

11.1 Medicines - intervention and comparator

Not applicable.

Table 32 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Not applicable.

Table 33 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference

11.4 Disease management costs

Not applicable.

11.4.1 On-demand treatment costs

Table 34 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference

11.5 Costs associated with management of adverse events

Not applicable.

Table 35 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
[Adverse event]		

11.6 Subsequent treatment costs

Not applicable.

Table 36 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing

[Name of the intervention]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]

11.7 Patient costs

Not applicable.

Table 37 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Activity	

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

Not applicable.

12.1 Base case overview

Not applicable.

Table 38 Base case overview

Feature	Description
Comparator	
Type of model	
Time horizon	
Treatment line	
Measurement and valuation of health effects	
Costs included	
Dosage of medicine	
Average time on treatment	
Parametric function for PFS	

Feature	Description
Parametric function for OS	
Inclusion of waste	

12.1.1 Base case results

Table 39 Base case results, discounted estimates

	Garadacimab	Lanadelumab	Difference
Medicine costs			
Medicine costs – co-administration			
Administration			
On-demand treatment acquisition			
On-demand treatment administration			
Resource use			
Costs associated with management of adverse events			
Subsequent treatment costs			
Patient costs			
Palliative care costs			
Total costs			
Life years gained (Prone to attack)			
Life years gained (Full attack freedom)			
Total life years			
QALYs (Prone to attack)			

	Garadacimab	Lanadelumab	Difference
QALYs (Full attack freedom)			
QALYs (adverse reactions)			
Total QALYs			
Incremental costs per life year gained			
Incremental cost per QALY gained (ICER)			

12.2 Sensitivity analyses

Not applicable.

12.2.1 Deterministic sensitivity analyses

Table 40 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					

12.2.2 Probabilistic sensitivity analyses

13. Budget impact analysis

Not applicable.

Table 41 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		

	Year 1	Year 2	Year 3	Year 4	Year 5
			Non-recommendation		

Budget impact

Table 42 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended					
The medicine under consideration is NOT recommended					
Budget impact of the recommendation					

14. List of experts

[redacted]

15. References

Austin, P. C. 2009. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med,* 28**,** 3083-107.

Banerji, A., Riedl, M. A., Bernstein, J. A., Cicardi, M., Longhurst, H. J., Zuraw, B. L., Busse, P. J., Anderson, J., Magerl, M., Martinez-Saguer, I., Davis-Lorton, M., Zanichelli, A., Li, H. H., Craig, T., Jacobs, J., Johnston, D. T., Shapiro, R., Yang, W. H., Lumry, W. R., Manning, M. E., Schwartz, L. B., Shennak, M., Soteres, D., Zaragoza-Urdaz, R. H., Gierer, S., Smith, A. M., Tachdjian, R., Wedner, H. J., Hebert, J., Rehman, S. M., Staubach, P., Schranz, J., Baptista, J., Nothaft, W., Maurer, M. & Investigators, H. 2018. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. *JAMA,* 320**,** 2108-2121.

Betschel, S., Badiou, J., Binkley, K., Borici-Mazi, R., Hebert, J., Kanani, A., Keith, P., Lacuesta, G., Waserman, S., Yang, B., Aygoren-Pursun, E., Bernstein, J., Bork, K., Caballero, T., Cicardi, M., Craig, T., Farkas, H., Grumach, A., Katelaris, C., Longhurst, H., Riedl, M., Zuraw, B., Berger, M., Boursiquot, J. N., Boysen, H., Castaldo, A., Chapdelaine, H., Connors, L., Fu, L., Goodyear, D., Haynes, A., Kamra, P., Kim, H., Lang-Robertson, K., Leith, E., McCusker, C., Moote, B., O'Keefe, A., Othman, I., Poon, M. C., Ritchie, B., St-Pierre, C., Stark, D. & Tsai,

E. 2019. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol,* 15**,** 72.

Bork, K., Anderson, J. T., Caballero, T., Craig, T., Johnston, D. T., Li, H. H., Longhurst, H. J., Radojicic, C. & Riedl, M. A. 2021. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. *Allergy Asthma Clin Immunol,* 17**,** 40.

Busse, P. & Kaplan, A. 2022. Specific Targeting of Plasma Kallikrein for Treatment of Hereditary Angioedema: A Revolutionary Decade. *J Allergy Clin Immunol Pract,* 10**,** 716-722.

Busse, P. J. & Christiansen, S. C. 2020. Hereditary Angioedema. *N Engl J Med,* 382**,** 1136-1148.

Busse, P. J., Christiansen, S. C., Riedl, M. A., Banerji, A., Bernstein, J. A., Castaldo, A. J., Craig, T., Davis-Lorton, M., Frank, M. M., Li, H. H., Lumry, W. R. & Zuraw, B. L. 2021. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract,* 9**,** 132-150 e3.

Bygum, A. 2009. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol,* 161**,** 1153-8.

Bygum, A. 2014. Hereditary angioedema - consequences of a new treatment paradigm in Denmark. *Acta Derm Venereol,* 94**,** 436-41.

Caballero, T., Aygoren-Pursun, E., Bygum, A., Beusterien, K., Hautamaki, E., Sisic, Z., Wait, S. & Boysen, H. B. 2014. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc,* 35**,** 47-53.

CADTH 2020. CADTH Common Drug Review Clinical Review Report for Lanadelumab (Takhzyro).

Canadian Agency for Drugs and Technologies in Health. 2019. *CADTH Canadian Drug Expert Committee Recommendation* [Online]. Available: https://www.cadth.ca/sites/default/files/cdr/complete/SR0618%20Takhzyro%20-%20CDEC%20Final%20Recommendation%20November%2022%2C%202019_for%20posting.pdf [Accessed 16 May 2024].

Canadian Agency for Drugs and Technologies in Health. 2020. *Clinical Review Report - Lanadelumab (Takhzyro)* [Online]. Available: https://www.cadth.ca/sites/default/files/cdr/clinical/sr0618-takhzyro-clinical-review-report.pdf [Accessed 12 August 2024].

Cao, H., Biondo, M., Lioe, H., Busfield, S., Rayzman, V., Nieswandt, B., Bork, K., Harrison, L. C., Auyeung, P., Farkas, H., Csuka, D., Pelzing, M., Dower, S., Wilson, M. J., Nash, A., Nolte, M. W. & Panousis, C. 2018. Antibody-mediated inhibition of FXIIa blocks downstream bradykinin generation. *J Allergy Clin Immunol,* 142**,** 1355-1358.

Craig, T., Magerl, M., Levy, D. S., Reshef, A., Lumry, W. R., Martinez-Saguer, I., Jacobs, J. S., Yang, W. H., Ritchie, B., Aygoren-Pursun, E., Keith, P. K., Busse, P., Feuersenger, H., Pawaskar, D., Jacobs, I., Pragst, I. & Doyle, M. K. 2022. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet,* 399**,** 945-955.

Craig, T. J., Levy, D. S., Reshef, A., Lumry, W. R., Martinez-Saguer, I., Jacobs, J. S., Yang, W. H., Ritchie, B., Aygoren-Pursun, E., Keith, P. K., Busse, P., Feuersenger, H., Alexandru Bica, M., Jacobs, I., Pragst, I. & Magerl, M. 2024. Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study. *Lancet Haematol,* 11**,** e436-e447.

Craig, T. J., Reshef, A., Li, H. H., Jacobs, J. S., Bernstein, J. A., Farkas, H., Yang, W. H., Stroes, E. S. G., Ohsawa, I., Tachdjian, R., Manning, M. E., Lumry, W. R., Saguer, I. M., Aygoren-Pursun, E., Ritchie, B., Sussman, G. L., Anderson, J., Kawahata, K., Suzuki, Y., Staubach, P., Treudler, R., Feuersenger, H., Glassman, F., Jacobs, I. & Magerl, M. 2023. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet,* 401**,** 1079-1090.

CSL Behring 2020. Clinical Study Protocol: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous

Administration of CSL312 (garadacimab) in the Prophylactic Treatment of Hereditary Angioedema.
CSL Behring 2022. 253590_CSL312_3001_Final_Tables_20220829.
CSL Behring GmbH 2022a. CSL312_2001 garadacimab CSR, final version. *Data on file*.
CSL Behring GmbH 2022b. CSL312_3001 VANGUARD garadacimab CSR, final version. *Data on file*.
CSL Behring GmbH 2022c. A Systematic Literature Review of Randomized Controlled Trials Investigating Prophylactic Interventions in HAE Among Adolescents and Adults. *Data on file*.
Dias, S., Welton, N. J., Sutton, A. J. & Ades, A. 2011. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials.
European Medicines Agency. 2025. *Andembry - Summary of Product Characteristics* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/andembry [Accessed].
EuroQol. 2025. *EQ-5D-5L* [Online]. Available: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/ [Accessed 15JAN2025].
Goodyear, D., Lumry, W., Anderson, J., Gagnon, R., Brouwer, E., Andriotti, T., Fei, K., Tachdjian, R., Yegin, A. & Craig, T. 2022. Treatment patterns among patients with HAE-C1-INH: Interim analysis findings from US and Canada participants in the EMPOWER study. *Journal of Allergy and Clinical Immunology,* 149**,** AB167.
Higgins JPT, L. T., Deeks JJ 2023a. Chapter 6.4.1: Effect measures for dichotomous outcomes. *In:* HIGGINS JPT, T. J., CHANDLER J, CUMPSTON M, LI T, PAGE MJ, WELCH VA (ed.) *Cochrane Handbook for Systematic Reviews of Interventions.* 6.4 ed.: Cochrane.
Higgins JPT, T. J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA 2023b. *Cochrane Handbook for Systematic Reviews of Interventions version 6.4* Cochrane.
Itzler, R., Brennan, C. J., Cabanday, D. & Lumry, W. R. 2024a. Assessing benefits of being attack-free for subjects with hereditary angioedema.
Itzler, R., Lumry, W. R., Sears, J., Braverman, J., Li, Y., Brennan, C. J. & Koch, G. G. 2024b. An international survey assessing the effects of the duration of attack-free period on health-related quality of life for patients with hereditary angioedema. *Orphanet J Rare Dis,* 19**,** 241.
Jean-Baptiste, M., Itzler, R., Prusty, S., Supina, D. & Martin, M. L. 2022. The symptom experience of hereditary angioedema (HAE) patients beyond HAE attacks: literature review and clinician interviews. *Orphanet J Rare Dis,* 17**,** 232.
Kiani, S., Jacobs, J., Deasi, B., Aggarwal, K., Murray, S. C., Iocca, H. & Lumry, W. R. 2021. Durable reduction in hereditary angioedema (HAE) attack rates with berotralstat over 24 months: Results from the phase 3 apeX-2 study. *European Journal of Allergy and Clinical Immunology,* 76**,** 16.
Longhurst, H. & Cicardi, M. 2012. Hereditary angio-oedema. *Lancet,* 379**,** 474-81.
Longhurst, H., Cicardi, M., Craig, T., Bork, K., Grattan, C., Baker, J., Li, H. H., Reshef, A., Bonner, J., Bernstein, J. A., Anderson, J., Lumry, W. R., Farkas, H., Katelaris, C. H., Sussman, G. L., Jacobs, J., Riedl, M., Manning, M. E., Hebert, J., Keith, P. K., Kivity, S., Neri, S., Levy, D. S., Baeza, M. L., Nathan, R., Schwartz, L. B., Caballero, T., Yang, W., Crisan, I., Hernandez, M. D., Hussain, I., Tarzi, M., Ritchie, B., Kralickova, P., Guilarte, M., Rehman, S. M., Banerji, A., Gower, R. G., Bensen-Kennedy, D., Edelman, J., Feuersenger, H., Lawo, J. P., Machnig, T., Pawaskar, D., Pragst, I., Zuraw, B. L. & Investigators, C. 2017. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. *N Engl J Med,* 376**,** 1131-1140.
Lopez Lera, A. 2021. Pathophysiology and underlying mechanisms in hereditary angioedema. *Balkan Med J,* 38**,** 82-88.
Lumry, W. R. 2013. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. *Am J Manag Care,* 19**,** s103-10.
Maurer, M., Magerl, M., Betschel, S., Aberer, W., Ansotegui, I. J., Aygoren-Pursun, E., Banerji, A., Bara, N. A., Boccon-Gibod, I., Bork, K., Bouillet, L., Boysen, H. B., Brodszki, N., Busse, P. J., Bygum, A., Caballero, T., Cancian, M., Castaldo, A., Cohn, D. M., Csuka, D., Farkas, H.,

Gompels, M., Gower, R., Grumach, A. S., Guidos-Fogelbach, G., Hide, M., Kang, H. R., Kaplan, A. P., Katelaris, C., Kiani-Alikhan, S., Lei, W. T., Lockey, R., Longhurst, H., Lumry, W. R., MacGinnitie, A., Malbran, A., Martinez Saguer, I., Matta, J. J., Nast, A., Nguyen, D., Nieto-Martinez, S. A., Pawankar, R., Peter, J., Porebski, G., Prior, N., Reshef, A., Riedl, M., Ritchie, B., Rafique Sheikh, F., Smith, W. B., Spaeth, P. J., Stobiecki, M., Toubi, E., Varga, L. A., Weller, K., Zanichelli, A., Zhi, Y., Zuraw, B. & Craig, T. 2022. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy,* 77**,** 1961-1990.

McKenzie, A., Roberts, A., Malandkar, S., Feuersenger, H., Panousis, C. & Pawaskar, D. 2022. A phase I, first-in-human, randomized dose-escalation study of anti-activated factor XII monoclonal antibody garadacimab. *Clin Transl Sci,* 15**,** 626-637.

Mendivil, J., Murphy, R., de la Cruz, M., Janssen, E., Boysen, H. B., Jain, G., Aygoren-Pursun, E., Hirji, I. & Devercelli, G. 2021. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. *Orphanet J Rare Dis,* 16**,** 94.

National Library of Medicine. 2021. *Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE* [Online]. Available: https://www.clinicaltrials.gov/study/NCT02586805?term=NCT02586805&rank=1 [Accessed 12 August 2024].

National Library of Medicine. 2022. *A Study to Investigate CSL312 in Subjects With Hereditary Angioedema (HAE)* [Online]. Available: https://www.clinicaltrials.gov/study/NCT03712228?term=NCT03712228&rank=1 [Accessed 7 May 2024].

National Library of Medicine. 2023. *CSL312 (Garadacimab) in the Prevention of Hereditary Angioedema Attacks* [Online]. Available: https://www.clinicaltrials.gov/study/NCT04656418?term=NCT04656418&rank=1 [Accessed 7 May 2023].

National Library of Medicine. 2024. *Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema Attacks* [Online]. Available: https://www.clinicaltrials.gov/study/NCT04739059?term=NCT04739059&rank=1 [Accessed 7 May 2024].

Nordenfelt, P., Nilsson, M., Lindfors, A., Wahlgren, C. F. & Bjorkander, J. 2017. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. *Allergy Asthma Proc,* 38**,** 447-455.

Okuno, K. 2023. Guideline for hereditary angioedema(HAE)by the Japanese Association for Complement Research: The 2023 revision and update. *Presented at the 59th Japanese Complement Symposium*.

Pawaskar, D., Chen, X., Glassman, F., May, F., Roberts, A., Biondo, M., McKenzie, A., Nolte, M. W., Jusko, W. J. & Tortorici, M. 2022. Pharmacokinetic/pharmacodynamic modeling for dose selection for the first-in-human trial of the activated Factor XII inhibitor garadacimab (CSL312). *Clin Transl Sci,* 15**,** 709-720.

Phillippo, D., Ades, T., Dias, S., Palmer, S., Abrams, K. & Welton, N. 2016. Methods for population-adjusted indirect comparisons in submissions to NICE. *Technical Support Document,* 18.

Phillippo, D. M., Ades, A. E., Dias, S., Palmer, S., Abrams, K. R. & Welton, N. J. 2018. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Med Decis Making,* 38**,** 200-211.

Shah, C. H., Princic, N., Evans, K. A. & Schultz, B. G. 2023. Real-world changes in costs over time among patients in the United States with hereditary angioedema on long-term prophylaxis with lanadelumab. *J Med Econ,* 26**,** 871-877.

Signorovitch, J. E., Wu, E. Q., Yu, A. P., Gerrits, C. M., Kantor, E., Bao, Y., Gupta, S. R. & Mulani, P. M. 2010. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics,* 28**,** 935-45.

Sinnathamby, E. S., Issa, P. P., Roberts, L., Norwood, H., Malone, K., Vemulapalli, H., Ahmadzadeh, S., Cornett, E. M., Shekoohi, S. & Kaye, A. D. 2023. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. *Adv Ther,* 40**,** 814-827.

Statistics Denmark. 2024. *Population figures* [Online]. Available: https://www.dst.dk/en/Statistik/emner/borgere/befolkning/befolkningstal [Accessed 26 September 2024].

Takeda Pharma. 2017. *HELP Study - Statistical Analysis Plan* [Online]. Available: https://cdn.clinicaltrials.gov/large-docs/05/NCT02586805/SAP_005.pdf [Accessed 14JAN2025].

The Danish Medicines Council. 2020a. *Baggrund for Medicinrådets anbefaling vedrørende lanadelumab som mulig standardbehandling til forebyggende behandling af arveligt angioødem* [Online]. Available: https://medicinraadet-classic.azureedge.net/media/kfshf5hu/baggrund-for-medicinraadets-anbefaling-vedr-lanadelumab-til-arveligt-angiooedem-vers-1-0_adlegacy.pdf [Accessed 11 April 2024].

The Danish Medicines Council. 2020b. *Lanadelumab (Takhzyro)* [Online]. Available: https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/l/lanadelumab-takhzyro-arveligt-angioodem [Accessed 27 September 2024].

The Danish Medicines Council. 2023. *Protokol for Medicinrådets behandlingsvejledning vedrørende lægemidler til rutinemæssig forebyggende behandling af arveligt angioødem* [Online]. Available: https://medicinraadet-dk.b-cdn.net/media/ypcbkyrk/protokol-for-medicinr%C3%A5dets-behandlingsvejl-vedr-l%C3%A6gemidler-til-arveligt-angio%C3%B8dem-vers-2-0.pdf [Accessed 18 December 2024].

The Danish Medicines Council. 2024. *Opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til forebyggende behandling af arveligt angioødem* [Online]. Available: https://medicinraadet-dk.b-cdn.net/media/4eedykfy/opsummering-af-medicinradets-evidensgennemgang-vedr-arveligt-angioodem-version-1-0.pdf [Accessed 8 January 2025].

The European Medicines Agency. 2024. *Takhzyro SmPC* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/takhzyro [Accessed 10 May 2024].

Weller, K., Groffik, A., Magerl, M., Tohme, N., Martus, P., Krause, K., Metz, M., Staubach, P. & Maurer, M. 2012. Development and construct validation of the angioedema quality of life questionnaire. *Allergy,* 67**,** 1289-98.

Weller, K., Magerl, M., Peveling-Oberhag, A., Martus, P., Staubach, P. & Maurer, M. 2016. The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. *Allergy,* 71**,** 1203-9.

Zuraw, B. L., Bernstein, J. A., Lang, D. M., Craig, T., Dreyfus, D., Hsieh, F., Khan, D., Sheikh, J., Weldon, D., Bernstein, D. I., Blessing-Moore, J., Cox, L., Nicklas, R. A., Oppenheimer, J., Portnoy, J. M., Randolph, C. R., Schuller, D. E., Spector, S. L., Tilles, S. A., Wallace, D., American Academy of Allergy, A., Immunology, American College of Allergy, A. & Immunology 2013. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol,* 131**,** 1491-3.

Zuraw, B. L. & Christiansen, S. C. 2011. Pathophysiology of hereditary angioedema. *Am J Rhinol Allergy,* 25**,** 373-8.

Appendix A. Main characteristics of studies included

Table 43 Main characteristic of studies included

Trial name: A Multicentre, Double-blind, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema	**NCT number: NCT04656418**
Objective	The objective of this study is to investigate the efficacy and safety of subcutaneous administration of garadacimab in the prophylactic treatment of HAE.
Publications – title, author, journal, year	Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Craig, T. J., Reshef, A., Li, H. H., Jacobs, J. S., Bernstein, J. A., Farkas, H., Yang, W. H., Stroes, E. S. G., Ohsawa, I., Tachdjian, R., Manning, M. E., Lumry, W. R., Saguer, I. M., Aygoren-Pursun, E., Ritchie, B., Sussman, G. L., Anderson, J., Kawahata, K., Suzuki, Y., Staubach, P., Treudler, R., Feuersenger, H., Glassman, F., Jacobs, I. & Magerl, M. *Lancet*. 2023
Study type and design	This is a multicentre, double-blind, randomized, placebo-controlled, parallel-arm study to investigate the efficacy and safety of subcutaneous administration of garadacimab in the prophylactic treatment of HAE. Patients with at least two HAE attacks during the run-in period were randomly assigned to garadacimab or placebo in a ratio 3:2 by an Interactive response technology (IRT) system. In case of emergencies, revealing the patients' treatment was permitted. Study start: 27.01.2021. Study completion: 07.06.2022
Sample size (n)	64 patients
Main inclusion criteria	Male or female ≥ 12 years of age; diagnosed with clinically confirmed C1-INH HAE; experience ≥ 3 attacks during the 3 months before screening. Note: For subjects 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.
Main exclusion criteria	Concomitant diagnosis of another form of angioedema such as idiopathic or acquired angioedema, recurrent angioedema associated with urticarial or HAE type 3 For adult patients: use of C1-INH products, androgens, antifibrinolytics or other small molecule medications for routine prophylaxis against HAE attacks within 2 weeks before the run-in period

Trial name: A Multicentre, Double-blind, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema	NCT number: NCT04656418
Intervention	Patients in the treatment arm (n=39) received an initial loading dose of twice 200 mg garadacimab and thereafter a monthly dose of 200 mg garadacimab.
Comparator(s)	Patients in the comparator arm (n=25) received placebo twice during the initial loading phase and thereafter once monthly.
Follow-up time	Follow-up visits occurred every two weeks from day 1 throughout the treatment period of 6 months. Another follow-up visit was performed at day 242.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoints:** • Time-normalized number of HAE attacks per month during treatment period **Secondary and exploratory endpoints:** • percentage change in the time-normalized number of HAE attacks per month during the treatment period compared to the run-in period • Time-normalized number of HAE attacks per month requiring on-demand treatment • Time-normalized number of moderate or severe HAE attacks per month • Time-normalized number of HAE attacks per month in the first 3-months and second 3-months of treatment period • Relative difference in means in the time-normalized number of HAE attacks per month between garadacimab to placebo • Percentage of participants with a response to SGART • Number of participants with at least one AE, SAE, and AESI • Number of participants with CSL312-induced anti-CSL312 antibodies • Number of participants with clinically significant abnormalities in laboratory assessments reported as TEAEs • Percentage of participants with at least one AE, SAE, and AESI • Percentage of participants with CSL312-induced anti-CSL312 antibodies • Percentage of participants with clinically significant abnormalities in laboratory assessments reported as TEAEs

Trial name: A Multicentre, Double-blind, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema	NCT number: NCT04656418
	Exploratory endpoints included the time to first attack after days 1 and 14, and garadacimab concentrations at scheduled timepoints during the treatment period and at follow-up visit.
Method of analysis	All efficacy analyses were ITT analyses. Attack rates during the treatment period were assessed by a linear model assuming a Poisson distribution. The primary endpoint was evaluated using a Wilcoxon test. Hierarchically tested secondary endpoints were assessed using a Wilcoxon test, Fisher exact test, and χ^2 test. All other secondary or exploratory endpoints were evaluated by Wilcoxon or Fisher exact test. Continues safety variables were presented using mean or median values. A p value of ≤ 0.05 was considered statistically significant.
Subgroup analyses	Not applicable.
Other relevant information	None.

Sources: (National Library of Medicine 2023, Craig et al. 2023)
Abbreviations: AE = Adverse event; AESI = Adverse event of special interest; C1-INH = C1 esterase inhibitor; HAE = Hereditary angioedema; IRT = Interactive response technology; ITT = Intention-to-treat; n = Number of observations or individuals; NCT = National clinical trial; SAE = Severe adverse event; SGART = Subject's global assessment of response to therapy; TEAE = Treatment-emergent adverse event.

Trial name: An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema	NCT number: NCT04739059
Objective	The objective of this study was to evaluate the long-term efficacy and safety of garadacimab when administered subcutaneously.
Publications – title, author, journal, year	Ongoing.
Study type and design	This study is a Phase 3b, multinational, multicentre, open-label study. Patients included were previously enrolled in the VANGUARD Phase 3 study, the CSL312_2001 Phase 2 study, or eligible garadacimab-naïve patients. Screening and run-in were only performed for garadacimab-naïve patients. After the treatment period, all patients entered a 2-month follow-up period. Study start: 29.03.2021. Estimated study completion: November 2025
Sample size (n)	171
Main inclusion criteria	• Males and females aged ≥ 12 years • Diagnosed with clinically confirmed C1-INH HAE • Experienced ≥ 3 HAE attacks during the 3 months before Screening

	• Participated in the Run-in Period for at least 1 month (CSL312-naïve subjects only) • Experienced at least an average of 1 HAE attack per month during the Run-in Period
Main exclusion criteria	• Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema or recurrent angioedema associated with urticaria • Use of C1-INH products, androgens, antifibrinolytics or other small molecule medications for routine prophylaxis against HAE attacks at least two weeks before the first day of the run-in period • Use of monoclonal antibodies such as lanadelumab 3 months before the first day of the run-in period. • Female subjects use oestrogen-containing oral contraceptives or hormone replacement therapy within four weeks prior to screening • Female or male subjects who are fertile and sexually active not using or not willing to use an acceptable method of contraception to avoid pregnancy during the study and for 30 days after receipt of the last dose of CSL312 • Pregnant, breastfeeding, or not willing to cease breastfeeding
Intervention	Patients received monthly dose of garadacimab 200 mg for at least 12 months. Garadacimab-naïve patients additionally received an initial loading dose of garadacimab 400 mg at the beginning of the treatment period.
Comparator(s)	No comparators are used in this study.
Follow-up time	Primary outcomes are followed for up to 45 months, secondary outcomes for up to 43 to 45 months. During the first year, outcomes are followed up every 3 months. After that, they are followed up every 6 months.
Is the study used in the health economic model?	No. VANGUARD extension study is not included based on being a single-arm study.
Primary, secondary and exploratory endpoints	**Primary endpoints:** • Number of subjects with TEAEs, percentage of subjects with TEAEs, TEAEs rates per injection, and TEAEs rates per subject year **Secondary and exploratory endpoints:** • Time-normalized number of HAE attacks per month (attack rate) during the run-in and treatment • The percentage reduction and the number of subjects experiencing at least ≥ 50% ≥ 70%, ≥ 90 or equal to 100% (attack free) reduction in the time-normalized number of HAE attacks on treatment compared to run-in period

	• The time-normalized number (per month and year) of HAE attacks requiring on-demand treatment in subjects on treatment • The time-normalized number (per month and year) of moderate and/or severe HAE attacks in subjects on treatment • Number and percentage of subjects rating their response to therapy as good or excellent • The number and percentage of subjects experiencing TEAEs • The number and percentage of subjects experiencing AESIs • The number and percentage of subjects experiencing SAEs, including deaths • The number and percentage of subjects experiencing garadacimab induced anti-CSL312 antibodies
Method of analysis	The primary safety analysis was performed in patients with HAE-C1INH, while secondary safety analyses were performed in the overall population (comprising patients with HAE-C1INH or HAE-nC1-INH). All secondary efficacy endpoints were analysed using the overall population. Continuous variables are presented using mean values with corresponding 95% confidence intervals (CIs) or standard deviation (SD) and median values with corresponding interquartile ranges (IQRs).
Subgroup analyses	Not applicable.
Other relevant information	None.

Source: (National Library of Medicine 2024)
Abbreviations: AESI = Adverse event of special interest; C1-INH = C1 esterase inhibitor; CI = Confidence interval HAE = Hereditary angioedema; HAE-nC1-INH = HAE with normal C1-INH; IQR = Interquartile ranges; NCT = National clinical trial; SAE = Severe adverse event; SD = Standard deviation; TEAE = treatment-emergent adverse event.

Trial name: A Multicenter, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in Subjects With Hereditary Angioedema	**NCT number: NCT03712228**
Objective	The objective of this study is to investigate the clinical efficacy, pharmacokinetics, and safety of garadacimab as prophylaxis to prevent attacks in subjects with HAE-C1-INH.
Publications – title, author, journal, year	Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary. Craig, T., Magerl, M., Levy, D. S., Reshef, A., Lumry, W. R., Martinez-Saguer, I., Jacobs, J. S., Yang, W. H., Ritchie, B., Aygoren-Pursun, E., Keith, P. K., Busse, P., Feuersenger, H., Pawaskar, D., Jacobs, I., Pragst, I. & Doyle, M. K. *Lancet*. 2022.
Study type and design	This study was a Phase 2, randomized, double-blind, placebo-controlled, multinational, multicentre, dose-finding study (TP1). All patients that met the eligibility criteria were randomly assigned 1:1:1:1

	using an IRT and block randomisation block sizes of 1 to 4. Randomisation codes could be revealed in case of emergency, using the interactive response technology. All patients and investigational site staff were masked to treatment assignment. No crossover was allowed.
Sample size (n)	44
Main inclusion criteria	• Male or female • Aged ≥ 18 to ≤ 65 years • A diagnosis of C1-INH HAE or FXII/PLG HAE; • For subjects with C1-INH HAE: ≥ 4 HAE attacks over a consecutive 2-month period during the 3 months before Screening, as documented in the subject's medical record.
Main exclusion criteria	• History of clinically significant arterial or venous thrombosis, or current clinically significant prothrombotic risk • History of an uncontrolled, abnormal bleeding event due to a coagulopathy, or a current clinically significant coagulopathy or clinically significant risks for bleeding events • Known incurable malignancies
Intervention	Patients received initial IV loading doses of placebo, 40 mg, 100 mg, or 300 mg garadacimab at day 1 according to their treatment arm. On day 6, patients received subcutaneous placebo, 75 mg, 200 mg, or 600 mg garadacimab and every four weeks after.
Comparator(s)	Placebo was used as the comparator as well as different doses of garadacimab.
Follow-up time	Patients were contacted every 2 weeks during the run-in period from week 1. During the 12-weeks treatment period, follow-up visits were performed every 2 weeks for the duration of the period. All patients entered an extension period (NCT03712228 open-label extension study).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoints:** • The mean time normalized number of HAE attacks per month **Secondary and exploratory endpoints:** • The number and percentage of responder subjects with C1-INH HAE • The number and percentage of HAE attack-free subjects with C1-INH HAE • The number and percentage of mild, moderate or severe HAE attacks • The mean time-normalized number of mild, moderate or severe HAE attacks per month

	• The number and percentage of subjects with at least 1 HAE attack treated with on-demand HAE medication • Maximum concentration of garadacimab • Area under the concentration-time curve in 1 dosing interval (AUC0-tau) of garadacimab • Time of maximum concentration, terminal elimination half-life, and clearance of garadacimab • Volume of distribution during the elimination phase of garadacimab • The number of subjects with C1-INH HAE with AEs, SAEs, AESI, ISRs, and binding antibodies to garadacimab • Exploratory endpoints were the number of days per month that patients experienced attacks, the number of rescue medication uses per month, pharmacodynamic biomarkers, and investigator-reported and patient-reported outcomes
Method of analysis	Demographic patient characteristics and primary, secondary, and exploratory endpoint data were analysed in the ITT population. Continuous variables were presented using mean values with their respective 95% CI or SD, IQR, and counts of missing and non-missing values. The number of monthly attacks was calculated by the length of the assessment period of each patient in days multiplied by 30.4375. P values of ≤0.05 were considered statistically significant.
Subgroup analyses	Not applicable.
Other relevant information	None.

Sources: (National Library of Medicine 2022, Craig et al. 2022)
Abbreviations: Abbreviations: AE = Adverse event; AESI = Adverse event of special interest; C1-INH = C1 esterase inhibitor; CI = Confidence interval; FXII = Factor XII; HAE = Hereditary angioedema; IQR = Interquartile range; IRT = Interactive response technology; ISR = Injection site reaction; ITT = Intention-to-treat; IV = Intravenous; NCT = National clinical trial; PLG = Plasminogen gene; SAE = Severe adverse event; SD = Standard deviation; SGART = Subject's global assessment of response to therapy; TEAE = Treatment-emergent adverse event.

Trial name: A Multicenter, Randomized, Placebo-controlled, Parallel-arm Open-label Extension Study to Investigate the Efficacy, Pharmacokinetics, and Safety of CSL312 in Subjects With Hereditary Angioedema	**NCT number: NCT03712228**
Objective	Objective of this study was to evaluate the efficacy and safety of garadacimab patient-reported, investigator-reported, and HRQoL outcomes for the treatment of patients with HAE.
Publications – title, author, journal, year	Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study. Craig, T. J., Levy, D. S., Reshef, A., Lumry, W. R., Martinez-Saguer, I., Jacobs, J. S., Yang, W. H., Ritchie, B.,

	Aygoren-Pursun, E., Keith, P. K., Busse, P., Feuersenger, H., Alexandru Bica, M., Jacobs, I., Pragst, I. & Magerl, M. *Lancet Haematol*. 2024
Study type and design	This study was a phase 2 study, with randomised, double-blind, placebo-controlled, and open-label extension periods (TP2). The extension period comprised 44 weeks or longer. Patients that received the placebo, garadacimab 75 mg, or garadacimab 400 mg were re-randomly distributed to the garadacimab 200 mg group or the garadacimab 600 mg group in a 1:1 ratio. Dose up- or downtitration was allowed on a case-to-case basis. Randomisation was stratified and used a fixed block size of 1–4 by means of a centralised IRT.
Sample size (n)	38
Main inclusion criteria	• Male or female • Aged ≥ 18 to ≤ 65 years • A diagnosis of C1-INH HAE or FXII/PLG HAE; • For subjects with C1-INH HAE: ≥ 4 HAE attacks over a consecutive 2-month period during the 3 months before Screening, as documented in the subject's medical record.
Main exclusion criteria	• History of clinically significant arterial or venous thrombosis, or current clinically significant prothrombotic risk • History of an uncontrolled, abnormal bleeding event due to a coagulopathy, or a current clinically significant coagulopathy or clinically significant risks for bleeding events • Known incurable malignancies
Intervention	All patients received subcutaneous garadacimab 200 mg or 600 mg once monthly for 44 weeks or longer. The first three doses were administered under supervision of the investigator. All further doses were self-administered. Patients at garadacimab 200 mg with more than three attacks within two months were eligible for garadacimab 400 mg. On March 20, 2020, patients receiving garadacimab 600 mg were down-titrated to garadacimab 200 mg for the remaining treatment period.
Comparator(s)	No comparators are used in this study.
Follow-up time	Patients reported the occurrence of HAE attacks in an electronic diary starting day 1 and were contacted by the investigator every two weeks for review. Study site assessments were performed every month for the first three months and every three months thereafter. Adverse events were followed up for at least 2 months after finalizing TP2.
Is the study used in the health economic model?	No.
Primary, secondary and exploratory endpoints	Primary endpoints:

	• time-normalised number of HAE attacks in patients C1-INH HAE deficiency or dysfunction receiving garadacimab 200 mg or 600 mg Secondary endpoints: • number and proportion of patients responding to treatment (≥50% relative reduction in attack rate vs the run-in period) • proportion of patients who were attack-free; proportion of patients with mild, moderate, or severe attacks • proportion of patients who experienced attacks treated with on-demand rescue medication • plasma pharmacokinetics in patients with C1-INH HAE deficiency • time-normalised number of HAE attacks per month • Exploratory endpoints included quality of life, patient-reported and investigatorreported outcomes, number of HAE attack-days per month, and time-normalised number of uses of on-demand HAE medication per month
Method of analysis	Demographic patient characteristics and primary, secondary, and exploratory efficacy endpoints were analysed in the ITT population. Patients were analysed according to the dose group they entered at the beginning of TP2. Continuous variables are presented using mean values (95% CIs or SD), IQR, and counts of missing and non-missing values. Categorical values are presented using counts and percentages.
Subgroup analyses	Patients that were down-titrated were reported under the garadacimab 200 mg group after receiving the first garadacimab 200 mg dose. Patients that were up-titrated to garadacimab 400 mg were analysed according to the 200 mg group.
Other relevant information	None.

Sources: (National Library of Medicine 2022, Craig et al. 2024)
Abbreviations: C1-INH = C1 esterase inhibitor, CI = Confidence interval; FXII = Factor XII; HAE = Hereditary angioedema; HRQoL = Health-related quality of life; IQR; Interquartile range; IRT = Interactive response technology; ITT = Intention-to-treat; NCT = National clinical trial; PLG = Plasminogen gene; SD = Standard deviation; TP2 = treatment period 2.

Appendix B. Efficacy results per study

Results per study

Table 44 Results per study

Results of VANGUARD (NCT04656418)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Time-Normalized Number of HAE Attacks	Garadacimab 200 mg	39	0.27 (0.05 to 0.49)	-1.74	N/A	<0.001	-87%	-96%, -58%	<0.001	The statistical method to evaluate the primary endpoint of the time-normalized number of HAE attacks vs placebo is a two-sided Wilcoxon test (α level 0.05), which showed that there was a statistically significant lower HAE attack rate in subjects receiving garadacimab compared to placebo. A sensitivity analysis adjusted for baseline attack rate using a Poisson model, was used to evaluate the mean attack number of	(Craig et al. 2023, CSL Behring GmbH 2022b)
	Placebo	25	2.01 (1.44 to 2.57)								

Results of VANGUARD (NCT04656418)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										HAE attacks per month in the garadacimab arm and the placebo arm, which corresponded to the 89% reduction in the mean attack rate of HAE attacks in the garadacimab arm compared to placebo noted in this table.	
Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment per month	Garadacimab 200 mg	39	0.23 (0.02 to 0.45)	-1.63	N/A	<0.001(nominal)	-88%	N/A		The analysis of the number of HAE attacks requiring on-demand treatment per month is based on a two-sided Wilcoxon test (α level 0.05), not adjusted for multiplicity. The percentage difference in means was calculated as 100% * (mean time-normalized number of HAE attacks requiring	(Craig et al. 2023, CSL Behring GmbH 2022b)
	Placebo	25	1.86 (1.26 to 2.46)								

Results of VANGUARD (NCT04656418)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										on-demand treatment ratio - 1).	
Time-Normalized Number of Moderate and/or Severe HAE Attacks per month	Garadacimab 200 mg	39	0.13 (0.03 to 0.22)	-1.22	N/A	<0.001(nominal)	-90%	N/A		The normalized number of moderate or severe HAE attacks was tested in an exploratory manner via a two-sided Wilcoxon Test (α level 0.05), not adjusted for multiplicity. The percentage difference in means was calculated as 100% * (mean time-normalized number of moderate and/or severe HAE attacks ratio - 1).	(Craig et al. 2023, CSL Behring GmbH 2022b)
	Placebo	25	1.35 (0.86 to 1.84)								
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	Garadacimab 200 mg	39	74% (29/39 subjects; 58.9, 85.4)				N/A	N/A	N/A	The proportion of Subjects who Achieved ≥90% Attack Rate Reduction compared to the run-in was calculated as part of the secondary endpoint	(Craig et al. 2023, CSL Behring GmbH 2022b)
	Placebo	25	8.3% (2/24 subjects; 2.3, 25.9)								

Results of VANGUARD (NCT04656418)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										evaluating the reduction in the attack rate during the treatment period compared to the run-in and its corresponding 95% CI was calculated.	
Proportion of Attack-Free Patients	Garadacimab 200 mg	39	61.5% (24/39 subjects; 45.9, 75.1)			<0.001 (nominal)	N/A	N/A	N/A	The percentage of subjects with a percentage reduction of 100%, i.e., who do not experience a HAE attack and so are attack-free, was presented and summarized with corresponding 95% CI for the 6-month treatment Period, a Fisher-Test was performed to assess for differences between treatment arms.	(Craig et al. 2023, CSL Behring GmbH 2022b)
	Placebo	25	0% (0/24 subjects; 0.1, 13.8)								
AE-QoL Change	Garadacimab 200 mg	39	-26.47 (-32.8, -20.1)	N/A	N/A	N/A	N/A	N/A	N/A	The AE-QoL was completed using a	(Craig et al. 2023, CSL

Results of VANGUARD (NCT04656418)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										provisioned eCOA solution. From the AE-QoL domain scores, total scores, and changes from baseline were summarized for each treatment arm by study visit. A mixed model for repeated measures (MMRM) was used to test for a treatment effect, a time effect, and a treatment-by-time interaction on the total and domain scores for study visits. This analysis was exploratory.	Behring GmbH 2022b)
	Placebo	25	-2.21 (-11.1, 6.7)								
Porportions of patients achieving an MCID ≥6 points in total score	Garadacimab 200 mg	39	87.9% (29/33 subjects; 71.8, 96.6)	43.88	21.46, 66.30	N/A	N/A	N/A	N/A	The GLMSELECT procedure was performed as a model selection procedure identifying if the minimal	(Craig et al. 2023, CSL Behring GmbH 2022b)

Results of VANGUARD (NCT04656418)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	25	55.0% (11/25 subjects; 31.5, 76.9)							clinically important difference of at least 6 points for the total score and domain scores from Day 1 to Day 182 was associated with: age, baseline attack rate, maximum severity of HAE attacks during Run-in Period, and the anatomical location of the HAE attacks. Logistic regression for total and domain scores with these variables was performed to analyse for a treatment effect on achieving a minimal clinically important difference of at least 6 points	

Results of CSL312_2001 (NCT03712228)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Time Normalized Number of HAE Attacks	Garadacimab 200 mg	8	0.0 (-0.06, 0.15)		N/A	<0.001	98.9%	98, 101		The mean time normalized number of HAE attacks per month was evaluated by dividing the number of attacks of each patient by the length of the patient's assessment period in days, multiplied by 30.4375. Further, it tested against placebo for a difference in the attack rate at an α level of 0.025. The 75 mg garadacimab dose was tested against placebo for the median number of monthly attacks in a post-hoc analysis.	(Craig et al. 2022)
	Placebo	8	4.24 (3.1, 5.0)								
Time-Normalized Number of HAE Attacks Requiring On-	Garadacimab 200 mg	8	0.045 (-0.06 to 0.15)		N/A	N/A	N/A	N/A	N/A	The number of attacks requiring	(Craig et al. 2022)

Results of CSL312_2001 (NCT03712228)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Demand Treatment per month.	Placebo	8	3.98 (2.5 to 5.45)							acute treatment was evaluated using the ITT population.	
Time-Normalized Number of Moderate and/or Severe HAE Attacks	Garadacimab 200 mg	8	Moderate: 0.05 (-0.06 to 0.15) Severe: 0.00 (0, 0)		N/A	N/A	N/A	N/A	N/A	The number and percentage of patients with moderate and/or severe HAE attacks in subjects according to the investigator's assessment based on the subject's description of the attack. The ITT population was used for assessment.	(Craig et al. 2022)
	Placebo	8	Moderate: 1.93 (0.76 to 3.11) Severe: 0.89 (0.25 to 2.03)								
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	Garadacimab 200 mg	8	8/8 (100%)		N/A	N/A	N/A	N/A	N/A	The proportion of Subjects who Achieved ≥90% Attack Rate Reduction compared to the run-in was calculated as part of the secondary	(Craig et al. 2022)
	Placebo	8	0/8 (0%)								

Results of CSL312_2001 (NCT03712228)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										endpoint evaluating Responder subjects and its corresponding 95% CI was calculated.	
Proportion of Attack-Free Patients	Garadacimab 200 mg	8	7/8 (88%)		N/A	N/A	N/A	N/A	N/A	The percentage of subjects with a percentage reduction of 100%, ie, who do not experience a HAE attack and so are attack-free, was presented and summarized with corresponding 95%.	(Craig et al. 2022)
	Placebo	8	0/8 (0%)								

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Rate of Investigator Confirmed HAE Attacks	Lanadelumab 300 mg (every 2 weeks)	27	0.26 (0.14 to 0.46)	−1.71	−2.09 to −1.33	<0.001	0.13	0.07 to 0.24	<0.001	Attack rates are model-based mean attacks per month, defined as 4 weeks. Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. The absolute differences were estimated from a nonlinear function of the model parameters. All P values (Wald test) are reported vs	(Banerji et al. 2018, Takeda Pharma 2017)
	Placebo	41	1.97 (1.64 to 2.36)								

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										placebo. For the estimated relative difference in effect, the P value was adjusted for multiple testing.	
Rate of Investigator Confirmed Hereditary HAE Attacks During Day 14 Through Day 182	Lanadelumab 300 mg (every 2 weeks)	27	0.22 (0.12 to 0.41)	−1.77	−2.16 to −1.38	<0.001	0.11	0.06 to 0.21	<0.001	Attack rates are model-based mean attacks per month, defined as 4 weeks. Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. The	(Banerji et al. 2018, Takeda Pharma 2017)
	Placebo	41	1.99 (1.65 to 2.39)								

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										absolute differences were estimated from a nonlinear function of the model parameters. All *P* values (Wald test) are reported vs placebo. For the estimated relative difference in effect, the *P* value was adjusted for multiple testing.	
Rate of Investigator Confirmed HAE Attack Requiring Acute Treatment	Lanadelumab 300 mg (every 2 weeks)	27	0.21 (0.11 to 0.40)	−1.43	−1.78 to −1.07	<0.001	0.13	0.07 to 0.25	<0.001	Attack rates are model-based mean attacks per month, defined as 4 weeks. Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were	(Banerji et al. 2018, Takeda Pharma 2017)
	Placebo	41	1.64 (1.34 to 2.00)								

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. The absolute differences were estimated from a nonlinear function of the model parameters. All *P* values (Wald test) are reported vs placebo. For the estimated relative difference in effect, the *P* value was adjusted for multiple testing.	
Rate of Moderate or Severe Investigator Confirmed HAE Attacks	Lanadelumab 300 mg (every 2 weeks)	27	0.20 (0.11 to 0.39)	−1.01	−1.32 to −0.71	<0.001	0.17	0.08 to 0.33	<0.001	Attack rates are model-based mean attacks per month,	(Banerji et al. 2018, Takeda Pharma 2017)

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	41	1.22 (0.97 to 1.52)							defined as 4 weeks. Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. The absolute differences were estimated from a nonlinear function of the model parameters. All *P* values (Wald test) are reported vs placebo. For the estimated relative difference in effect,	

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										the *P* value was adjusted for multiple testing.	
Proportion of Subjects who Achieved ≥90% Attack Rate Reduction	Lanadelumab 300 mg (every 2 weeks)	27	18 (66.7%)	16	N/A	N/A	61.8%	39.5 to 78.8	<0.001	Proportion of Subjects who Achieved ≥90% Attack Rate Reduction for each lanadelumab treatment group were compared with the placebo group without adjustment for multiplicity, using Fisher's exact test and t-test, respectively. The observed portion of the treatment period was used for the analysis of binary outcomes.	(Banerji et al. 2018, Takeda Pharma 2017)
	Placebo	41	2 (4.9%)								

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of Attack-Free Patients	Lanadelumab 300 mg (every 2 weeks)	27	12 (44.4%)	11	N/A	N/A	42.0	18.1 to 61.8	<0.001	Proportion of attack-free patients for each lanadelumab treatment group were compared with the placebo group without adjustment for multiplicity, using Fisher's exact test and t-test, respectively. The observed portion of the treatment period was used for the analysis of binary outcomes.	(Banerji et al. 2018, Takeda Pharma 2017)
	Placebo	8	1 (2.4%)								
Attack-Free Days per Month	Lanadelumab 300 mg (every 2 weeks)	27	27.3 (SD 1.3)	4.7	N/A	<0.001	N/A	N/A	N/A	Attack-free days per month for each lanadelumab treatment group were compared with the placebo group without adjustment for multiplicity, using	Banerji et al. 2018b(Takeda Pharma 2017)

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										Fisher's exact test and t-test, respectively. The observed portion of the treatment period was used for the analysis of binary outcomes	
	Placebo	41	22.6 (SD 4.4)								
AE-QoL Change	Lanadelumab 300 mg (every 2 weeks)	26	–21.29 (–28.21 to –14.37)	–16.57	–28.53 to –4.62	0.003	N/A	N/A	N/A	Change in AE-QoL total and domain scores from days 0-182 were compared across the lanadelumab dose regimens and placebo using analysis of covariance adjusting for baseline scores with pairwise t test using the Tukey-	Banerji et al. 2018b(Takeda Pharma 2017)

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										Kramer approximation.	
	Placebo	38	–4.72 (−10.46 to 1.02)								
Proportion of patients achieving an MCID ≥6 points in total score	Lanadelumab 300 mg (every 2 weeks)	26	80.8% (21/26 subjects)	7	N/A	0.001	N/A	N/A	N/A	Chi-squared tests were used to assess the difference in the proportion of patients achieving a responder definition (minimal clinically important difference of –6) in change in the total AE-QoL score from days 0-182, across treatments vs placebo. Logistic regression models were fit to estimate treatment effects on achievement of responder definition,	Banerji et al. 2018b(Takeda Pharma 2017)
	Placebo	38	36.8% (14/38 subjects)								

Results of HELP (NCT02586805)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										adjusting for other relevant covariates.	

Abbreviations: AE = Adverse event; AESI = Adverse events of special interest; AE-QoL = Angioedema Quality of Life Questionnaire; C1-INH = C1 esterase inhibitor; CI = Confidence interval; Cmax = Maximum concentration; eCOA = Electronic clinical outcome assessment; HAE = Hereditary Angioedema; ISRs = Injection site reactions; ITT = Intention-to-treat; MCID = Minimal clinically important difference; NR = Not reported; PT = preferred term; SAE = Serious adverse event; SGART = Subject's Global Assessment of Response to Therapy; SOC = System organ class; T1/2 = Terminal Elimination Half-life; TEAE = Treatment-emergent adverse event; Tmax = Time of maximum concentration

Sources: (Banerji et al. 2018, Craig et al. 2022, Craig et al. 2023)

B.1 Outcomes in VANGUARD – detailed description

B.1.1 Time-normalized number of HAE attacks (primary efficacy endpoint)

During the treatment period, a total of 63 and 264 HAE attacks were experienced across the garadacimab 200 mg and placebo arms of the ITT population, respectively. This yielded a significantly lower mean (95% CI) HAE attack rate of 0.27 (0.05, 0.49) per month with garadacimab 200 mg compared to 2.01 (1.44, 2.57) with placebo (p<0.001), which is equivalent to an 87% reduction in the number of HAE attacks (Figure 4). Similarly, there was an 100% reduction in the median (interquartile range [IQR]) number of HAE attacks per month with garadacimab 200 mg (0 [0.00, 0.31]) compared with placebo (1.35 [1.00, 3.20]).

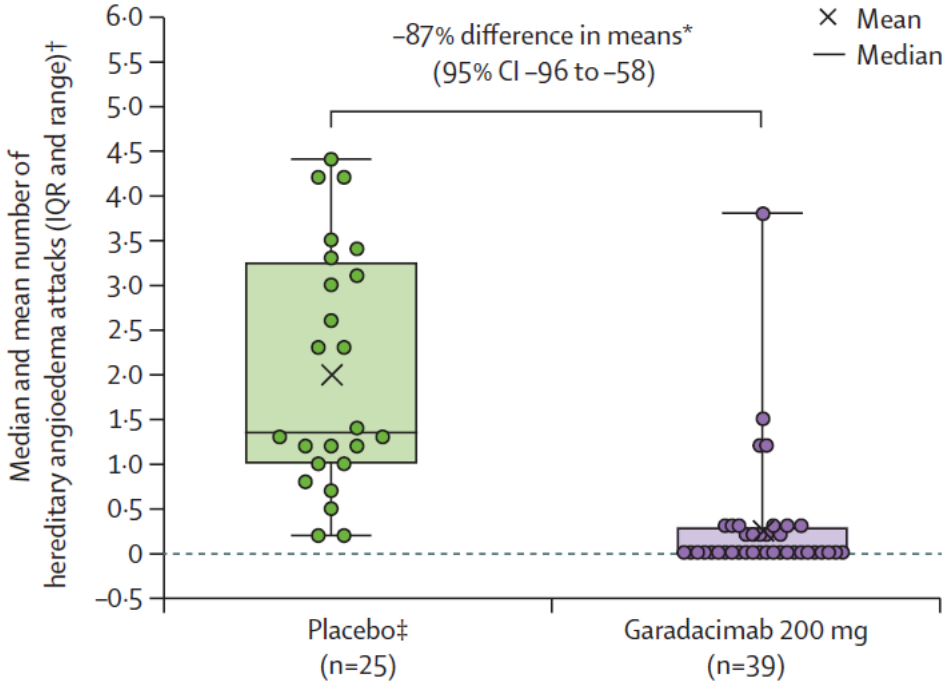


Figure 4 Time-normalized number of HAE attacks (primary efficacy endpoint) – VANGUARD Phase 3 study ITT population (N=64)

* p<0.0001; two-sided Wilcoxon test, hierarchical testing.
† The shaded boxes and error bars represent IQRs and minimum and maximum values, respectively; each dot represents the patient's mean number of HAE attacks per month during the treatment period.
‡ One patient in the placebo group with less than 30 days of treatment was excluded from the analyses, as prespecified in the clinical trial protocol.
Abbreviations: CI = Confidence interval; HAE = Hereditary angioedema; IQR = Interquartile range, ITT: Intention-to-treat; n = Number of observations or individuals.
Source: (Craig et al. 2023)

In a sensitivity analysis, after adjusting for baseline number of attacks, the difference in the least squares (LS) mean (95% CI) monthly number of attacks was –89% (–95, –76). This analysis compared the number of HAE attacks in the treatment period using a generalized linear model for count data assuming a Poisson distribution. The time-

normalized number of HAE attacks in the run-in period as a covariate and the logarithm of the length of subject treatment as an offset variable were included (Craig et al. 2023).

B.1.2 Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment

Overall, garadacimab 200 mg led to an 88% reduction in HAE attacks requiring on-demand treatment per month compared to patients treated with placebo (mean [95% CI]: 0.23 [0.02, 0.45] vs 1.86 [1.26, 2.46], p<0.001) (Figure 5). Findings were similar when the mean number of HAE attacks requiring on-demand treatment per month were calculated over the first 3 months of the treatment period (mean [95% CI]: 0.24 [0.00, 0.48] vs 1.76 [1.18, 2.35], p<0.001) and the second 3 months of the treatment period (mean [95% CI]: 0.23 [0.03, 0.43] vs 1.80 [1.08, 2.52], p<0.001) (Figure 5), suggesting a rapid onset of action and stable treatment response to garadacimab (Craig et al. 2023).

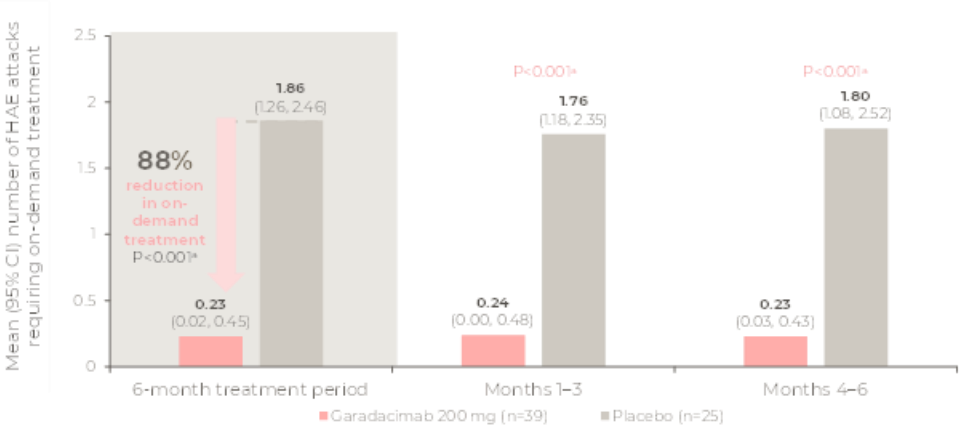


Figure 5 Number of HAE attacks requiring on-demand treatment (secondary efficacy endpoint) – VANGUARD Phase 3 study ITT population (N=64)

[a] Two-sided Wilcoxon test, nominal p-value.
Abbreviations: CI = Confidence interval; ITT = Intention-to-treat; n = Number of observations or individuals.
Source: (Craig et al. 2023)

B.1.3 Time-Normalized Number of Moderate and/or Severe HAE Attacks

Moreover, a significant reduction in moderate or severe HAE attacks (indicative of being highly burdensome) was demonstrated with garadacimab. As shown in Figure 6, there was a 90% reduction in moderate or severe HAE attacks per month in patients treated with garadacimab 200 mg compared with placebo (mean [95% CI]: 0.13 [0.03, 0.22] vs 1.35 [0.86, 1.84], p<0.001).

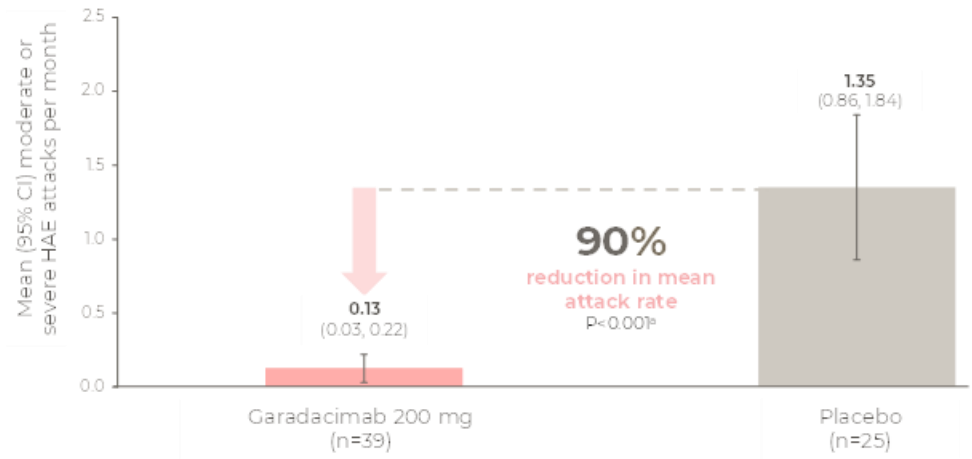


Figure 6 Time-normalized number of moderate or severe HAE attacks (secondary efficacy endpoint) – VANGUARD Phase 3 study ITT population (N=64)

[a] Two-sided Wilcoxon test, nominal p-value.
Abbreviations: CI = Confidence interval; HAE = Hereditary angioedema; ITT = Intention-to-treat; n = Number of observations or individuals.
Source: (Craig et al. 2023)

B.1.4 Proportion of Subjects who Achieved ≥90% Attack Rate Reduction

During the 6-month Treatment Period, the majority of subjects receiving CSL312 (94.9%) were considered responders with a ≥ 50% reduction in the time-normalized number of HAE attacks, compared to 33.3% of subjects receiving placebo. The percentage of subjects with ≥ 70% reduction in HAE attacks in the CSL312 Arm was comparable to the percentage of responders with a ≥ 50% reduction. The percentage of subjects with reductions in HAE attacks of ≥ 90% in the CSL312 Arm was 74.4% (29 / 39 subjects) and in the Placebo Arm 8.3% (2 / 24 subjects).

B.1.5 Proportion of Attack-Free Patients

Achieving attack freedom is a key goal of HAE management. A significantly higher proportion of patients were attack-free over the course of the overall treatment period (61.5% vs 0%, p<0.0001). Of note, a significantly greater proportion of patients treated with garadacimab were also attack-free during the first 3 months of treatment compared with placebo (71.8% vs 8.3%, p<0.001), potentially indicative of the rapid onset of action of garadacimab (Figure 7).

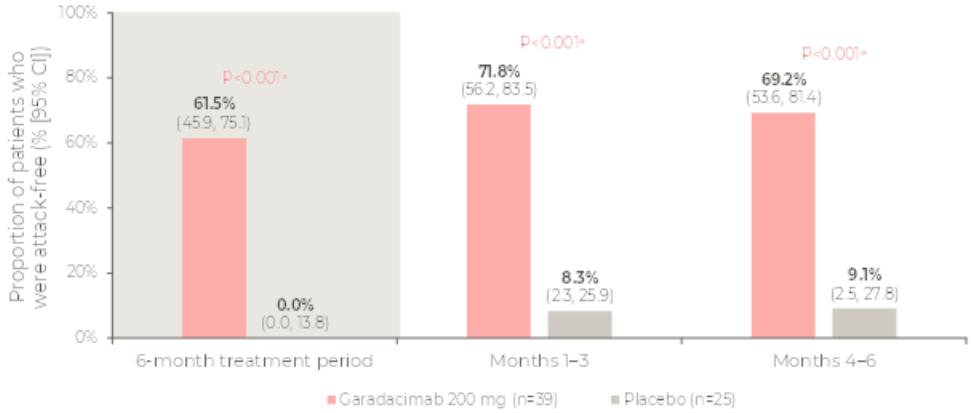


Figure 7 Proportion of patients who were attack-free (secondary efficacy endpoint) – VANGUARD Phase 3 study ITT population (N=64)

a Two-sided Wilcoxon test, nominal p-value.
Abbreviations: CI = Confidence interval; ITT = Intention-to-treat; n = Number of observations or individuals.
Source: (Craig et al. 2023)

B.1.6 AE-QoL Change

The mean (SD) and the change from baseline in mean scores in subjects receiving CSL312 or placebo for all 4 domains (functioning, fatigue and mood, fears and shame, and nutrition) as well as the total score of the Angioedema QoL questionnaire at Day 1 (baseline), Day 31, and Day 182 were collected in evaluable subjects. For subjects in the CSL312 treatment arm, improvement in the mean scores were observed from Day 31. Over the 6-month Treatment Period, further improvements in mean scores were observed and maintained, through Day 182. In the CSL312 Arm, the reduction in mean (SD) total score was -23.702 (15.8377) from baseline to Day 31 and -26.471 (17.8943) from baseline to Day 182. By contrast, in the Placebo Arm, the reduction in mean (SD) total score was -4.972 (10.1830) from baseline to Day 31 and -2.206 (19.1296) from baseline to Day 182. These results were similar for each of the domain scores. Analysis of Angioedema QoL using MMRM for fixed effects showed nominally statistically significant effects of treatment, visit, and treatment-by-visit interaction for total score and for all 4 domain scores (each nominal $p \leq 0.004$), except for the treatment-by-visit interaction for fatigue and mood and visit for nutrition. The baseline HAE attack rate variable did not show a nominally statistically significant effect in any of the domains or total score.

For change from baseline in Angioedema QoL, linear regression with selected variables (treatment [all domains and total score] and anatomical location of HAE attack [functioning and total score]) showed a nominally significant treatment effect in the domains of functioning (nominal $p < 0.001$; mean [SD] change from baseline in CSL312 Arm of -35.8 [23.243]), fatigue and mood (nominal $p = 0.032$; mean [SD] change from baseline in CSL312 Arm of -21.06 [22.870]), fears and shame (nominal $p < 0.001$; mean [SD] change from baseline in CSL312 Arm of -28.03 [24.100]), nutrition (nominal $p = 0.010$; mean [SD] change from baseline in CSL312 Arm of -16.67 [23.316]), and total score (nominal $p < 0.001$; mean [SD] change from baseline in CSL312 Arm of -26.47 [17.894]).There was a nominally statistically significant effect of the anatomical location

of the HAE attacks on the domains of functioning (nominal p = 0.043) and total score (nominal p = 0.033). None of the other variables, including age, baseline HAE attack rate, and maximum severity of HAE attacks, were included in the final model.

B.1.7 Proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182

The clinical meaningfulness of the improvement in scores for the Angioedema QoL was assessed by calculating the proportion of subjects who achieved a minimal clinically important difference (defined as a 6-point change (Weller et al. 2016)) in domain and total scores. From Day 1 to Day 182, there was a higher proportion of subjects who achieved a minimal clinically important difference in the CSL312 Arm compared to the Placebo Arm in all 4 domains of the Angioedema QoL as well as total score (range: 66.7%-90.9% in the CSL312 Arm and 35.0%-55.0% in the Placebo Arm). Logistic regression with selected variables (all domains and total score: treatment, age, maximum severity of HAE attacks during the Run-in Period; functioning, fears and shame, and total score: baseline HAE attack rate; functioning, fatigue and mood, fears and shame, and total score: anatomical location of HAE attack) showed a nominally significant treatment effect in all domains and total score: functioning (nominal p = 0.001); fatigue and mood (nominal p = 0.010); fears and shame (nominal p = 0.014); nutrition (nominal p = 0.040); and total score (nominal p = 0.004). There was a nominally significant effect of age for the domain of fatigue and mood (nominal p = 0.047). No nominally significant treatment effects were observed in the variables of baseline HAE attack rate, maximum severity of HAE attacks during the Run-in Period, and anatomical location of HAE attack for the domains where these variables were included in the final model.

B.2 Outcomes in CSL312_2001 – detailed description

B.2.1 Number of HAE attacks per month (primary efficacy endpoint)

The median (IQR) number of HAE attacks per month during the 12-week treatment period was 4.6 (3.1, 5.0) with placebo. This equated to a significant median (95% CI) reduction in HAE attacks per month of 100% (98, 101) with garadacimab 200 mg (p=0.0002) vs placebo (Figure 8). These results are shown in Craig et al. (2022).

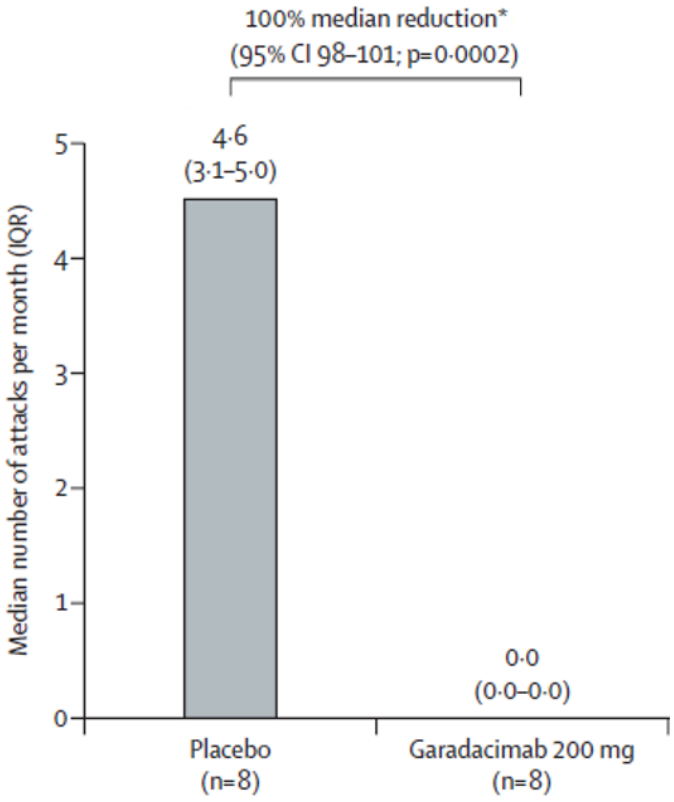


Figure 8 Median number of HAE attacks per month – CSL312_2001 Phase 2 study ITT population (N=32)

* Median reduction in the number of HAE attack per month vs placebo.
Abbreviations: CI = Confidence interval; HAE = Hereditary angioedema; IQR = Interquartile range; ITT = Intention-to-treat; n = Number of observations or individuals.
Source: modified from (Craig et al. 2022)

B.2.2 Proportion of subjects with HAE attacks requiring on-demand treatment

All patients in the placebo arm had ≥1 HAE attack requiring on-demand treatment, compared with 13% in the garadacimab 200 mg arm. Similarly, 94% (89/95) and 100% (1/1) of overall HAE attacks required on-demand treatment in the placebo and garadacimab 200 mg arm (Craig et al. 2022).

B.2.3 Proportion of attack-free patients and subjects who achieved ≥90% attack rate reduction

A summary of secondary efficacy endpoints is reported in Table 44. Overall, there were 95 HAE attacks in the placebo arm and only one HAE attack in the garadacimab 200 mg arm which was of moderate severity (Craig et al. 2022).

No patients in the placebo arm were attack free during the treatment period compared with 88% in the garadacimab 200 mg arm. Similarly, no patients in the placebo arm achieved ≥50% reduction in HAE attacks per month (compared with the run-in period), whereas all patients in the garadacimab 200 mg arm achieved ≥90% reduction in HAE attacks per month (Craig et al. 2022) (Figure 9).

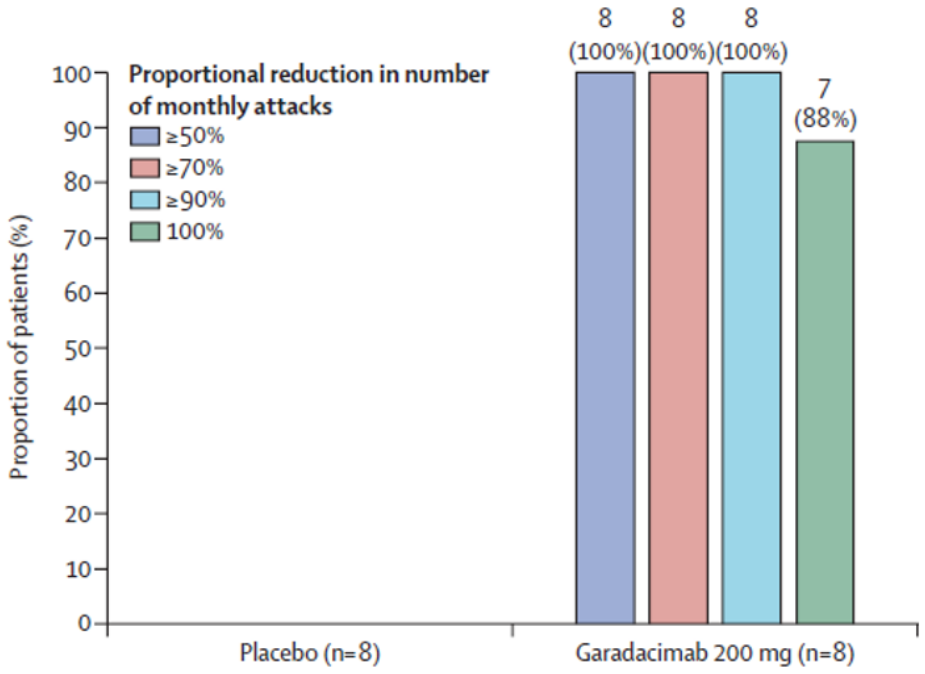


Figure 9 Patients with proportional reduction in the HAE attacks per month – CSL312_2001 Phase 2 study ITT population (N=32)

Abbreviations: HAE = Hereditary angioedema; ITT = Intention-to-treat; n = Number of observations or individuals.
Source: modified from (Craig et al. 2022)

B.3 Outcomes in HELP – detailed description

B.3.1 Rate of investigator confirmed HAE attacks during treatment period (primary efficacy endpoint)

The mean number of monthly HAE attacks during the run-in period ranged from 3.2 to 4.0 attacks across the treatment groups placebo (n=41) and lanadelumab every two weeks 300 mg. Upon lanadelumab treatment the monthly number of attacks throughout the treatment period day 0 to day 182 was 0.26 (95% CI, 0.14-0.46) in the 300 mg every two weeks group, compared to 1.97 (95% CI, 1.64-2.36) in the placebo group. This equated to a significant reduction (mean difference) in HAE attacks per month between the treatment arms versus the placebo arm. The mean difference between the treatment arms versus placebo were −1.71 (95% CI, −2.09 to −1.33) in the 300 mg every two weeks group (adjusted $P < .001$ for all comparisons). This results in a mean rate ratio of 0.13 (95% CI, 0.07 to 0.24) for the 300 mg every two weeks group (adjusted $P < .001$ for all comparisons), relative to placebo. Attack rates per month are shown in Figure 10.

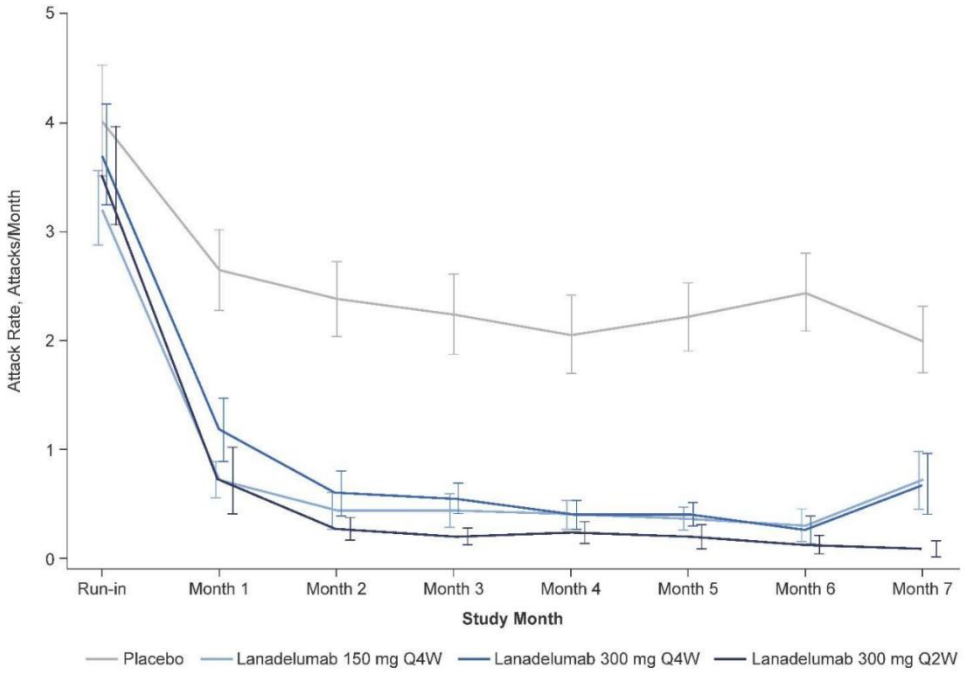


Figure 10 Mean HAE attack rates by study month and treatment group

Abbreviations: Q2W = Every two weeks; Q4W = Every four weeks
Source: (Banerji et al. 2018)

Moreover, the evaluation of the mean number of monthly HAE attacks between day 14 to day 182 resulted in slightly lower numbers compared to the mean number of attacks per month between day 0 to day 182. Mean monthly HAE attack numbers between day 14 to day 182 were 1.99 (95% CI, 1.65 to 2.39) in the placebo group, compared to 0.22 (95% CI, 0.12 to 0.41) in the 300 mg every two weeks group (Table 16).

B.3.2 Number of moderate and/or severe HAE attacks per month

Compared with placebo, lanadelumab regimens led to statistically significant reductions in the number of attacks requiring acute treatment (all adjusted $p<0.001$), the number of moderate or severe attacks (all adjusted $p<0.001$), and the number of attacks from Days 14 to 182 (all adjusted $p<0.001$) (Table 16).

Patients experienced 0.20 (95% CI, 0.11 to 0.39) moderate or severe monthly attacks from day 0 to day 182 in the 300-mg every two weeks group, and 1.22 (95% CI, 0.97 to 1.52) in the placebo group (adjusted $p<0.001$).

B.3.3 HAE attacks per month requiring on-demand treatment

The mean number of monthly HAE attacks requiring acute treatment between day 0 to day 182 was 0.21 (95% CI, 0.11 to 0.40) in the 300 mg every two weeks group, compared to 1.64 (95% CI, 1.34 to 2.00) in the placebo group (Table 16).

B.3.4 Proportion of attack-free patients

The percentage of patients who were attack-free for the entire treatment period was 44% in the lanadelumab 300 mg every 2 weeks group (Table 16).

B.3.5 Attack-free days per month

The number of attack-free days per month was reduced by 4.7 (3.2 to 6.2) in the lanadelumab 300 mg every 2 weeks group compared to placebo (p<0.001) (Table 16).

Table 45 Primary and secondary outcomes among patients with HAE attacks taking lanadelumab vs placebo[a]

Endpoint	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Placebo (n = 41)
Number of attacks per month, day 0-182		
Mean (95% CI)[b,c]	0.26 (0.14 to 0.46)	1.97 (1.64 to 2.36)
Difference (95% CI)[d]	−1.71 (−2.09 to −1.33)	
P value	<.001	
Rate ratio (95% CI)[c]	0.13 (0.07 to 0.24)	
P value[e]	<.001	
Number of attacks requiring acute treatment per month, day 0-182		
Mean (95% CI)[b,c]	0.21 (0.11 to 0.40)	1.64 (1.34 to 2.00)
Difference (95% CI)[d]	−1.43 (−1.78 to −1.07)	
P value	<.001	
Rate ratio (95% CI)[c]	0.13 (0.07 to 0.25)	
P value[e]	<.001	
Number of moderate or severe attacks per month, day 0-182		
Mean (95% CI)[b,c]	0.20 (0.11 to 0.39)	1.22 (0.97 to 1.52)
Difference (95% CI)[d]	−1.01 (−1.32 to −0.71)	

P value	<.001	
Rate ratio (95% CI)[c]	0.17 (0.08 to 0.33)	
P value[e]	<.001	
Number of attacks per month, day 14-182		
Mean (95% CI)[b,c]	0.22 (0.12 to 0.41)	1.99 (1.65 to 2.39)
Difference (95% CI)[d]	−1.77 (−2.16 to −1.38)	
P value	<.001	
Rate ratio (95% CI)[c]	0.11 (0.06 to 0.21)	
P value[e]	<.001	
Responder analysis, number (%)[f]		
≥50% Reduction	27 (100)	13 (31.7)
Difference (95% CI)	68.3 (47.9 to 83.8)	
P value[g]	<0.001	
≥70% Reduction	24 (88.9)	4 (9.8)
Difference (95% CI)	79.1 (60.0 to 91.6)	
P value[g]	<0.001	
≥90% Reduction	18 (66.7)	2 (4.9)
Difference (95% CI)	61.8 (39.5 to 78.8)	
P value[g]	<0.001	
Maximum attack severity, number (%)		
Attack free	12 (44.4)	1 (2.4)
Difference (95% CI)	42.0 (18.1 to 61.8)	

P value[g]	<0.001	
Mild	3 (11.1)	1 (2.4)
Difference (95% CI)	8.7 (−15.6 to 32.0)	
P value[g]	0.29	
Moderate	10 (37.0)	25 (61.0)
Difference (95% CI)	−23.9 (−46.7 to 0.7)	
P value[g]	0.08	
Severe	2 (7.4)	14 (34.1)
Difference (95% CI)	−26.7 (−48.9 to −2.8)	
P value[g]	0.02	
Attack-free days per month, mean (SD), days	27.3 (1.3)	22.6 (4.4)
Difference (95% CI)	4.7 (3.2 to 6.2)	
P value[h]	<0.001	
Number of high-morbidity attacks per month		
Mean (95% CI)[i,j]	0.03 (0.01 to 0.13)	0.22 (0.14 to 0.35)
Difference (95% CI)[k]	−0.19 (−0.30 to −0.07)	
P value	0.001	
Rate ratio (95% CI)[j]	0.15 (0.04 to 0.65)	
P value	0.01	

[a]All patients received injections every 2 weeks, with those in the every-4-week groups receiving placebo in between active treatments.
[b]Attack rates are model-based mean attacks per month, defined as 4 weeks.
[c]Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. All *P* values (Wald test) reported vs placebo.
[d]Estimated from a nonlinear function of the model parameters. All *P* values (Wald test) reported vs placebo.
[e]*P* value adjusted for multiple testing.

[f] Achievement of a prespecified reduction from the run-in period in the hereditary angioedema attack rate. The percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100.
[g] The difference vs placebo was analyzed using Fisher exact test.
[h] The difference vs placebo was analyzed using a *t* test.
[i]Attack rates are model-based mean attacks per month, defined as 4 weeks.
[j] Results are from a Poisson regression model accounting for overdispersion; treatment group and the normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. All *P* values (Wald test) reported vs placebo.
[k] Estimated from a nonlinear function of the model parameters. All *P* values (Wald test) reported vs placebo.
Abbreviations: CI = Confidence interval; SD = Standard deviation; n = Number of scores or individuals
Source: (Banerji et al. 2018)

Appendix C. Comparative analysis of efficacy

C.1 Data sources

This study used IPD for garadacimab versus placebo from the VANGUARD, i.e. VANGUARD, (NCT04656418) and CSL312_2001 (NCT03712228) trials and SLD for lanadelumab versus placebo from the HELP trial (NCT02586805). The HELP trial was identified through an SLR (CSL Behring GmbH 2022c). Key study characteristics are summarised in Table 46, with a more detailed overview of the studies provided in Section 6.1.1.

Table 46. Key characteristics of studies included in the matching-adjusted indirect comparison

	VANGUARD NCT04157348	CSL312_2001 NCT03712228	HELP NCT02586805
Intervention	Garadacimab 200 mg: QM	Garadacimab 75 mg: QM 200 mg: QM 600 mg: QM	Lanadelumab 300 mg: Q2W 300 mg: Q4W 150 mg: Q4W
Comparator	Placebo	Placebo	Placebo
Study design	Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel arm, 26-week trial	Phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel arm, 12-week trial	Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel arm, 26-week trial
Study site locations	Canada, Germany, Hungary, Israel, Netherlands, US	Canada, Germany, Israel, US	Canada, Germany, Italy, Puerto Rico, UK, US
Sample size	Total N = 64 Garadacimab 200 mg QM N = 39 Placebo N = 25	Total N = 32 Garadacimab 75 mg QM N = 9 Garadacimab 200 mg QM N =8 Garadacimab 600 mg QM N = 7 Placebo N = 8	Total N = 125 Lanadelumab 300 mg Q2W N = 27 Lanadelumab 300 mg Q4W N = 29 Lanadelumab 150 mg Q4W N = 28 Placebo N = 41

Abbreviations: n = Number of observations or individuals; NCT = National clinical trial; Q2W = Every 2 weeks; Q4W = Every 4 weeks; QM = Once monthly¸ UK = United Kingdom; US = the United States.
Source: (National Library of Medicine 2023, National Library of Medicine 2022, National Library of Medicine 2021)

Table 47 Availability of Efficacy and Patient-reported Outcomes of Interest

Intervention	Study Group (N)	Time-normalized number of HAE attacks during treatment period	Mean attack ratio (attack rate ratio) vs. placebo*	Normalized number of HAE attacks requiring on-demand treatment	Normalized number of moderate and /or severe attacks	% patient attack free over trial period	Proportion of subjects who achieved at least 90% attack rate reduction compared to run-in	Number of attack free days (attack-free time period)	Time to first HAE attack	Proportion of pf patients who had ≤1 attack in 6 months	Attack-free time per year	Change from baseline in AE-QoL total score	Proportion of patients achieving an MCID ≥6points in total score from visit day 1 to last visit day
Garadacimab (VANGUARD)	ITT (N=64)	✓	✓	✓	✓	✓	✓	✓+	✓	✓	NR	✓	✓
Garadacimab (CSL312_2001)	ITT (N=32)	✓	NR	✓	✓+	✓	✓	✓+	NR	NR	NR	NR	NR
Lanadelumab (HELP)	ITT (N=125)	✓	✓	✓	✓	✓	✓	✓	NR	NR	NR	✓	✓

+ These outputs were not reported in the CSR/main publications of these studies but provided separately

* This measure is a relative measure of time normalized HAE attacks versus placebo, rather than a distinct clinical outcome; We therefore suggest that this outcome may not be needed.

✓ = Results reported; however, definitions/measurement may not be identical across all trials

Abbreviations: AE-QoL = Angioedema quality of life questionnaire; CSR = Clinical study report; HAE = Hereditary angioedema; ITT = Intention-to-treat; MCID = Minimal clinically important difference; NR = Not reported.

C.2 Patient populations used in comparative analyses

For the VANGUARD and CSL312_2001 trials, the analysis populations were the ITT populations, which consisted of all patients who were randomized and received at least one dose of the investigational product, irrespective of their protocol adherence and continued participation in the study (N = 39 [garadacimab], N = 25 [placebo] from VANGUARD and N = 8 [garadacimab], N = 8 [placebo] from CSL312_2001). IPD for the licensed dosage of garadacimab from both VANGUARD (garadacimab 200 mg monthly and placebo) and CSL312_2001 (garadacimab 200 mg Q4W and placebo) trials will be pooled into one dataset (where applicable) prior to the analysis.

For the HELP trial, the analysis population was the ITT population, which consisted of all patients who were randomized and received at least one dose of the investigational product. Only licensed doses for lanadelumab were considered for the MAIC analyses. Therefore, only lanadelumab 300 mg Q2W (N = 27), lanadelumab 300 mg Q4W (N = 29), and the placebo (N = 41) arms were included in the analysis.

C.3 Alignment of key trial design characteristics

Participants enrolled in the VANGUARD, CSL312_2001 and HELP trials were required to satisfy the key eligibility criteria outlined in Table 48. Key eligibility criteria were generally aligned between the three trials.

Table 48 Key eligibility criteria of patients included in the matching-adjusted indirect comparison

Eligibility Criteria	VANGUARD NCT04157348	CSL312_2001 NCT03712228	HELP NCT02586805	Interpretation
Inclusion criteria				
Diagnosis	HAE type I or II	HAE type I or II	HAE type I or II	Similar
HAE attack	Experienced ≥ 3 documented HAE attacks during the 3 months before screening At least an average of 1 HAE attack per month during Run-in period	Experienced ≥4 HAE attacks of any severity over 2 consecutive months, within the 3 months prior to screening or initiation of previous HAE prophylaxis	Baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period	Criteria prior to screening for VANGUARD and CSL312_2001 is narrower than for HELP. Criteria during run-in is narrower for CSL312_2001 than for HELP. Criteria for VANGUARD and HELP is approximately aligned.
Treatment management	Must stop using C1-INH products, androgens, antifibrinolytics or other small molecules for	Willing to stop using C1-INH therapy, androgens, or	Must not use short-term prophylactic therapy for HAE	Criteria for VANGUARD is narrower than for HELP.

	routine prophylaxis against HAE attacks within 2 weeks prior to run-in period	antifibrinolytics for routine attack prophylaxis at the start of the run-in period (allowing for ≥4 weeks wash-out)	within 7 days of the run-in period, including C1 inhibitors, attenuated androgens, or antifibrinolytics	Criteria for CSL312_2001 is broader than for HELP, but unable to match due to lack of granularity in IPD.
C1-INH functional activity	≤50%, and C4 antigen level below the lab reference range	≤50% of the lower limit of the reference range, and C4 antigen level below the lab reference range	<40% of normal level, or 40-50% of normal level if C4 antigen is below normal range	Criteria for VANGUARD and CSL312_2001 is narrower than for HELP.
Clinical abnormalities	No clinical abnormalities assessed as clinically significant in results of haematology, chemistry, or urinalysis assessments.	NR	NR	Criteria for VANGUARD is narrower than for HELP. Criteria for CSL312_2001 and HELP are aligned.
Sex	Male or female	Male or female	Male or female	Similar
Age	≥ 12 years	18 to 65 years	≥ 12 years	Criteria for CSL312_2001 is narrower than for HELP. Criteria for VANGUARD and HELP are aligned.
Exclusion criteria				
Concomitant diagnosis	Concomitant diagnosis of another form of angioedema	Concomitant diagnosis or history of significant arterial/venous thrombosis, prothrombotic risk, abnormal bleeding, or known incurable malignancies	Concomitant diagnosis of another form of chronic, recurrent angioedema	Similar
Previous studies	Participation in another interventional clinical	Participation in another interventional	Participation in a prior lanadelumab	Similar

	study during the 30 days before Screening	clinical study during the 30 days before Screening	(DX-2930) study	
Contraception	Lack of effective contraception	Lack of effective contraception	Lack of effective contraception	Similar
Pregnancy	Intention to become pregnant or to father a child at any time during the study and breastfeeding	Intention to become pregnant or to father a child, or pregnant or nursing	Pregnant or breastfeeding	Similar
Investigational drugs	Received investigational product in a previous interventional study within within 5 half-lives	Any investigational drug or device was prohibited during the study and during the 30 days before Screening	Received investigational drug or device within 4 weeks of screening	Similar
Monoclonal antibodies	Use of monoclonal antibodies within 3 months prior to the Run-in Period.	Any previous treatment with any monoclonal antibody at any time during study	NR	Criteria for VANGUARD and CSL312_2001 is narrower than for HELP.
Oestrogen-containing medications or ACE inhibitors	Use of oestrogen-containing medications with systemic Angiotensin-converting enzyme (ACE) enzyme inhibitor within 4 weeks prior to the Run-in Period, or currently receiving a therapy not permitted during the study	ACE inhibitors or anticoagulant or antiplatelet therapy, including low-dose aspirin therapy taken prophylactically in the 3 months before Screening and at any time during the study	Exposure to ACE inhibitors, or oestrogen-containing medications within 4 weeks of screening	Criteria for CSL312_2001 is narrower than for HELP. Criteria for VANGUARD and HELP are aligned.
CSL312	Previously administered CSL312 in another interventional clinical study	NR	NR	Criteria for VANGUARD is narrower than for HELP.

				Criteria for CSL312_2001 and HELP are aligned.
Recombinant protein bearing an Fc domain, ribonucleic acid silencing, or gene transfer technologies	NR	Any previous treatment with any recombinant protein bearing an Fc domain, ribonucleic acid silencing, or gene transfer technologies at any time during study	NR	Criteria for CSL312_2001 is narrower than for HELP. Criteria for VANGUARD and HELP are aligned.
Androgens	For adult subjects: exposure to androgens within 2 weeks prior to entering the run-in period. For adolescent subjects: Use of long-term androgen therapy for HAE before screening.	NR	Exposure to androgens within 2 weeks prior to entering the run-in period	Criteria for CSL312_2001 is broader than for HELP, but unable to match due to lack of granularity in IPD. Criteria for VANGUARD is narrower than for HELP.
Prophylactic therapy	Adult subjects: Use of C1-INH products, androgens, antifibrinolytics or other small molecule medications within 2 weeks prior to the Run-in Period Adolescent subjects: Long-term prophylactic therapy for HAE pre-screening	LTP to prevent HAE attacks with the use of C1-INH products or antifibrinolytics at any time during the study	Use of long-term (short-term) prophylactic therapy for HAE within 2 weeks (7 days) prior to entering the run-in period	Criteria is defined differently between CSL312_2001, VANGUARD, and HELP.
Liver function abnormalities	Subjects with ≥2 x ULN for AST and/or ALT may be eligible if there is an explanation, and results are not clinically significant.	Subjects with ≥2 x ULN for AST and/or ALT may be eligible if there is an explanation, and results are not clinically significant.	ALT > 3x ULN, or AST > 3x ULN, or Total bilirubin > 2x ULN	Criteria for VANGUARD and CSL312_2001 is broader than for HELP, but unable to match because HELP does not report ULN values.

Surgery and hypersensitivity	Any preplanned major surgeries or procedures during the clinical study Known or suspected hypersensitivity to monoclonal antibody therapy or hypersensitivity to the investigational product or to any excipients of the investigational product	Had any pre-planned surgeries during the trial that had an inherent clinically significant risk for thrombotic events or bleeding. Had a known or suspected hypersensitivity to investigational product or to any excipients of investigational product.	NR	Criteria for VANGUARD and CSL312_2001 is narrower than for HELP.

Abbreviations: ACE = Angiotensin-converting enzyme; ALT = Alanine transaminase; AST = Aspartate aminotransferase; C1-INH = C1 esterase inhibitor; HAE = Hereditary angioedema; IPD = Individual patient data; LTP = Long-term prophylaxis; MAIC = Matching-adjusted indirect comparison; NR = Not reported; ULN = Upper limit of normal
Sources: (National Library of Medicine 2023, National Library of Medicine 2022, National Library of Medicine 2021)

C.4 Estimating indirect treatment effects

For each outcome type, estimates for the relative effect of garadacimab versus lanadelumab were derived using both (a) an estimate of the relative treatment effect for garadacimab versus placebo (if analysis was anchored) or an estimate of the absolute treatment effect for garadacimab (if analysis was unanchored) based on the IPD from the pooled (where applicable) garadacimab trials, and (b) the estimated relative treatment effect for lanadelumab versus placebo (if analysis was anchored) or the estimated absolute treatment effect for lanadelumab (if analysis was unanchored) based on the published SLD from HELP. Two categories of comparisons that used a unique version of data from the garadacimab trials were conducted for each outcome:

Unadjusted – the relative treatment effect estimate was derived using data from the original pooled (where applicable) garadacimab trials without having adjusted (i.e., weighted patients) for treatment effect modifiers.

Adjusted (i.e., MAIC analysis) – the relative treatment effect estimate was derived using data from the pooled (where applicable) garadacimab trials after having adjusted (i.e., weighted patients) for treatment effect modifiers. The target estimand for the MAIC was perceived as the average treatment effect in the comparator; a mapping of the outcome for patients taking garadacimab to the HELP population.

All MAIC analyses were performed using R version 3.6.1 or higher, based on the code provided in the NICE Decision Support Unit Technical Support Document 18 (the R code is available to HTA bodies upon request). Statistical significance testing was defined using a two-tailed p-value of <0.05.

C.4.1 Binary endpoints

Three binary endpoints were included in this study:

- proportion of attack-free patients over the trial period;
- proportion of subjects who achieved ≥90% attack rate reduction compared to run-in; and
- proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182.

Given that zero subjects achieved an attack-free status over the trial period in the placebo arms of VANGUARD and CSL312_2001, it was inappropriate to conduct an anchored MAIC. However, since only one subject achieved an attack-free status in the placebo arm of HELP, this suggests that prognostic differences across trials may be minimal. Therefore, absolute effects between garadacimab and lanadelumab for proportion of attack-free patients over the trial period were compared using unanchored MAICs which excluded the placebo arms from each trial. Similarly, only two patients in each of the VANGUARD and HELP placebo arms, and zero patients in the CSL312_2001 placebo arm achieved a ≥90% attack rate reduction. Though technically feasible to conduct an anchored MAIC for the proportion of subjects with ≥90% attack rate reduction compared to run-in outcome, the rare event numbers in the placebo arms will lead to high levels of uncertainty in the resulting MAIC relative treatment effects. Therefore, given the zero or rare event numbers and to ensure consistent methodology across these two outcomes, unanchored MAICs were considered the primary analysis for proportion of subjects who achieved ≥90% attack rate reduction compared to run-in.

Further follow-up is likely to result in more events for these endpoints. Therefore, to account for differences in trial durations, pseudo IPD was generated for HELP with follow-up set to 182 days (26 weeks) for each pseudo patient and included together with the pooled IPD for the garadacimab trials in a weighted generalized linear model. The log HR for garadacimab versus lanadelumab was estimated using a binomial likelihood and complementary log-log (cloglog) link function with the outcome and covariates for treatment (i.e., garadacimab or lanadelumab). The logarithm of time (days) of the maximum follow-up for each patient in their respective trial (84 days [12 weeks] for CSL312_2001 and 182 days [6 months] for VANGUARD) was included as an offset variable in the model. The corresponding variance was estimated using a robust sandwich estimator (Phillippo et al. 2016). Effect estimates were exponentiated and reported as HRs with 95% confidence intervals (CIs).

Anchored MAICs were conducted to compare proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182, since events are not rare. The methods are as described above, except that an additional model-adjustment covariate for study (i.e., garadacimab study or HELP) was included in the generalized linear model to distinguish between the placebo arms of the different trials. However, since this

outcome was not reported for CSL312_2001, and both VANGUARD and HELP have the same maximum follow-up (182 days), an offset variable was not required.

Anchored MAICs were also conducted as a sensitivity analysis for proportion of subjects who achieved ≥90% attack rate reduction compared to run-in. In this case, an additional model-adjustment covariate for study (i.e., garadacimab study or HELP) was included in the generalized linear model.

C.4.2 Continuous endpoints

Two continuous outcomes were included in this study:

- number of attack-free days per month; and
- AE-QoL change from baseline to day 182.

For the pooled garadacimab versus placebo population, the mean difference (MD) was estimated using weighted generalized linear model using a Gaussian likelihood and identity link function with the outcome and the binary treatment indicator. Since AE-QoL change from baseline to day 182 is not reported for CSL312_2001, the mean difference of this outcome for garadacimab versus placebo was estimated from VANGUARD only. The corresponding variance was estimated using a robust sandwich estimator (Phillippo et al. 2016). For lanadelumab versus placebo, the MD and variance was obtained from HELP. The relative treatment effect was calculated as the difference in estimated MDs, and the corresponding variance was calculated as the sum of the variances of the MDs. Effect estimates were reported as a MD with 95% CIs.

C.4.3 Rate endpoints

Three rate outcomes were included in this study:

- time-normalized number of HAE attacks; and
- time-normalized number of HAE attacks requiring on-demand treatment; and
- time-normalized number of moderate and/or severe HAE attacks

For the pooled garadacimab versus placebo population, the log rate ratio was estimated using weighted generalized linear model using a Poisson likelihood and log link function with the outcome and the binary treatment indicator. Normalized baseline attack rate was included as a covariate in the model to align with the statistical analysis methodology reported for HELP (Banerji et al. 2018). The logarithm of time (days) for each patient that was observed during the treatment period (i.e., the exposure time prior to discontinuation) was included as an offset variable in the model. Overdispersion was investigated and not detected. The corresponding variance was estimated using a robust sandwich estimator (Phillippo et al. 2016). For lanadelumab versus placebo, the estimated rate ratio and variance was obtained from HELP and its log rate ratio and variance derived. The log relative treatment effect was calculated as the difference of the log rate ratios, and the corresponding variance was calculated as the sum of the variances of the log rate ratios. Effect estimates were exponentiated and reported as rate ratios with 95% CIs.

C.5 Identification and rank ordering of treatment effect modifiers for balancing

Table 49 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety before matching

	VANGUARD		CSL312_2001		HELP	
	Garadacimab 200 mg (n=39)	Placebo (n = 25)	Garadacimab 200 mg (n=8)	Placebo (n=8)	Lanadelumab Q2W 300 mg (n=27)	Placebo (n=41)
Age, years	43 (17%)	38 (13%)	38.5 (30–49)	39 (33-53)	40 (13)	40 (17)
Gender						
Female	24 (62%)	14 (56%)	2 (25%)	4 (50%)	15 (56%)	34 (83%)
Male	15 (39%)	11 (44%)	6 (75%)	4 (50%)	12 (44%)	7 (17%)
Ethnicity						
Non-white	7 (19%)	5 (20%)	0 (0%)	1 (13%)	1 (4%)	2 (5%)
White	33 (85%)	22 (88%)	8 (100%)	7 (88%)	26 (96%)	39 (95%)
Unknown or not reported	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hereditary angioedema type						
I	34 (87%)	22 (88%)	7 (88%)	7 (88%)	23 (85%)	38 (92%)
II	5 (13%)	3 (12%)	1 (13%)	1 (13%)	4 (15%)	3 (7%)

Patients on prophylactic therapy during the 3 months before screening*	14 (36%)	7 (28%)	1 (13%)	1 (13%)	14 (52%)	24 (59%)
Number of hereditary angioedema attacks during the 3 months before screening or at the start of prophylaxis	9 (6-11)	9 (6-12)	NR	NR	NR	NR
Number of hereditary angioedema attacks during the run-in period	3 (2.4-3.7)	3 (2.1-2.9)	NR	NR	NR	NR
Mean number of attacks per month during run-in period	NR	NR	6 (4)	5 (2)	NR	NR
Run-in hereditary angioedema attack rate, mean (SD), attacks per month	NR	NR	NR	NR	4 (2)	4 (3)
History of laryngeal attacks	21 (54%)	17 (68%)	NR	NR	20 (74)	27 (66)
Location of hereditary angioedema attacks during the 3 months before screening						
Cutaneous (extremities)	30 (77%)	20 (80%)	NR	NR	NR	NR
Abdominal	30 (77%)	18 (72%)	NR	NR	14 (51.9%)	27 (65.9%)

Facial	13 (33%)	8 (32%)	NR	NR	NR	NR
Throat, larynx, or tongue	3 (8%)	2 (8%)	NR	NR	1 (3.7%)	0
Peripheral	1 (3%)	0	NR	NR	24 (88.9%)	33 (80.5%)

Notes: VANGUARD: Data are n (%), mean (SD), mean (SD), or mean (95% CI); CSL312_2001: Data are n (%), mean (SD), or median (IQR); HELP: Data are mean (SD)
References: (Craig et al. 2023); (National Library of Medicine 2023); (Craig et al. 2022); (Banerji et al. 2018)
Abbreviations: NR = Not reported; SD = Standard deviation; Q2W = Every two weeks; n = Number of scores or individuals.

A list of potentially important treatment effect modifiers was created as described in Appendix C Appendix C. The list of treatment effect modifiers, their availability in VANGUARD and CSL312_2001 and HELP trials, and their individual and final rankings are shown in Table 50**.** The final list of ranked modifiers was applied to all outcomes of interest. Modifiers were considered for adjustment in the MAICs based on availability across trials.

Table 50 Final ranking of treatment effect modifiers and availability in the VANGUARD, CSL312_2001 and HELP trials

Characteristic	Interim Pooled Ranking (incorporating feedback from internal clinical experts only)	Final Pooled Ranking (incorporating feedback from internal and external clinical experts)	Available in VANGUARD Trial?	Available in CSL312_2001 Trial?	Available in HELP Trial?	Considered for Adjustment in the MAIC
Baseline HAE attack rate (during run-in)	1	1	Yes	Yes	Yes	**Yes**
BMI (or weight if BMI not available)	3	2	Yes	Yes	Yes	**Yes**
History of anxiety	4	3	Yes	Yes	No	No
History of depression	5	4	Yes	Yes	No	No
Age	8	5	Yes	Yes	Yes	**Yes**
Sex	6	6	Yes	Yes	Yes	**Yes**
Race	2	Not important	Yes	Yes	Yes	No
Any prior treatment	7	Not important	Yes	Yes	Yes	No
HAE Type (I or II)	Not important	Not important	Yes	Yes	Yes	No
HAE prophylaxis	Not important	Not important	Yes	Yes	Yes	No

during 3 months before screening						
Prior plasma-derived C1 inhibitor	Not important	Not important	Yes	Yes	Yes	No

Abbreviations: BMI = Body mass index; HAE = Hereditary angioedema; MAIC = Matching-adjusted indirect comparison.
Source: (National Library of Medicine 2023, National Library of Medicine 2022, National Library of Medicine 2021)

A summary of the outcomes of the MAIC is provided in Table 51.

Table 51 Comparative analysis of studies comparing garadacimab to lanadelumab for patients with HAE

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Time-normalized number of HAE attacks	VANGUARD CSL312_2001 HELP	NA	NA	NA	RR = 0.55	(0.22, 1.37)	NA	Detailed description available in C.4.3	No
Time-normalized number of HAE attacks requiring on-demand treatment	VANGUARD CSL312_2001 HELP	NA	NA	NA	RR = 0.52	(0.20, 1.35)	NA	Detailed description available in C.4.3	No
Time-normalized number of moderate and/or severe HAE attacks	VANGUARD CSL312_2001 HELP	NA	NA	NA	RR = 0.25	(0.07, 0.84)	<0.05	Detailed description available in C.4.3	No
Proportion of patients with ≥90% attack rate reduction compared to run-in[1]	VANGUARD CSL312_2001 HELP	NA	NA	NA	HR = 1.50	(0.77, 2.90)	NA	Given the rare event numbers in the placebo arms of the garadacimab studies, unanchored MAIC was used. More detailed description available in C.4.1.	No

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Proportion of attack-free patients over the trial period[2]	VANGUARD CSL312_2001 HELP	NA	NA	NA	HR = 1.93	(0.92, 4.03)	NA	Given the zero event numbers in the placebo arms of the garadacimab studies, unanchored MAIC was used. More detailed description available in C.4.1.	Yes
Number of attack-free days per month	VANGUARD CSL312_2001 HELP	MD = 0.44	(-1.76, 2.63)	NA	NA	NA	NA	Detailed description available in C.4.2	No
AE-QoL change from baseline to day 182[3]	VANGUARD HELP	MD = -17.38	(-33.67, -1.08)	NA	NA	NA	NA	Detailed description available in C.4.2	No
Proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182[3]	VANGUARD HELP	NA	NA	NA	HR=0.97	(0.31, 3.05)	NA	Since events are not rare, anchored MAICs were conducted. More detailed description available in C.4.1.	No

Abbreviations: AE-QoL = Angioedema Quality of Life questionnaire; CI = Confidence interval; HAE = Hereditary angioedema; MD = Mean deviation; MAIC = Matching-adjusted indirect comparison; MCID = Minimal clinically important difference; RR = Risk ratio

C.6 Results of the comparative analysis of efficacy

C.6.1 Efficacy – results per Time-normalized number of HAE attacks

C.6.1.1 GARA 200 QM versus TAK 300 Q2W

C.6.1.1.1 Balance of Populations

Table 52 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the anchored analysis. Before adjustment, there were substantial differences in the percentage of patients with weight <75 kg (SMD = 0.357) and percentage of female patients (SMD = 0.347), a moderate difference in HAE attack rate during run-in (SMD = 0.165), and a small difference in the percentage of patients with age <40 years (SMD = 0.005) when comparing the pooled VANGUARD and CSL312_2001 population to the HELP population. In the primary scenario that adjusted for all four factors, there was a 23% reduction in ESS and the pooled patient characteristics of VANGUARD and CSL312_2001 matched those of HELP.

Table 52 Unadjusted and Adjusted Baseline Characteristics for VANGUARD and CSL312_2001 (Pooled) and HELP in Anchored Analysis for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, Time-normalized Number of Moderate and/or Severe Attacks, and Proportion of Patients with ≥90% Attack Rate Reduction (Anchored)

Characteristics	HELP (LANA 300 Q2W & PBO arms)[a]	Pooled VANGUARD & CSL312_2001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 68	N = 79[b]		ESS = 74		ESS = 64		ESS = 64		ESS = 61	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.8 (2.9)[c]	3.4 (2.28)	0.165	3.8 (2.95)	0	3.8 (2.96)	0	3.8 (2.96)	0	3.8 (2.96)	0
Weight, <75 kg, %	52.9%[d]	35.4%	0.357	33.8%	0.392	52.9%	0	52.9%	0	52.9%	0
Age, <40 years, %	47.1%[d]	46.8%	0.005	46.3%	0.017	46.2%	0.017	47.1%	0	47.1%	0
Sex, female, %	72.1%[c]	55.7%	0.347	54.4%	0.373	61.4%	0.228	61.3%	0.231	72.1%	0

[a] HELP SLD was pooled for the LANA300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.
[b] Note that one subject who received placebo in VANGUARD had missing outcome data and was removed from the analysis.
Source: (Banerji et al. 2018, Canadian Agency for Drugs and Technologies in Health 2019)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; MAIC = Matching-adjusted indirect comparison; PBO = Placebo; SD = Standard deviation; SLD = Summary-level data; SMD = Standardized mean difference; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.1.1.2 MAIC results

The results for time-normalized number of HAE attacks comparing GARA 200 QM versus LANA300 Q2W before and after adjustment are presented in Figure 11. The unadjusted comparison of time-normalized number of HAE attacks for patients treated with GARA 200 QM versus LANA 300 Q2W produced a RR of 0.48 (95% CI: 0.20, 1.18; P = 0.111) in favour of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favourable for GARA 200 QM (RR: 0.55 [95% CI: 0.22, 1.37; P = 0.200]), but not statistically significant.

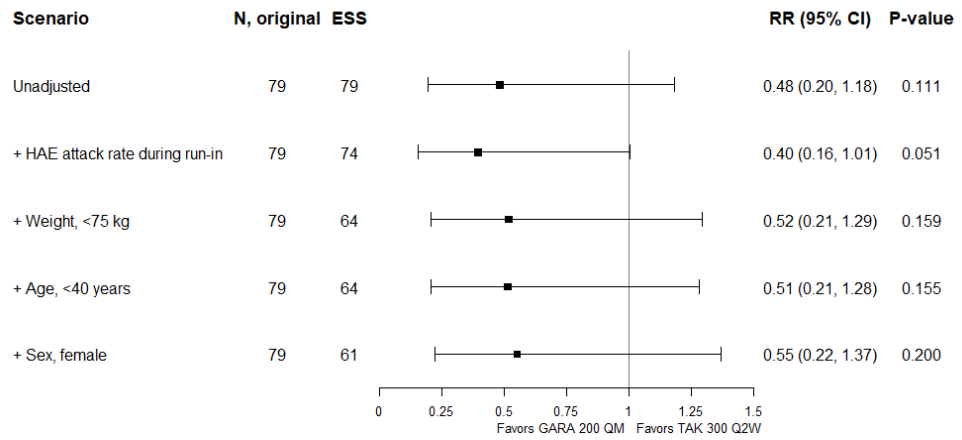


Figure 11 Summary of Time-normalized Number of HAE Attacks Versus LANA 300 Q2W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = Confidence interval; ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; RR = rate ratio; LANA 300 Q2W, = Lanadelumab 300 mg every two weeks

C.6.1.1.3 Sensitivity analysis excluding CSL312_2001

When comparing the CSL312_3001 population to the HELP population before adjustment, substantial differences were observed in HAE attack rate during run-in (SMD = 0.392), the percentage of patients with weight <75 kg (SMD = 0.267), and percentage of female patients (SMD = 0.251), and a small difference in the percentage of patients with age <40 years (SMD = 0.053) (Table 53). In the scenario that adjusted for all four factors, there was a 51% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

The unadjusted comparison of time-normalized number of HAE attacks for patients treated with GARA 200 QM versus TAK 300 Q2W produced a RR of 0.77 (95% CI: 0.30, 2.01; P = 0.599) in favor of GARA 200 QM, however this was not statistically significant (Figure 12). In the scenario that adjusted for all four factors, the result was also

numerically favorable for GARA 200 QM (RR: 0.98 [95% CI: 0.34, 2.83; P = 0.968]), but not statistically significant.

Table 53 Sensitivity Excluding CSL312_2001: Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Anchored Analysis for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, Time-normalized Number of Moderate and/or Severe Attacks, and Proportion of Patients with ≥90% Attack Rate Reduction (Anchored)

Characteristics	HELP (TAK 300 Q2W & PBO arms)[a]	CSL312_3001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 68	N = 63[b]		ESS = 35		ESS = 31		ESS = 31		ESS = 31	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.8 (2.9)[c]	2.9 (1.73)	0.392	3.8 (2.96)	0	3.8 (2.97)	0	3.8 (2.97)	0	3.8 (2.97)	0
Weight, <75 kg, %	52.9%[d]	39.7%	0.267	33.6%	0.398	52.9%	0	52.9%	0	52.9%	0
Age, <40 years, %	47.1%[d]	44.4%	0.053	52.5%	0.109	52.3%	0.105	47.1%	0	47.1%	0
Sex, female, %	72.1%[c]	60.3%	0.251	62.6%	0.204	69.8%	0.050	71.3%	0.018	72.1%	0

[a] HELP SLD was pooled for the TAK 300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.(CSL Behring 2022)
[b] Note that one subject who received placebo in CSL312_3001 had missing outcome data and was removed from the analysis.
Source: [c] (Banerji et al. 2018) [d] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SLD = summary-level data; SMD = standardized mean difference; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

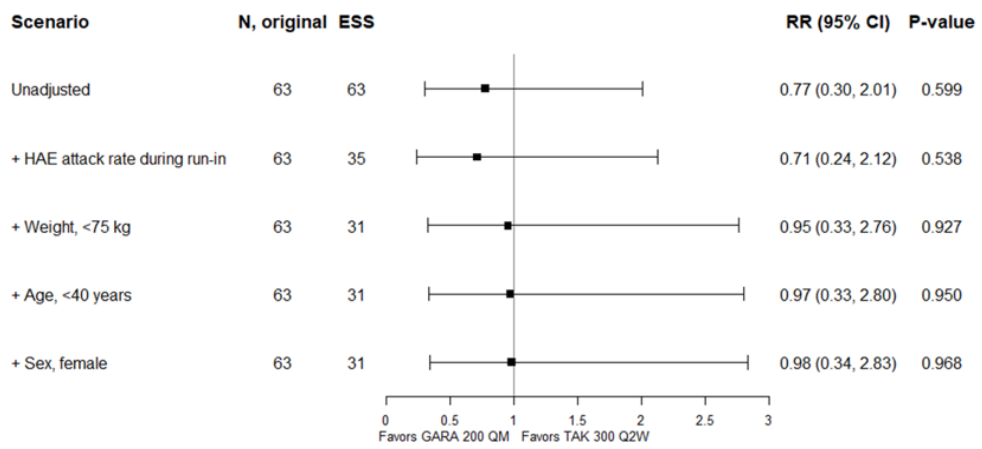


Figure 12 Sensitivity Excluding CSL312_2001: Summary of Time-normalized Number of HAE Attacks Versus TAK 300 Q2W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.

Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.

Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.1.2 GARA 200 QM versus TAK 300 Q4W

C.6.1.2.1 Balance of Populations

Table 54 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the anchored analysis. Before adjustment, there were substantial differences in the percentage of patients with weight <75 kg (SMD = 0.445), the percentage of female patients (SMD = 0.431), and the HAE attack rate during run-in (SMD = 0.201), and a small difference in the percentage of patients who were age <40 years (SMD = 0.051). In the primary scenario that adjusted for all four factors, there was a 30% reduction in ESS and the pooled patient characteristics of CSL312_3001 and CSL312_2001 matched those of HELP.

Table 54 Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and CSL312_2001 (Pooled) and HELP in Anchored Analysis for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, Time-normalized Number of Moderate and/or Severe Attacks, and Proportion of Patients with ≥90% Attack Rate Reduction (Anchored)

Characteristics	HELP (TAK 300 Q4W & PBO arms)[a]	Pooled CSL312_3001 & CSL312_2001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 70	N = 79[b]		ESS = 73		ESS = 58		ESS = 58		ESS = 55	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.9 (3.0)[c]	3.4 (2.28)	0.201	3.9 (3.00)	0	3.9 (3.00)	0	3.9 (3.00)	0	3.9 (3.00)	0
Weight, <75 kg, %	57.1%[d]	35.4%	0.445	33.4%	0.490	57.1%	0	57.1%	0	57.1%	0
Age, <40 years, %	44.3%[d]	46.8%	0.051	46.1%	0.037	46.3%	0.040	44.3%	0	44.3%	0
Sex, female, %	75.7%[c]	55.7%	0.431	54.4%	0.459	63.2%	0.275	63.4%	0.269	75.7%	0

[a] HELP SLD was pooled for the TAK 300 Q4W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.(CSL Behring 2022)
[b] Note that one subject who received placebo in CSL312_3001 had missing outcome data and was removed from the analysis.
Source: [c] (Banerji et al. 2018) [d] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.

Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SLD = summary-level data; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.1.2.2 MAIC results

The results for time-normalized number of HAE attacks comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 13. The unadjusted comparison of time-normalized number of HAE attacks for patients treated with GARA 200 QM versus TAK 300 Q4W produced a RR of 0.23 (95% CI: 0.11, 0.50; P < 0.001) in favour of GARA 200 QM, which was statistically significant. In the primary MAIC scenario, the result was favourable for GARA 200 QM and statistically significant (RR: 0.29 [95% CI: 0.13, 0.63; P = 0.002]).

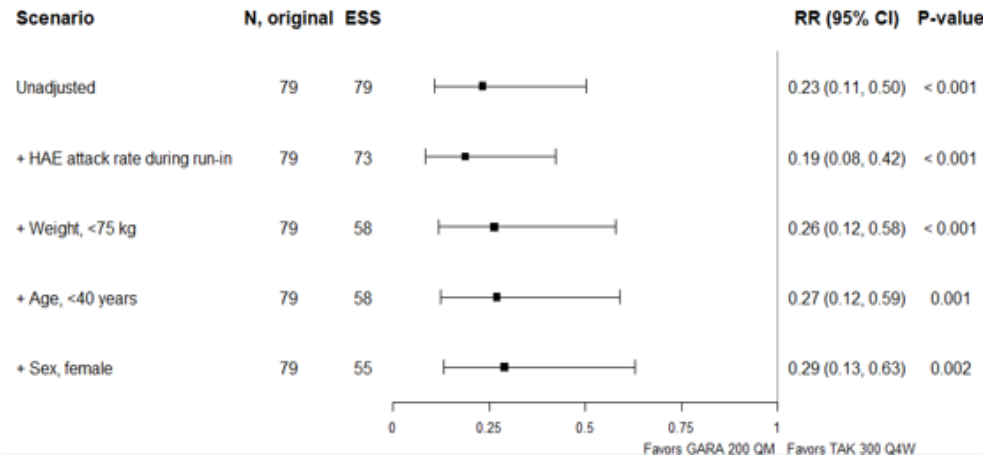


Figure 13 Summary of Time-normalized Number of HAE Attacks Versus TAK 300 Q4W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.1.2.3 Sensitivity analysis excluding CSL312_2001

When comparing the CSL312_3001 population to the HELP population before adjustment, substantial differences were observed in HAE attack rate during run-in (SMD = 0.428), the percentage of patients with weight <75 kg (SMD = 0.354), and percentage of female patients (SMD = 0.334), and a small difference in the percentage of patients with age <40 years (SMD = 0.003) (Table 55). In the scenario that adjusted for all four factors, there was a 57% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

The unadjusted comparison of time-normalized number of HAE attacks for patients treated with GARA 200 QM versus TAK 300 Q4W produced a RR of 0.37 (95% CI: 0.16, 0.86; P = 0.020) in favor of GARA 200 QM, which was statistically significant (Figure 14). In the scenario that adjusted for all four factors, the result was also numerically favorable

for GARA 200 QM (RR: 0.53 [95% CI: 0.20, 1.39; P = 0.198]), but not statistically significant.

Table 55 Sensitivity Excluding CSL312_2001: Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Anchored Analysis for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, Time-normalized Number of Moderate and/or Severe Attacks, and Proportion of Patients with ≥90% Attack Rate Reduction (Anchored)

Characteristics	HELP (TAK 300 Q4W & PBO arms)[a]	CSL312_3001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 70	N = 63[b]		ESS = 33		ESS = 28		ESS = 27		ESS = 27	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.9 (3.0)[c]	2.9 (1.73)	0.428	3.9 (3.01)	0	3.9 (3.01)	0	3.9 (3.01)	0	3.9 (3.01)	0
Weight, <75 kg, %	57.1%[d]	39.7%	0.354	33.0%	0.499	57.1%	0	57.1%	0	57.1%	0
Age, <40 years, %	44.3%[d]	44.4%	0.003	52.7%	0.169	52.4%	0.163	44.3%	0	44.3%	0
Sex, female, %	75.7%[c]	60.3%	0.334	62.8%	0.283	71.9%	0.086	74.3%	0.033	75.7%	0

[a] HELP SLD was pooled for the TAK 300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.[12]
[b] Note that one subject who received placebo in CSL312_3001 had missing outcome data and was removed from the analysis.
Sources: [c] (Banerji et al. 2018) [d] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SLD = summary-level data; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

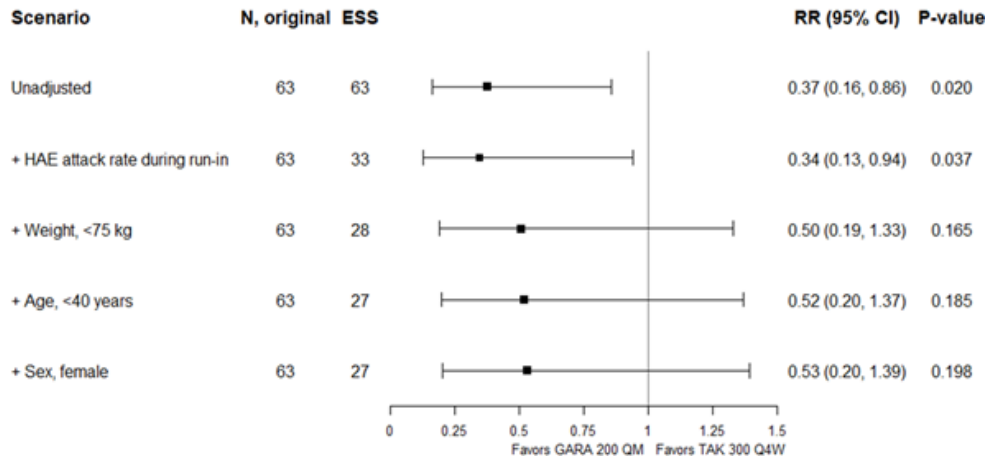


Figure 14 Sensitivity Excluding CSL312_2001: Summary of Time-normalized Number of HAE Attacks Versus TAK 300 Q4W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.2 Efficacy – results per Time-Normalized Number of HAE Attacks Requiring On-Demand Treatment

C.6.2.1 GARA 200 QM versus TAK 300 Q2W

C.6.2.1.1 Balance of Populations

For a detailed summary pertaining to population balancing after adjustment for the time-normalized number of HAE attacks requiring on-demand treatment, refer to Appendix C.6.1.1.1.

C.6.2.1.2 MAIC results

The results for time-normalized number of HAE attacks requiring on-demand treatment comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 15. The unadjusted comparison of time-normalized number of HAE attacks requiring on-demand treatment for patients treated with GARA 200 QM versus LANA 300 Q2W produced a RR of 0.44 (95% CI: 0.17, 1.13; P = 0.086) in favour of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favourable for GARA 200 QM (RR: 0.52 [95% CI: 0.20, 1.35; P = 0.180]), but not statistically significant.

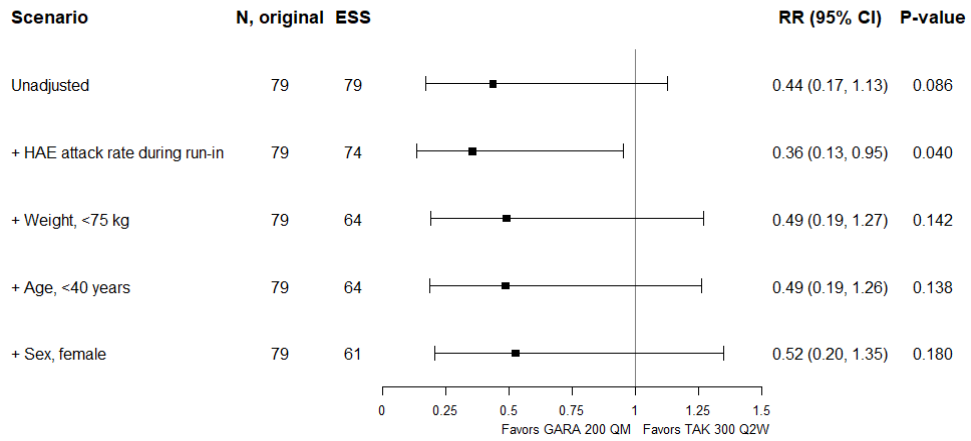


Figure 15 Summary of Time-normalized Number of HAE Attacks Requiring On-demand Treatment Versus LANA 300 Q2W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = Confidence interval; ESS= Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; RR = Rate ratio; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.2.1.3 Sensitivity analysis excluding CSL312_2001

For a detailed summary pertaining to population balancing after adjustment for the time-normalized number of HAE attacks requiring on-demand treatment, refer to Appendix C.6.1.1.3.

The unadjusted comparison of time-normalized number of HAE attacks requiring on-demand treatment for patients treated with GARA 200 QM versus TAK 300 Q2W produced a RR of 0.68 (95% CI: 0.25, 1.87; P = 0.455) in favour of GARA 200 QM, however this was not statistically significant (Figure 16). In the scenario that adjusted for all four factors, the result was also numerically favourable for GARA 200 QM (RR: 0.93 [95% CI: 0.31, 2.81; P = 0.893]), but not statistically significant.

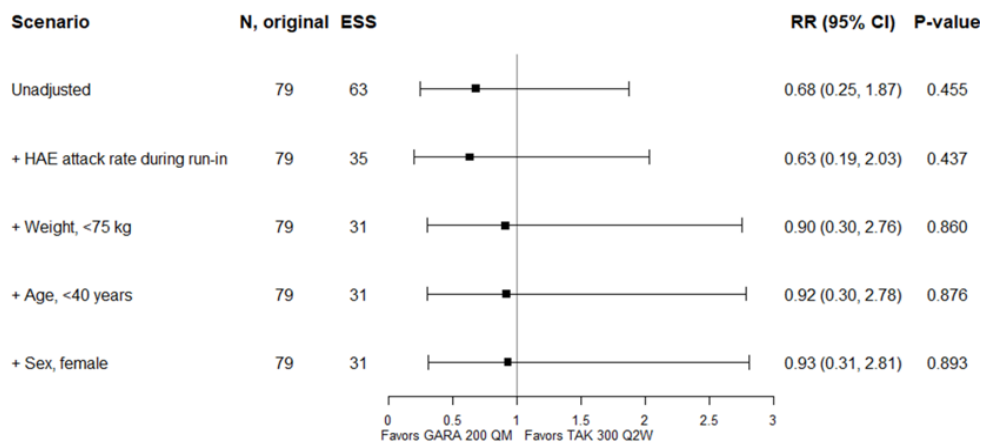


Figure 16 Sensitivity Excluding CSL312_2001: Summary of Time-normalized Number of HAE Attacks Requiring On-demand Treatment Versus TAK 300 Q2W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.2.2 GARA 200 QM versus TAK 300 Q4W

C.6.2.2.1 Balance of Populations

For a detailed summary pertaining to population balancing after adjustment, refer to Appendix C.6.1.2.1.

C.6.2.2.2 MAIC Results

The results for time-normalized number of HAE attacks requiring on-demand treatment comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 17. The unadjusted comparison of time-normalized number of HAE attacks requiring on-demand treatment for patients treated with GARA 200 QM versus TAK 300 Q4W produced a RR of 0.22 (95% CI: 0.09, 0.51; P < 0.001) in favor of GARA 200 QM, which was statistically significant. In the primary MAIC scenario, the result was also favorable for GARA 200 QM and statistically significant (RR: 0.29 [95% CI: 0.13, 0.66; P = 0.003]).

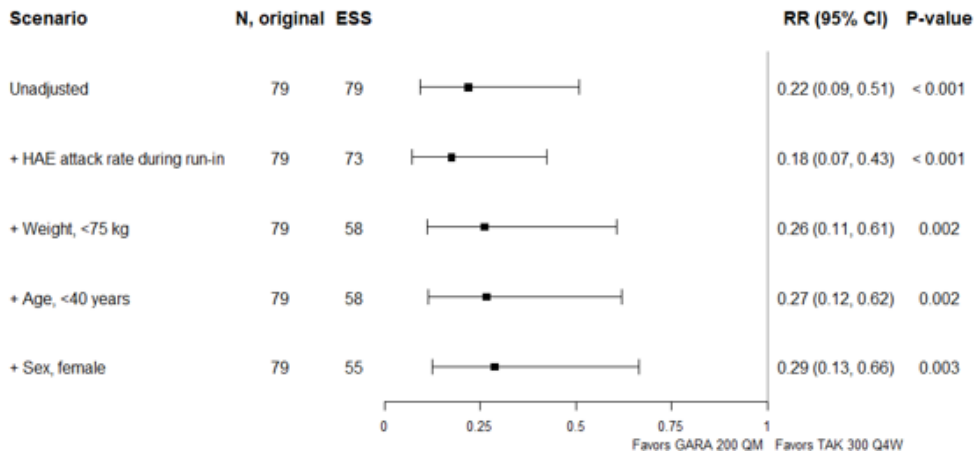


Figure 17 Summary of Time-normalized Number of HAE Attacks Requiring On-demand Treatment Versus TAK 300 Q4W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.2.2.3 Sensitive analysis excluding CSL312_2001

For a detailed summary pertaining to population balancing after adjustment for the time-normalized number of HAE attacks requiring on-demand treatment, refer to Appendix C.6.1.2.3.

The unadjusted comparison of time-normalized number of HAE attacks requiring on-demand treatment for patients treated with GARA 200 QM versus TAK 300 Q4W produced a RR of 0.34 (95% CI: 0.14, 0.85; P = 0.021) in favor of GARA 200 QM, which was statistically significant (Figure 18). In the scenario that adjusted for all four factors, the result was also numerically favorable for GARA 200 QM (RR: 0.53 [95% CI: 0.19, 1.47; P = 0.222]), but not statistically significant.

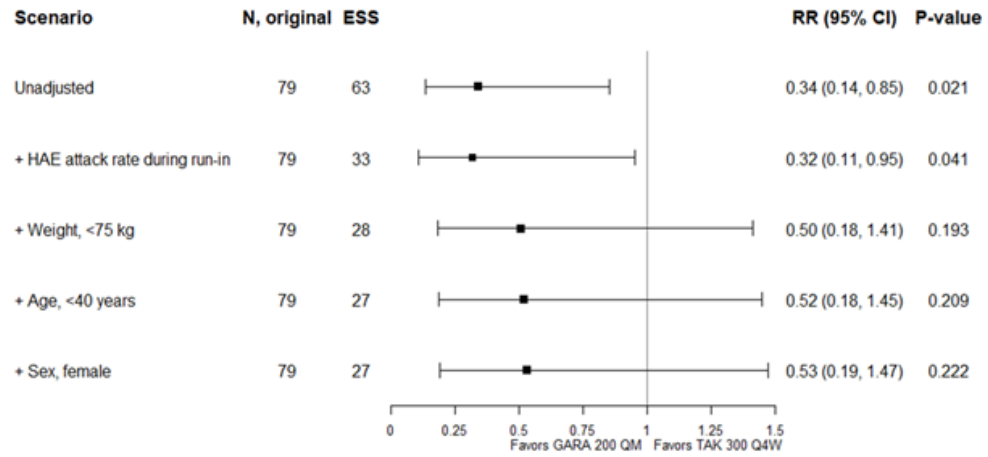


Figure 18 Sensitivity Excluding CSL312_2001: Summary of Time-normalized Number of HAE Attacks Requiring On-demand Treatment Versus TAK 300 Q4W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.3 Efficacy – results per Time-Normalized Number of Moderate and/or Severe HAE Attacks

C.6.3.1 GARA 200 QM versus TAK 300 Q2W

C.6.3.1.1 Balance of populations

For a detailed summary pertaining to population balancing after adjustment for the time-normalized number of HAE attacks requiring on-demand treatment, refer to Appendix C.6.1.1.1.

C.6.3.1.2 MAIC results

The results for time-normalized number of moderate and/or severe HAE attacks comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 19. The unadjusted comparison of time-normalized number of moderate and/or severe HAE attacks for patients treated with GARA 200 QM versus LANA 300 Q2W produced a RR of 0.26 (95% CI: 0.08, 0.83; P = 0.024) in favour of GARA 200 QM, which was statistically significant. In the primary MAIC scenario, the result was also favourable for GARA 200 QM and statistically significant (RR: 0.25 [95% CI: 0.07, 0.84; P = 0.026]).

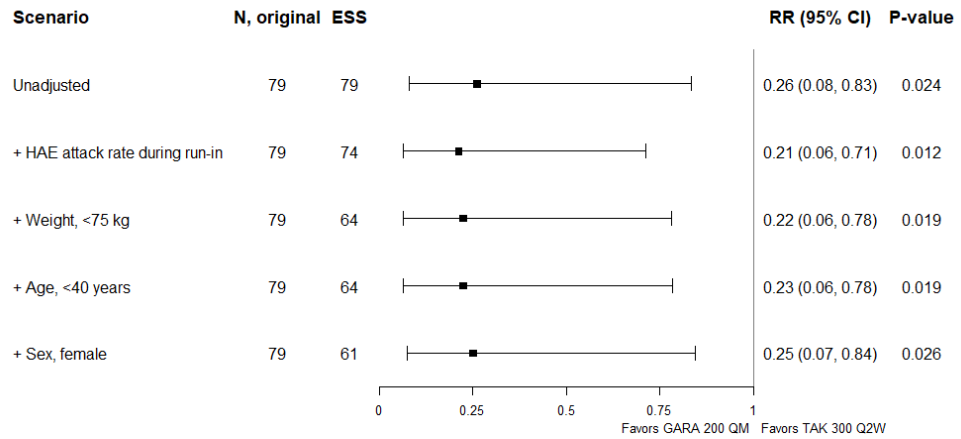


Figure 19 Summary of Time-normalized Number of Moderate and/or Severe HAE Attacks Versus LANA 300 Q2W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = Confidence interval; ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; RR = Rate ratio; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.3.1.3 Sensitivity analysis excluding CSL312_2001

For a detailed summary pertaining to population balancing after adjustment for the time-normalized number of moderate and/or severe HAE attacks, refer to Appendix C.6.1.1.3.

The unadjusted comparison of time-normalized number of moderate and/or severe HAE attacks for patients treated with GARA 200 QM versus TAK 300 Q2W produced a RR of 0.42 (95% CI: 0.12, 1.45; P = 0.171) in favour of GARA 200 QM, however this was not statistically significant (Figure 20). In the scenario that adjusted for all four factors, the result was also numerically favourable for GARA 200 QM (RR: 0.49 [95% CI: 0.11, 2.11; P = 0.339]), but not statistically significant.

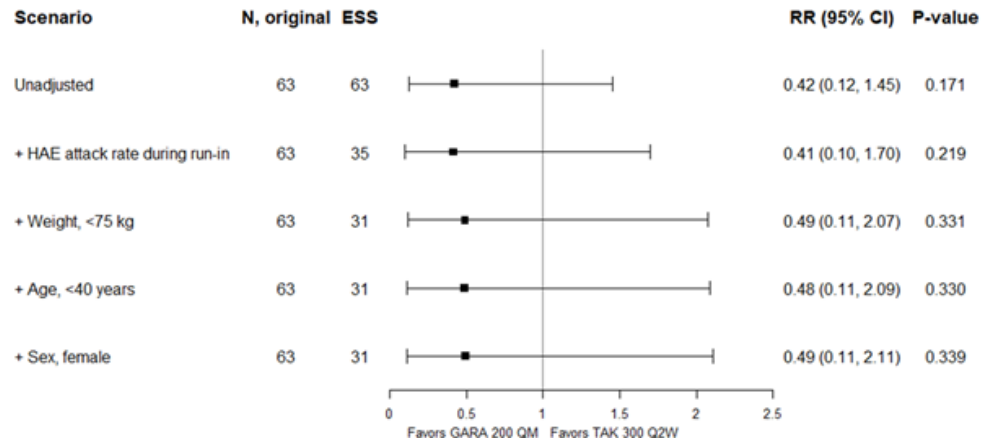


Figure 20 Sensitivity Excluding CSL312_2001: Summary of Time-normalized Number of Moderate and/or Severe HAE Attacks Versus TAK 300 Q2W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.3.2 GARA 200 QM versus TAK 300 Q4W

C.6.3.2.1 Balance of Populations

For a detailed summary pertaining to population balancing after adjustment, refer to Appendix C.6.1.2.1.

C.6.3.2.2 MAIC results

The results for time-normalized number of moderate and/or severe HAE attacks comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 21. The unadjusted comparison of time-normalized number of moderate and/or severe HAE attacks for patients treated with GARA 200 QM versus TAK 300 Q4W produced a RR of 0.16 (95% CI: 0.06, 0.48; P < 0.001) in favour of GARA 200 QM, which was statistically significant. In the primary MAIC scenario, the result was also favourable for GARA 200 QM and statistically significant (RR: 0.15 [95% CI: 0.05, 0.49; P = 0.001]).

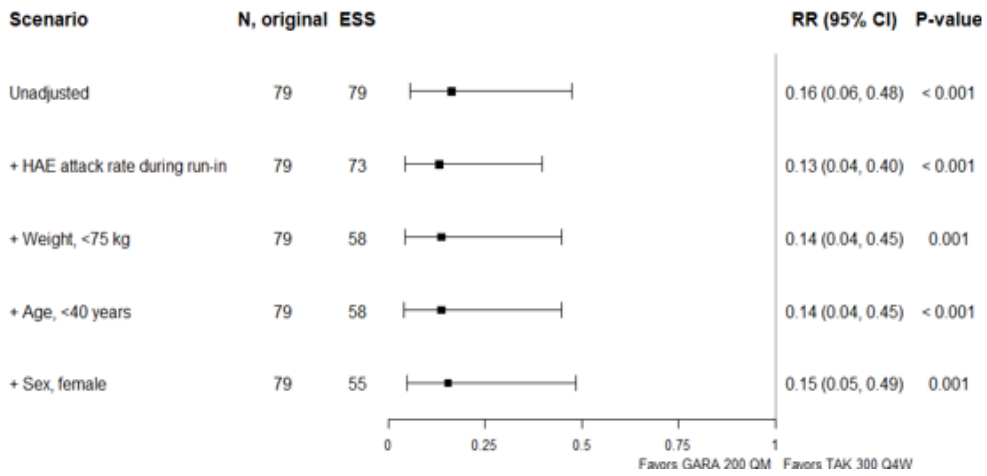


Figure 21 Summary of Time-normalized Number of Moderate and/or Severe HAE Attacks Versus TAK 300 Q4W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.3.2.3 Sensitivity analysis excluding SL312_2001

For a detailed summary pertaining to population balancing after adjustment for the time-normalized number of moderate and/or severe HAE attacks, refer to Appendix C.6.1.2.3.

The unadjusted comparison of time-normalized number of moderate and/or severe HAE attacks for patients treated with GARA 200 QM versus TAK 300 Q4W produced a RR of 0.26 (95% CI: 0.08, 0.83; P = 0.023) in favor of GARA 200 QM, which was statistically significant (Figure 22). In the scenario that adjusted for all four factors, the result was also numerically favorable for GARA 200 QM (RR: 0.32 [95% CI: 0.08, 1.36; P = 0.123]), but not statistically significant.

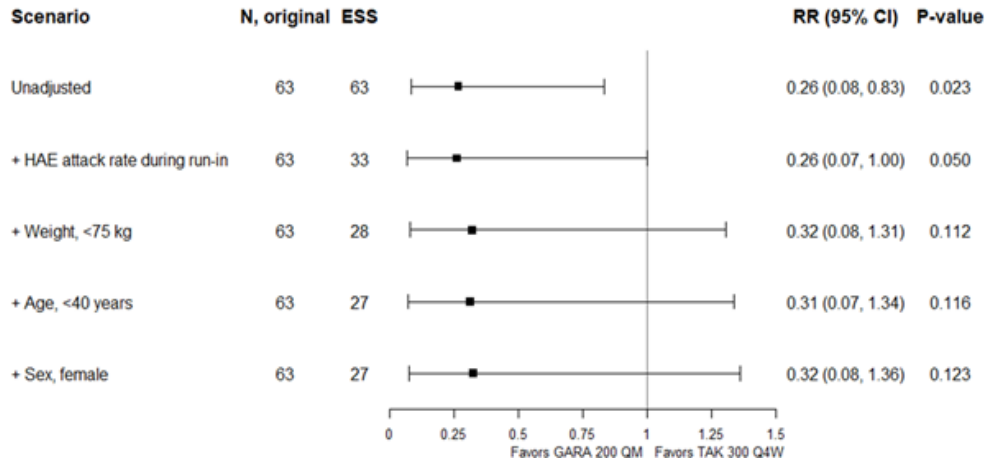


Figure 22 Sensitivity Excluding CSL312_2001: Summary of Time-normalized Number of Moderate and/or Severe HAE Attacks Versus TAK 300 Q4W

Note: An RR below 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To align with the statistical analysis methodology reported for HELP, normalized baseline HAE attack rate was included as a model covariate and the logarithm of time (days) for each patient that was observed during the treatment period was included as an offset in the model that estimates the relative treatment effect of GARA 200 QM vs placebo. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; RR = rate ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.4 Efficacy – results per Proportion of subjects who achieved ≥90% attack rate reduction

C.6.4.1 GARA 200 QM versus TAK 300 Q2W

C.6.4.1.1 Balance of Populations

Table 56 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the unanchored analysis. Before adjustment, there was a moderate difference in the percentage of patients with age <40 years (SMD = 0.188) and small differences in the percentage of patients with weight <75 kg (SMD = 0.017), the HAE attack rate during run-in (SMD = 0.006), and the percentage of female patients (SMD = 0.006) when comparing the pooled VANGUARD and CSL312_2001 population to the HELP population. In the primary scenario that adjusted for all four factors, there was a 4% reduction in ESS and the pooled patient characteristics of VANGUARD and CSL312_2001 matched those of HELP.

Table 56 Unadjusted and Adjusted Baseline Characteristics for VANGUARD and CSL312_2001 (Pooled) and HELP in Unanchored Analyses for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Characteristics	HELP (LANA 300 Q2W)	Pooled VANGUARD & CSL312_2001 (GARA 200 QM)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 27	N = 47		ESS = 47		ESS = 47		ESS = 45		ESS = 45	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.5 (2.3)[a]	3.5 (2.56)	0.006	3.5 (2.33)	0	3.5 (2.33)	0	3.5 (2.33)	0	3.5 (2.33)	0
Weight, <75 kg, %	37.0%[b]	36.2%	0.017	36.2%	0.016	37.0%	0	37.0%	0	37.0%	0
Age, <40 years, %	51.9%[b]	42.6%	0.188	42.5%	0.189	42.5%	0.190	51.9%	0	51.9%	0
Sex, female, %	55.6%[a]	55.3%	0.006	55.9%	0.006	56.0%	0.008	54.3%	0.026	55.6%	0

Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; MAIC = Matching-adjusted indirect comparison; PBO = Placebo; SD = Standard deviation; SMD = Standardized mean difference; LANA 300 Q2W = Lanadelumab 300 mg every two weeks
Source: (Banerji et al. 2018, Canadian Agency for Drugs and Technologies in Health 2020)

C.6.4.1.2 MAIC results

The results for proportion of subjects who achieved ≥90% attack rate reduction comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 23. The unadjusted comparison of proportion of subjects who achieved ≥90% attack rate for patients treated with GARA 200 QM versus LANA 300 Q2W produced a HR of 1.51 (95% CI: 0.83, 2.77; P = 0.181) in favour of GARA 200 QM, however this was not statistically significant. In the scenario that adjusted for all four factors, the result was also numerically favourable for GARA 200 QM (HR: 1.50 [95% CI: 0.77, 2.90; P = 0.230]), but not statistically significant.

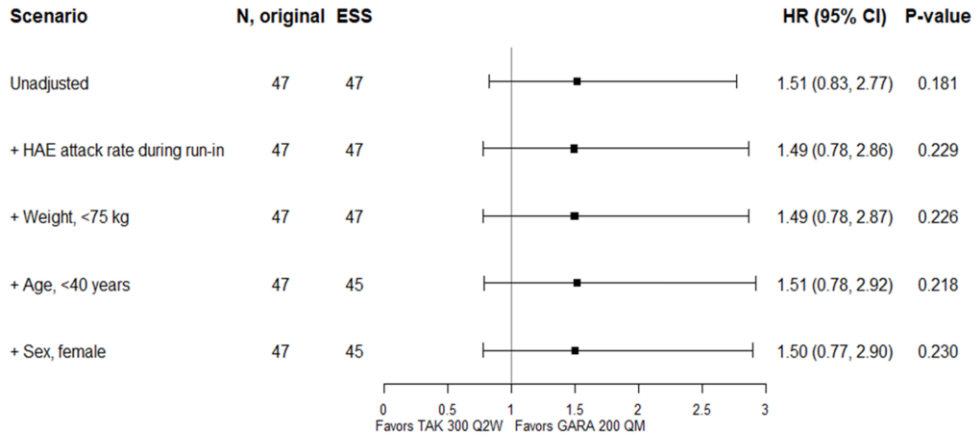


Figure 23 Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus LANA 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS= Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; HR = Hazard ratio; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.4.1.3 Sensitivity analysis excluding CSL312_2001

When comparing the CSL312_3001 population to the HELP population before adjustment, substantial differences were observed in the percentage of patients with age <40 years (SMD = 0.273), a moderate difference in HAE attack rate during run-in (SMD = 0.197) and percentage of female patients (SMD = 0.121), and a small difference in the percentage of patients with weight <75 kg (SMD = 0.030) (Table 57). In the scenario that adjusted for all four factors, there was a 10% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

The unadjusted comparison of proportion of subjects who achieved ≥90% attack rate for patients treated with GARA 200 QM versus TAK 300 Q2W produced a HR of 1.24 (95% CI: 0.66, 2.31; P = 0.501) in favour of GARA 200 QM, however this was not statistically

significant (Figure 24). In the scenario that adjusted for all four factors, the result was also numerically favourable for GARA 200 QM (RR: 1.23 [95% CI: 0.63, 2.38; P = 0.542]), but not statistically significant.

Table 57 Sensitivity Excluding CSL312_2001: Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Unanchored Analysis for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Characteristics	HELP (TAK 300 Q2W arm)	CSL312_3001 (GARA 200 QM arm)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 27	N = 39		ESS = 38		ESS = 38		ESS = 35		ESS = 35	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.5 (2.3)[a]	3.1 (2.05)	0.197	3.5 (2.33)	0	3.5 (2.33)	0	3.5 (2.33)	0	3.5 (2.33)	0
Weight, <75 kg, %	37.0%[b]	38.5%	0.030	35.7%	0.027	37.0%	0	37.0%	0	37.0%	0
Age, <40 years, %	51.9%[b]	38.5%	0.273	38.9%	0.264	38.9%	0.263	51.9%	0	51.9%	0
Sex, female, %	55.6%[a]	61.5%	0.121	61.5%	0.121	61.7%	0.124	57.9%	0.047	55.6%	0

Source: [a] (Banerji et al. 2018) [b] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SMD = standardized mean difference; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

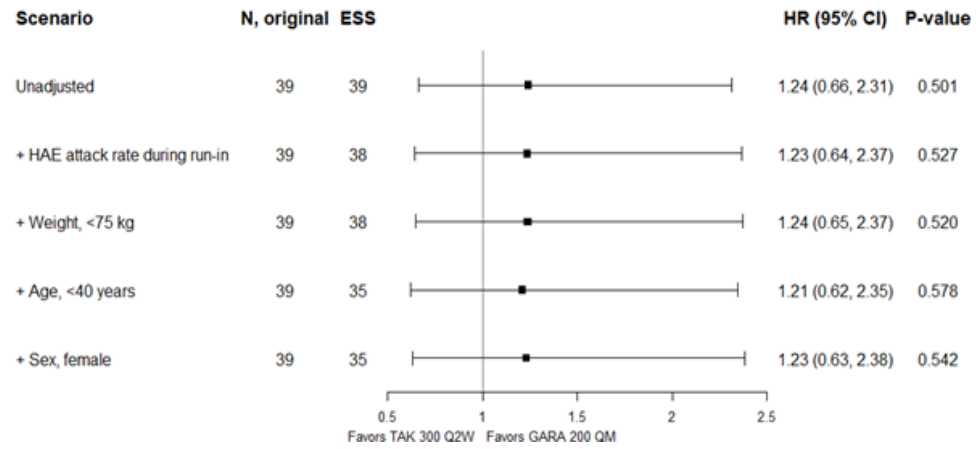


Figure 24 Sensitivity Excluding CSL312_2001: Summary of Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.4.1.4 Sensitivity analysis anchored MAIC

For a detailed summary pertaining to population balancing after adjustment for the proportion of subjects achieving ≥90% attack rate reduction, refer to Appendix C.6.1.1.1 for the pooled CSL312_3001 and CSL312_2001 population and Appendix C.6.1.1.3 for the CSL312_3001 only population.

For the anchored analysis including the pooled CSL312_3001 and CSL312_2001 population, the unadjusted comparison of subjects who achieved ≥90% attack rate reduction for patients treated with GARA 200 QM versus TAK 300 Q2W produced a HR of 1.01 (95% CI: 0.13, 7.84; P = 0.993) in favor of GARA 200 QM, however this was not statistically significant (Figure 25). In the primary MAIC scenario, the result was numerically favorable for TAK 300 Q2W (HR: 0.96 [95% CI: 0.09, 9.74; P = 0.973]), but not statistically significant.

For the anchored analysis excluding CSL312_2001, the unadjusted comparison of subjects who achieved ≥90% attack rate reduction for patients treated with GARA 200 QM versus TAK 300 Q2W produced a HR of 0.71 (95% CI: 0.09, 5.57; P = 0.746) in favor of TAK 300 Q2W, however this was not statistically significant (Figure 26). In the primary MAIC scenario, the result was also numerically favorable for TAK 300 Q2W (HR: 0.84 [95% CI: 0.09, 7.89; P = 0.882]), but not statistically significant.

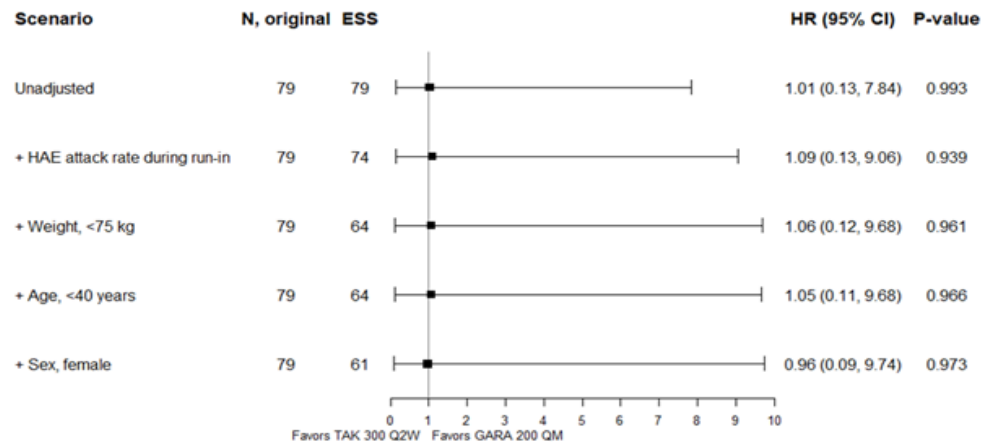


Figure 25 Sensitivity of Anchored MAIC for Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Note: Since the MAIC was anchored through placebo, a binary study indicator (garadacimab study or HELP) was included in the model. Additionally, to account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

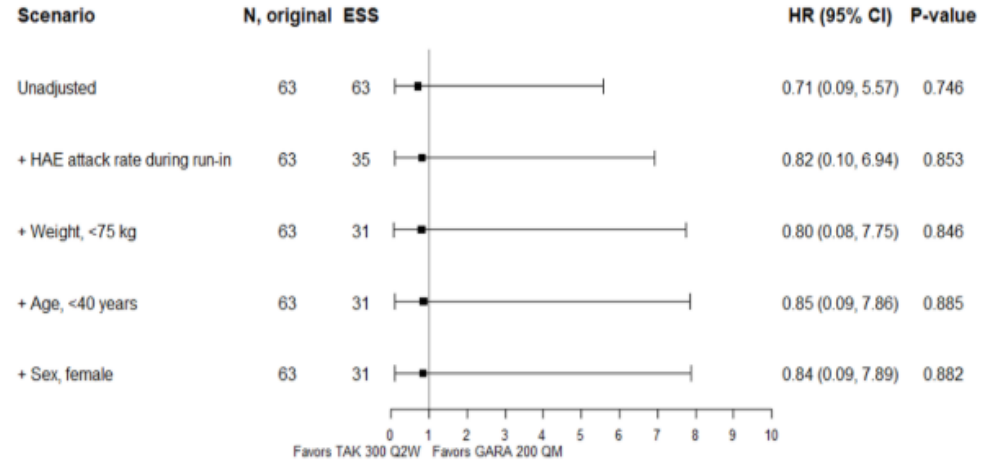


Figure 26 Sensitivity of Anchored MAIC and Excluding CSL312_2001 for Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Note: Since the MAIC was anchored through placebo, a binary study indicator (garadacimab study or HELP) was included in the model. Additionally, to account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.4.2 GARA 200 QM versus TAK 300 Q4W

C.6.4.2.1 Balance of Populations

Table 58 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the unanchored analysis. Before adjustment, there were substantial differences in the percentage of patients with weight <75 kg (SMD = 0.247) and the percentage of female patients (SMD = 0.209), and small differences in the HAE attack rate during run-in (SMD = 0.073) and the percentage of patients who were age <40 years (SMD = 0.045). In the primary scenario that adjusted for all four factors, there was a 11% reduction in ESS and the pooled patient characteristics of CSL312_3001 and CSL312_2001 matched those of HELP.

Table 58 Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and CSL312_2001 (Pooled) and HELP in Unanchored Analyses for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Characteristics	HELP (TAK 300 Q4W)	Pooled CSL312_3001 & CSL312_2001 (GARA 200 QM)									
		Unadjusted			Adjusted						
					1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 29	N = 47			ESS = 47		ESS = 43		ESS = 43		ESS = 42	
	Stat.	Stat.		SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.7 (2.5)[a]	3.5 (2.56)		0.073	3.7 (2.53)	0	3.7 (2.53)	0	3.7 (2.53)	0	3.7 (2.53)	0
Weight, <75 kg, %	48.3%[b]	36.2%		0.247	35.1%	0.269	48.3%	0	48.3%	0	48.3%	0
Age, <40 years, %	44.8%[b]	42.6%		0.045	42.7%	0.042	42.5%	0.047	44.8%	0	44.8%	0
Sex, female, %	65.5%[a]	55.3%		0.209	55.5%	0.205	57.4%	0.167	57.0%	0.176	65.5%	0

Source: [a] (Banerji et al. 2018) [b] (CADTH 2020)

Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.

Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.4.2.2 MAIC results

The results for proportion of subjects who achieved ≥90% attack rate reduction comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 27. The unadjusted comparison of proportion of subjects who achieved ≥90% attack rate for patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 2.07 (95% CI: 1.11, 3.85; P = 0.021) in favour of GARA 200 QM, which was statistically significant. In the scenario that adjusted for all four factors, the result was also favourable for GARA 200 QM (HR: 2.03 [95% CI: 1.03, 4.02; P = 0.041]), and statistically significant.

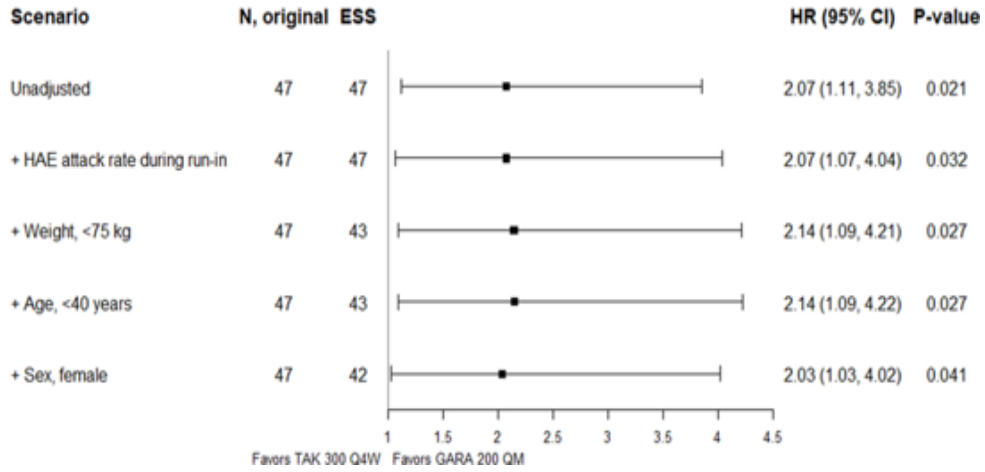


Figure 27 Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks

C.6.4.2.3 Sensitivity analysis excluding CSL312_2001

When comparing the CSL312_3001 population to the HELP population before adjustment, substantial differences were observed in HAE attack rate during run-in (SMD = 0.276) and in the percentage of patients with weight <75 kg (SMD = 0.200), a moderate difference in the percentage of patients with age <40 years (SMD = 0.129), and a small difference in the percentage of female patients (SMD = 0.082)(Table 59). In the scenario that adjusted for all four factors, there was a 15% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

The unadjusted comparison of proportion of subjects who achieved ≥90% attack rate for patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 1.70 (95% CI: 0.90, 3.21; P = 0.105) in favour of GARA 200 QM, however this was not statistically significant (Figure 28). In the scenario that adjusted for all four factors, the result was

also numerically favourable for GARA 200 QM (RR: 1.72 [95% CI: 0.87, 3.40; P = 0.121]), but not statistically significant.

Table 59 Sensitivity Excluding CSL312_2001: Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Unanchored Analysis for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Characteristics	HELP (TAK 300 Q4W arm)	CSL312_3001 (GARA 200 QM arm)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 29	N = 39		ESS = 36		ESS = 33		ESS = 33		ESS = 33	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.7 (2.5)[a]	3.1 (2.05)	0.276	3.7 (2.53)	0	3.7 (2.54)	0	3.7 (2.54)	0	3.7 (2.54)	0
Weight, <75 kg, %	48.3%[b]	38.5%	0.200	34.3%	0.287	48.3%	0	48.3%	0	48.3%	0
Age, <40 years, %	44.8%[b]	38.5%	0.129	40.5%	0.087	41.2%	0.072	44.8%	0	44.8%	0
Sex, female, %	65.5%[a]	61.5%	0.082	61.7%	0.080	63.2%	0.047	61.8%	0.076	65.5%	0

Source: [a] (Banerji et al. 2018) [b] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

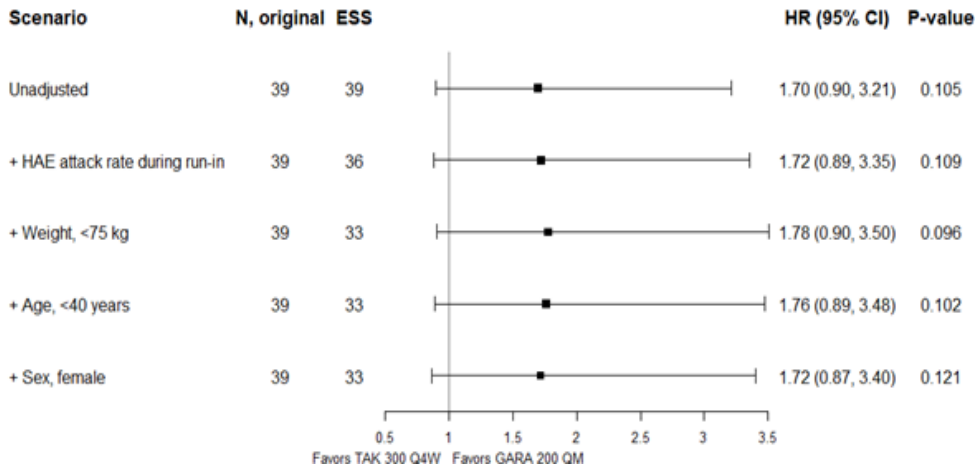


Figure 28 Sensitivity Excluding CSL312_2001: Summary of Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.4.2.4 Sensitivity analysis anchored MAIC

For a detailed summary pertaining to population balancing after adjustment for proportion of garadacimab subjects who achieved ≥90% attack rate reduction, refer to Appendix C.6.1.2.1 for the pooled CSL312_3001 and CSL312_2001 population and Appendix C.6.1.2.3 for the CSL312_3001 only population.

For the anchored analysis including the pooled CSL312_3001 and CSL312_2001 population, the unadjusted comparison of subjects who achieved ≥90% attack rate reduction for patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 1.38 (95% CI: 0.18, 10.78; P = 0.758) in favour of GARA 200 QM, however this was not statistically significant (Figure 29). In the primary MAIC scenario, the result was also numerically favourable for GARA 200 QM (HR: 1.38 [95% CI: 0.13, 14.58; P = 0.790]), but not statistically significant.

For the anchored analysis excluding CSL312_2001, the unadjusted comparison of subjects who achieved ≥90% attack rate reduction for patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 0.97 (95% CI: 0.12, 7.66; P = 0.981) in favour of GARA 200 QM, however this was not statistically significant (Figure 30). In the primary MAIC scenario, the result was also numerically favourable for GARA 200 QM (HR: 1.25 [95% CI: 0.13, 12.24; P = 0.848]), but not statistically significant.

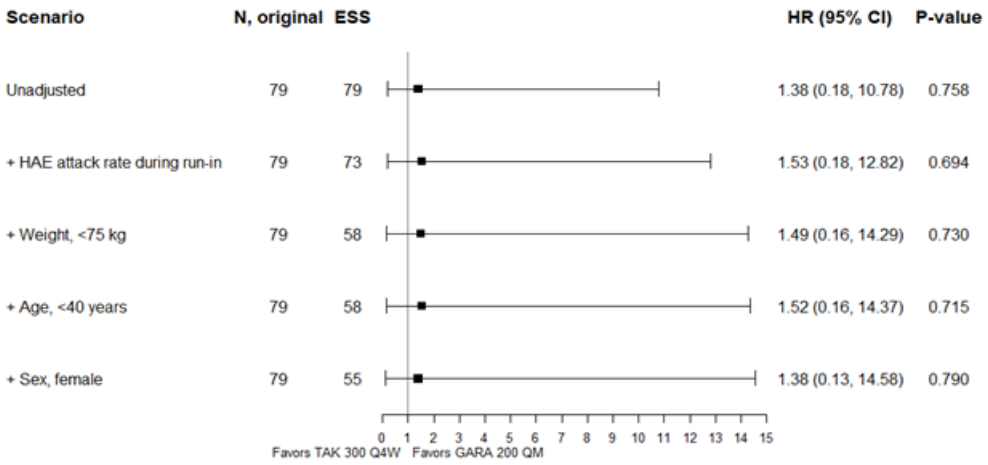


Figure 29 Sensitivity of Anchored MAIC for Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: Since the MAIC was anchored through placebo, a binary study indicator (garadacimab study or HELP) was included in the model. Additionally, to account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

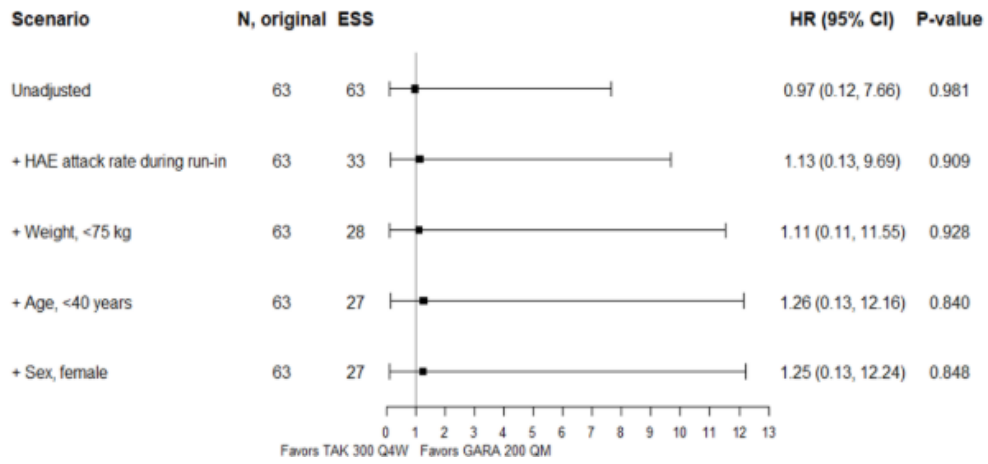


Figure 30 Sensitivity of Anchored MAIC and Excluding CSL312_2001 for Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: Since the MAIC was anchored through placebo, a binary study indicator (garadacimab study or HELP) was included in the model. Additionally, to account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This model-adjustment covariate and offset were included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.5 Efficacy – results per Proportion of Attack-free Patients

C.6.5.1 GARA 200 QM versus TAK 300 Q2W

C.6.5.1.1 Balance of populations

For a detailed summary pertaining to population balancing after adjustment for proportion of attack-free patients, refer to Appendix C.6.4.1.1.

C.6.5.1.2 MAIC results

The results for proportion of attack-free patients comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 31. The unadjusted comparison of proportion of attack-free patients for patients treated with GARA 200 QM versus LANA 300 Q2W produced a HR of 1.98 (95% CI: 1.00, 3.93; P = 0.051) in favour of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favourable for GARA 200 QM (HR: 1.93 [95% CI: 0.92, 4.03; P = 0.080]), but not statistically significant.

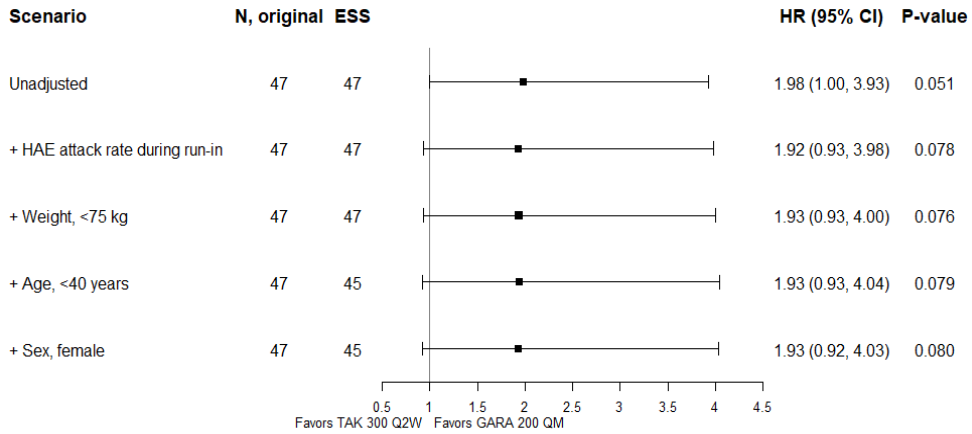


Figure 31 Summary of Proportion of Attack-free Patients Versus LANA 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = Confidence interval; ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; HR = Hazard ratio; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.5.1.3 Sensitivity analysis excluding CSL312_2001

For a detailed summary pertaining to population balancing after adjustment for the proportion of attack-free patients, refer to Appendix C.6.4.1.3.

The unadjusted comparison of proportion of attack-free patients treated with GARA 200 QM versus TAK 300 Q2W produced a HR of 1.63 (95% CI: 0.80, 3.30; P = 0.179) in favour of GARA 200 QM, however this was not statistically significant (Figure 32). In the scenario that adjusted for all four factors, the result was also numerically favourable for GARA 200 QM (HR: 1.44 [95% CI: 0.67, 3.09; P = 0.347]), but not statistically significant.

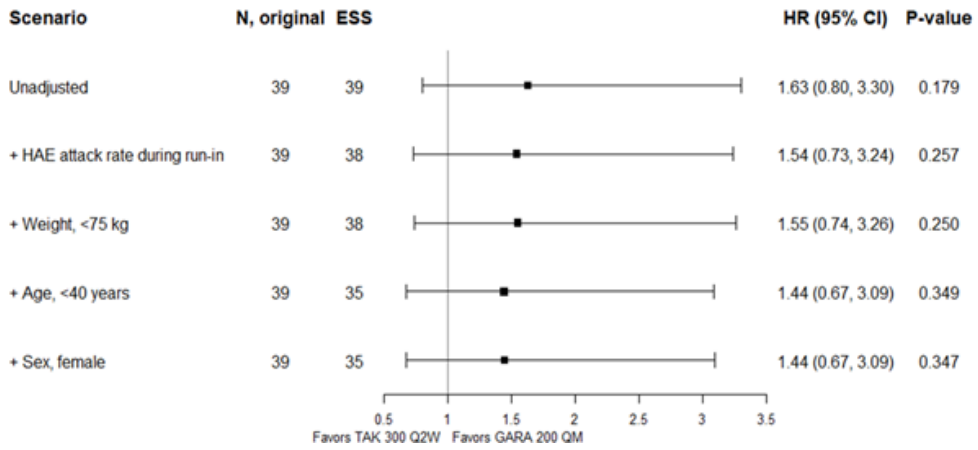


Figure 32 Sensitivity Excluding CSL312_2001: Summary of Proportion of Attack-free Patients Versus TAK 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.5.2 GARA 200 QM versus TAK 300 Q4W

C.6.5.2.1 Balance of Populations

For a detailed summary pertaining to population balancing after adjustment for proportion of attack-free patients, refer to Appendix C.6.4.2.1.

C.6.5.2.2 MAIC results

The results for proportion of attack-free patients comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 33. The unadjusted comparison of proportion of attack-free patients for patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 3.13 (95% CI: 1.47, 6.67; P = 0.003) in favour of GARA 200 QM, which was statistically significant. In the primary MAIC scenario, the result was also favourable for GARA 200 QM and statistically significant (HR: 3.25 [95% CI: 1.45, 7.29; P = 0.004]).

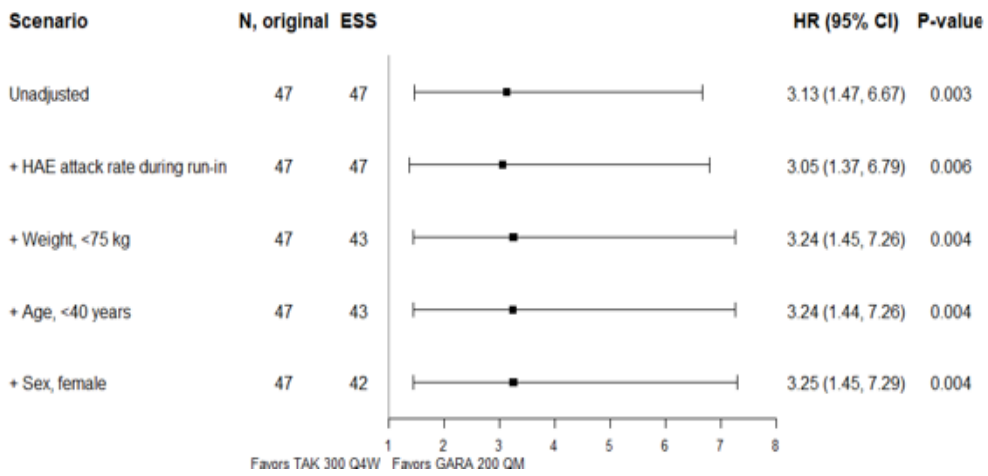


Figure 33 Summary of Proportion of Attack-free Patients Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: to account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.5.2.3 Sensitivity analysis excluding CSL312_2001

For a detailed summary pertaining to population balancing after adjustment for the proportion of attack-free patients, refer to Appendix C.6.4.2.3.

The unadjusted comparison of proportion of attack-free patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 2.57 (95% CI: 1.18, 5.60; P = 0.017) in favour of GARA 200 QM, which was statistically significant (Figure 34). In the scenario that adjusted for all four factors, the result was also favourable for GARA 200 QM (HR: 2.55 [95% CI: 1.11, 5.83; P = 0.027]), and statistically significant.

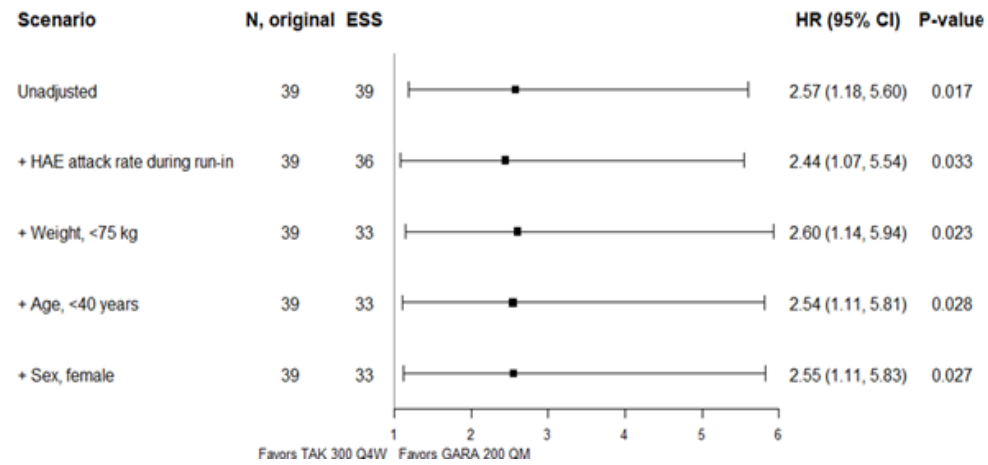


Figure 34 Sensitivity Excluding CSL312_2001: Summary of Proportion of Attack-free Patients Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.

Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.6 Efficacy – results per Attack-Free days per Month

C.6.6.1 GARA 200 QM versus TAK 300 Q2W

C.6.6.1.1 Balance of Populations

Table 60 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the anchored analysis. The VANGUARD population assessed for this outcome had one additional patient in the placebo arm compared to the analysis in Section C.6.1.1.1. Similarly, before adjustment, there were substantial differences in the percentage of patients with weight <75 kg (SMD = 0.367) and percentage of female patients (SMD = 0.361), a moderate difference in HAE attack rate during run-in (SMD = 0.168), and a small difference in the percentage of patients with age <40 years (SMD = 0.008) when comparing the pooled VANGUARD and CSL312_2001 population to the HELP population. In the primary scenario that adjusted for all four factors, there was a 24% reduction in ESS and the pooled patient characteristics of VANGUARD and CSL312_2001 matched those of HELP.

Table 60 Unadjusted and Adjusted Baseline Characteristics for VANGUARD and CSL312_2001 (Pooled) and HELP in Anchored Analysis for Number of Attack-free Days per Month

Characteristics	HELP (LANA 300 Q2W & PBO arms)[a]	Pooled VANGUARD & CSL312_2001 (GARA 200 QM & PBO arms)											
		Unadjusted		Adjusted									
				1 Characteristic			2 Characteristics		3 Characteristics		4 Characteristics		
	N = 68	N = 80		ESS = 74			ESS = 64		ESS = 64		ESS = 61		
	Stat.	Stat.	SMD	Stat.		SMD	Stat.	SMD	Stat.	SMD	Stat.		SMD
HAE attack rate during run-in, mean (SD)	3.8 (2.9)[b]	3.4 (2.26)	0.168	3.8 (2.95)	0	3.8 (2.96)	0	3.8 (2.96)	0	3.8 (2.96)	0		
Weight, <75 kg, %	52.9%[c]	35.0%	0.367	33.4%	0.401	52.9%	0	52.9%	0	52.9%	0		
Age, <40 years, %	47.1%[c]	47.5%	0.008	46.8%	0.005	46.6%	0.009	47.1%	0	47.1%	0		
Sex, female, %	72.1%[b]	55.0%	0.361	53.7%	0.387	61.1%	0.235	61.0%	0.236	72.1%	0		

[a] HELP SLD was pooled for the LANA 300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.

Source: (Banerji et al. 2018, Canadian Agency for Drugs and Technologies in Health 2020)Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.

Abbreviations: ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; MAIC = Matching-adjusted indirect comparison; PBO = Placebo; SD = Standard deviation; SLD = Summary-level data; SMD = Standardized mean difference; LANA 300 Q2W = Lanadelumab 300 mg every two weeks.

C.6.6.1.2 MAIC results

The results for attack-free days per month comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 35. The unadjusted comparison of attack-free days per month for patients treated with GARA 200 QM versus LANA 300 Q2W produced an MD of 0.90 (95% CI: -1.25, 3.05; P = 0.413) in favor of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favorable for GARA 200 QM (MD: 0.44 [95% CI: -1.76, 2.63; P = 0.696]), but not statistically significant.

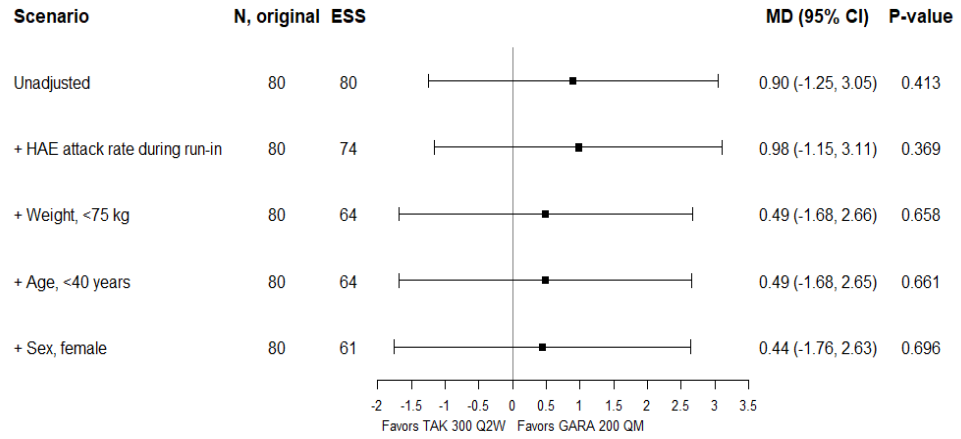


Figure 35 Summary of Proportion of Attack-free Patients Versus LANA 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: To account for differences in trial duration, an offset of the logarithm of time (days) of the maximum follow-up for each patient was included in the model. This offset was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; LANA 300 Q2W = lanadelumab 300 mg every two weeks

C.6.6.1.3 Sensitivity analysis excluding CSL312_2001

When comparing the CSL312_3001 population to the HELP population before adjustment, a substantial difference was observed in HAE attack rate during run-in (SMD = 0.393), percentage of patients with weight <75 kg (SMD = 0.280), and the percentage of female patients (SMD = 0.271), and a small difference in the percentage of patients with age <40 years (SMD = 0.036) (Table 61). In the scenario that adjusted for all four factors, there was a 53% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

The unadjusted comparison of attack-free days per month for patients treated with GARA 200 QM versus TAK 300 Q2W produced an MD of -0.15 (95% CI: -2.37, 2.06; P = 0.894) in favour of TAK 300 Q2W, however this was not statistically significant (Figure 36). In the scenario that adjusted for all four factors, the result was also numerically favourable for TAK 300 Q2W (MD: -0.79 [95% CI: -3.05, 1.46; P = 0.491]), but not statistically significant.

Table 61 Sensitivity Excluding CSL312_2001: Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Anchored Analysis for Number of Attack-free Days per Month

Characteristics	HELP (TAK 300 Q2W & PBO arms)[a]	CSL312_3001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 68	N = 64		ESS = 35		ESS = 31		ESS 31		ESS = 30	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.8 (2.9)[b]	2.9 (1.71)	0.393	3.8 (2.96)	0	3.8 (2.97)	0	3.8 (2.97)	0	3.8 (2.97)	0
Weight, <75 kg, %	52.9%[c]	39.1%	0.280	33.1%	0.408	52.9%	0	52.9%	0	52.9%	0
Age, <40 years, %	47.1%[c]	45.3%	0.036	53.3%	0.124	52.8%	0.114	47.1%	0	47.1%	0
Sex, female, %	72.1%[b]	59.4%	0.271	61.9%	0.218	69.5%	0.056	71.2%	0.021	72.1%	0

[a] HELP SLD was pooled for the TAK 300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.
Sources: [b] (Banerji et al. 2018) [c] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SMD = standardized mean difference; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

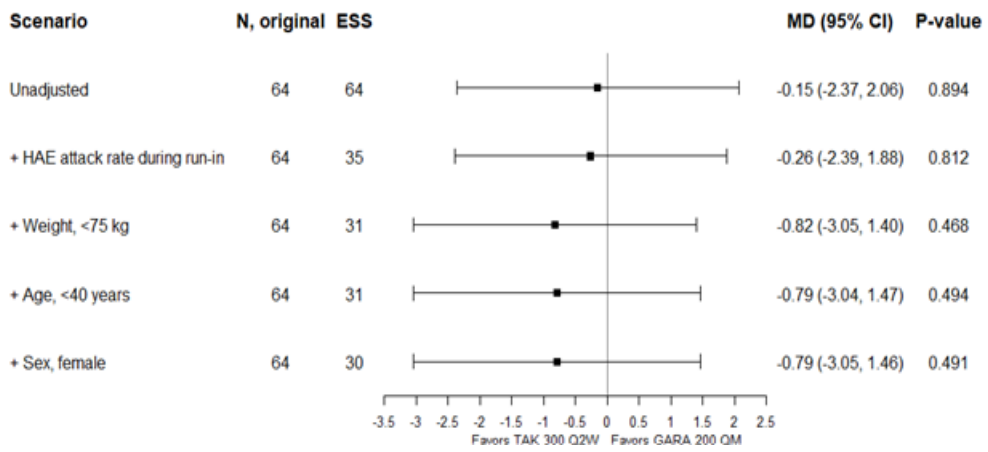


Figure 36 Sensitivity Excluding CSL312_2001: Summary of Attack-free Days per Month Versus TAK 300 Q2W

Note: An MD above 0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MD = mean difference; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.6.2 GARA 200 QM versus TAK 300 Q4W

C.6.6.2.1 Balance of Populations

Table 62 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the anchored analysis. The CSL312_3001 population assessed for this outcome had one additional patient in the placebo arm compared to the analysis in Appendix C.6.1.2.1. Similarly, before adjustment, there were substantial differences in the percentage of patients with weight <75 kg (SMD = 0.455), the percentage of female patients (SMD = 0.446), and the HAE attack rate during run-in (SMD = 0.204), and a small difference in the percentage of patients who were age <40 years (SMD = 0.064). In the primary scenario that adjusted for all four factors, there was a 31% reduction in ESS and the pooled patient characteristics of CSL312_3001 and CSL312_2001 matched those of HELP.

Table 62 Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and CSL312_2001 (Pooled) and HELP in Anchored Analysis for Number of Attack-free Days per Month

Characteristics	HELP (TAK 300 Q4W & PBO arms)[a]	Pooled CSL312_3001 & CSL312_2001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 70	N = 80		ESS = 73		ESS = 59		ESS = 59		ESS = 55	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.9 (3.0)[b]	3.4 (2.26)	0.204	3.9 (3.00)	0	3.9 (3.00)	0	3.9 (3.00)	0	3.9 (3.00)	0
Weight, <75 kg, %	57.1%[c]	35.0%	0.455	33.0%	0.499	57.1%	0	57.1%	0	57.1%	0
Age, <40 years, %	44.3%[c]	47.5%	0.064	46.7%	0.049	46.7%	0.047	44.3%	0	44.3%	0
Sex, female, %	75.7%[b]	55.0%	0.446	53.7%	0.473	62.9%	0.281	63.2%	0.274	75.7%	0

[a] HELP SLD was pooled for the TAK 300 Q4W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.(CSL Behring 2022)
Source: [b] (Banerji et al. 2018) [c] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD = standard deviation; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.6.2.2 MAIC results

The results for attack-free days per month comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 37. The unadjusted comparison of attack-free days per month for patients treated with GARA 200 QM versus TAK 300 Q4W produced an MD of 1.30 (95% CI: -0.85, 3.45; P = 0.237) in favour of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favourable for GARA 200 QM (MD: 0.84 [95% CI: -1.40, 3.08; P = 0.462]), but not statistically significant.

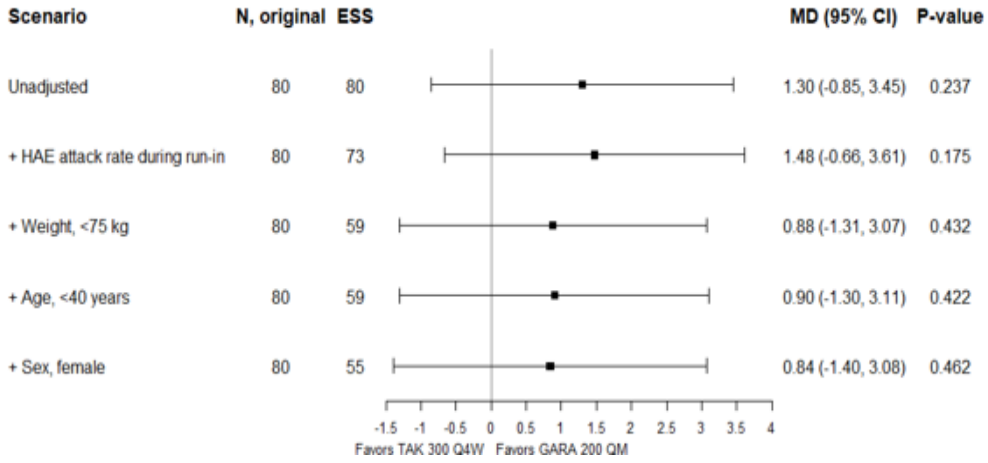


Figure 37 Summary of Attack-free Days per Month Versus TAK 300 Q4W

Note: An MD above 0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q2W.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MD = mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.6.2.3 Sensitivity analysis excluding CSL312_2001

When comparing the CSL312_3001 population to the HELP population before adjustment, a substantial difference was observed in HAE attack rate during run-in (SMD = 0.429), percentage of patients with weight <75 kg (SMD = 0.367), and the percentage of female patients (SMD = 0.354), and a small difference in the percentage of patients with age <40 years (SMD = 0.020) (Table 63). In the scenario that adjusted for all four factors, there was a 58% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

The unadjusted comparison of attack-free days per month for patients treated with GARA 200 QM versus TAK 300 Q4W produced an MD of 0.25 (95% CI: -1.97, 2.46; P = 0.825) in favour of GARA 200 QM, however this was not statistically significant (Figure 38). In the scenario that adjusted for all four factors, the result was numerically favourable for TAK 300 Q4W (MD: -0.48 [95% CI: -2.79, 1.84; P = 0.686]), but not statistically significant.

Table 63 Sensitivity Excluding CSL312_2001: Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Anchored Analysis for Number of Attack-free Days per Month

Characteristics	HELP (TAK 300 Q4W & PBO arms)[a]	CSL312_3001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 70	N = 64		ESS = 33		ESS = 28		ESS = 27		ESS = 27	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.9 (3.0)[b]	2.9 (1.71)	0.429	3.9 (3.01)	0	3.9 (3.01)	0	3.9 (3.01)	0	3.9 (3.01)	0
Weight, <75 kg, %	57.1%[c]	39.1%	0.367	32.5%	0.510	57.1%	0	57.1%	0	57.1%	0
Age, <40 years, %	44.3%[c]	45.3%	0.020	53.5%	0.184	52.8%	0.170	44.3%	0	44.3%	0
Sex, female, %	75.7%[b]	59.4%	0.354	62.1%	0.297	71.7%	0.091	74.2%	0.035	75.7%	0

[a] HELP SLD was pooled for the TAK 300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.[12]
Sources: [b] (Banerji et al. 2018) [c] (CADTH 2020)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; PBO = placebo; SD =standard deviation; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

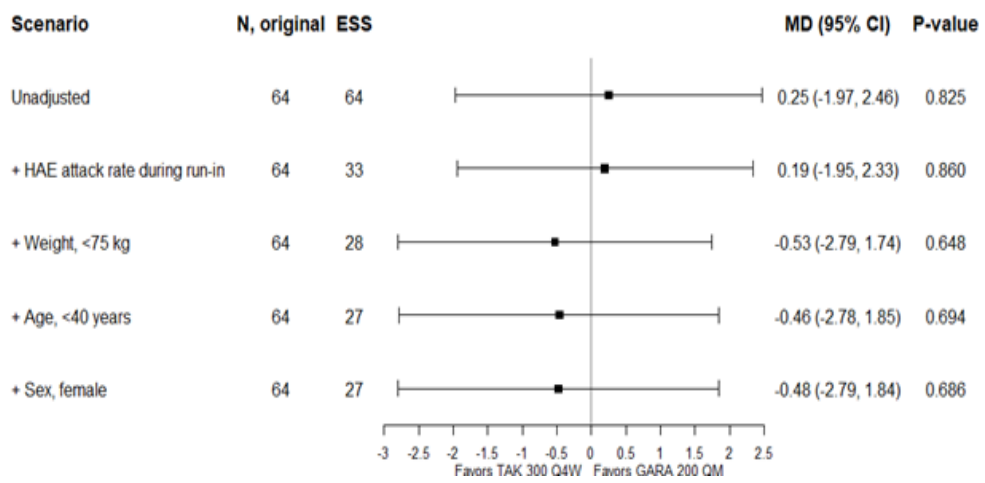


Figure 38 Sensitivity Excluding CSL312_2001: Summary of Attack-free Days per Month Versus TAK 300 Q4W

Note: An MD above 0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MD = mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.7 Efficacy – results per AE-QoL Change from Baseline to Day 182

C.6.7.1 GARA 200 QM versus TAK 300 Q2W

C.6.7.1.1 Balance of Populations

Table 64 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the anchored analysis. Before adjustment, there were substantial differences in the percentage of patients with HAE attack rate during run-in (SMD = 0.304), weight <75 kg (SMD = 0.348), and percentage of female patients (SMD = 0.250), and a moderate difference in the percentage of patients with age <40 years (SMD = 0.113) when comparing the VANGUARD population to the HELP population. In the primary scenario that adjusted for all four factors, there was a 49% reduction in ESS and the patient characteristics of VANGUARD matched those of HELP.

Table 64 Unadjusted and Adjusted Baseline Characteristics for VANGUARD and HELP in Anchored Analysis for AE-QoL Change from Baseline to Day 182, and Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182

Characteristics	HELP (LANA 300 Q2W & PBO arms)[a]	Pooled VANGUARD (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 68[b]	N = 53[c]		ESS = 31		ESS = 27		ESS = 27		ESS = 27	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.8 (2.9)[d]	3.1 (1.80)	0.304	3.8 (2.97)	0.000	3.8 (2.97)	0.000	3.8 (2.97)	0.000	3.8 (2.97)	0.000
Weight, <75 kg, %	52.9%[e]	35.8%	0.348	31.0%	0.454	52.9%	0.000	52.9%	0.000	52.9%	0.000
Age, <40 years, %	47.1%[e]	41.5%	0.113	51.0%	0.078	49.8%	0.054	47.1%	0.000	47.1%	0.000
Sex, female, %	72.1%[d]	60.4%	0.250	63.0%	0.195	69.7%	0.052	70.7%	0.032	72.1%	0.000

a HELP SLD was pooled for the LANA 300 Q2W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.
b Note: the HELP baseline characteristics presented are for all subjects included in ITT population, however the HELP AE-QoL outcome data is only based on 64 patients.
c Note that 11 subjects in VANGUARD had missing outcome data and was removed from the analysis.
Source: (Banerji et al. 2018, Canadian Agency for Drugs and Technologies in Health 2019)
Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.
Abbreviations: AE-QoL = Angioedema quality of life questionnaire; ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; MAIC = Matching-adjusted indirect comparison; MCID = Minimal clinically important difference; PBO = Placebo; SD = Standard deviation; SLD = Summary-level data; SMD = Standardized mean difference; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.7.1.2 MAIC Results

The results for AE-QoL change from baseline to day 182 comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 39.The unadjusted comparison of AE-QoL change from baseline to day 182 for patients treated with GARA 200 QM versus LANA 300 Q2W produced a MD of -7.69 (95% CI: -23.41, 8.02; P = 0.337) in favour of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also favourable for GARA 200 QM and statistically significant (MD: -17.38 [95% CI: -33.67, -1.08; P = 0.037]).

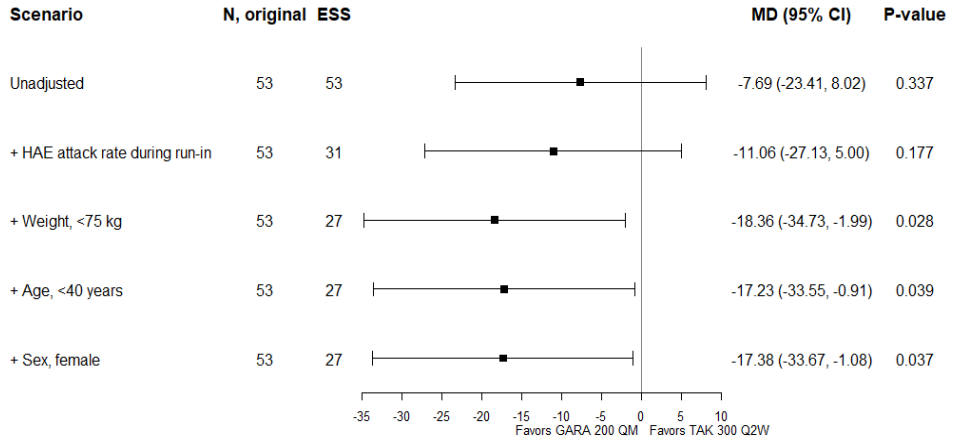


Figure 39 Summary of AE-QoL Change from Baseline to Day 182 Versus LANA 300 Q2W

Note: An MD below 0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; CI = Confidence interval; ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; MD = Mean difference; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.7.2 GARA 200 QM versus TAK 300 Q4W

C.6.7.2.1 Balance of Populations

Table 65 presents the distribution of baseline characteristics before adjusting and after the adjustment process for the anchored analysis. Before adjustment, there were substantial differences in the percentage of patients with HAE attack rate during run-in (SMD = 0.341), weight <75 kg (SMD = 0.436), and percentage of female patients (SMD = 0.333), and a small difference in the percentage of patients with age <40 years (SMD = 0.056) when comparing the CSL312_3001 population to the HELP population. In the primary scenario that adjusted for all four factors, there was a 55% reduction in ESS and the patient characteristics of CSL312_3001 matched those of HELP.

Table 65 Unadjusted and Adjusted Baseline Characteristics for CSL312_3001 and HELP in Anchored Analysis for AE-QoL Change from Baseline to Day 182, and Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182

Characteristics	HELP (TAK 300 Q4W & PBO arms)[a]	Pooled CSL312_3001 (GARA 200 QM & PBO arms)									
		Unadjusted		Adjusted							
				1 Characteristic		2 Characteristics		3 Characteristics		4 Characteristics	
	N = 70[b]	N = 53[c]		ESS = 30		ESS = 24		ESS = 24		ESS = 24	
	Stat.	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD	Stat.	SMD
HAE attack rate during run-in, mean (SD)	3.9 (3.0)[d]	3.1 (1.80)	0.341	3.9 (3.01)	0.000	3.9 (3.02)	0.000	3.9 (3.02)	0.000	3.9 (3.02)	0.000
Weight, <75 kg, %	57.1%[e]	35.8%	0.436	30.5%	0.556	57.1%	0.000	57.1%	0.000	57.1%	0.000
Age, <40 years, %	44.3%[e]	41.5%	0.056	51.2%	0.139	49.7%	0.108	44.3%	0.000	44.3%	0.000
Sex, female, %	75.7%[d]	60.4%	0.333	63.2%	0.274	71.6%	0.093	73.5%	0.051	75.7%	0.000

[a] HELP SLD was pooled for the TAK 300 Q4W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4.(CSL Behring 2022)

[b] Note: the HELP baseline characteristics presented are for all subjects included in ITT population, however the HELP AE-QoL outcome data is only based on 65 patients.

[c] Note that 11 subjects in CSL312_3001 had missing outcome data and was removed from the analysis.

Source: [d] (Banerji et al. 2018) [e] (CADTH 2020)

Note: An SMD between 0 and 0.1 is considered a small difference, an SMD >0.1 and ≤0.2 is a moderate difference, and an SMD >0.2 is a substantial difference. ESS is rounded to whole numbers.

Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; MCID = minimal clinically important difference; PBO = placebo; SD = standard deviation; SLD = summary-level data; SMD = standardized mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.7.2.2 MAIC results

The results for AE-QoL change from baseline to day 182 comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 40. The unadjusted comparison of AE-QoL change from baseline to day 182 for patients treated with GARA 200 QM versus TAK 300 Q4W produced a MD of -11.60 (95% CI: -27.24, 4.03; P = 0.146) in favour of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also favourable for GARA 200 QM and statistically significant (MD: -21.29 [95% CI: -37.39, -5.18; P = 0.010]).

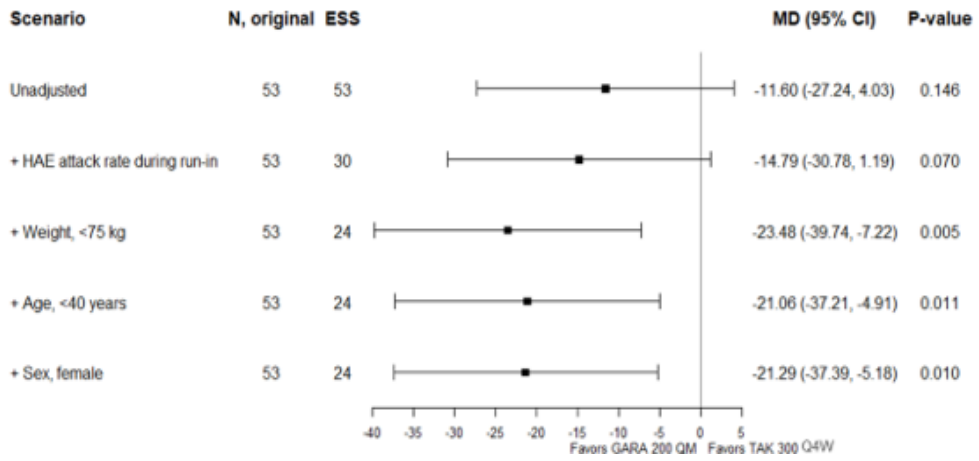


Figure 40 Summary of AE-QoL Change from Baseline to Day 182 Versus TAK 300 Q4W

Note: An MD below 0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MD = mean difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.8 Efficacy – results per Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182

C.6.8.1 GARA 200 QM versus TAK 300 Q2W

C.6.8.1.1 Balance of Populations

For a detailed summary pertaining to population balancing after adjustment for the proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182, please refer to Appendix C.6.7.1.1.

C.6.8.1.2 MAIC Results

The results for the proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182 comparing GARA 200 QM versus LANA 300 Q2W before and after adjustment are presented in Figure 41. The unadjusted comparison of the proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182 for patients treated with GARA 200 QM versus LANA 300 Q2W produced a HR of 0.74 (95% CI: 0.26, 2.07; P = 0.562) in favour of LANA 300 Q2W, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favourable for LANA 300 Q2W (HR: 0.97 [95% CI: 0.31, 3.05; P = 0.953]), but not statistically significant.

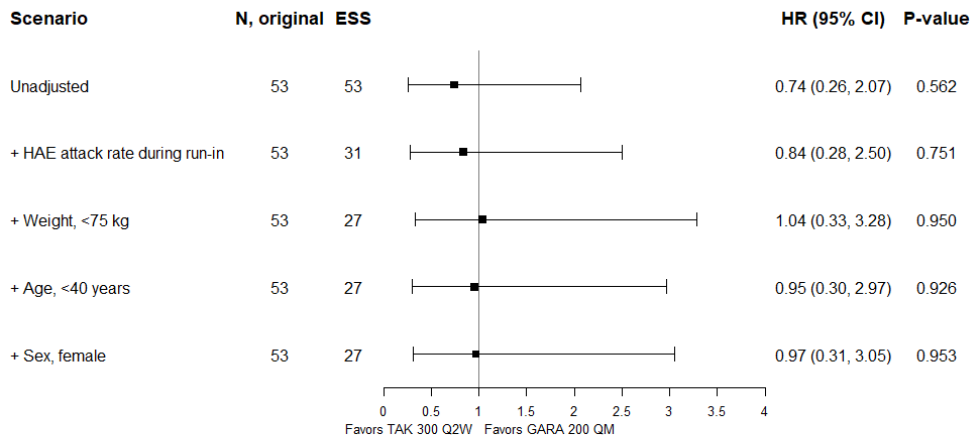


Figure 41 Summary of the Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182 Versus LANA 300 Q2W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to LANA 300 Q2W.
Note: Since the MAIC was anchored through placebo, a binary study indicator (garadacimab study or HELP) was included in the model. This model-adjustment covariate was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = Confidence interval; ESS = Effective sample size; GARA 200 QM = Garadacimab 200 mg once monthly; HAE = Hereditary angioedema; HR = Hazard ratio; MCID = Minimal clinically important difference; LANA 300 Q2W = Lanadelumab 300 mg every two weeks

C.6.8.2 GARA 200 QM versus TAK 300 Q4W

C.6.8.2.1 Balance of Populations

For a detailed summary pertaining to population balancing after adjustment for the proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182, refer to Appendix C.6.7.2.1.

C.6.8.2.2 MAIC results

The results for the proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182 comparing GARA 200 QM versus TAK 300 Q4W before and after adjustment are presented in Figure 42. The unadjusted comparison of the proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182 for patients treated with GARA 200 QM versus TAK 300 Q4W produced a HR of 1.22 (95% CI: 0.43, 3.46; P = 0.705) in favor of GARA 200 QM, however this was not statistically significant. In the primary MAIC scenario, the result was also numerically favorable for GARA 200 QM (HR: 1.52 [95% CI: 0.47, 4.97; P = 0.485]), but not statistically significant.

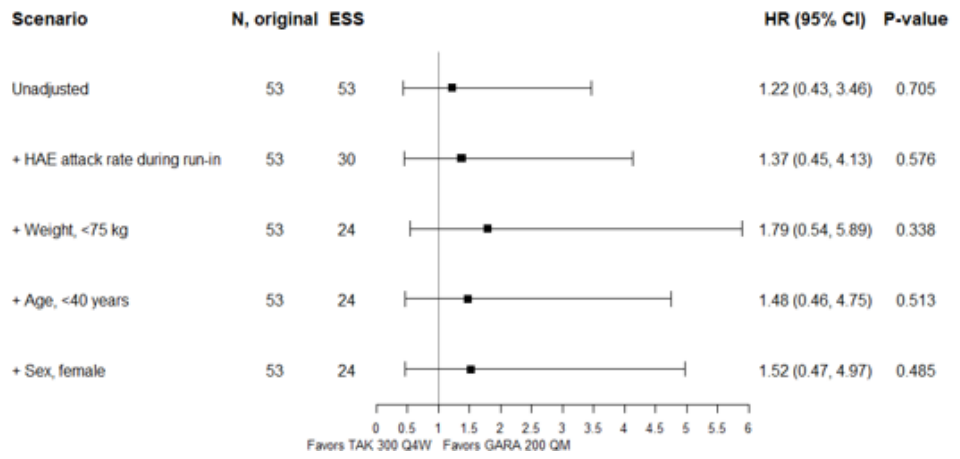


Figure 42 Summary of the Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182 Versus TAK 300 Q4W

Note: An HR above 1.0 indicates an improved outcome for GARA 200 QM relative to TAK 300 Q4W.
Note: Since the MAIC was anchored through placebo, a binary study indicator (garadacimab study or HELP) was included in the model. This model-adjustment covariate was included in every MAIC scenario as well as the "unadjusted" analysis.
Abbreviations: CI = confidence interval; ESS = effective sample size; GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; HR = hazard ratio; MCID = minimal clinically important difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.9 MAIC Patient Weights

C.6.9.1 GARA 200 QM versus TAK 300 Q2W

C.6.9.1.1 Primary analysis (CSL312_3001 and CSL312_2001 pooled)

Table 66 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, and Time-normalized Number of Moderate and/or Severe Attacks

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	79	74	0.92	0.92	0.95	0.98	3.35
2 Characteristics	79	64	0.61	0.61	0.71	1.42	3.35
3 Characteristics	79	64	0.60	0.62	0.70	1.44	3.33
4 Characteristics	79	61	0.43	0.50	0.83	1.51	2.96

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

Table 67 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Unanchored Analyses of GARA 200 QM versus TAK 300 Q2W for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum

1 Characteristic	47	47	0.53	0.96	1.02	1.07	1.12
2 Characteristics	47	47	0.53	0.94	1.01	1.08	1.15
3 Characteristics	47	45	0.40	0.86	0.92	1.20	1.41
4 Characteristics	47	45	0.39	0.84	0.93	1.19	1.45

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

Table 68 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for Number of Attack-free Days per Month

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	80	74	0.92	0.92	0.95	0.98	3.42
2 Characteristics	80	64	0.60	0.61	0.70	1.44	3.42
3 Characteristics	80	64	0.60	0.61	0.70	1.45	3.40
4 Characteristics	80	61	0.42	0.49	0.83	1.54	3.02

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

Table 69 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for AE-QoL Change from Baseline to Day 182, and Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	53	31	0.65	0.70	0.79	0.98	6.92
2 Characteristics	53	27	0.40	0.43	0.67	1.35	7.26
3 Characteristics	53	27	0.37	0.44	0.64	1.34	7.29
4 Characteristics	53	27	0.36	0.46	0.62	1.30	7.34

Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; MCID = minimal clinically important difference; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.9.1.2 Sensitivity analysis (excluding CSL312_2001)

Table 70 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, and Time-normalized Number of Moderate and/or Severe Attacks

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	63	35	0.75	0.76	0.85	0.93	8.02
2 Characteristics	63	31	0.46	0.49	0.57	1.30	8.40
3 Characteristics	63	31	0.39	0.51	0.65	1.35	8.47
4 Characteristics	63	31	0.38	0.51	0.63	1.36	8.50

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

Table 71 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Unanchored Analyses of GARA 200 QM versus TAK 300 Q2W for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	39	38	0.76	0.86	0.95	1.05	1.67
2 Characteristics	39	38	0.76	0.84	0.94	1.08	1.68

3 Characteristics	39	35	0.54	0.73	0.92	1.20	1.95
4 Characteristics	39	35	0.53	0.72	0.97	1.18	2.03

Abbreviations: GARA 200 QM, garadacimab 200 mg once monthly; MAIC, matching-adjusted indirect comparison; TAK 300 Q2W, Takhzyro 300 mg every two weeks.

Table 72 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for Number of Attack-free Days per Month

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	64	35	0.74	0.76	0.84	0.92	8.20
2 Characteristics	64	31	0.46	0.48	0.57	1.31	8.57
3 Characteristics	64	31	0.38	0.50	0.61	1.38	8.64
4 Characteristics	64	30	0.37	0.50	0.61	1.38	8.68

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q2W = Takhzyro 300 mg every two weeks.

C.6.9.1.3 Sensitivity analysis (CSL312_3001 and CSL312_2001 pooled; Anchored MAIC for proportion of subjects who achieved ≥90% Attack Rate Reduction)

Table 73 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for Proportion of Patients with ≥90% Attack Rate Reduction*

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	79	74	0.92	0.92	0.95	0.98	3.35
2 Characteristics	79	64	0.61	0.61	0.71	1.42	3.35
3 Characteristics	79	64	0.60	0.62	0.70	1.44	3.33
4 Characteristics	79	61	0.43	0.50	0.83	1.51	2.96

Abbreviations: GARA 200 QM, garadacimab 200 mg once monthly; HAE, hereditary angioedema; MAIC, matching-adjusted indirect comparison; TAK 300 Q2W, Takhzyro 300 mg every two weeks.

* Note: The weights used in this sensitivity analysis are identical to the weights used in the primary analysis of GARA 200 QM versus TAK 300 Q2W for time-normalized number of HAE attacks, time-normalized number of HAE attacks requiring on-demand treatment, and time-normalized number of moderate and/or severe attacks (Table 66).

C.6.9.1.4 Sensitivity analysis (excluding CSL312_2001; Anchored MAIC for proportion of subjects who achieved ≥90% Attack Rate Reduction)

Table 74 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q2W for Proportion of Patients with ≥90% Attack Rate Reduction*

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	63	35	0.75	0.76	0.85	0.93	8.02
2 Characteristics	63	31	0.46	0.49	0.57	1.30	8.40
3 Characteristics	63	31	0.39	0.51	0.65	1.35	8.47
4 Characteristics	63	31	0.38	0.51	0.63	1.36	8.50

Abbreviations: GARA 200 QM, garadacimab 200 mg once monthly; HAE, hereditary angioedema; MAIC, matching-adjusted indirect comparison; TAK 300 Q2W, Takhzyro 300 mg every two weeks.

* Note: The weights used in this sensitivity analysis are identical to the weights used in the sensitivity analysis (excluding CSL312_2001) of GARA 200 QM versus TAK 300 Q2W for time-normalized number of HAE attacks, time-normalized number of HAE attacks requiring on-demand treatment, and time-normalized number of moderate and/or severe attacks (Table 70).

C.6.9.2 GARA 200 QM versus TAK 300 Q4W

C.6.9.2.1 Primary analysis (CSL312_3001 and CSL312_2001)

Table 75 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, and Time-normalized Number of Moderate and/or Severe Attacks

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	79	73	0.92	0.92	0.92	0.94	3.48
2 Characteristics	79	58	0.49	0.53	0.67	1.48	3.48
3 Characteristics	79	58	0.47	0.53	0.69	1.50	3.55
4 Characteristics	79	55	0.36	0.38	0.76	1.70	3.36

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

Table 76 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Unanchored Analyses of GARA 200 QM versus TAK 300 Q4W for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	47	47	0.81	0.91	0.99	1.09	1.21
2 Characteristics	47	43	0.59	0.72	1.02	1.21	1.77

3 Characteristics	47	43	0.56	0.73	1.01	1.18	1.87
4 Characteristics	47	42	0.46	0.74	0.93	1.22	2.15

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

Table 77 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for Number of Attack-free Days per Month

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	80	73	0.92	0.92	0.92	0.94	3.55
2 Characteristics	80	59	0.49	0.53	0.67	1.49	3.54
3 Characteristics	80	59	0.46	0.53	0.68	1.51	3.62
4 Characteristics	80	55	0.35	0.38	0.76	1.72	3.41

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

Table 78 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for AE-QoL Change from Baseline to Day 182, and Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum

1 Characteristic	53	30	0.67	0.72	0.78	0.96	7.30
2 Characteristics	53	24	0.34	0.36	0.51	1.47	7.76
3 Characteristics	53	24	0.28	0.38	0.49	1.47	7.82
4 Characteristics	53	24	0.27	0.40	0.51	1.50	7.90

Abbreviations: AE-QoL = Angioedema Quality of Life Questionnaire; GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; MCID = minimal clinically important difference; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.9.2.2 Sensitivity analysis (excluding CSL312_2001)

Table 79 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for Time-normalized Number of HAE Attacks, Time-normalized Number of HAE Attacks Requiring On-demand Treatment, and Time-normalized Number of Moderate and/or Severe Attacks

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	63	33	0.76	0.77	0.83	0.91	8.46
2 Characteristics	63	28	0.38	0.39	0.43	1.41	8.98
3 Characteristics	63	27	0.29	0.44	0.54	1.47	9.10
4 Characteristics	63	27	0.28	0.43	0.51	1.37	9.16

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

Table 80 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Unanchored Analyses of GARA 200 QM versus TAK 300 Q4W for Proportion of Patients with ≥90% Attack Rate Reduction and Proportion of Attack-free Patients

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	39	36	0.75	0.83	0.91	1.00	2.42
2 Characteristics	39	33	0.51	0.62	1.00	1.28	2.61
3 Characteristics	39	33	0.46	0.64	0.96	1.25	2.57
4 Characteristics	39	33	0.40	0.67	0.97	1.22	2.68

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

Table 81 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for Number of Attack-free Days per Month

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	64	33	0.75	0.77	0.82	0.91	8.65
2 Characteristics	64	28	0.38	0.39	0.43	1.43	9.16
3 Characteristics	64	27	0.28	0.44	0.51	1.44	9.27
4 Characteristics	64	27	0.27	0.42	0.51	1.35	9.33

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

C.6.9.2.3 Sensitivity analysis (CSL312_3001 and CSL312_2001 pooled; Anchored MAIC for proportion of subjects who achieved ≥90% Attack Rate Reduction)

Table 82 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 and CSL312_2001 (Pooled) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for Proportion of Patients with ≥90% Attack Rate Reduction*

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	79	73	0.92	0.92	0.92	0.94	3.48
2 Characteristics	79	58	0.49	0.53	0.67	1.48	3.48
3 Characteristics	79	58	0.47	0.53	0.69	1.50	3.55
4 Characteristics	79	55	0.36	0.38	0.76	1.70	3.36

Abbreviations: GARA 200 QM = garadacimab 200 mg once monthly; HAE = hereditary angioedema; MAIC = matching-adjusted indirect comparison; TAK 300 Q4W = Takhzyro 300 mg every four weeks.

* Note: The weights used in this sensitivity analysis are identical to the weights used in the primary analysis of GARA 200 QM versus TAK 300 Q4W for time-normalized number of HAE attacks, time-normalized number of HAE attacks requiring on-demand treatment, and time-normalized number of moderate and/or severe attacks (Table 75).

C.6.9.2.4 Sensitivity analysis (excluding CSL312_2001; Anchored MAIC for proportion of subjects who achieved ≥90% Attack Rate Reduction)

Table 83 Distribution of Rescaled MAIC Patient Weights for CSL312_3001 (Excluding CSL312_2001) Used in Anchored Analysis of GARA 200 QM versus TAK 300 Q4W for Proportion of Patients with ≥90% Attack Rate Reduction*

Scenario	N	ESS	Minimum	Q25	Median	Q75	Maximum
1 Characteristic	63	33	0.76	0.77	0.83	0.91	8.46
2 Characteristics	63	28	0.38	0.39	0.43	1.41	8.98
3 Characteristics	63	27	0.29	0.44	0.54	1.47	9.10
4 Characteristics	63	27	0.28	0.43	0.51	1.37	9.16

Abbreviations: GARA 200 QM, garadacimab 200 mg once monthly; HAE, hereditary angioedema; MAIC, matching-adjusted indirect comparison; TAK 300 Q4W, Takhzyro 300 mg every four weeks.

* Note: The weights used in this sensitivity analysis are identical to the weights used in the sensitivity analysis (excluding CSL312_2001) of GARA 200 QM versus TAK 300 Q4W for time-normalized number of HAE attacks, time-normalized number of HAE attacks requiring on-demand treatment, and time-normalized number of moderate and/or severe attacks (Table 79).

C.7 Bucher analysis

As a supplement to the MAIC described in Section 7, a Bucher analysis was undertaken to estimate the relative efficacy and impact on quality of life of garadacimab (200 mg QM) vs lanadelumab (300 mg Q2W) for the prophylactic treatment of adolescents/adults with type I or II HAE. Individual patient data were leveraged from the VANGUARD trial to derive a pooled estimate for garadacimab versus placebo and summary-level data were leveraged from the HELP trial for lanadelumab versus placebo.

C.7.1 Data sources

This study used individual patient data (IPD) for garadacimab versus placebo from the VANGUARD (NCT04656418) and SLD for lanadelumab versus placebo from the HELP trial (NCT02586805). These studies are described in sections 6.1.1.1 and 6.1.1.3.

C.7.2 Patient populations used in comparative analyses

For VANGUARD, the analysis population was the ITT population, which consisted of all patients who were randomized and received at least one dose of the investigational product, irrespective of their protocol adherence and continued participation in the study (N = 39 [garadacimab], N = 25 [placebo] from VANGUARD).

For the HELP trial, the analysis population was the ITT population, which consisted of all patients who were randomized and received at least one dose of the investigational product. Only licensed doses for lanadelumab were considered for the Bucher analyses. Therefore, only lanadelumab 300 mg Q2W (N = 27), lanadelumab 300 mg Q4W (N = 29), and the placebo (N = 41) arms were included in the analysis.

C.7.3 Key trial design characteristics

The general trial design characteristics of VANGUARD and the HELP trials are described in sections 6.1.1.1 and 6.1.1.3.

Participants enrolled in the VANGUARD and HELP trials were required to satisfy the key eligibility criteria outlined in Table 48. Key eligibility criteria were generally aligned between the three trials although some differences exist.

C.7.4 Key trial baseline characteristics

The key baseline characteristics for the VANGUARD and HELP trials are presented in Table 84 for the pooled active treatment and placebo arms.

Table 84 Key Baseline Characteristics

Characteristic	VANGUARD	HELP	
	Pooled Garadacimab 200 QM & PBO arms (N=64)	Pooled Lanadelumab 300 Q2W & PBO arms[a] (N=68)	Pooled Lanadelumab 300 Q4W & PBO arms[a] (N=70)
HAE attack rate during run-in, mean (SD)	2.9 (1.71)	3.8 (2.9)[b]	3.9 (3.0)[b]
Weight, <75 kg, %	39.1%	52.9%[c]	57.1%[c]
Age, <40 years, %	45.3%	47.1%[c]	44.3%[c]
Sex, female, %	59.4%	72.1%[b]	75.7%[b]

[a] HELP SLD was pooled for the lanadelumab 300 Q4W and PBO arms following the methods reported in the Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (Higgins JPT 2023b)
[b] Data source: Table 1 in (Banerji et al. 2018)
[c] Data source: Table 7 in Lanadelumab (Takhzyro) CADTH Clinical Review Report (Canadian Agency for Drugs and Technologies in Health 2020)
Abbreviations: HAE, hereditary angioedema; PBO, placebo; Q4W, every four weeks; QM, once monthly; SD, standard deviation.

C.7.5 Outcomes

The following outcomes were assessed:

1. Time-normalized number of HAE attacks,
2. Time-normalized number of moderate and/or severe HAE attacks,
3. Proportion of attack-free patients,
4. Proportion of patients who achieved ≥90% attack rate reduction compared to run-in,
5. Angioedema Quality of Life Questionnaire (AE-QoL) change from baseline to day 182, and
6. Proportion of patients achieving a minimal clinically important difference (MCID) ≥6 points in total score from baseline to day 182.

C.7.5.1 Time-Normalized Number of HAE Attacks

Time-normalized number of HAE attacks for garadacimab treatment is defined as the number of investigator-confirmed HAE attacks per month during treatment period from day 1 (first study drug administration) through day 182 (6-month) (CSL Behring 2020). The outcome definition is similar in the HELP trial (Banerji et al. 2018).

C.7.5.2 Time-Normalized Number of Moderate and/or Severe HAE Attacks

Time-normalized number of moderate or severe HAE attacks for garadacimab treatment is defined as the number of investigator-confirmed HAE attacks per month during treatment period from day 1 (first study drug administration) through day 182 (6-month) (CSL Behring 2020). The outcome definition is similar in the HELP trial (Banerji et al. 2018).

C.7.5.3 Proportion of Attack-Free Patients

Proportion of attack-free patients for the garadacimab population is defined as the percentage of subjects with a percentage reduction of 100% (ie, who do not experience an HAE attack and so are attack-free for the 6-month treatment period (CSL Behring 2020). The outcome definition is similar in the HELP trial (Banerji et al. 2018).

C.7.5.4 Proportion of Subjects who Achieved ≥90% Attack Rate Reduction

This outcome is defined as the proportion of patients who achieved at least a 90% attack rate reduction at 6-months compared to the run-in period (CSL Behring 2020). The outcome definition is similar in the HELP trial, with a treatment period of 26 weeks (Banerji et al. 2018).

C.7.5.5 AE-QoL Change from Baseline to Day 182

For both the garadacimab and lanadelumab populations, AE-QoL change from baseline (day 1 for garadacimab (CSL Behring 2020) and day 0 for lanadelumab (Banerji et al. 2018)) to day 182 was assessed from a questionnaire consisting of four domains (functioning, fatigue and mood, fears and shame, and nutrition). In the VANGUARD trial, the questionnaire responses were provided via electronic case report form (eCRF) data, and this outcome was reported for patients of age ≥18 years (CSL Behring 2020). In the HELP trial, the questionnaire was administered pre-dose (Banerji et al. 2018).

C.7.5.6 Proportion of Patients Achieving an MCID ≥6 Points in Total Score from Baseline to Day 182

This outcome is defined as the proportion of patients with MCID change (≥6 points) in AE-QoL total score from day 1 to day 182 (garadacimab) (CSL Behring 2020) through day 182 (lanadelumab) (Banerji et al. 2018). In the VANGUARD trial, this outcome was reported for patients of age ≥18 years (CSL Behring 2020).

C.7.6 Methodology

The methodology and considerations used to conduct the analyses are summarized below.

C.7.6.1 Estimating Indirect Treatment Effects

The Bucher ITC contrasted effect estimates from garadacimab versus placebo and lanadelumab versus placebo for each outcome of interest. Prior to conducting the Bucher comparison, IPD was leveraged from VANGUARD to derive the effect estimates for garadacimab versus placebo. The effect estimates for lanadelumab versus placebo were obtained or derived from HELP. Input data for the Bucher ITC analyses are provided in Table 85.

Details for each outcome are described below.

C.7.6.2 Binary Endpoints

Three binary endpoints were included in this study:

1. proportion of attack-free patients over the trial period;

2. proportion of patients who achieved ≥90% attack rate reduction compared to run-in; and

3. proportion of patients achieving an MCID ≥6 points in total score from baseline to day 182.

An odds ratio (OR) and standard error (SE) for garadacimab versus placebo was estimated using event counts from a 2x2 table (Higgins JPT 2023a). The OR was calculated as the odds of the event in the garadacimab group (ie, number of patients with events in the garadacimab group / number of patients without events in the garadacimab group) divided by the odds of the event in the placebo group (ie, number of patients with events in the placebo group / number of patients without events in the placebo group). The log odds ratio was then derived, and the corresponding variance was calculated by summing the reciprocals of the number of patients with events and the number of patients without events in both the garadacimab and placebo groups and then taking the square root of this sum. Notably, there were zero subjects in the VANGUARD placebo arm that achieved an attack-free status. A zero-cell correction was therefore applied (ie, 1 was added to the denominator and 0.5 was added to the numerator for all treatment arms) to facilitate obtaining an estimate for this outcome (Dias et al. 2011).

For lanadelumab versus placebo, the log OR and its variance was estimated similarly using published event counts for HELP. Since the placebo arm did not have any zero events, zero-cell correction was not required for the HELP data.

The log relative treatment effect of garadacimab versus lanadelumab was calculated as the difference in estimated ORs, and the corresponding variance was calculated as the

sum of the variances of the log ORs. Effect estimates were exponentiated and reported as ORs with 95% confidence intervals (CIs).

C.7.6.3 Continuous Endpoints

One continuous outcome was included in this study:

1. AE-QoL change from baseline to day 182.

The mean difference (MD) and SE for garadacimab versus placebo was estimated using a Gaussian likelihood with an identity link function. Treatment was included as a model-adjustment covariate.

For lanadelumab versus placebo, the MD and variance was obtained from HELP.

The relative treatment effect of garadacimab versus lanadelumab was calculated as the difference in estimated MDs, and the corresponding variance was calculated as the sum of the variances of the MDs. Effect estimates were reported as a MD with 95% CIs.

C.7.6.4 Rate Endpoints

Two rate outcomes were included in this study:

1. time-normalized number of HAE attacks; and

2. time-normalized number of moderate and/or severe HAE attacks.

The log rate ratio (RR) and SE for garadacimab vs placebo were estimated using a Poisson likelihood with a log link function. Treatment and normalized baseline HAE attack-rate during run-in were included as model-adjustment covariates and the logarithm of time (days) each subject was observed during the treatment period was included as an offset variable to align with the statistical analysis methodology reported for HELP (Banerji et al. 2018).

For lanadelumab versus placebo, the estimated RR and variance was obtained from HELP and its log RR and variance derived.

The log relative treatment effect of garadacimab versus lanadelumab was calculated as the difference of the log RRs, and the corresponding variance was calculated as the sum of the variances of the log RRs. Effect estimates were exponentiated and reported as RRs with 95% CIs.

Table 85 Summary of Bucher ITC inputs

Outcome Outcome type	Comparator	N Gara Pbo	Event Gara Pbo	Prop Gara Pbo	N Lan Pbo	Event Lan Pbo	Prop Lan Pbo	Relative Treatment Effect Gara vs Pbo (95% CI)	Relative Treatment Effect Lan vs Pbo (95% CI)
Time-normalized number of HAE attacks Rate	Lan Q2W	39 24[1]			27 41			RR: 0.10 (0.05, 0.21)	RR: 0.13 (0.07, 0.24)
	Lan Q4W	39 24[1]			29 41			RR: 0.10 (0.05, 0.21)	RR: 0.27 (0.18, 0.41)
Time-normalized number of moderate and/or severe HAE attacks Rate	Lan Q2W	39 24[1]			27 41			RR: 0.07 (0.03, 0.20)	RR: 0.17 (0.08, 0.33)
	Lan Q4W	39 24[1]			29 41			RR: 0.07 (0.03, 0.20)	RR: 0.27 (0.16, 0.46)
	Lan Q2W	40[2] 25[1,2]	24.5[3] 0.5[3]	0.613 0.02	27 41	12 1	0.444 0.024	OR: 77.45 (4.39, 1367.86)	OR: 32.00 (3.82, 267.82)

Proportion of attack-free patients Binary	Lan Q4W	40[2] 25[1,2]	24.5[3] 0.5[3]	0.613 0.020	29 41	9 1	0.310 0.024	OR: 77.45 (4.39, 1367.86)	OR: 18.00 (2.13, 152.17)
Proportion of subjects who achieved ≥90% attack rate reduction Binary	Lan Q2W	39 24[1]	29 2	0.744 0.083	27 41	18 2	0.667 0.049	OR: 31.90 (6.34, 160.58)	OR: 39.00 (7.64, 199.21)
	Lan Q4W	39 24[1]	29 2	0.744 0.083	29 41	16 2	0.552 0.049	OR: 31.90 (6.34, 160.58)	OR: 24.00 (4.85, 118.68)
Proportion of patients achieving an MCID ≥6 points in total score Binary	Lan Q2W	33[4] 20[5]	29 11	0.879 0.550	26 38	21 14	0.808 0.368	OR: 5.93 (1.51, 23.28)	OR: 7.20 (2.22, 23.37)
	Lan Q4W	33[4] 20[5]	29 11	0.879 0.550	27 38	17 14	0.630 0.368	OR: 5.93 (1.51, 23.28)	OR: 2.91 (1.05, 8.10)
Change from baseline in AE-QoL total score Continuous	Lan Q2W	33[4] 20[5]			26 38			MD: -24.26 (-34.46, -14.06)	MD: -16.57 (-28.53, -4.62)
	Lan Q4W	33[4] 20[5]			27 38			MD: -24.26 (-34.46, -14.06)	MD: -12.66 (-24.51, -0.80)

[1]Note that one subject who received placebo in VANGUARD had missing outcome data and was removed from the analysis.
[2]Zero-cell correction of 1 patient applied.
[3]Zero-cell correction of 0.5 event applied.
[4]Note that six subject who received garadacimab in VANGUARD had missing outcome data and was removed from the analysis.
[5]Note that five subjects who received placebo in VANGUARD had missing outcome data and was removed from the analysis.
Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; Gara, garadacimab; HAE, hereditary angioedema; CI, confidence interval; Lan, lanadelumab; MCID, minimal clinically important difference; MD, mean difference; OR, odds ratio; Pbo, placebo; Pop, population; Prop, proportion; Q2W, every two weeks; Q4W, every four weeks; RR, rate ratio.

C.7.7 Results

The Bucher ITC results for garadacimab 200 QM versus lanadelumab 300 Q2W and lanadelumab 300 Q4W for each outcome are presented in Table 86.

Compared to lanadelumab 300 Q4W, Bucher ITC results were statistically significantly favorable for garadacimab 200 QM for time-normalized number of moderate and/or severe HAE attacks. Garadacimab 200 QM was numerically favorable vs lanadelumab 300 Q2W and Q4W across all other outcomes, except proportion of patients achieving an MCID ≥6 points in total score, where lanadelumab 300 Q2W was numerically superior, but this was not statistically significant.

Table 86 Summary of Results

Outcome	Treatment effect	Bucher ITC results	
		Garadacimab 200 QM vs. Lanadelumab 300 Q2W	Garadacimab 200 QM vs. Lanadelumab 300 Q4W
Time-normalized number of HAE attacks	RR (95% CI)	*0.77 (0.30, 2.01)*	**0.37 (0.16, 0.86)**
Time-normalized number of moderate and/or severe HAE attacks	RR (95% CI)	*0.42 (0.12, 1.45)*	**0.26 (0.08, 0.83)**
Proportion of attack-free patients[1]	OR (95% CI)	*2.42 (0.07, 86.13)*	*4.30 (0.12, 154.03)*
Proportion of subjects who achieved ≥90% attack rate reduction	OR (95% CI)	0.82 (0.08, 8.13)	*1.33 (0.14, 12.91)*
Proportion of patients achieving an MCID ≥6 points in total score	OR (95% CI)	0.82 (0.14, 5.00)	*2.04 (0.37, 11.22)*
Change from baseline in AE-QoL total score	MD (95% CI)	*-7.69 (-23.41, 8.02)*	*-11.60 (-27.24, 4.03)*

Bold values indicate statistical significance and correspond to a two-tailed p-value <0.05.
Italic values indicate numberical trend favoring garadacimab 200 QM over lanadelimab 300 Q2W or Q4W
Shaded cells indicate numerical trend favoring lanadelumab 300 Q2W over garadacimab 200 QM.
An RR < 1 indicates an improved outcome for garadacimab 200 QM relative to lanadelumab 300 Q2W or Q4W.
An OR > 1 indicates an improved outcome for garadacimab 200 QM relative to lanadelumab 300 Q2W or Q4W.
An MD < 0 indicates an improved outcome for garadacimab 200 QM relative to lanadelumab 300 Q2W or Q4W.
[1] The Bucher analysis for proportion of attack-free patients used a zero-cell correction.
Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; CI, confidence

interval; MCID, minimal clinically important difference; MD, mean difference; OR, odds ratio; Q2W, every two weeks; Q4W, every four weeks; QM, once monthly; RR, rate ratio.

C.7.8 Discussion

Garadacimab and lanadelumab have demonstrated favorable outcomes as long-acting prophylactic treatments for HAE (Craig et al. 2023, Banerji et al. 2018) but have not been compared in any head-to-head trials. To fill this knowledge gap, the present study conducted Bucher ITCs to estimate the comparative efficacy and impact on QoL of garadacimab and two licensed doses of lanadelumab.

Given the availability of a common comparator, the Bucher method was deemed feasible for estimating the relative effects of garadacimab versus lanadelumab. The present analysis used IPD from VANGUARD, and SLD from HELP. These two effect estimates were then used as inputs (Table 85) in the traditional Bucher ITCs to estimate the relative effect of garadacimab versus lanadelumab.

Bucher results were statistically significantly in favor of garadacimab 200 QM for time-normalized number of moderate and/or severe HAE attacks in the comparison vs lanadelumab 300 mg Q4W. Compared with lanadelumab 300 Q4W, garadacimab 200 QM was numerically favorable with respect to all other outcomes.

In the comparison to lanadelumab 200 Q2W, garadacimab 200 QM was numerically favorable with respect to time-normalized number of HAE attacks, proportion of attack-free patients over the trial period, and change from baseline in AE-QoL total score in the treatment of patients with type I or II HAE. For proportion of patients who achieved ≥90% attack rate reduction, and proportion of patients achieving an MCID ≥6 points in total score, the Bucher results were numerically favorable for lanadelumab 300 Q2W, however this was not statistically significant.

In contrast to the results from the MAIC analysis (reported in Section 7.1.4.2), the statistical significance was lost for garadacimab 200 QM when compared to lanadelumab 300 Q2W for time-normalized number of moderate and/or severe HAE attacks, and AE-QoL change from baseline to day 182. Additionally, Bucher analysis results shifted in favor of lanadelumab 300 Q2W for proportion of subjects who achieved ≥90% attack rate reduction, however this was not statistically significant. All other Bucher analysis results remained consistent with the primary analysis.

This study was not without limitations. First, the VANGUARD and HELP populations leveraged for the Bucher analyses differed in their distribution of key baseline characteristics. As the Bucher method does not adjust for treatment effect modifiers and relies on the assumption of homogeneity and similarity, the observed differences in key baseline characteristics across analysis populations may have contributed bias to the Bucher ITC results (Table 84). Additionally, although key trial design characteristics were broadly similar across trials, VANGUARD was narrower for some eligibility criteria compared to HELP (Table 48) and there were also some differences in baseline characteristics between the two trials (HAE attack rate during run-in, weight, age, and sex; Table 84), resulting in unresolved heterogeneity between trials.

In contrast to the Bucher analysis reported here, the MAIC reported in Section 7 and Appendix C.1 - C.6 accounts for the differences in baseline HAE attack rate during run-in, weight, age, and sex (see Appendix C.6.1.1), thereby reducing the uncertainty associated with between trial-heterogeneity.

Appendix D. Extrapolation

Not applicable.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Overview of adverse events from VANGUARD, TEAEs by system organ class, and TEAEs related to study treatment by system organ class are shown in the tables below.

Table 87 Overview of adverse events (VANGUARD, Safety Analysis Set)

	Garadacimab 200 mg (N=39)		Placebo (N=25)	
	Patients, n (%)*	Events, n (%)*	Patients, n (%)*	Events, n (%)*
Any TEAE	25 (64.1)	75 (100)	15 (60.0)	54 (100)
Related to study treatment	4 (10.3)	9 (12.0)	3 (12.0)	5 (9.3)
Leading to study discontinuation	0	0	0	0
TEAEs by outcome				
Death	0	0	0	0
TEAEs identified as injection site reaction†	2 (5.1)	3 (4.0)	3 (12.0)	3 (5.6)
Related to study treatment	2 (5.1)	3 (4.0)	2 (8.0)	2 (3.7)
Serious TEAEs‡	1 (2.6)	1 (1.3)	0	0
Number and proportion of patients who discontinue treatment regardless of reason	0 (0.0)	0 (0.0)	3 (12.0)	3 (12.0)

Abbreviations: AESI = Adverse event of special interest; n = Number of scores or individuals; SC = Subcutaneous; TEAE = Treatment-emergent adverse event.
* Percentages for patients are based on the number of patients in the Safety Analysis Set. Percentages for events are based on the total number of events.
†Injection-site reaction is summarised by System Organ Class and Preferred Term forming a virtual System Organ Class of Injection Site Reactions
‡One severe, serious adverse event (laryngeal attack) was assessed as not related to trial treatment. The patient made a full recovery and was kept under hospital observation overnight.
Source: Craig et al., 2023,(Craig et al. 2023) CSL Behring Data on File, CSL312_3001 CSR (2022) (CSL Behring GmbH 2022b)

Table 88 TEAEs related to study treatment by System Organ Class and Preferred Term (VANGUARD, Safety Analysis Set)

MedDRA System Organ Class and MedDRA Preferred Term*	Garadacimab 200 mg (N=39)		Placebo (N=25)	
	Patients, n (%)†	Events, n (%)†	Patients, n (%)†	Events, n (%)†
Any TEAE related to study treatment	4 (10.3)	9 (100.0)	3 (12.0)	5 (100)
Injection site reactions‡	2 (5.1)	3 (33.3)	2 (8.0)	2 (40)
Injection site erythema	1 (2.6)	1 (11.1)	2 (8.0)	2 (40)
Injection site bruising	1 (2.6)	1 (11.1)	0	0
Injection site pruritus	1 (2.6)	1 (11.1)	0	0
Investigations	1 (2.6)	1 (11.1)	0	0
Prothrombin fragment 1+2 increased	1 (2.6)	1 (11.1)	0	0
Headache	1 (2.6)	5 (55.6)	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = Number of scores or individuals; TEAE = Treatment-emergent adverse event
*Adverse events are coded using MedDRA version 26.1
†Percentages for patients are based on the number of patients in the Safety Analysis Set. Percentages for events are based on the total number of events.
‡Injection-site reaction is summarised by System Organ Class and Preferred Term forming a virtual System Organ Class of Injection Site Reactions
Source: (Craig et al. 2023) (CSL Behring GmbH 2022b).

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

Not applicable.

Table 89 Overview of parameters in the probabilistic sensitivity analyses

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A SLR was conducted to identify clinical evidence that summarizes the efficacy and safety data from randomized controlled trials (RCTs) for pharmacological prophylactic therapies in adolescent and/or adult patients with HAE. The SLR adhered to established methods for conducting systematic reviews and were reported on in accordance with the Preferred Reporting Items for SLRs and Meta-Analyses (PRISMA) statement. The search was conducted across multiple databases through the Ovid® search interface (Embase, MEDLINE®, the Cochrane Library databases, and the Centre for Reviews and Dissemination database), using a combination of controlled vocabulary and keywords developed by a medical information specialist and peer reviewed by a second information specialist before execution. Disagreements were discussed and a third reviewer involved to resolve if required. The electronic database search was conducted on April 8, 2024 for the original review and August 5, 2024 for the updated review. For the update review duplicate database hits were also checked for between the original and update reviews. The database searches retrieved 1934 references, of which 522 were duplicates. In the original review, of the 1412 titles and abstracts screened with the eligibility criteria, 995 references did not meet the criteria. Hence, full texts of the remaining 417 references were retrieved and reviewed based on the eligibility criteria, plus 44 publications identified through grey literature searches. Of these, 320 publications were included overall, of which 206 were extracted, with the remaining 114 being non-RCT publications. The 206 clinical publications extracted from were on 20 different studies. Of the 20 studies, 14 were RCTs and 6 OLE studies.

Table 90 PICOS statement for the clinical SLR for HAE

Clinical SLR PICOS	
Patient population	Adolescent and adult patients with recurrent HAE attacks.
Intervention and Comparators	**Intervention** Garadacimab (CSL312) **Comparators** Lanadelumab (Takeda, Takhzyro, SHP643) and berotralstat (BioCryst Pharmaceuticals, Orladeyo, BCX7353)
Outcomes measures	Number of Attacks Requiring Acute Treatment Time-Normalized Number of Moderate and/or Severe HAE Attacks

	Proportion of Subjects who Achieved ≥90% Attack Rate Reduction Proportion of Attack-Free Patients Attack-Free Days per Month AE-QoL Change
Study design	Randomised clinical trials (including extension studies)

Abbreviations: AE-QoL = Angioedema Quality of Life questionnaire; HAE = Hereditary angioedema; SLR = Systematic literature review.

The key biomedical literature databases (Medical Literature Analysis and Retrieval System Online [MEDLINE®], Excerpta Medica Database [Embase®]), Cochrane collaboration and Centre for Reviews and Dissemination database were consulted as described in Table 91 below.

Table 91 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to present	02.08.2024
Medline	Ovid	1946 to present	02.08.2024
Cochrane Library databases	Wiley platform	2024	05.08.2024
Centre for Reviews and Dissemination database	york.ac.uk/crd	2024	05.08.2024

Other sources were used to enrich the search. The websites of the regulatory and HTA authorities in countries of particular interest were consulted, which included the UK (England and Scotland), Wales, Ireland, and Canada: NICE - National Institute for Health and Care Excellence, SMC - Scottish Medicines Consortium, AWMSG - All Wales Medicines Strategy Group, NCPE - National Centre for Pharmacoeconomics, CADTH - Canadian Agency for Drugs and Technologies in Health. The selected countries represent larger reimbursement markets in Europe and North America, and provide the most robust resources for the identification of relevant documents. These other sources are detailed in Table 92 below.

Furthermore, conferences and networks were searched to identify key information, using the search terms ''Hereditary angioedema'' and ''HAE''. The conference proceedings of the following organisations were searched manually for abstracts: ISPOR (2021-2024), BSI Clinical Immunology Professional Network (BSI-CIPN [2021-2023]),

EAACI (2021-2023), European Society for Immunodeficiencies (ESID) Biennial Meeting (2022), and American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting (2021-2024). This is detailed in Table 93 below.

In addition, a SLR handsearch was conducted to identify further publications according to the inclusion criteria.

Table 92 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
SMC	https://www.scottishmedicines.org.uk/	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
AWMSG	http://www.awmsg.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
NCPE	https://www.ncpe.ie/	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
CADTH	https://www.cadth.ca/	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
Clinical trials US	https://clinicaltrials.gov	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
Clinical trials EU	https://www.clinicaltrialsregister.eu	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024
Clinical trials UK	http://www.isrctn.com	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024

Source name	Location/source	Search strategy	Date of search
World Health Organization	www.who.int/ictrp/en/	Searches for relevant literature using key words in website-based search function.	Final search conducted in August 2024

Abbreviations: AWMSG = All Wales medicines strategy group; CADTH = Canadian agency for drugs and technologies in health; EU = European Union; NCPE = National centre for pharmacoeconomics; NICE = National institute for health and care excellence; SMC = Scottish medicines consortium; UK = United Kingdom; US = the United States.

Table 93 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISPOR	Presentation database	Manual search (2021-2024)	''Hereditary angio*'' and ''HAE''	August 2024
BSI	Network website	Manual search (2021-2023)	''Hereditary angioedema'' and ''HAE''	August 2024
EAACI	Search in onlinelibrary.wiley.com	Manual search (2021-2023)	''Hereditary angioedema'' and ''HAE''	August 2024
ESID	Search in Abstract book	Manual search (2022)	''Hereditary angioedema'' and ''HAE''	August 2024
AAAAI	Search in jacionline.org and sciencedirect.com	Manual search (2021-2024)	''Hereditary angioedema'' and ''HAE''	August 2024

Abbreviations: AAAAI = American academy of allergy, asthma, and immunology; BSI = British standards institution; EAACI = the European academy of allergy and clinical immunology; ESID = European society for immunodeficiencies; ISPOR = The professional society for health economics and outcomes research.

H.1.1 Search strategies

The Ovid platform was used to conduct searches in the mentioned literature databases. Ovid is a search platform that provides standardised access to a wide range of clinical literature databases and is an accepted tool by HTA agencies for conducting SLRs. Data were obtained by combining extensive lists of search terms for the indication, interventions, and study designs. Results were cross-checked against utility/disutility-containing publications identified from the clinical and economic SLR to ensure the completeness of the evidence. Furthermore, the Cochrane Library databases and the Centre for Reviews and Dissemination database was searched. The search strings included in the literature search are detailed in Table 94, Table 95, Table 96, and Table 97 below.

Table 94 Search strategy table for MEDLINE (via Ovid)

No.	Query	Results
#1	ANGIOEDEMAS, HEREDITARY/ or (((Heredit* or C1*) adj4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*)) or c1 esterase inhibitor deficiency or c1 inhibitor deficiency or (HAE adj5 Attack) or C1-INH-HAE or (heredit* adj10 (HAE or HANE or C1-INH)) or (heredit* adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica*))).mp.	3 796
#2	(Garadacimab or "CSL312" or "CSL 312" or "2162134 62 3" or "2162134623").mp.	15
#3	(Cinryze* or "1018837-94-9" or haegarda* or "csl 830" or "csl830" or "rvg19303" or "rvg319303").mp.	54
#4	(Berinert* or "ce 1145" or "ce1145").mp.	78
#5	(Lanadelumab* or "dx 2930" or "dx2930" or lanadelumab flyo or lanadelumabflyo or "shp 643" or "shp643" or "tak 743" or "tak743" or takhzyro or "1426055-14-2").mp.	118
#6	(Berotralstat* or "bcx 7353" or "bcx7353" or orladeyo or "1809010-50-1" or "1809010-52-3" or (aminomethyl* adj10 cyanophenyl) or (cyclopropylmethylamino* adj5 fluorophenyl)).mp.	54
#7	Antibodies, Monoclonal/ or ((factor XII or factor XIIa or "factor 12a" or kallikrein or FXIIa or anti-FXII) adj3 (inhibitor* or antagonist* or antibod*)).mp.	205 312
#8	exp complement c1 inactivator proteins/ or (C1-INH* or C1inh* or pdC1-INH* or pdC1inh* or rhC1-INH* or rhC1inh* or ((C1* or "C 1" or complement 1* or "complement component 1") adj3 (inhibit* or inactivat*)) or complement component inactivator or complement inactivating factor or "serping1" or "serpin family g member 1" or cetor or rhucin or "alpha 1 neuraminoglycoprotein" or "80295-37-0" or "80295-38-1").mp.	7 210
#9	or/2-6	273
#10	or/7-8	212 102
#11	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or placebos/	1 362 991
#12	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or controlled clinical trial or multicenter study or clinical trial).pt.	896 062

No.	Query	Results
#13	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$) or (open-label or open label or extension)).mp.	1 649 707
#14	or/11-13	2 214 688
#15	1 and 9	238
#16	1 and (9 or 10) and 14	365
#17	15 or 16	499
#18	limit 17 to dt=20240405-20240831	13

Table 95 Search strategy table for Embase (via Ovid)

No.	Query	Results
#1	(angioneurotic edema/ and (hereditary or (C1* adj3 inhibit*)).mp.) or (((Heredit* or C1*) adj4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*)) or c1 esterase inhibitor deficiency or c1 inhibitor deficiency or (HAE adj5 Attack) or C1-INH-HAE or (heredit* adj10 (HAE or HANE or C1-INH)) or (heredit* adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica*))).mp.	7 398
#2	Garadacimab/ or (Garadacimab or "CSL312" or "CSL 312" or "2162134 62 3" or "2162134623").mp.	75
#3	(Cinryze* or "1018837-94-9" or haegarda* or "csl 830" or "csl830" or "rvg19303" or "rvg319303").mp.	419
#4	(Berinert* or "ce 1145" or "ce1145").mp.	674
#5	Lanadelumab/ or (Lanadelumab* or "dx 2930" or "dx2930" or lanadelumab flyo or lanadelumabflyo or "shp 643" or "shp643" or "tak 743" or "tak743" or takhzyro or "1426055-14-2").mp.	519
#6	Berotralstat/ or (Berotralstat* or "bcx 7353" or "bcx7353" or orladeyo or "1809010-50-1" or "1809010-52-3" or (aminomethyl* adj10 cyanophenyl) or (cyclopropylmethylamino* adj5 fluorophenyl)).mp.	229
#7	monoclonal antibody/ or blood clotting factor 12a inhibitor/ or kallikrein inhibitor/ or ((factor XII or factor XIIa or "factor 12a" or kallikrein or FXIIa or anti-FXII) adj3 (inhibitor* or antagonist* or antibod*)).mp.	239 542
#8	exp complement component C1s inhibitor/ or (C1-INH* or C1inh* or pdC1-INH* or pdC1inh* or rhC1-INH* or rhC1inh* or ((C1* or "C 1" or	11 813

No.	Query	Results
	complement 1* or "complement component 1") adj3 (inhibit* or inactivat*)) or complement component inactivator or complement inactivating factor or "serping1" or "serpin family g member 1" or cetor or rhucin or "alpha 1 neuraminoglycoprotein" or "80295-37-0" or "80295-38-1").mp.	
#9	or/2-6	1488
#10	or/7-8	250 579
#11	Clinical Trial/ or Randomized Controlled Trial/ or controlled clinical trial/ or multicenter study/ or Phase 3 clinical trial/ or phase 4 clinical trial/ or exp RANDOMIZATION/ or Single Blind Procedure/ or Double Blind Procedure/ or Crossover Procedure/ or PLACEBO/ or Prospective Study/	2 862 090
#12	(randomi?ed controlled trial$ or rct or (random$ adj2 allocat$) or single blind$ or double blind$ or ((treble or triple) adj blind$) or placebo$ or open-label or open label or extension).mp.	1 901 312
#13	or/11-12	3 503 512
#14	1 and 9	1 190
#15	1 and (9 or 10) and 13	1 105
#16	limit 15 to dc=20240405-20240831	16

Table 96 Search strategy table for the Cochrane Library (via Wiley online platform)

No.	Query	Results
#1	[mh "ANGIOEDEMAS, HEREDITARY"] or (((Heredit* or "C1") NEAR/4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*)) or "c1 esterase inhibitor deficiency" or "c1 inhibitor deficiency" or (HAE NEAR/5 Attack) or "C1-INH-HAE" or (heredit* NEAR/10 (HAE or HANE or "C1-INH")) or (heredit* NEAR/4 ((giant or gigantea or milton or edematosa or oedematosa) NEAR/2 urtica*))):ti,ab,kw	501
#2	(Garadacimab or "CSL312" or "CSL 312" or "2162134 62 3" or "2162134623"):ti,ab,kw	33
#3	(Cinryze* or "1018837-94-9" or haegarda* or "csl 830" or "csl830" or "rvg19303" or "rvg319303"):ti,ab,kw	50
#4	(Berinert* or "ce 1145" or "ce1145"):ti,ab,kw	32

No.	Query	Results
#5	(Lanadelumab* or "dx 2930" or "dx2930" or lanadelumab flyo or lanadelumabflyo or "shp 643" or "shp643" or "tak 743" or "tak743" or takhzyro or "1426055-14-2"):ti,ab,kw	69
#6	(Berotralstat* or "bcx 7353" or "bcx7353" or orladeyo or "1809010-50-1" or "1809010-52-3" or (aminomethyl* NEAR/10 cyanophenyl) or (cyclopropylmethylamino* NEAR/5 fluorophenyl)):ti,ab,kw	56
#7	[mh "Antibodies, Monoclonal"] or ((factor XII or factor XIIa or "factor 12a" or kallikrein or FXIIa or anti-FXII) NEAR/3 (inhibitor* or antagonist* or antibod*)):ti,ab,kw	27 009
#8	[mh "complement c1 inactivator proteins"] or ("C1-INH" or "C1inh" or "pdC1-INH" or "pdC1inh" or "rhC1-INH" or "rhC1inh" or (("C1" or "C 1" or "complement 1" or "complement component 1") NEAR/3 (inhibit* or inactivat*)) or complement component inactivator or complement inactivating factor or "serping1" or "serpin family g member 1" or cetor or rhucin or "alpha 1 neuraminoglycoprotein" or "80295-37-0" or "80295-38-1"):ti,ab,kw	439
#9	or #2-#6	233
#10	or #7-#8	27 383
#11	[mh "Randomized Controlled Trials as Topic"] or [mh "randomized controlled trial"] or [mh "Random Allocation"] or [mh "Double Blind Method"] or [mh "Single Blind Method"] or [mh "clinical trial"] or [mh "Clinical Trials as topic"] or [mh "placebos"]	291 008
#12	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or controlled clinical trial or multicenter study or clinical trial):ti,ab,kw	837 467
#13	((clinical NEAR/1 trial$) or ((singl$ or doubl$ or treb$ or tripl$) NEAR/1 (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated NEAR/2 random$) or (open-label or open label or extension)):ti,ab,kw	819 086
#14	or #11-#13	1 158 721
#15	#1 and #9	191
#16	#1 and (#9 or #10) and #14	341
#17	#15 or #16	356 1 Cochrane review 355 Trials

No.	Query	Results
#18	with Publication Year from 2024 to 2024, with Cochrane Library publication date from Apr 2024 to Sep 2024, in Trials	4

Table 97 Search strategy table for the Database of Abstract Reviews of Effects, NHS Economic Evaluation Database, HTA Database (via York.ac.uk/crd interface)

No.	Query	Results
#1	MeSH DESCRIPTOR Angioedemas, Hereditary EXPLODE ALL TREES	5
#2	((Heredit* or C1*) AND (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*))	13
#3	(c1 esterase inhibitor deficiency or c1 inhibitor deficiency)	3
#4	(HAE AND Attack)	1
#5	(C1-INH-HAE)	0
#6	((heredit* AND (HAE or HANE or C1-INH)) or (heredit* AND ((giant or gigantea or milton or edematosa or oedematosa) AND urtica*)))	3
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	13

H.1.2 Systematic selection of studies

Methods followed were in line with the guidance provided by the DMC, NICE, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. For each review, 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 to resolve if required. For the update review duplicate database hits were also checked for between the original and update reviews. dFull text copies of all potentially relevant records were then obtained and evaluated in more detail against the eligibility criteria. This assessment was also undertaken by two independent reviewers, with disagreements discussed and a third reviewer involved to resolve if required.

Methods followed were in line with the guidance provided by the DMC, NICE, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. For each review, 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 to resolve if required. For the update review duplicate database hits were also checked for between the original and update reviews. For each review, data were extracted by one reviewer and checked by a second, into NICE submission template tables. A comprehensive critical appraisal of the RCT/OLE studies was conducted.

Table 98 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Study populations or subgroups of patients (humans only; men or women) with: • Age ≥12 years • Diagnosed with HAE	Study populations or subgroups: Non-human • Age <12 years • No confirmation of HAE	NR
Intervention	The following treatments for HAE as prophylaxis, provided as a single agent: • Garadacimab • Cinryze • Haegarda • Berinert • Takhzyro • Orladeyo Publications using the following 'generic' treatment terms for the intervention were also included for the RCTs only: Monoclonal antibodies Factor 12a inhibitor Kallikrein inhibitors Complement c1 inactivator proteins (C1-	• Combination of treatments listed in the inclusion criteria • Those not listed in the inclusion criteria	NR

	INH, pdC1-INH, rhC1-INH)		
Comparators	No restriction, any or no comparator	No restriction	NR
Outcomes	Clinical efficacy or effectiveness (all mild, moderate or severe): Time-normalized number of HAE attacks (requirement of on-demand treatment and severity to be recorded) including the change/percentage change in number of attacks N and % attack-free patients QoL (including AE-QoL) N and % of participants with a response on the SGART Safety: N and % of subjects with adverse events (including but not limited to, TEAEs and SAEs, and ISRs) N and % mortality N and % discontinuations due to AEs N and % discontinuations from the trial Adverse event rates (including but not limited to, TEAEs rates per injection, TEAEs rates per subject year)	Those not listed in the inclusion criteria	NR

Study design/publication type	Randomised controlled trials Non-randomised controlled studies Non-controlled studies	Animal studies In-vitro studies Pharmacokinetic studies Editorials Reviews Letters Comments Notes Erratum SLRs were included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.	NR
Language restrictions	No restriction	No restriction	NR

Abbreviations: AE = Adverse events; AE-QoL = Angioedema quality of life questionnaire; HAE = hereditary angioedema; N = Number of scores or individuals; NR = Not reported; pdC1-INH = Plasma-derived C1 esterase inhibitor; QoL = Quality of life; RCT = Randomised controlled study; SGART = Subject's global assessment of response to therapy; SLR = Systematic literature review; TEAE = Treatment-emergent adverse events.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram illustrated in Figure 43 presents how clinical references were reviewed and extracted. The database searches retrieved 1934 references, of which 522 were duplicates.

In the original review (Figure 43), of the 1412 titles and abstracts screened with the eligibility criteria, 995 references did not meet the criteria. Hence, full texts of the remaining 417 references were retrieved and reviewed based on the eligibility criteria, plus 44 publications identified through grey literature searches. Of these, 320 publications were included overall, of which 206 were extracted, with the remaining 114 being non-RCT publications. The 206 clinical publications extracted from were on 20 different studies. Of the 20 studies, 14 were RCTs and 6 OLE studies. In the update review (Figure 44), of the 24 titles and abstracts screened with the eligibility criteria, 15 references did not meet the criteria. Hence, full texts of the remaining 9 references were retrieved and reviewed based on the eligibility criteria. Of these, 5 publications were included. Of the 5 publications, one reported on both RCT and OLE stages of a study (Craig 2024 - CSL312_2001 NCT03712228), and one OLE only (Anderson 2024 -

VANGUARD OLE NCT04739059). Both of these studies were identified in the original review, so across the two reviews, 208 publications on 20 studies were extracted.

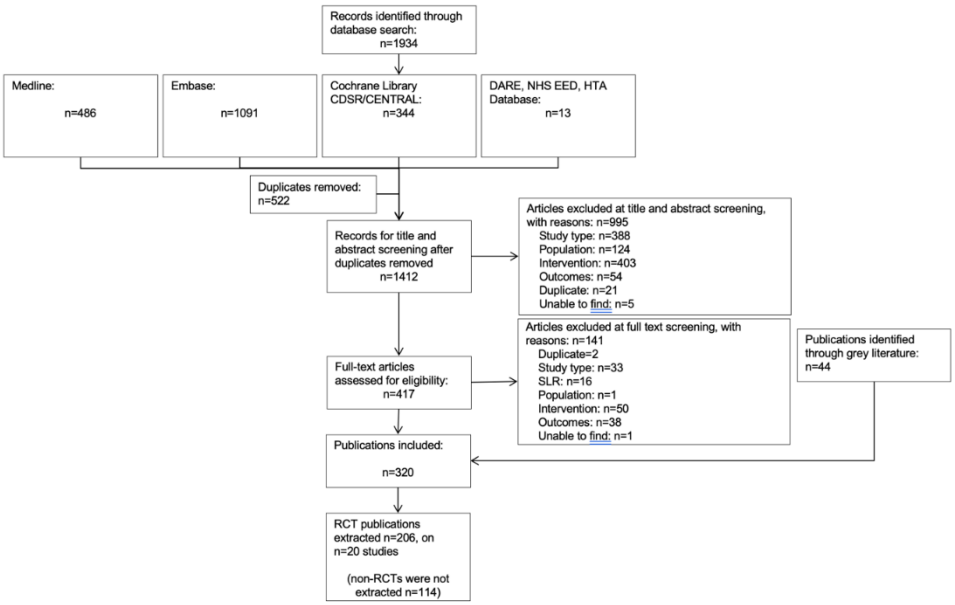


Figure 43 PRISMA flow diagram for Clinical Literature Search – original review (08/04/2024)

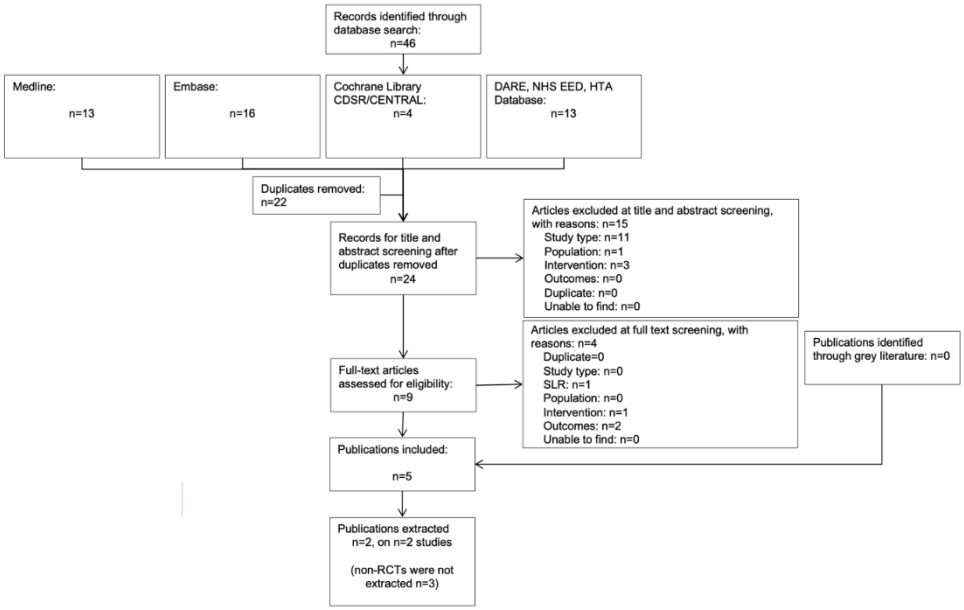


Figure 44 PRISMA flow diagram for Clinical Literature Search – updated review (05/08/2024)

Details of 147 studies are presented in Table 99, as well as all 144 excluded studies including reasons for exclusion into the application in Table 100.

Table 99 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
VANGUARD/NCT04656418 Craig, T. J., Reshef, A., Li, H. H., Jacobs, J. S., Bernstein, J. A., Farkas, H., ... & Magerl, M. (2023). Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 401(10382), 1079-1090.	To investigate the efficacy and safety of subcutaneous administration of garadacimab in the prophylactic treatment of HAE	A multicenter, double-blind, randomized, placebo-controlled, parallel-arm study	Patients with C1-INH HAE and frequent attacks	Garadacimab (n=39) and Placebo (n=25)	Time-normalized number of HAE attacks per month during treatment period from first injection up to 6 months	Secondary outcomes were the percentage change in the time-normalized number of HAE attacks per month during the treatment period compared to the run-in period during the first and second 3 months, the time-normalized number of HAE attacks per month requiring on-demand treatment during the first and second 3 months, the time-normalized number of moderate or severe HAE attacks per month during the first and second 3 months, the time-normalized number of HAE attacks per month in the first 3-months and second 3-months of treatment period, the

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						relative difference in means in the time-normalized number of HAE attacks per month between garadacimab and placebo during the first and second 3 months, the percentage of participant with a response to SGART up to 6 months, the number and percentage of participant with at least one AE, SAE, and AESI from the first dose of garadacimab up to 3 months after the last injection, the number and percentage of participant with garadacimab-induced anti-garadacimab antibodies up to 8 months, and the number and percentage of participant with clinically significant abnormalities in laboratory assessments

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						reported as TEAEs from the first dose of garadacimab up to 3 months after the last injection
ACT03712228 Craig T, Magerl M, Levy DS, et al. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2022;10328(399):945-955.	To investigate the clinical efficacy, pharmacokinetics, and safety of CSL312 as prophylaxis to prevent attacks in subjects with HAE.	This is a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 study	Patients with C1-INH HAE and frequent attacks	Garadacimab 75 mg (n=9), garadacimab 200 mg (n=8), garadacimab 600 mg (n=7), and Placebo (n=8)	The mean time normalized number of HAE attacks per month in subjects with C1-INH HAE during treatment period 1 (13 weeks follow up)	The number and percentage of responder subjects, the number and percentage of HAE attack-free subjects, the number and percentage of mild, moderate or severe HAE attacks, the mean time-normalized number of mild, moderate or severe HAE attacks per month, the number and percentage of subjects with at least 1 HAE attack treated with on-demand HAE medication, and the pharmacokinetics of garadacimab. All secondary outcomes were measured in subjects with C1-INH HAE

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						during treatment period 1 (13 weeks follow up).
HELP/NCT02586805 Banerji A, Riedl MA, Bernstein JA et al. ; HELP Investigators. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121. doi: 10.1001/jama.2018.16773. Erratum in: JAMA. 2019 Apr 23;321(16):1636. doi: 10.1001/jama.2019.4254. PMID: 30480729; PMCID: PMC6583584.	To evaluate the efficacy and safety of lanadelumab in preventing acute angioedema attacks	This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Patients with Type I and Type II HAE.	Lanadelumab 150 mg every 4 weeks (n=28), lanadelumab 300 mg every 4 weeks (n=29), lanadelumab 300 mg every 2 weeks (n=27), and Placebo (n=41)	The rate of investigator confirmed HAE attacks during the treatment period from day 0 to day 182	The rate of investigator confirmed HAE attacks requiring acute treatment from day 0 to day 182, the rate of moderate and severe investigator confirmed HAE attacks from day 0 to day 182, and the rate of investigator confirmed HAE attacks during day 14 through day 182

Abbreviations: AE = Adverse events; AESI = Adverse events of special interest; C1-INH = C1-Inhibitor; HAE = Hereditary angioedema; SAE = Serious adverse events; TEAE = Treatment-emergent adverse event.

H.1.3 Excluded fulltext references

Clinical publications were excluded for multiple reasons, among those the study design and wrong PICO. All excluded publications (original and updated review combined) are depicted in Table 100.

Table 100 Clinical publications excluded, original and updated review

Reference details of publication	Reason for exclusion
Correction to: 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. *JAMA.* 2019;321(16):1636	Study design
Craig TJ, Reshef A, Li HH, Jacobs JS, Bernstein JA, Farkas H, Yang WH, Stroes ES, Ohsawa I, Tachdjian R, Manning ME. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2023 Apr 1;401(10382):1079-90. Department of Error. Lancet. 2023;401(10384):1266.	Study design
Ahuja M, Dorr A, Bode E, Boulton APR, Buckland M, Chee S, et al. Berotralstat for the prophylaxis of hereditary angioedema-Real-world evidence data from the United Kingdom. Allergy. 2023;78(5):1380-3.	Study design
Alves PB. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. Revista Portuguesa de Imunoalergologia. 2021;29(3):219-20.	Study design
Anonymous. Correction: Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. (JAMA - Journal of the American Medical Association (2018) 320:20 (2108-2121) DOI: 10.1001/jama.2018.16773). JAMA - Journal of the American Medical Association. 2019;321(16):1636.	Study design

Anonymous. Erratum: Department of Error (The Lancet (2023) 401(10382) (1079-1090), (S0140673623003501), (10.1016/S0140-6736(23)00350-1)). The Lancet. 2023;401(10384):1266.	Study design
Bernardino AG, Ferreira MB, Costa C, Caiado J, Pedro E, Santos AS. Experience of lanadelumab administration in hereditary angioedema: A case series of 4 patients in Portugal. Asia Pacific allergy. 2023;13(2):91-4.	Study design
Busse P, Baker J, Martinez-Saguer I, Bernstein JA, Craig T, Magerl M, Riedl M, Shapiro R, Frank M, Lumry W, Rosch J, Edelman J, Williams-Herman D, Feuersenger H, Rojavin M. Safety of C1-inhibitor concentrate use for hereditary angioedema in pediatric patients. The journal of allergy and clinical immunology. 2017;5(4)1142-1145.	Study design
Chapman RG, Phillips M, Agostoni A. C1-inhibitor concentrate for treatment of hereditary angioedema. New England Journal of Medicine. 1980;303(9):526-7.	Study design
Chipps BE. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. Pediatrics. 2011;128(SUPPL. 3):S143.	Study design
Cicardi M, Henry Li H, Chase C, Anderson JT, Bernstein JA, Farkas H, et al. Risk for attacks in hereditary angioedema (HAE) population correlates with C1-inhibitor functional activity (C1-INHact). Journal of Allergy and Clinical Immunology. 2017;139(2 Supplement 1):AB233.	Study design
Cicardi M, Li HH, Anderson J, Bernstein JA, Farkas H, Zhang Y, et al. Pharmacodynamic effects of subcutaneous C1-INH for the prevention of HAE attacks. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	Study design
Craig T, Lumry W, Cicardi M, Zuraw B, Bernstein JA, Anderson J, et al. Treatment effect of switching from intravenous to subcutaneous C1-inhibitor for prevention of hereditary angioedema attacks: COMPACT subgroup findings. The journal of allergy and clinical immunology In practice. 2019;7(6):2035-8.	Study design

Craig T, Riedl M, Dykewicz MS, Gower RG, Baker J, Edelman FJ, Hurewitz D, Jacobs J, Kalfus I. When is prophylaxis for hereditary angioedema necessary?. Annals of Allergy, Asthma & Immunology. 2009 May 1;102(5):366-72.	Study design
De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert® P) in hereditary angioedema: a review. Transfusion and apheresis science. 2003 Dec 1;29(3):247-54.	Study design
Dorr AD, Chopra C, Coulter TI, Dempster J, Dziadzio M, El-Shanawany T, et al. Lanadelumab for the prevention of hereditary angioedema attacks: A real-world UK audit. Allergy. 2023;78(5):1369-71.	Study design
Farkas H, Aygoren-Pursun E, Martinez-Saguer I, Kessel A, Hao J, Lu P, et al. The use of a C1 esterase inhibitor concentrate to manage hereditary angioedema attacks in children. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):101.	Study design
Farkas H, Csuka D, Zotter Z, Varga L, Fust G. Prophylactic therapy in children with hereditary angioedema. Journal of Allergy and Clinical Immunology. 2013;131(2):579-82.e2.	Study design
Garcia JFB, Takejima P, Veronez CL, Aun MV, Motta AA, Kalil J, et al. Use of pdC1-INH concentrate for long-term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH. Journal of Allergy and Clinical Immunology: In Practice. 2018;6(4):1406-8.	Study design
Iaboni A, Kanani A, Lacuesta G, Song C, Kan M, Betschel SD. Impact of lanadelumab in hereditary angioedema: a case series of 12 patients in Canada. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2021;17(1):78.	Study design
Javaud N, Bouillet L, Rabetrano H, Bitoun A, Launay D, Lapostolle F, et al. Hereditary angioedema: Clinical presentation and socioeconomic cost of 200 French patients. The journal of allergy and clinical immunology In practice. 2019;7(1):328-30.	Study design
Johnston DT, Busse PJ, Riedl MA, Maurer M, Anderson J, Nurse C, et al. Effectiveness of lanadelumab for preventing hereditary angioedema attacks: Subgroup analyses from the HELP study. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2021;51(10):1391-5.	Study design
Kelbel T. A case of normal C1 esterase inhibitor hereditary angioedema successfully treated with berotralstat. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2022;128(4):462-3.	Study design

Lumry WR, Zuraw B, Cicardi M et al. Correction to: Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet J Rare Dis. 2021;16:329. https://doi.org/10.1186/s13023-021-01975-2	Study design
Martinez-Saguer I, Knop J, Flemming A, Thomann M, Maurer M. Real World treatment patterns of hereditary angioedema with lanadelumab in Germany: A prescription data analysis. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2022;20(8):1127-9.	Study design
Saharia P, Soni P, Chatterjee M. PRO7 A NETWORK META-ANALYSIS COMPARING C1 AND KALLIKREIN INHIBITORS APPROVED FOR PROPHYLAXIS OF HEREDITARY ANGIOEDEMA IN THE UNITED STATES. Value in Health. 2019;22(Supplement 2):S336.	Study design
Sardana N, Craig TJ. Recent advances in management and treatment of hereditary angioedema. Pediatrics. 2011;128(6):1173-80.	Study design
Wang Y, Marier JF, Kassir N, Gosselin NH, Martin P. Exposure-Response Analyses of Lanadelumab in Patients with Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2019;143(2 Supplement):AB40.	Study design
Xu YY, Buyantseva LV, Agarwal NS, Olivieri K, Zhi YX, Craig TJ. Update on treatment of hereditary angioedema. Clinical and Experimental Allergy. 2013;43(4):395-405.	Study design
Zhang Y, Tortorici MA, Pawaskar D, Pragst I, Machnig T, Hutmacher M, et al. Exposure-Response Model of Subcutaneous C1-Inhibitor Concentrate to Estimate the Risk of Attacks in Patients With Hereditary Angioedema. CPT: pharmacometrics & systems pharmacology. 2018;7(3):158-65.	Study design
Zozaya N, Caballero T, Gonzalez-Quevedo T, Setien PG, Gonzalez MA, Jodar R, et al. A multicriteria decision analysis (MCDA) applied to three long-term prophylactic treatments for hereditary angioedema in Spain. Global & regional health technology assessment. 2022;9:14-21.	Study design

Zuraw BL, Christiansen SC. New promise and hope for treating hereditary angioedema. Expert opinion on investigational drugs. 2008;17(5):697-706.	Study design
Zuraw BL, Cicardi M, Craig TJ, Longhurst HJ, Lumry WR, Bernstein JA, et al. Subcutaneous (SC) vs intravenous (IV) C1-esterase-inhibitor (C1-INH) replacement treatment for the prevention of attacks of hereditary angioedema (HAE): A Population based exposure-response analysis. Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB52.	Study design
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.	Study design - SLR
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.	Study design - SLR
Anonymous. Clinical Review Report Lanadelumab (Takhzyro): (Shire Pharma Canada ULC): Indication: For routine prevention of attacks of hereditary angioedema in adolescents and adults. 2020.	Study design - SLR
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.	Study design - SLR
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.	Study design - SLR

Berotralstat (Orladeyo): CADTH Reimbursement Review: Therapeutic area: Hereditary angioedema (HAE)	Study design - SLR
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.	Study design - SLR
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.	Study design - SLR
Bork K, Steffensen I, Machnig T. Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: a systematic literature review. Allergy and asthma proceedings. 2013;34(4):312-27.	Study design - SLR
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.	Study design - SLR
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).	Study design - SLR
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.	Study design - SLR

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.	Study design - SLR
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.	Study design - SLR
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.	Study design - SLR
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.	Study design - SLR
Ahmed M, Wang Y, Yu M, Marier JF, Bhattacharya I. Pharmacokinetics (PK), Pharmacodynamics (PD), and Exposure-Response (E-R) Analyses Confirm the Effectiveness of Lanadelumab in Patients 2 to <12 Years Old With Hereditary Angioedema (HAE). Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB130.	Population
Aygoren-Pursun E, Johnston D, Lumry W, Li H, Banerji A, Zuraw B, et al. Patterns of Treatment and Retreatment of Acute Attacks of Hereditary Angioedema (HAE) with Standard of Care (SOC) On-Demand Medication: Results from the APeX-2 Study. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB107.	Outcomes
Banerji A, Phadke NA, Gottumukkala R, Sharma R, Murali MR. Case 8-2022: A 54-Year-Old Woman with Episodes of Swelling. The New England journal of medicine. 2022;386(11):1071-9.	Outcomes
Beard N, Frese M, Mere P, Katelaris C, Mills K. Interventions for the long-term prevention of hereditary angioedema attacks. Cochrane Database of Systematic Reviews. 2019;2019(8):CD013403.	Outcomes

Bernstein J, Soteres D, Stolz L. Ecallantide treatment of acute attacks of hereditary angioedema in patients treated prophylactically with C1-inhibitor therapy: Case study. Allergy: European Journal of Allergy and Clinical Immunology. 2011;66(SUPPL. 94):420.	Outcomes
Betschel S, Radojicic C, van Kooten S, Malloy N, Heckmann M, Ulloa J, et al. Characterizing the HAE Patient Perspective on First-Line Prophylactic Treatment. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB86.	Outcomes
Bouillet L, Fain O, Armengol G, Aubineau M, Blanchard-Delaunay C, Dalmas M-C, et al. Long-term prophylaxis in hereditary angioedema management: Current practices in France and unmet needs. Allergy and asthma proceedings. 2022;43(5):406-12.	Outcomes
Bygum A, Martinez-Saguer I, Bas M, Rosch J, Edelman J, Rojavin M, et al. Use of a C1 Inhibitor Concentrate in Adults >=65 Years of Age with Hereditary Angioedema: Findings from the International Berinert R (C1-INH) Registry. Drugs & aging. 2016;33(11):819-27.	Outcomes
Castaldo AJ, Jervelund C, Corcoran D, Boysen HB, Christiansen SC, Zuraw BL. Assessing the cost and quality-of-life impact of on-demand-only medications for adults with hereditary angioedema. Allergy and asthma proceedings. 2021;42(2):108-17.	Outcomes
Chapovsky F, Hirsh J, Pawaskar D, Jacobs I, Feuersenger H. Pharmacokinetic profile of subcutaneous c1-esterase inhibitor (C1-INH [SC]) in adolescent and adult patients with hereditary angioedema (HAE). Pediatrics. 2019;144(2).	Outcomes
Dayno J, Miller DP, Hautamaki E, Newcomer S, Fitts D, Lumry WR. Relationship between angioedema attacks and health-related quality of life outcomes in patients with hereditary angioedema (HAE). Journal of Allergy and Clinical Immunology. 2014;133(2 SUPPL. 1):AB33.	Outcomes
Dempster J. Practicalities of a reduced volume formulation of a C1-INH concentrate for the treatment of hereditary angioedema: real-life experience. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2018;14:44	Outcomes
Ebo DG, Van der Poorten MM, Van Gasse AL, Schrijvers R, Hermans C, Bartiaux M, et al. Clinical practice of hereditary angioedema in Belgium: opportunities for optimized care. Acta Clinica Belgica: International Journal of Clinical and Laboratory Medicine. 2023;78(6):431-7.	Outcomes
Euctr BG. A clinical trial to assess 2 different doses of BCX7353 compared to placebo as an oral treatment for the prevention of attacks in people with HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-003966-29-BG. 2018.	Outcomes

Euctr CZ. A clinical trial to assess 2 different doses of BCX7353 compared to placebo as an oral treatment for the prevention of attacks in people with HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-003966-29-CZ. 2018.	Outcomes
Euctr DE. A study to evaluate the long-term clinical safety and efficacy of subcutaneously administered C1-esterase inhibitor in the prevention of hereditary angioedema. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2014-001054-42-DE. 2014.	Outcomes
Euctr DE. Study to determine the efficacy and safety of C1 Esterase Inhibitor liquid for injection compared to placebo in the prevention of Angioedema attacks in adolescents and adults with hereditary angioedema. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2015-002478-19-DE. 2015.	Outcomes
Euctr DE. A study to investigate CSL312 in subjects with hereditary angioedema (HAE). https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2018-000605-24-DE. 2018.	Outcomes
Euctr GB. A placebo controlled trial of of three doses of BCX7353 to evaluate the safety and efficacy in the prevention of attacks in patients with HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2015-003923-74-GB. 2015.	Outcomes
Euctr GB. Long Term Safety Study of BCX7353 in HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-003281-27-GB. 2017.	Outcomes
Euctr HU. A Study of the Safety and Efficacy of Subcutaneous Administration of Cinryze with Recombinant Human Hyaluronidase for the Prevention of HAE Attacks. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2012-000083-24-HU. 2012.	Outcomes
Euctr HU. BCX7353 for the prevention of HAE attacks. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2016-001272-29-HU. 2016.	Outcomes
Euctr NL. CSL312 (garadacimab) in the prevention of hereditary angioedema attacks. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2020-000570-25-NL. 2020.	Outcomes
Glassman F, Hu Z, Yuraszeck T, Pragst I, Pawaskar D. A population pharmacokinetic/pharmacodynamic/exposure response model to relate complement 4 antigen concentrations and risk of attacks in hereditary angioedema patients. Clinical Pharmacology and Therapeutics. 2020;107(Supplement 1):S60.	Outcomes
Greve J, Hoffmann TK, Hahn J. Efficacy of lanadelumab, a monoclonal antibody to plasma kallikrein, in patients with hereditary angioedema type i and ii, outside of controlled clinical trials. Laryngo- Rhino- Otologie. 2020;99(SUPPL 2):S38.	Outcomes

Hettiarachchi A, Tsang SY, Jin C, Leang X, Chatelier J, Godsell J, et al. THE CHANGING LANDSCAPE OF HEREDITARY ANGIOEDEMA MANAGEMENT IN AUSTRALIA: A RETROSPECTIVE SINGLE CENTRE ANALYSIS. Internal Medicine Journal. 2022;52(Supplement 5):26-7.	Outcomes
Hyatt D, Watkins N, Kyrychenko P, Avalos-Reyes E. CHANGES IN UTILIZATION OF ACUTE MEDICATIONS AFTER INITIATION OF PROPHYLACTIC TREATMENTS FOR HEREDITARY ANGIOEDEMA. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S5.	Outcomes
Jens G, Robin L, Susanne T, Hoffmann TK, Janina H. Efficacy of lanadelumab, a monoclonal antibody to plasma kallikrein, in patients with Hereditary Angioedema Type I and II, outside of controlled clinical trials. Laryngo- Rhino- Otologie. 2022;101(Supplement 2):S249-S50.	Outcomes
jRct. CSL312 (garadacimab) in the prevention of hereditary angioedema attacks. https://trialsearchwhoint/Trial2aspx?TrialID=JPRN-jRCT2031210056. 2021.	Outcomes
Kardum Z, Prus V, Milas Ahic J, Kardum D. Successful treatment with Cinryze R replacement therapy of a pregnant patient with hereditary angioedema: a case report. Journal of medical case reports. 2021;15(1):20.	Outcomes
Lindsay K, Chua I, Jordan A, Stephens S. National audit of a hereditary and acquired angioedema cohort in New Zealand. Internal medicine journal. 2022;52(12):2124-9.	Outcomes
Lumry WR, Bernstein JA, Li HH, Levy DS, Jones DH, Padilla BE, et al. An expert panel's review on patients with hereditary angioedema switching from attenuated androgens to oral prophylactic therapy. Allergy and asthma proceedings. 2024;45(1):44-9.	Outcomes
Kreuz J. Berinert P Study of Subcutaneous Versus Intravenous Administration (PASSION). ClinicalTrials. gov NCT00748202, published Sep. 2008;4.	Outcomes
Nct. A Study of Lanadelumab in Teenagers and Adults to Prevent Acute Attacks of Non-histaminergic Angioedema With Normal C1-Inhibitor (C1-INH). https://clinicaltrialsgov/ct2/show/NCT04206605. 2019.	Outcomes
Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: Follow-up survey of US physicians. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2021;126(3):264-72.	Outcomes
Shah CH, Princic N, Evans KA, Schultz BG. Real-world changes in costs over time among patients in the United States with hereditary angioedema on long-term prophylaxis with lanadelumab. Journal of medical economics. 2023;26(1):871-7.	Outcomes

Staubach P, Soteres D, Aygoren-Pursun E, Tachdjian R, Lumry W, Hao J, et al. Use of short term prophylaxis during treatment with lanadelumab does not impact the risk of an attack: Analysis of data from the HELP study and HELP OLE. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74(Supplement 106):211-2.	Outcomes
Umin. A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema. https://trialsearchwhoint/Trial2aspx?TrialID=JPRN-UMIN000034869. 2018.	Outcomes
Varga L, Szeplaki G, Visy B, Fust G, Harmat G, Miklos K, et al. C1-inhibitor (C1-INH) autoantibodies in hereditary angioedema. Strong correlation with the severity of disease in C1-INH concentrate naive patients. Molecular Immunology. 2007;44(6):1454-60.	Outcomes
Aranzabal MA, Joral A, Lasa EM, Echenagusia MA. Retrospective analysis of patients with hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) followed-up in the real-world setting in guipuzcoa, spain. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):369.	Intervention
Arcoleo F, Cancian M, Cicardi M, De Pasquale T, Di Maulo R, Guarino DM, et al. Long-term prophylaxis in hereditary angioedema patients followed in ITAlian Centers for Angioedema (ITACA) and enrolled in HAE Global Registry (HGR). Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 4).	Intervention
Baynova K, Cimbollek S, Quiralte J, Lucena JM, Garcia R, Gonzalez-Quevedo T. Effectiveness of subcutaneous human C1 esterase inhibitor concentrate for the prevention of hereditary angioedema acute episodes during the COVID19 pandemic period: A case series. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):204.	Intervention
Baynova K, Reguero M, R AV, Ochando M, Lucena JM, Garcia JR, et al. COVID-19 infection in patients with severe hereditary angioedema in long term prophylaxis with subcutaneous C1-inhibitor -A prospective study. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):412-3.	Intervention
Bernstein J, Kanarek H, Soteres D, Mutschelknaus D, Cala M, Schultz B, et al. DIAGNOSTIC PATHWAYS IN LANADELUMAB-TREATED PATIENTS WITH NORMAL C1-INHIBITOR HEREDITARY ANGIOEDEMA (NC1-INH-HAE): A MULTICENTER CHART REVIEW. Annals of Allergy, Asthma and Immunology. 2022;129(5 Supplement):S29.	Intervention
Boccon-Gibod I, Wu MA, Di Maulo R, De Munari M, De Roberto L, Pagnier A, et al. The French side of the global angioedema registry. Allergy: European Journal of Allergy and Clinical Immunology. 2018;73(Supplement 105):727-8.	Intervention

Boccon-Gibod I, Wu MA, Di Maulo R, De Munari M, De Roberto L, Pagnier A, et al. The French side of the Global Angioedema Registry. Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 4).	Intervention
Boccon-Gibod I, Wu MA, Di Maulo R, De Munari M, Pagnier A, Mansard C, et al. The French Side of the Global Angioedema Registry. Journal of Allergy and Clinical Immunology. 2019;143(2 Supplement):AB47.	Intervention
Bouillet L, Boccon-Gibod I, Gompel A, Floccard B, Martin L, Blanchard-Delaunay C, et al. Hereditary angioedema with normal C1 inhibitor: clinical characteristics and treatment response with plasma-derived human C1 inhibitor concentrate (Berinert R) in a French cohort. European journal of dermatology : EJD. 2017;27(2):155-9.	Intervention
Bouillet L, Boccon-Gibod IA, Pagnier A, Gompel A, Floccard B, Martin L, et al. Hereditary angioedema: Analysis of 287 attacks treated with C1 esterase inhibitor in the French cohort cobra. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):593.	Intervention
Bouillet L, Fain O, Armengol G, Aubineau M, Blanchard-Delaunay C, Dalmas M, et al. ATHENEE survey: Unmet medical needs in hereditary angioedema (HAE) in France. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):96-7.	Intervention
Bouillet L, Launay D, Fain O, Boccon-Gibod I, Laurent J, Martin L, et al. Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2013;111(4):290-4.	Intervention
Caminoa M, Caballero T, Perez-Fernandez E, Gomez-Traseira C, Gaya F, Aabom A, et al. Hereditary angioedema due to C1 inhibitor deficiency: Clinical descriptive study in an international cohort. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):61.	Intervention
Cicardi M, Mannucci PM, Castelli R, Rumi MG, Agostoni A. Reduction in transmission of hepatitis C after the introduction of a heat-treatment step in the production of C1-inhibitor concentrate. Transfusion. 1995;35(3):209-12.	Intervention
Craig T, Riedl M, Baker J, Banerji A, Hurewitz D, Kalfus I, et al. Open-label use of nanofiltered C1 esterase inhibitor (human) for treatment or prophylaxis of acute attacks of hereditary angioedema in pregnant subjects. Allergy: European Journal of Allergy and Clinical Immunology. 2011;66(SUPPL. 94):419.	Intervention
Dempster J, Gompels M, Bright P, Longhurst H. Case series of UK experience of icatibant for acute attacks of hereditary angioedema. Clinical and Experimental Immunology. 2010;160(SUPPL. 1):11-2.	Intervention

Dominas N, Hoffmann TK, Bas M, Greve J. Improving patient outcomes in hereditary angioedema: reducing attack frequency using routine prevention with C1 inhibitor concentrate. BMJ case reports. 2014;2014.	Intervention
Euctr HU. An open-label exploratory Phase II study of the safety and prophylactic effect of a weekly 50 U/kg rC1INH treatment in asymptomatic patients with hereditary C1INH deficiency (HAE) - OPERA. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2009-010736-18-HU. 2009.	Intervention
Euctr IT. Pharmacokinetics and Safety of Human Pasteurised C1-Inhibitor Concentrate (Berinert/CE1145) in Subjects with Congenital C1-INH Deficiency. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2010-019670-32-IT. 2012.	Intervention
Farinha IC, Tavares B, Sousa N, Almeida E, Lozoya C, Regateiro FS, et al. COVID-19 infection and vaccination in patients with hereditary angioedema: a multicentric study. European annals of allergy and clinical immunology. 2024;56(1):34-41.	Intervention
Fragnan NTML, Veronez C, Moreno A, Arruda LKP, Goncalves RF, Valle S, et al. Treatment of Patients with Hereditary Angioedema with Normal C1 Inhibitor: Evaluation of 295 Patients. Journal of Allergy and Clinical Immunology. 2019;143(2 Supplement):AB40.	Intervention
Fukunaga A, Morita E, Miyagi T, Eto K, Shimizu A, Kagami S, et al. [EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF INTRAVENOUS C1 INHIBITOR FOR LONG-TERM PROPHYLAXIS AND TREATMENT OF BREAKTHROUGH ATTACKS IN JAPANESE SUBJECTS WITH HEREDITARY ANGIOEDEMA: A PHASE 3 OPEN-LABEL STUDY]. Arerugi = [Allergy]. 2020;69(3):192-203.	Intervention
Gidaro A, Perego F, Colombo E, Cancian M, Zanichelli A, Wu MA, et al. Effect of long term prophylaxis with attenuated androgen (AA-LTP) on the risk for cardiovascular and neoplastic diseases in a cohort of 289 patients with Hereditary Angioedema (HAE) due to C1 inhibitor deficiency. Journal of Allergy and Clinical Immunology. 2017;139(2 Supplement 1):AB237.	Intervention
Graham C, Machnig T, Knox H, Supina D, Krishnarajah G. Attacks avoided and cost offsets associated with subcutaneous C1-inhibitor (human) longterm prophylaxis of hereditary angioedema. Annals of Allergy, Asthma and Immunology. 2017;119(5 Supplement 1):S40-S1.	Intervention
Hack CE, Relan A, Baboeram A, Oortwijn B, Versteeg S, Van Ree R, et al. Immunosafety of recombinant human C1-inhibitor in hereditary angioedema: Evaluation of IgE antibodies. Clinical Drug Investigation. 2013;33(4):275-81.	Intervention

Hofstra JJ, Kleine Budde I, van Twuyver E, Choi G, Levi M, Leebeek FW, et al. Treatment of hereditary angioedema with nanofiltered C1-esterase inhibitor concentrate (Cetor®): multi-center phase II and III studies to assess pharmacokinetics, clinical efficacy and safety. Clinical immunology (Orlando, Fla). 2012;142(3):280-90.	Intervention
Horiuchi T, Hide M, Yamashita K, Ohsawa I. The use of tranexamic acid for on-demand and prophylactic treatment of hereditary angioedema—A systematic review. Journal of Cutaneous Immunology and Allergy. 2018 Oct;1(4):126-38.	Intervention
Johnson F, Strassen U. ETIOLOGY AND PREDICTORS OF HEREDITARY ANGIOEDEMA (HAE) CLUSTER-ATTACKS DESPITE PHARMACEUTICAL TREATMENT. Annals of Allergy, Asthma and Immunology. 2019;123(5 Supplement):S96.	Intervention
Johnson F, Strassen U, Greve J, Magerl M, Wirth M. Etiology and predictors of clusterattacks following the treatment of acute hereditary angioedema (HAE) attacks. Laryngo- Rhino- Otologie. 2019;98(Supplement 2):S13.	Intervention
Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: Implications for future therapies. Allergy and asthma proceedings. 2018;39(1):74-80.	Intervention
Jung J-W, Suh DI, Park HJ, Kim S, Kwon HS, Yang MS, et al. Clinical Features of Hereditary Angioedema in Korean Patients: A Nationwide Multicenter Study. International archives of allergy and immunology. 2018;176(3-4):272-9.	Intervention
Li H, Chiao J, Jacobs I. Comparison of the safety profiles of 40 IU/kg and 60 IU/kg doses of subcutaneous C1-esterase inhibitor (C1- INH [SC]) in the prophylactic treatment of hereditary angioedema (HAE): Results from a phase 3 trial. Allergy and Asthma Proceedings. 2017;38(5):397.	Intervention
Magerl M, Bernstein JA, Banerji A, Li HH, Lumry WR, Maurer M, et al. Response to subcutaneous human C1-Inhibitor for the prevention of angioedema attacks in patients with hereditary angioedema: Subgroups based on prior intravenous C1-inhibitor use. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70(SUPPL. 101):60.	Intervention
Manto I, Latysheva E, Bliznetz E, Timoshenko D, Aleshina L, Bocherova Y, et al. Clinical features of patients with hereditary angioedema with a mutation in the plasminogen gene. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):557.	Intervention
Martinez-Saguer I, Bork K, Latysheva T, Zabrodska L, Chopyak V, Nenasheva N, et al. Plasma-derived C1 esterase inhibitor pharmacokinetics and safety in patients with hereditary angioedema. The journal of allergy and clinical immunology Global. 2024;3(1):100178.	Intervention

Mendivil J, Dersarkissian M, Chang R, Cheng M, Duh MS, Sarda SP, et al. The relationship between treatment with long-term prophylaxis and attack rate in hereditary angioedema (HAE): A multinational chart review study. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(SUPPL 109):85.	Intervention
Nct 2014. A Phase 2 HAE Prophylaxis Study With Recombinant Human C1 Inhibitor. https://clinicaltrials.gov/show/NCT02247739	Intervention
Nunes FL, Ferriani MPL, Moreno AS, Langer SS, Maia LSM, Ferraro MF, et al. Decreasing Attacks and Improving Quality of Life through a Systematic Management Program for Patients with Hereditary Angioedema. International Archives of Allergy and Immunology. 2021;182(8):697-708.	Intervention
Phillips-Angles E, Lluncor M, Pedrosa M, Lamacchia D, Hernanz A, Alvez-Liste A, et al. Determinant factors of disease activity in hereditary angioedema due to C1 inhibitor deficiency. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74(Supplement 106):757-8.	Intervention
Reshef A, Moldovan D, Obtulowicz K, Visscher S, Relan A. Efficacy and safety of a weekly infusion of recombinant human C1 inhibitor (rhC1INH) for the prophylaxis of hereditary angioedema attacks. Allergy: European Journal of Allergy and Clinical Immunology. 2012;67(SUPPL. 96):353-4.	Intervention
Reshef A, Moldovan D, Obtulowicz K, Leibovich I, Mihaly E, Visscher S, et al. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: A pilot study. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(1):118-24.	Intervention
Riedl M, Zuraw B, Baker J, Hurewitz D, White M, Vegh A, et al. Open-label use of nanofiltered C1 esterase inhibitor (human) for the prophylaxis of hereditary angioedema attacks. Allergy: European Journal of Allergy and Clinical Immunology. 2011;66(SUPPL. 94):420-1.	Intervention
Rosado-Quinones AM, Zaragoza-Urdaz R. Hereditary Angioedema: An Updated Experience with Patients with Angioedema in Puerto Rico. Puerto Rico health sciences journal. 2019;38(4):248-54.	Intervention
Sanchez MD, Cuervo J, Rave D, Clemen G, Yepes-Nunez JJ, Ortiz-Reyes B, et al. Hereditary angioedema in Medellin (Colombia): Clinical evaluation and quality of life appraisal. Biomedica : revista del Instituto Nacional de Salud. 2015;35(3):419-28.	Intervention
Schranz J, Levy R, Lumry W, Manning M, Jacobs J, Dychter SS, et al. Safety, pharmacokinetics (PK), and pharmacodynamics (PD) of subcutaneous (SC) cinryze(C1 inhibitor (C1 INH) with recombinant human hyaluronidase (rHuPH20) in subjects with hereditary angioedema (HAE). Journal of Allergy and Clinical Immunology. 2012;129(2 SUPPL. 1):AB369.	Intervention

Slade C, DerSarkissian M, Katelaris C, Devercelli G, Smith W. Patient characteristics, treatment, and outcomes of hereditary angioedema in Australia: Findings from a chart review study. Internal Medicine Journal. 2021;51(SUPPL 4):22-3.	Intervention
Strassen U. Etiology and predictors of hereditary angioedema cluster-attacks despite pharmaceutical treatment. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB108.	Intervention
Triggianese P, Senter R, Petraroli A, Zoli A, Lo Pizzo M, Bignardi D, et al. Pregnancy in women with hereditary angioedema due to C1-inhibitor deficiency: Results from the ITACA cohort study on outcome of mothers and children with in utero exposure to plasma-derived C1-inhibitor. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):401-2.	Intervention
Valerieva A, Staevska MT, Grivcheva-Panovska V, Jesenak M, Kohalmi KV, Hrubiskova K, et al. Recombinant human C1 esterase inhibitor for hereditary angioedema attacks: A European registry. The World Allergy Organization journal. 2021;14(4):100535.	Intervention
Zanichelli A, Triggiani M, Bova M, Cancian M, Moldovan D, Cicardi M. An international registry for angioedema without urticaria. Journal of Allergy and Clinical Immunology. 2017;139(2 Supplement 1):AB235.	Intervention
Jain G, Sussman G, Lumry WR, Lu P, Lewis H, Maurer M. Lanadelumab improves health-related quality of life in patients with hereditary angioedema (HAE): findings from the HELP study. Allergy, asthma and clinical immunology. 2019;15.	Duplicate
Maurer M, Gierer S, Hebert J, Hao J, Lu P, Banerji A. Lanadelumab is highly efficacious at steady-state in hereditary angioedema (HAE): results of the phase 3 HELP study. Allergy. 2018;73:289.	Duplicate
Martinez-Saguer IC, M.; Aygren-Prsn, E.; Rusicke, E.; Klingebiel, T.; Kreuz, W. Pharmacokinetic berinert P study of subcutaneous versus intravenous administration in subjects with moderate hereditary angioedema - The passion study. Journal of allergy and clinical immunology. 2011; 127:2 Suppl 1:AB257	Unable to find
Longhurst HJ, Bouillet L, Cancian M, Grivcheva-Panovska V, Koleilat M, Magerl M, Savic S, Stobiecki M, Tachdjian R, Yea CM and Audhya PK. Hereditary angioedema attacks in patients receiving long-term prophylaxis: a systematic review. Allergy and Asthma Proceedings . 2024;45(3):213.	SLR

Lumry W, Craig T, Anderson J, Riedl M, Henry Li H, Tachdjian R, Manning M, Bajcic P, Rodino F, Wang S and Bernstein J. Retrospective analysis of patient outcomes associated with subcutaneous c1inh prophylaxis for hereditary angioedema. Allergy and Asthma Proceedings. 2024;45(3):212-213.	Intervention
Itzler R, Lumry WR, Sears J, Braverman J, Li Y, Brennan CJ and Koch GG. An international survey assessing the effects of the duration of attack-free period on health-related quality of life for patients with hereditary angioedema. Orphanet journal of rare diseases. 2024;19(1):241.	Outcomes
O'Connor M, Busse P, Christiansen S, Radojicic C, Ulloa J, Danese S, Desai V, Andriotti T, Audhya P and Craig T. Quality of life among prophylaxis and on-demand users in hae. Allergy and Asthma Proceedings. 2024;45(3):212.	Outcomes

A local adaption of the SLR was made for the Danish setting. Included studies are shown in Section 5.1. Studies included were the clinical trials on which the relative efficacy is based. None of the other studies were assessed to be as suitable as the included studies. The most prevalent reasons for exclusion were outcomes used, study design, as well as the intervention of the study. The final sample was deemed to be of high relevance for the decision problem.

H.1.4 Quality assessment

Of the 20 studies, 14 were RCTs and 6 OLE studies. The RCTs and OLE quality assessments are reported in Table 101 and Table 102.

Table 101 Quality assessment results for RCTs (studies n=14 – the six OLEs are reported in the next table)

Trial	PASSION NCT00748202 933	SAHARA NCT02584959 880	APEX-2 NCT03485911 1385	COMPACT NCT01912456 823	HELP-03 NCT02586805 125	APEX-1 NCT02870972 81	384 VANGUARD NCT04656418 384[a]	DX-2930-02 (lanadelumab) NCT02093923 115
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear
Was the concealment of treatment allocation adequate?	N/A	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	N/A	Yes	Yes	Yes	Yes	Yes	No	Not clear
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	No	No	No
Is there any evidence to suggest that the authors	No	No	No	No	No	No	No	No

measured more outcomes than they reported?								
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	No	Yes	No	No	No	No	No
Trial		**CHANGE NCT01005888 1391**	**C1 3201 NCT02247739 1161[a]**	**APeX-J NCT03873116 1039**	**NCT01095497 1003**	**CSL312_2001363**	**Waytes 1996 1314**	
							Trial 1	**Trial 2**
Was randomisation carried out appropriately?		Not clear	Yes	Yes	Not clear	Yes	Not clear	Not clear
Was the concealment of treatment allocation adequate?		Not clear	Yes	Yes	N/A	Yes	Not clear	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?		Yes	Not clear	Yes	Yes	No	Yes	Not clear
Were the care providers, participants, and outcome		No (ID1002)	Yes	Yes	N/A	No	Not clear; double blinded study,	Not clear; double blinded study,

assessors blind to treatment allocation?						details of blinding were not reported	details of blinding were not reported
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	Yes	Yes	Not clear	Yes	Yes	Yes

Table from Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24) (Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care [University of York Centre for Reviews and Dissemination].)

Table 102 Quality assessment results for non-randomised and non-controlled studies (studies n=6)

Study name	LEVP2006-4 CHANGE 3 1397	APEX-2 OLE 731	VANGUARD OLE 31	HELP-04 OLE 113	COMPACT OLE 374	CSL312_2001 OLE 1020
Was the cohort recruited in an acceptable way?	Yes	Yes	Not clear	Yes	Yes	Yes

Was the exposure accurately measured to minimise bias?	Not clear	Yes	Not clear	No	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Not clear	No	Yes	Yes
Have the authors identified all important confounding factors?	Not clear	Yes	Not clear	Yes	Yes	Not clear
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	N/A	Not clear	No	N/A	Not clear
Was the follow-up of patients complete?	Not clear	Yes	Not clear	Yes	Yes	Yes
Are the results (for example, in terms of confidence interval and p-values) suitably precise?	Not clear	Yes	Not clear	Yes	Yes	Not clear

Table from Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24) (Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study)

H.1.5 Unpublished data

No unpublished data was used in this review. In the application, the published data from the VANGUARD and CSL312_2001 trials was supplemented with further unpublished details on the efficacy and safety of garadacimab.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search information

Table 103 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Via ovid.com	1974 – 05.04.2024 Updated: -31.08.2024	31.08.2024
Medline	Via ovid.com	1946 – 05.04.2024 Updated: -31.08.2024	31.08.2024
The Cochrane Library databases	Via Wiley online platform	01.01.2024 – 31.04.2024 Updated: - 31.08.2024	31.08.2024
EconLIT	Via ovid.com	1886 – 29.03.2024 Updated: - 18.07.2024	18.07.2024

Table 104 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Centre for Reviews and Dissemination database	via york.ac.uk/crd	No restriction – 08.04.2024 Updated: -05.08.2024	05.08.2024

Table 105 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISPOR	2024/2023/2022/2021: https://www.ispor.org/heor-resources/presentations-database/search	Electronic search	Hereditary angio* OR HAE	2024
BSI Clinical Immunology Professional Network (BSI-CIPN)	2023: https://www.bsicongress.com/bsi/frontend/reg/titem.csp?pageID=10796&eventID=13 2022: https://www.bsicongress.com/bsi/frontend/reg/titem.csp?pageID=6769&eventID=10&eventID=10 2021: https://www.bsicongress.com/bsi/frontend/reg/titem.csp?pageID=5087&eventID=8	Electronic search	Hereditary angioedema, Hereditary angioedema, HAE	2024
European Academy of Allergy and Clinical Immunology Hybrid Congress (EAACI)	2023: https://onlinelibrary.wiley.com/toc/13989995/2023/78/S112	Electronic search	Hereditary angioedema, Hereditary angioedema, HAE	2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	2022: https://onlinelibrary.wiley.com/toc/13989995/2023/78/S111 2021: https://onlinelibrary.wiley.com/toc/13989995/2021/76/S110			
European Society for Immunodeficiencies (ESID) Biennial Meeting	2022: https://2022.esidmeeting.org/esid-2022-abstracts-book/	Electronic search	Hereditary angioedema, Hereditary angioedema, HAE	2024
American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting	2024: https://www.jacionline.org/programs_abstracts 2023: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/151/issue/2/suppl/S#article-3 2022: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/149/issue/2/suppl/S#article-3	Electronic search	Hereditary angioedema, Hereditary angioedema, HAE	2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	2021: https://www.sciencedirect.com/journal/journal-of-allergy-and-clinical-immunology/vol/147/issue/2/suppl/S			
National Institute for Health and Care Excellence (NICE) **Scottish Medicines Consortium (SMC)** **All Wales Medicines Strategy Group (AWMSG)** **National Centre for Pharmacoeconomics (NCPE)** **Canadian Agency for Drugs and Technologies in Health (CADTH)**	https://www.nice.org.uk/ https://www.scottishmedicines.org.uk/ http://www.awmsg.org/ https://www.ncpe.ie/ https://www.cadth.ca/	Electronic search	Hereditary angioedema, Hereditary angioedema, HAE	2024
https://clinicaltrials.gov **https://www.clinicaltrialsregister.eu** **http://www.isrctn.com** **www.who.int/ictrp/en/**	https://clinicaltrials.gov https://www.clinicaltrialsregister.eu http://www.isrctn.com www.who.int/ictrp/en/	Electronic search	Hereditary angioedema, Hereditary angioedema, HAE	2024

I.1.1 Search strategies

Table 106 Search strategy for MEDLINE (via Ovid)

No.	Query	Results (original search)	Results (updated search)
1	ANGIOEDEMAS, HEREDITARY/ or (((Heredit* or C1*) adj4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*)) or c1 esterase inhibitor deficiency or c1 inhibitor deficiency or (HAE adj5 Attack) or C1-INH-HAE or (heredit* adj10 (HAE or HANE or C1-INH)) or (heredit* adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica*))).mp.	3 723	3 796
2	exp quality-adjusted life years/ or sickness impact profile/	23 421	23 823
3	((quality adj2 (wellbeing or well-being)) or quality of life or sickness impact profile or disability adjusted life or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or health utilit* or utility score* or disutilit* or utility value* or hui or hui1 or hui2 or hui3 or health* year* equivalent* or hye or hyes or discrete choice* or rosser or willingness to pay or time tradeoff or time trade off or tto or standard gamble* or sf36 or “sf 36” or “short form 36” or “shortform 36” or shortform36 or sf20 or “sf 20” or “short form 20” or “shortform 20” or shortform20 or sf12 or “sf 12” or “short form 12” or “shortform 12” or shortform12 or sf8 or “sf 8” or “short form 8” or “shortform 8” or shortform8 or sf6 or “sf 6” or “short form 6” or “shortform 6” or shortform6).ti,ab.	440 220	453 837
4	2 or 3	445 861	459 500
5	1 and 4	261	273
6	limit 5 to dt=20240405-20240831		13

Table 107 Search strategy for Embase (via Ovid)

No.	Query	Results (original search)	Results (updated search)
1	(angioneurotic edema/ and (hereditary or (C1* adj3 inhibit*)).mp.) or (((Heredit* or C1*) adj4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio	7 248	7 398

No.	Query	Results (original search)	Results (updated search)
	edema* or angioneurotic* or angio neurotic*)) or c1 esterase inhibitor deficiency or c1 inhibitor deficiency or (HAE adj5 Attack) or C1-INH-HAE or (heredit* adj10 (HAE or HANE or C1-INH)) or (heredit* adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica*))).mp.		
2	Quality adjusted life year/ or "quality of life index"/ or short form 12/ or short form 20/ or short form 36/ or short form 8/ or sickness impact profile/	93 331	95 973
3	((quality adj2 (wellbeing or well-being)) or quality of life or sickness impact profile or disability adjusted life or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or health utility* or utility score* or disutilit* or utility value* or hui or hui1 or hui2 or hui3 or health* year* equivalent* or hye or hyes or rosser or discrete choice or willingness to pay or time tradeoff or time trade off or tto or standard gamble* or sf36 or "sf 36" or "short form 36" or "shortform 36" or shortform36 or sf20 or "sf 20" or "short form 20" or "shortform 20" or shortform20 or sf12 or "sf 12" or "short form 12" or "shortform 12" or shortform12 or sf8 or "sf 8" or "short form 8" or "shortform 8" or shortform8 or sf6 or "sf 6" or "short form 6" or "shortform 6" or shortform6).ti,ab.	690 446	711 827
4	2 or 3	706 395	728 304
5	1 and 4	594	620
6	limit 5 to dc=20240405-20240831		25

Table 108 Search strategy for the Cochrane Library (via Wiley online platform)

No.	Query	Results (original search)	Results (updated search)
1	[mh "ANGIOEDEMAS, HEREDITARY"] or (((Heredit* or "C1") NEAR/4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*)) or "c1 esterase inhibitor deficiency" or "c1 inhibitor deficiency" or (HAE NEAR/5 Attack) or "C1-INH-HAE" or (heredit* NEAR/10 (HAE or HANE or "C1-INH")) or (heredit* NEAR/4 ((giant or gigantea or milton or edematosa or oedematosa) NEAR/2 urtica*))):ti,ab,kw	480	501

2	[mh “quality adjusted life years”] or [mh “sickness impact profile”]	2 955	2 998
3	((quality NEAR/2 (wellbeing or well-being)) or quality of life or sickness impact profile or disability adjusted life or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or health utilit* or utility score* or disutilit* or utility value* or hui or hui1 or hui2 or hui3 or health* year* equivalent* or hye or hyes or discrete choice* or rosser or willingness to pay or time tradeoff or time trade off or tto or standard gamble* or sf36 or "sf 36" or "short form 36" or "shortform 36" or shortform36 or sf20 or "sf 20" or "short form 20" or "shortform 20" or shortform20 or sf12 or "sf 12" or "short form 12" or "shortform 12" or shortform12 or sf8 or "sf 8" or "short form 8" or "shortform 8" or shortform8 or sf6 or "sf 6" or "short form 6" or "shortform 6" or shortform6):ti,ab	177 608	185 859
4	#2 or #3	177 950	186 201
5	#1 and #4	63	70
6	#1 and #4 with Publication Year from 2024 to 2024, with Cochrane Library publication date from Apr 2024 to Aug 2024, in Trials		2

Table 109 Search strategy for the Database of Abstract Reviews of Effects, NHS Economic Evaluation Database, HTA Database (via York.ac.uk/crd interface)

No.	Query	Results (original search)	Results (updated search)
1	MeSH DESCRIPTOR Angioedemas, Hereditary EXPLODE ALL TREES	5	5
2	((Heredit* or C1*) AND (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*))	13	13
3	(c1 esterase inhibitor deficiency or c1 inhibitor deficiency)	3	3
4	(HAE AND Attack)	1	1
5	(C1-INH-HAE)	0	0
6	((heredit* AND (HAE or HANE or C1-INH)) or (heredit* AND ((giant or gigantea or milton or edematosa or oedematosa) AND urtica*)))	3	3

7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	13	13

Table 110 Search strategy for EconLit (via Ovid)

No.	Query	Results (original search)	Results (updated search)
1	(((Heredit* or C1*) adj4 (edema* or oedema* or angioedema* or angiooedema* or angio oedema* or angio edema* or angioneurotic* or angio neurotic*)) or c1 esterase inhibitor deficiency or c1 inhibitor deficiency or (HAE adj5 Attack) or C1-INH-HAE or (heredit* adj10 (HAE or HANE or C1-INH)) or (heredit* adj4 ((giant or gigantea or milton or edematosa or oedematosa) adj2 urtica*))).mp.	0	0

Table 111 Search strategy for ISPOR (all meetings)

Query	Results
Hereditary angio* OR HAE: 7	26

Table 112 Search strategy for BSI Clinical Immunology Professional Network (BSI-CIPN)

No.	Query	Results
1	Hereditary angioedema OR HAE	0

Table 113 Search strategy for European Academy of Allergy and Clinical Immunology Hybrid Congress (EAACI)

No.	Query	Results
1	Hereditary angioedema OR HAE	233

Table 114 Search strategy for European Society for Immunodeficiencies (ESID) Biennial Meeting

No.	Query	Results
1	Hereditary angioedema OR HAE	14

Table 115 Search strategy for American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting

No.	Query	Results
1	Hereditary angioedema OR HAE	138

Table 116 Search strategy for National Institute for Health and Care Excellence (NICE)

No.	Query	Results
1	Hereditary angioedema OR HAE	67

Table 117 Search strategy for https://clinicaltrials.gov and https://www.clinicaltrialsregister.eu

No.	Query	Results
1	Hereditary angioedema OR HAE	312

I.1.2 Study selection

Methods followed were in line with the guidance provided by NICE and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. For each review, 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 to resolve if required. For the update review duplicate database hits were also checked for between the original and update reviews. Full text copies of all potentially relevant records were then obtained and evaluated in more detail against the eligibility criteria. This assessment was also undertaken by

two independent reviewers, with disagreements discussed and a third reviewer involved to resolve if required. For each review, data were extracted by one reviewer and checked by a second.

Table 118 Quality of life eligibility criteria

PICOS category	Inclusion	Exclusion
Population	Study populations or subgroups of patients (humans only; men or women) with: • Age ≥12 years • Diagnosed with hereditary angioedema (HAE)	Study populations or subgroups: • Non-human • Age <12 years • No confirmation of HAE
Intervention/ Comparators	Any or no treatment	No restriction
Outcomes	• Utilities (for example, TTO, SG, EQ-5D, SF-6D, HUI) • Health-related QoL (for example, SF-36)	Any other outcomes
Study design	• Any primary publication in humans	Animal studies In-vitro studies Editorials Reviews Letters Comments Notes Erratum SLRs will be included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.
Geographical location	No restriction	No restriction
Language	No restriction	No restriction
Publication date	No restriction; any study date	No restriction

Abbreviations: HAE = Hereditary angioedema; TTO = Time trade-off; SG = Standard gamble; EQ-5D; EuroQol-5 dimensions; SF-6D = Short form-6 dimensions; HUI = Health utilities index; SLR = Systematic literature review; SF-36 = Short form-36 health survey.

I.1.3 Results

The PRISMA diagram illustrated in Figure 45 presents how the health-related quality of life references were reviewed and extracted. The database searches retrieved 931 references, of which 270 were duplicates. Of the 661 titles and abstracts screened with the eligibility criteria, 332 references did not meet the criteria. Hence, full texts of the

remaining 329 references were retrieved and reviewed based on the eligibility criteria, after which 196 publications (reporting on 117 studies) were included, of which 180 publications were extracted. These 180 publications reported on 107 studies.

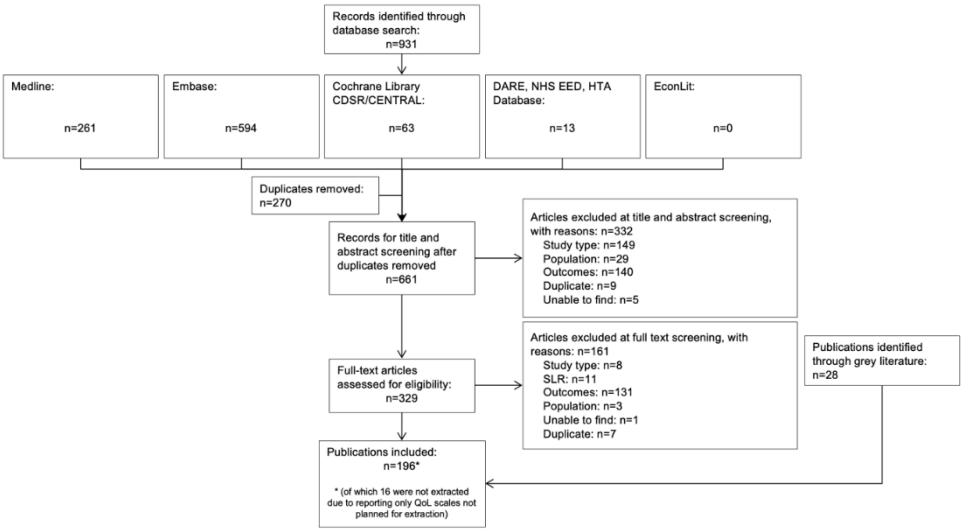


Figure 45 PRISMA health-related quality of life – original review

The PRISMA diagram illustrated in Figure 46 presents how the health-related quality of life references were reviewed and extracted through the update review. The database searches retrieved 53 references, of which 28 were duplicates. Of the 25 titles and abstracts screened with the eligibility criteria, 8 references did not meet the criteria. Hence, full texts of the remaining 17 references were retrieved and reviewed based on the eligibility criteria, after which 10 publications were included and extracted. These 10 publications reported on 9 studies. Seven were reporting on studies not already identified in the original review, so across both reviews 206 publications (on 124 studies) were included, of which 190 publications on 114 studies were extracted.

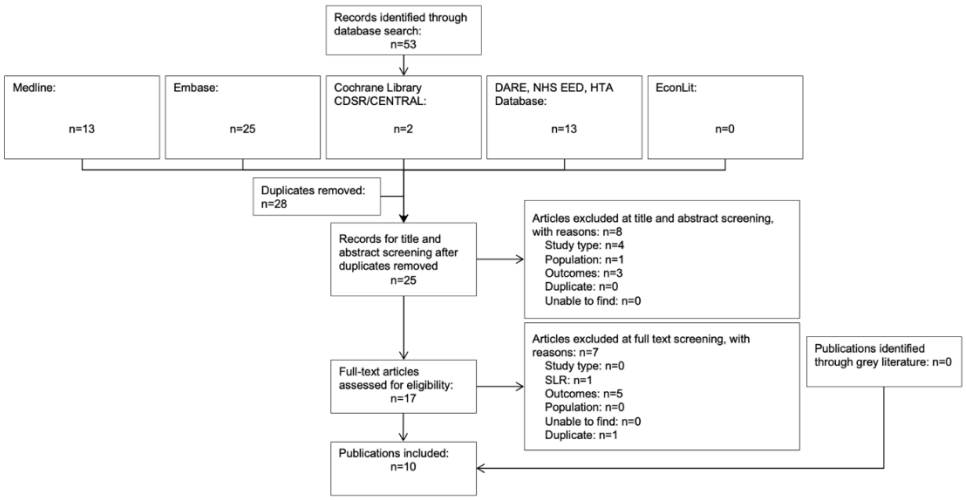


Figure 46 PRISMA health-related quality of life – update review

Table 119 shows the studies included in the SLR from the original and updated search.

Table 119 Publications included (publications n=206, studies n=124) – original and update review

ID	Reference details of publications included	Study
1 Aabom 2015	Aabom A, Andersen KE, Perez-Fernandez E, Caballero T, Bygum A. Health-related quality of life in Danish patients with hereditary angioedema. Acta dermato-venereologica. 2015;95(2):225-6.	1 Aabom 2015
2 Aabom 2017	Aabom A, Nguyen D, Fisker N, Bygum A. Health-related quality of life in Danish children with hereditary angioedema. Allergy and asthma proceedings. 2017;38(6):440-6.	2 Aabom 2017
15 Anderson 2022	Anderson J, Soteres D, Mellor J, Connolly H, Wynne-Cattanach K, Earl L, et al. PHYSICIAN AND PATIENT REPORTED OUTCOMES BY HEREDITARY ANGIOEDEMA TYPE: DATA FROM A REAL-WORLD STUDY. Annals of Allergy, Asthma and Immunology. 2022;129(5 Supplement):S27-S8.	15 Anderson 2022
24 Arce-Ayala 2019	Arce-Ayala YM, Diaz-Algorri Y, Craig T, Ramos-Romey C. Clinical profile and quality of life of Puerto Ricans with hereditary angioedema. Allergy and asthma proceedings. 2019;40(2):103-10.	24 Arce-Ayala 2019
26 Arjunji 2019	Arjunji R, Venkitaramani D, Wiesner T, Maru B, Dabbous O. PRO18 ASSESSMENT OF COST-EFFECTIVENESS RESULTS FROM ICER ULTRA-RARE DISORDER REVIEWS. Value in Health. 2019;22(Supplement 2):S338.	26 Arjunji 2019
31Ayazi 2017	Ayazi M, Fazlollahi MR, Saghafi S, Mohammadian S, Deshiry SN, Bidad K, et al. Quality of life in 41 patients with hereditary angioedema: First report from Iranian National Registry of Hereditary Angioedema. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	31 Ayazi 2017
37 Aygören-Pürsün 2018	,Aygoren-Pursun E, Bygum A, Grivcheva-Panovska V, Magerl M, Graff J, Steiner UC, et al. Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema. New England journal of medicine. 2018;379(4):352-62.	37 Aygören-Pürsün 2018
416 Magerl 2018	Magerl M, Rae W, Aygoren-Pursun E, Bygum A, Panovska VG, Steiner UC, et al. BCX7353 improves health-related quality of life in hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE): findings from the APeX-1 study. Allergy. 2018;73:724.	

GL114 NCT02870972	ClinicalTrials NCT02870972. Efficacy and Safety of BCX7353 to Prevent Angioedema Attacks in Subjects With Hereditary Angioedema (APeX-1). Available from: https://clinicaltrials.gov/study/NCT02870972?term=NCT02870972&rank=1	
36 Aygoren-Pursun 2016	Aygoren-Pursun E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Boysen HB, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. Patient preference and adherence. 2016;10:1699-707.	36 Aygoren-Pursun 2016
GL141 Caballero 2014*	Caballero T, Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Wait S, Boysen HB. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. InAllergy & Asthma Proceedings 2014 Jan 1;35(1):.	
48 Balla 2021	Balla Z, Ignacz B, Varga L, Kohalmi KV, Farkas H. How Angioedema Quality of Life Questionnaire Can Help Physicians in Treating C1-Inhibitor Deficiency Patients? Clinical reviews in allergy & immunology. 2021;61(1):50-9.	48 Balla 2021
293 Ignacz 2019	Ignacz B, Tohati R, Kohalmi KV, Farkas H. The relationship between disease activity and quality of life-a frst-time survey in hereditary angioedema. Allergy, Asthma and Clinical Immunology. 2019;15(S4):.	
54 Banerji 2020	Banerji A, Davis KH, Brown TM, Hollis K, Hunter SM, Long J, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2020;124(6):600-7.	54 Banerji 2020
195 Devercelli 2018	Devercelli G, Davis K, Brown M, Hollis K, Hunter S, Long J, et al. Burden of hereditary angioedema: Findings from a US patient survey. Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB57.	
77 Bernstein 2020	Bernstein JA, Tyson C, Relan A, Adams P, Magar R. Modeling Cost-Effectiveness of On-Demand Treatment for Hereditary Angioedema Attacks. Journal of managed care & specialty pharmacy. 2020;26(2):203-10.	77 Bernstein 2020
590 Tyson 2019	Tyson C, Magar R, Adams P, Relan A. Cost-effectiveness model for on-demand treatment of hae attacks. Journal of Managed Care and Specialty Pharmacy. 2019;25(3-A SUPPL.):S37-S8.	
591 Tyson 2019	Tyson C, Relan A, Adams P, Haynes A, Magar R. Cost-effectiveness model for on-demand treatment of hereditary angioedema (HAE) attacks. Allergy and Asthma Proceedings. 2019;40(5):359.	
82 Bewtra 2012	Bewtra AK, Levy RJ, Jacobson KW, Wasserman RL, Machnig T, Craig TJ. C1-inhibitor therapy for hereditary angioedema attacks: prospective patient assessments	82 Bewtra

	of health-related quality of life. Allergy and asthma proceedings. 2012;33(5):427-31.	2012
80 Bewtra 2009	Bewtra A, Jacobson KW, Craig T, Packer F. C1-INH therapy improves health-related quality of life measures in patients with hereditary angioedema. Journal of Allergy and Clinical Immunology. 2009;123(2 SUPPL. 1):S103.	
81 Bewtra 2009	Bewtra A, Levy R, Wasserman R, Jacobson K, Craig T. Patients receiving Cl-INH treatment for hereditary angioedema report few health-related limitations on quality of life survey. Annals of Allergy, Asthma and Immunology. 2009;103(5 SUPPL. 3):A115.	
99 Bostan 2021	Bostan OC, Tuncay G, Damadoglu E, Karakaya G, Kalyoncu AF. Effect of COVID-19 on hereditary angioedema activity and quality of life. Allergy and Asthma Proceedings. 2021;42(5):403-8.	99 Bostan 2021
103 Bouillet 2020	Bouillet L, Boccon-Gibod I, Launay D, Debord-Peguet S, Lenkei C, Boudjemia K, et al. Effectiveness of lanadelumab in the real-world setting: Findings from a temporary authorization of use (ATU) in France for the treatment of hereditary angioedema type 1/2. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(S109):87.	103 Bouillet 2020
108 Bouillet 2013	Bouillet L, Launay D, Fain O, Boccon-Gibod I, Laurent J, Martin L, et al. Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2013;111(4):290-4.	108 Bouillet 2013
109 Bouillet 2012	Bouillet L, Montauban V, Finck K, Bouee S. Observational study on the treatment and quality of life of subjects with hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2012;67(SUPPL. 96):199.	109 Bouillet 2012
111 Boursiquot 2024	Boursiquot J-N, Chapdelaine H, St-Pierre C, Hebert J. The Disease Burden of Hereditary Angioedema: Insights from a Survey in French-Canadians from Quebec. Journal of immunology research. 2024;2024:3028617.	111 Boursiquot 2024
136 Bygum 2009	Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. European journal of dermatology : EJD. 2009;19(2):147-51.	136 Bygum 2009
141 Bykova 2023	Bykova GA, Beltyukov EK, Naumova VV, Karakina ML. Organization of medical care for patients with hereditary angioedema and experience in treating patients with lanadelumab in the Sverdlovsk region. Russian Journal of Allergy. 2023;20(2):177-86.	141 Bykova 2023

154 Castaldo 2019	Castaldo AJ, Jervelund C, Kirk AR, Corcoran D, Balle Boysen H, Long JF, et al. A Comprehensive Approach to Assessing the Value of Prophylactic Therapy for the Ultra Rare Disease Hereditary Angioedema Using Real World Patient Data. Journal of Allergy and Clinical Immunology. 2019;143(S2):AB426.	154 Castaldo 2019
153 Castaldo 2021	Castaldo AJ, Jervelund C, Corcoran D, Boysen HB, Christiansen SC, Zuraw BL. Assessing the cost and quality-of-life impact of on-demand-only medications for adults with hereditary angioedema. Allergy and asthma proceedings. 2021;42(2):108-17.	153 Castaldo 2021
155 Castaldo 2023	Castaldo T, Selva C, Johnson P, Hunter AG, Tse J, Martinez A, et al. Comparison of Selected Health and Well Being Characteristics in Seniors with Hereditary Angioedema (HAE) and a Non-HAE Patient Matched Cohort. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB136.	155 Castaldo 2023
169 Cottrell 2011	Cottrell S, Tilden D, Jayaram N, Sinani R, Barnes D. Hereditary angioedema health state utility valuation study from the perspective of a representative sample of the Australian general public. Value in Health. 2011;14(7):A324.	169 Cottrell 2011
585 Tilden 2011	Tilden D, Cottrell S, Tocchini L, Jayaram N, Sinani R, Barnes D. A modelled economic evaluation of firazyr (icatibant) for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor (C1-INH) deficiency. Value in Health. 2011;14(7):A322-A3.	
174 Craig 2023	Craig T, Magerl M, Reshef A, Li H, Jacobs J, Bernstein J, et al. Efficacy and Safety of Subcutaneous Garadacimab for the Prophylaxis of Hereditary Angioedema Attacks in Adults and Adolescent Patients with HAE: Results from a Multicenter, Placebo-Controlled Phase 3 Trial. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB132.	174 Craig 2023
GL10 Lumry 2023	Lumry W, Magerl M, Craig TJ, Farkas H, Yang W, Stroes ES, Martinez Saguer I, Aygören- Pürsün E, Staubach P, Treudler R, Itzler R, Feuersenger H, Pragst I, Reshef A. Garadacimab prophylaxis improves quality of life in adult and adolescent patients with hereditary angioedema: Results from a multicentre Phase 3 study. European Journal of Allergy and Clinical Immunology - Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):114.	
216 EUCTR2021-000136-59-HU	Euctr HU. A study to assess whether different doses of KVD824 are effective in preventing attacks of Hereditary Angiodedema Type I or Type II. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2021-000136-59-HU. 2021.	216 EUCTR2021-000136-59-HU 2021
GL98 EU-CTR	GL98: EU Clinical Trials Register. 2021-000136-59. A study to assess whether different doses of KVD824 are effective in preventing attacks of Hereditary	

2021-000136-59	Angiodedema Type I or Type II. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-000136-59/CZ	
229 Farkas 2021	Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygoren-Pursun E, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. Clinical and translational allergy. 2021;11(4):e12035.	229 Farkas 2021
14 Anderson 2021	Anderson J, Sheridan W, Desai B, Tomita D, Manning M. CONSISTENTLY LOW HEREDITARY ANGIOEDEMA (HAE) ATTACK RATES OBSERVED IN US PATIENTS TREATED WITH BEROTRALSTAT. Annals of Allergy, Asthma and Immunology. 2021;127(5 Supplement):S14.	
502 Peter 2023	Peter JG, Desai B, Tomita D, Collis P, Stobiecki M. Assessment of HAE prophylaxis transition from androgen therapy to berotralstat: A subset analysis of the APeX-S trial. The World Allergy Organization journal. 2023;16(11):100841.	
529 Reshef 2020	Reshef A, Maurer M, Kiani S, Wu AY, Stobiecki M, Kinaciyan T, et al. Long-term effectiveness of berotralstat (BCX7353) for the prophylaxis of hereditary angioedema (HAE) attacks: results from the APeX-S study. Allergy. 2020;75(SUPPL 109):91-2.	
72* Bernstein 2021	Bernstein J, Desai B, Tomita D, Cornpropst M, Sublett J. IMPROVED PATIENT SATISFACTION WITH BEROTRALSTAT IN PATIENTS SWITCHING FROM INJECTABLE HEREDITARY ANGIOEDEMA (HAE) PROPHYLACTIC TREATMENTS. Annals of Allergy, Asthma and Immunology. 2021;127(5 Supplement):S27.	
235 Fijen 2023	Fijen LM, Klein PCG, Cohn DM, Kanters TA. The Disease Burden and Societal Costs of Hereditary Angioedema. The journal of allergy and clinical immunology In practice. 2023;11(8):2468-75.e2.	235 Fijen 2023
236 Fijen 2022	Fijen LM, Riedl MA, Bordone L, Bernstein JA, Raasch J, Tachdjian R, et al. Inhibition of Prekallikrein for Hereditary Angioedema. New England journal of medicine. 2022;386(11):1026-33.	236 Fijen 2022
233 Fijen 2022	Fijen LA, Bordone L, Newman K, Alexander V, Riedl M, Schneider E, et al. The Impact on Quality of Life Following Treatment with Plasma Prekallikrein Targeted Oligonucleotide Antisense Therapy in Hereditary Angioedema Patients. Journal of Allergy and Clinical Immunology. 2022;149(2 Supplement):AB169.	
GL119 NCT04030598	ClinicalTrials NCT04030598. A Study to Assess the Clinical Efficacy of Donidalorsen (Also Known as IONIS-PKK-LRx and ISIS 721744) in Participants With Hereditary Angioedema. Available from: https://clinicaltrials.gov/study/NCT04030598?term=NCT04030598&rank=1	
GL95 EU-CTR	EU Clinical Trials Register. 2019-001044-22. A Randomized, Double Blind, Placebo Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a	

2019-001044-22	Second Generation Ligand Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001044-22/results	
U5 Buttgereit 2024	Buttgereit T, Vera Ayala C, Aykanat S, Weller K, Gutsche A, Maurer M and Magerl M. The real life experience goes on: update after 4 years on the first cohort treated with lanadelumab at our center. Frontiers in Immunology. 2024;15():1405317.	U5 Buttgereit 2024
238 Fijen 2023	Fijen LM, Vera C, Buttgereit T, Bonnekoh H, Maurer M, Magerl M, et al. Sensitivity to change and minimal clinically important difference of the angioedema control test. Clinical and translational allergy. 2023;13(9):e12295.	
240 Forjaz 2021	Forjaz MJ, Ayala A, Caminoa M, Prior N, Perez-Fernandez E, Caballero T. HAE-AS: A Specific Disease Activity Scale for Hereditary Angioedema With C1-Inhibitor Deficiency. Journal of investigational allergology & clinical immunology. 2021;31(3):246-52.	240 Forjaz 2021
143 Caballero 2011	Caballero T, Caminoa M, Prior N, Gomez-Traseira C, Perez E, Forjaz M. Health-related quality of life in adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) assessed by SF-36v2: Preliminary results of an international study. Allergy: European Journal of Allergy and Clinical Immunology. 2011;66(SUPPL. 94):685-6.	
144 Caballero 2014	Caballero T, Caminoa MJ, Perez-Fernandez E, Gomez-Traseira C, Aabom A, Aberer W, et al. Health-related quality of life (HRQoL) in adult patients with hereditary angioedema due to c1 inhibitor deficiency (HAEC1-INH) assessed by SF-36V2. Journal of Allergy and Clinical Immunology. 2014;133(2 SUPPL. 1):AB34.	
494 Palao-Ocharan 2022	Palao-Ocharan P, Prior N, Perez-Fernandez E, Caminoa M, Aberer W, Betschel S, et al. Psychometric study of the SF-36v2 in hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE). Orphanet Journal of Rare Diseases. 2022;17(1):88.	
520 Prior 2014	Prior N, Remor E, Perez-Fernandez E, Gomez-Traseira C, Caminoa MJ, Gaya F, et al. IHAE-QoL: Specific health-related quality of life (HRQoL) questionnaire in hereditary angioedema due to C1 inhibitor deficiency (HAE-C1INH). Journal of Allergy and Clinical Immunology. 2014;133(2 SUPPL. 1):AB33.	
518 Prior 2016	Prior N, Remor E, Perez-Fernandez E, Caminoa M, Gomez-Traseira C, Gaya F, et al. Psychometric Field Study of Hereditary Angioedema Quality of Life Questionnaire for Adults: HAE-QoL. The journal of allergy and clinical immunology In practice. 2016;4(3):464-73.e4.	
244 Fukunaga 2020	Fukunaga A, Morita E, Miyagi T, Eto K, Shimizu A, Kagami S, et al. Efficacy, pharmacokinetics, pharmacodynamics, and safety of intravenous C1 inhibitor for long-term prophylaxis and treatment of breakthrough attacks in Japanese subjects with hereditary angioedema: A phase 3 open-label study. Japanese Journal of Allergology. 2020;69(3):192-203.	244 Fukunaga 2020

247 Garcia-Rosas 2023	Garcia-Rosas C, Lopez-Tiro JJ, Contreras-Contreras A, Ruiz-Penaloza M, Ortiz-Monteon ZE. [Experiencia inicial de Lanadelumab en una paciente mexicana con angioedema hereditario tipo I]. Revista alergia Mexico (Tecamachalco, Puebla, Mexico : 1993). 2023;70(4):194.	247 Garcia-Rosas 2023
253 Gomide 2013	Gomide MACMS, Toledo E, Valle SOR, Campos RA, Franca AT, Gomez NP, et al. Hereditary angioedema: quality of life in Brazilian patients. Clinics (Sao Paulo, Brazil). 2013;68(1):81-3.	253 Gomide 2013
268 Greve 2016	Greve J, Hahn J, Nordmann M, Schuler PJ, Bas M, Hoffmann TK, et al. Nanofiltrated C1-esterase-inhibitor in the prophylactic treatment of bradykinin-mediated angioedema. Transfusion. 2016;56(5):1022-9.	268 Greve 2016
274 Groser 2012	Groser M, Simon J, Treudler R. Clinical characteristics of thirty German patients with suspicion of hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2012;67(SUPPL. 96):351.	274 Groser 2012
280 Hahn 2020	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;36333(6):907-11.	280 Hahn 2020
281 Hahn 2020	Hahn J, Trainotti S, Wigand MC, Schuler PJ, Hoffmann TK, Greve J. Prospective Analysis in Patients With HAE Under Prophylaxis With Lanadelumab: A Real-life Experience. Journal of drugs in dermatology : JDD. 2020;19(10):978-83.	281 Hahn 2020
283 Helbert 2012	Helbert M, Pang F, Alvarez-Reyes M, Pearson I, Wolowacz S, Diwakar L. A cost-effectiveness comparison of icatibant and c1-esterase inhibitor concentrate for the symptomatic treatment of acute attacks of types I and II hereditary angioedema in the UK setting. Value in Health. 2012;15(7):A513.	283 Helbert 2012
285 Hews-Girard 2021	Hews-Girard J, Goodyear MD. Psychosocial burden of type 1 and 2 hereditary angioedema: a single-center Canadian cohort study. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2021;17(1):61.	285 Hews-Girard 2021
284 Hews-Girard 2019	Hews-Girard J, Dawn Goodyear M. Psychosocial burden of hereditary angioedema in a Canadian cohort. Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 4).	
286 Hioki 2024	Hioki C, Oda Y, Moriwaki S, Fukunaga A. Effect of lanadelumab on attack frequency and QoL in Japanese patients with hereditary angioedema: Report of five cases. The Journal of dermatology. 2024 Jun;51(6):873-7.	286 Hioki 2024
288 Honda 2024	Honda D, Hide M, Fukuda T, Koga K, Morita E, Moriwaki S, et al. Berotralstat for long-term prophylaxis of hereditary angioedema in Japan: parts 2 and 3 of the	288 Honda

	randomized APeX-J Phase III trial. World Allergy Organization journal. 2024;17(3):100882.	2024
HS1 Ohsawa 2021	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.	
GL118 NCT03873116	ClinicalTrials NCT03873116. Study to Evaluate the Efficacy and Safety of BCX7353 as an Oral Treatment for the Prevention of HAE Attacks in Japan (APeX-J). Available from: https://clinicaltrials.gov/study/NCT03873116	
300 Javaud 2018	Javaud N, Fain O, Durand-Zaleski I, Launay D, Bouillet L, Gompel A, et al. Specialist Advice Support for Management of Severe Hereditary Angioedema Attacks: a Multicenter Cluster-Randomized Controlled Trial. Annals of emergency medicine. 2018;72(2):194-203.e1.	300 Javaud 2018
306 Jindal 2017	Jindal NL, Harniman E, Prior N, Perez-Fernandez E, Caballero T, Betschel S. Hereditary angioedema: health-related quality of life in Canadian patients as measured by the SF-36. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2017;13:4.	306 Jindal 2017
307 Johnson 2023	Johnson F, Stenzl A, Hofauer B, Heppt H, Ebert E-V, Wollenberg B, et al. A Retrospective Analysis of Long-Term Prophylaxis with Berotralstat in Patients with Hereditary Angioedema and Acquired C1-Inhibitor Deficiency-Real-World Data. Clinical reviews in allergy & immunology. 2023;65(3):354-64.	307 Johnson 2023
332 Kawalec 2013	Kawalec P, Holko P, Paszulewicz A. Cost-utility analysis of Ruconest(R) (conestat alfa) compared to Berinert(R) P (human C1 esterase inhibitor) in the treatment of acute, life-threatening angioedema attacks in patients with hereditary angioedema. Postepy dermatologii i alergologii. 2013;30(3):152-8.	332 Kawalec 2013
334 Kessel 2017	Kessel A, Farkas H, Kivity S, Veszeli N, Kohalmi KV, Engel-Yeger B. The relationship between anxiety and quality of life in children with hereditary angioedema. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2017;28(7):692-8.	334 Kessel 2017
205 Engel-Yeger 2017	Engel-Yeger B, Farkas H, Kivity S, Veszeli N, Kohalmi KV, Kessel A. Health-related quality of life among children with hereditary angioedema. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2017;28(4):370-6.	
335 Kessel 2017	Kessel A, Farkas H, Veszeli N, Kohalmi K, Kivity S, Engel-Yeger B. C1-INH-HAE: The relationship between parents and children's emotional status, children's disease activity and health related quality of life. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):591.	
338 Kiani-Alikhan 2024	Kiani-Alikhan S, Gower R, Craig T, Wedner HJ, Kinaciyan T, Aygören-Pürsün E, et al. Once-daily oral berotralstat for long-term prophylaxis of hereditary angioedema: the open-label extension of the APeX-2 randomized trial. The journal of allergy and clinical immunology In practice. 2024;12(3):733-43.e10.	338 Kiani-Alikhan 2024

256 Gower 2022	Gower R, Banerji A, Collis P, Desai B, Tomita D, Lumry W. Sustained Improvement Observed in Patient-Reported Quality of Life (QoL) with 96 Weeks of Oral Berotralstat Treatment. Journal of Allergy and Clinical Immunology. 2022;149(2 Supplement):AB164.	
311 Johnston 2020	Johnston D, Banerji A, Riedl M, Soteres D, Bernstein J, Best J, et al. BEROTRALSTAT IMPROVES PATIENT-REPORTED QUALITY OF LIFE THROUGH 48 WEEKS IN THE PHASE 3 APEX-2 TRIAL. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S22.	
561 Soteres 2023	Soteres D, Lumry W, Magerl M, Gagnon R, Desai B, Tomita D, et al. Berotralstat Improved Quality of Life through 96 Weeks Across Multiple Subgroups of Patients with Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB139.	
GL116 NCT03485911	ClinicalTrials NCT03485911. Efficacy and Safety Study of BCX7353 as an Oral Treatment for the Prevention of Attacks in HAE (APeX-2). Available from: https://clinicaltrials.gov/study/NCT03485911?term=NCT03485911&rank=1	
GL93 EU-CTR 2017-003966-29	EU Clinical Trials Register. 2017-003966-29. A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003966-29/results	
294* Jacobs 2020	Jacobs J, Aygoren-Pursun E, Sitz K, Tachdjian R, Li H, Best J, et al. BEROTRALSTAT POSITIVELY IMPACTS PATIENT-REPORTED SATISFACTION: RESULTS FROM THE PHASE 3 APEX-2 TRIAL. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S25.	
339 Knipps 2023	Knipps L, Scherer A, Smola A, Wagenmann M. Subcutaneous C1-esterase inhibitor therapy in a patient with hereditary angioedema with normal C1-esterase inhibitor: A case report. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):361.	339 Knipps 2023
351 Kucharczyk 2024	Kucharczyk A, Matuszewski T, Kurowski M, Juchacz A, Tomasial-Lozowska M, Trebas-Pietras E, et al. Real-world Treatment Outcomes of Lanadelumab in the Prevention of Hereditary Angioedema Attacks: an Interim Analysis of a Polish, Prospective, Multicenter, Observational Study (CHOPIN). Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB9.	351 Kucharczyk 2024
354 Kuman 2019	Kuman Tuncel O, Gokmen NM, Demir E, Gulbahar O, Pirildar S. The impact of hereditary angioedema on quality of life and family planning decisions. International journal of psychiatry in medicine. 2019;54(6):377-94.	354 Kuman 2019
353 Kuman 2017	Kuman O, Demir E, Gulbahar O, Pirildar S, Mete Gokmen N. Health related quality of life in hereditary angioedema patients. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):585.	

357 Latysheva 2023	Latysheva EA, Manto IA, Aleshina LV, Bobrikova EN, Viktorova EA, Gracheva EM, et al. Preliminary results of a non-interventional single-center study evaluating the efficacy of long-term use of lanadelumab in routine clinical practice in the Russian Federation. Russian Journal of Allergy. 2023;20(2):164-76.	357 Latysheva 2023
364 Lee 2021	Lee EY, Hsieh J, Borici-Mazi R, Caballero T, Kanani A, Lacuesta G, et al. Quality of life in patients with hereditary angioedema in Canada. Annals of Allergy, Asthma and Immunology. 2021;126(4):394-400.e3.	364 Lee 2021
374 Liu 2019	Liu S, Wang X, Xu Y, Xu Q, Zhi Y. Health-related quality of life and its risk factors in Chinese hereditary angioedema patients. Orphanet journal of rare diseases. 2019;14(1):191.	374 Liu 2019
376 Lluncor 2018	Lluncor M, Lamacchia D, Hernanz A, Pedrosa M, Alvez A, Cabanas R, et al. Determinants of health related quality of life (HRQoL) in adult patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE). Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement):AB266.	376 Lluncor 2018
356 Lamacchia 2017	Lamacchia D, Hernanz A, Alvez A, Lluncor M, Pedrosa M, Cabanas R, et al. Health related quality of life in adult patients with C1-INH-HAE. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	
378 Lo 2022	Lo SH, Lloyd A, Elkhalifa S, Sisic Z, van Nooten FE. Time Trade-Off Utilities for Hereditary Angioedema Health and Caregiver States. PharmacoEconomics - open. 2022;6(2):231-9.	378 Lo 2022
377 Lo 2021	Lo SH, Lloyd A, Elkhalifa S, Sisic Z, Van Nooten F. PSY17 Time Trade-Off Utilities for Hereditary Angioedema Health States. Value in Health. 2021;24(Supplement 1):S232.	
396 Lumry 2010	Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. Allergy and asthma proceedings. 2010;31(5):407-14.	396 Lumry 2010
152 Castaldo 2009	Castaldo A, Lumry W, Caballero T, Vernon M, Blaustein M, Wilson D. Humanistic burden of hereditary angioedema: Health-related quality of life, depression, productivity, and social consequences. Allergy: European Journal of Allergy and Clinical Immunology. 2009;64(SUPPL. 90):232.	
628 Wilson 2009	Wilson DA, Castaldo AJ, Vernon MK, Rentz AM, Blaustein MB. Effect of hereditary angioedema: Health-related quality of life, depression, productivity, and social consequences. Journal of Allergy and Clinical Immunology. 2009;123(2 SUPPL. 1):S142.	
398 Lumry 2018	Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of	398 Lumry

	Hereditary Angioedema. The journal of allergy and clinical immunology In practice. 2018;6(5):1733-41.e3.	2018
388 Lumry 2017	Lumry W, Craig TJ, Farkas H, Feuersenger H. Health-related quality of life (HRQoL) and changes in work productivity measures with subcutaneous C1-Inhibitor [C1-INH(SC)] for the Prevention of Hereditary Angioedema (HAE) Attacks: Findings from the compact study. Journal of Allergy and Clinical Immunology. 2017;139(2 Supplement 1):AB233.	
397* Lumry 2017	Lumry WR, Craig T, Cicardi M, Zuraw BL, Longhurst H, Farkas H, et al. Can routine prophylactic subcutaneous C1-inhibitor [C1-INH(SC)] alleviate psychological and physical disabilities caused by HAE? Findings from the COMPACT study (NCT01912456). Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	
403 Lumry 2014	Lumry WR, Miller DP, Newcomer S, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy and asthma proceedings. 2014;35(5):371-6.	403 Lumry 2014
190 Dayno 2014	Dayno J, Miller DP, Hautamaki E, Newcomer S, Fitts D, Lumry WR. Relationship between angioedema attacks and health-related quality of life outcomes in patients with hereditary angioedema (HAE). Journal of Allergy and Clinical Immunology. 2014;133(2 SUPPL. 1):AB33.	
401 Lumry 2013	Lumry WR, Miller DP, Beusterien K, Hautamaki E, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving nanofiltered C1 inhibitor for prophylaxis: Results of a randomized, placebocontrolled cross-over study. Annals of Allergy, Asthma and Immunology. 2013;111(5 SUPPL. 1):A105.	
402 Lumry 2014	Lumry WR, Miller DP, Beusterien K, Hautamaki E, Fitts D, Dayno J. Health-related quality of life (HRQoL) in patients with hereditary angioedema (HAE) receiving nanofiltered C1 inhibitor (C1 INH-nf) for prophylaxis: Results of a randomised, placebo-controlled, cross-over study. Allergy: European Journal of Allergy and Clinical Immunology. 2014;69(SUPPL. 99):491.	
400 Lumry 2023	Lumry WR, Maurer M, Weller K, Riedl MA, Watt M, Yu M, et al. Long-term lanadelumab treatment improves health-related quality of life in patients with hereditary angioedema. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2023;131(1):101-8.e3.	400 Lumry 2023
51 Banerji 2022	Banerji A, Bernstein JA, Johnston DT, Lumry WR, Magerl M, Maurer M, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. Allergy. 2022;77(3):979-90.	
176 Craig 2020	Craig T, Soteres D, Anderson J, Paes K, Hao J, Hashemi L, et al. QUALITY OF LIFE OF HEREDITARY ANGIOEDEMA (HAE) PATIENTS WITH DEPRESSION OR ANXIETY RECEIVING LANADELUMAB. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S25.	

177 Craig 2022	Craig T, Tachdjian R, Bernstein J, Anderson J, Nurse C, Watt M, et al. LONG-TERM EFFICACY, SAFETY, AND QUALITY OF LIFE WITH LANADELUMAB TREATMENT IN ADOLESCENTS WITH HEREDITARY ANGIOEDEMA. Annals of Allergy, Asthma and Immunology. 2022;129(5 Supplement):S28.	
391 Lumry 2019	Lumry W, Maurer M, Magerl M, Jain G, Devercelli G, Regnault A, et al. LONG-TERM LANADELUMAB TREATMENT IMPROVES HEALTH-RELATED QUALITY OF LIFE: HELP OPEN-LABEL EXTENSION STUDY INTERIM FINDINGS. Annals of Allergy, Asthma and Immunology. 2019;123(5 Supplement):S29.	
613 Watt 2022	Watt M, Devercelli G, Lumry W, Maurer M, Weller K, Riedl M, et al. SUSTAINED IMPROVEMENT IN HEALTH-RELATED QUALITY OF LIFE WITH CONTINUED LANADELUMAB TREATMENT IN HEREDITARY ANGIOEDEMA. Annals of Allergy, Asthma and Immunology. 2022;129(5 Supplement):S27.	
614 Watt 2021	Watt M, Maurer M, Devercelli G, Paes K, Regnault A, Meunier J, et al. Long-term Impact of Lanadelumab on Patients with Hereditary Angioedema (HAE) Type 1/2: Patient Reported Outcome (PRO) Findings from the HELP Open-label Extension Study (OLE). Journal of Allergy and Clinical Immunology. 2021;147(2 Supplement):AB24.	
406 Lumry 2021	Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy. 2021;76(4):1188-98.	406 Lumry 2021
55 Banerji 2018	Banerji A, Riedl M, Zuraw B, Lumry W, Lu P, Hao J, et al. LANADELUMAB 300MG EVERY 2 WEEKS EFFECTIVELY PREVENTED HEREDITARY ANGIOEDEMA ATTACKS IN THE HELP STUDY. Annals of Allergy, Asthma and Immunology. 2018;121(5 Supplement):S5.	
297 Jain 2019	Jain G, Sussman G, Lumry WR, Lu P, Lewis H, Maurer M. Lanadelumab improves health-related quality of life in patients with hereditary angioedema (HAE): Findings from the HELP study. Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 1).	
381 Longhurst 2018	Longhurst H, Lumry W, Weller K, Magerl M, Lu P, Jain G, et al. Lanadelumab improves health-related quality of life in patients with hereditary Angioedema (HAE): Findings from the HELP study. Clinical and Experimental Allergy. 2018;48(11):1524-5.	
407 Lumry 2018	Lumry WR, Weller K, Magerl M, Lu P, Jain G, Lewis H, et al. Lanadelumab markedly improves health-related quality of life in hereditary angioedema patients in the HELP study. Swiss Medical Weekly. 2018;148(Supplement 231):28S.	
408 Lumry 2018	Lumry WR, Weller K, Magerl M, Schranz J, Jain G, Doll H, et al. Lanadelumab markedly improves health-related quality of life in hereditary angioedema patients in the HELP study. Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB47.	

SLR26 Banerji 2018	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.	
409 Lumry 2021	Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet journal of rare diseases. 2021;16(1):86.	409 Lumry 2021
173 Craig 2019	Craig T, Longhurst H, Lumry W, Chiao J, Feuersenger H, Prusty S, et al. Efficacy and quality of life outcomes with long-term subcutaneous C1 inhibitor prophylaxis in the COMPACT open-label extension trial. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74(Supplement 106):209-10.	
399 Lumry 2019	Lumry WR, Craig TJ, Magerl MAK, Farkas H, Lawo JP, Chiao J, et al. Long-term Health-related Quality of Life in Patients Treated With Subcutaneous C1-Inhibitor Replacement Therapy for the Prevention of Hereditary Angioedema Attacks. Journal of Allergy and Clinical Immunology. 2019;143(2 Supplement):AB38.	
411 Luz 2011	Luz S, da Silva JA, Barbosa F, Santos AS, Ferreira MB, Barbosa MP. Quality of life evaluation in patients with hereditary angioedema. Revista Portuguesa de Imunoalergologia. 2011;19(3):143-9.	411 Luz 2011
414 Magerl 2015	Magerl M, Aygören-Pürsün E, Graff J, Martinez-Saguer I, Kreuz W, Longhurst H. BCX4161, an oral kallikrein inhibitor, showed significant benefits on reducing disease burden and improving quality of life in subjects with hereditary angioedema in the Opus-1 study. Journal of allergy and clinical immunology. 2015;135(2):AB278.	414 Magerl 2015
419 Magliano 2016	Magliano CA, Tura BR, Santos M, Senna K, Costa MG. Cost Effectiveness of Icatibant for Hereditary Angioedema in Brazil: Challenges in the Economic Evaluation of Orphan Drugs. Value in Health. 2016 May 1;19(3):A248.	419 Magliano 2016
435 Martinez-Saguer 2023	Martinez-Saguer I, Grumach A, Zwiener R, Simon A, Murphy R, Cruz MDL, et al. BURDEN OF ILLNESS IN ADULT PATIENTS WITH HEREDITARY ANGIOEDEMA: Results: FROM A MULTINATIONAL SURVEY. Annals of Allergy, Asthma and Immunology. 2023;131(5 Supplement 1):S29-S30.	435 Martinez-Saguer 2023
275 Grumach 2024	Grumach A, Zwiener R, Martinez-Saguer I, Simon A, Murphy R, De La Cruz M, et al. Burden of Illness in Adult Patients With Controlled and Poorly Controlled Hereditary Angioedema: Findings From a Multinational Survey. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB92.	
648 Zwiener 2024	Zwiener R, Martinez-Saguer I, Grumach A, Simon A, Murphy R, De La Cruz M, et al. Burden of Illness in Female and Male Adult Patients With Hereditary Angioedema: Findings From a Multinational Survey. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB93.	

445 Medina 2023	Medina I, Josviack D, Berardi A, Cavallo C, Chinigo M, Chorzepa G, et al. [Health related to quality life of patients with hereditary angioedema in Argentina. A multicenter study]. Calidad de vida relacionada con la salud en pacientes con angioedema hereditario de Argentina Estudio multicentrico. 2023;70(2):64-71.	445 Medina 2023
449 Mendivil 2021	Mendivil J, Murphy R, de la Cruz M, Janssen E, Boysen HB, Jain G, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. Orphanet journal of rare diseases. 2021;16(1):94.	449 Mendivil 2021
450 Mendivil 2019	Mendivil J, Murphy R, Janssen E, Aygoeren-Puersuen E, Devercelli G, Boysen HB. Burden of hereditary angioedema: Findings from a multinational patient survey in EU, Canada, and Australia. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74(Supplement 106):756-7.	
464 Nadasan 2024	Nadasan V, Nadasan A, Borka-Balas R, Bara N. A Cross-Sectional Study of Quality of Life in Patients Enrolled in the Romanian Hereditary Angioedema Registry. Cureus. 2024;16(1):e51959.	464 Nadasan 2024
468 Nicolas 2021	Nicolas A, Launay D, Duprez C, Citerne I, Morell-Dubois S, Sobanski V, et al. Impact of disease on daily activities, emotions and quality of life of patients with hereditary angioedema. Revue de Medecine Interne. 2021;42(9):608-15.	468 Nicolas 2021
472 Nordenfelt 2014	Nordenfelt P, Dawson S, Wahlgren C-F, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy and asthma proceedings. 2014;35(2):185-90.	472 Nordenfelt 2014
85 Bjorkander 2013	Bjorkander J, Nordenfelt P, Lindfors A, Lofdahl K, Mallbris L, Werner S, et al. Burden of hereditary angioedema for patients in Sweden; results from a retrospective patient registry survey implemented by a population based census SWEHA of patients with HAE type 1 and 2. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):612.	
473 Nordenfelt 2017	Nordenfelt P, Nilsson M, Lindfors A, Wahlgren C-F, Bjorkander J. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. Allergy and asthma proceedings. 2017;38(6):447-55.	473 Nordenfelt 2017
474 Nordenfelt 2017	Nordenfelt P, Nilsson M, Lindfors A, Wahlgren CF, Bjorkander J. Study of health-related quality of life and disease activity in adults with HAE in Sweden. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	
476 Nuez 2020	Nuez AL. HEREDITARY ANGIOEDEMA: ASSOCIATION BETWEEN QUALITY OF LIFE AND DISSEASE ACTIVITY. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB106.	476 Nuez 2020

477 Nuez 2019	Nuez AL, Gutierrez IG, Alvarez-Perea A, Garcia AP, Ochoa De Ocariz MLB. Hereditary angioedema: Quality of life in 19 patients. Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 4).	
479 Nunes 2021	Nunes FL, Ferriani MPL, Moreno AS, Langer SS, Maia LSM, Ferraro MF, et al. Decreasing Attacks and Improving Quality of Life through a Systematic Management Program for Patients with Hereditary Angioedema. International archives of allergy and immunology. 2021;182(8):697-708.	479 Nunes 2021
462 Moreno 2020	Moreno A, Nunes F, Langer S, Ferriani M, Aragon D, Caballero T, et al. A multidisciplinary intervention resulted in improvement in qualilty of life among patients with hereditary angioedema. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB108.	
480 Nunes 2019	Nunes FL, Moreno AS, Langer SS, Ferriani MP, Maia L, Bessa JJ, et al. Multidisciplinary management of Brazilian patients with hereditary angioedema: Impact on quality of life. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74(Supplement 106):146.	
497 Park 2023	Park K, Yeich A, Craig T. Evaluating the Impact of Acute Versus Prophylaxis Therapy in Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB135.	497 Park 2023
503 Petersen 2024	Petersen RS, Bordone L, Riedl MA, Tachdjian R, Craig TJ, Lumry WR, et al. A phase 2 open-label extension study of prekallikrein inhibition with donidalorsen for hereditary angioedema. Allergy. 2024;79(3):724-34.	503 Petersen 2024
95 Bordone 2023	Bordone L, Newman K, Lui C, Alexander V, Riedl M, Schneider E, et al. Phase 2 Open-Label Extension Study With Donidalorsen in Patients With Hereditary Angioedema: Updated Interim Analysis With Quality-of-Life Data. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB129.	
96 Bordone 2024	Bordone L, Newman KB, Deng Y, Alexander VJ, Riedl MA, Schneider E, et al. One-year results from an open-label study of donidalorsen in patients with hereditary angioedema. Allergy and Asthma Proceedings. 2024;45(1):75-6.	
422 Manning 2024	Manning M, Bordone L, Newman K, Deng Y, Alexander V, Dorow S, et al. The Impact of Donidalorsen Taken Every 8 Weeks in Patients With Hereditary Angioedema: Two-Year Update. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB2.	
466 Newman 2023	Newman K, Riedl M, Lui C, Bordone L, Alexander V, Schneider E, et al. The Impact of Donidalorsen Taken Every 8 Weeks in Patients With Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB134.	
575 Tachdjian	Tachdjian R, Bordone L, Dorow S, Cohn D, Schneider E, Deng Y, et al. Phase 2 Open-Label Extension Study With Donidalorsen in Patients With Hereditary	

2024	Angioedema: 1 Year Versus 2 Years. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB11.	
507 Phillips-Angles 2019	Phillips-Angles E, Lluncor M, Pedrosa M, Lamacchia D, Hernanz A, Alvez-Liste A, et al. Determinant factors of disease activity in hereditary angioedema due to C1 inhibitor deficiency. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74(Supplement 106):757-8.	507 Phillips-Angles 2019
511 Piotrowicz-Wojcik 2024	Piotrowicz-Wojcik K, Bulanda M, Czarnobilska E, Porebski G. Clinical Characteristics and Quality of Life in a Cohort of Polish Pediatric Patients with Hereditary Angioedema. Children. 2024;11(2):237.	511 Piotrowicz-Wojcik 2024
532 Riedl 2018	Riedl MA, Aygören-Pürsün E, Baker J, Farkas H, Anderson J, Bernstein JA, et al. Evaluation of avoralstat, an oral kallikrein inhibitor, in a Phase 3 hereditary angioedema prophylaxis trial: the OPuS-2 study. Allergy. 2018;73(9):1871-80.	532 Riedl 2018
548 Sanchez 2015	Sanchez MD, Cuervo J, Rave D, Clemen G, Yepes-Nunez JJ, Ortiz-Reyes B, et al. Hereditary angioedema in Medellin (Colombia): Clinical evaluation and quality of life appraisal. Biomedica : revista del Instituto Nacional de Salud. 2015;35(3):419-28.	548 Sanchez 2015
563 Spano 2018	Spano R, Di Paola N, Bova M, Barbarino A. Value co-creation in healthcare: evidence from innovative therapeutic alternatives for hereditary angioedema. BMC health services research. 2018;18(1):571.	563 Spano 2018
564 Squeglia 2016	Squeglia V, Barbarino A, Bova M, Gravante C, Petraroli A, Spadaro G, et al. High attack frequency in patients with angioedema due to C1-inhibitor deficiency is a major determinant in switching to home therapy: a real-life observational study. Orphanet journal of rare diseases. 2016;11(1):133.	
569 Stobiecki 2023	Stobiecki M, Redel K, Czarnobilska E. Subcutaneous C1-esterase inhibitor prophylactic treatment during a pregnancy -The case report of a hereditary angioedema patient with frequent abdominal attacks. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):385.	569 Stobiecki 2023
572 Symons 2019	Symons CC, Bethune CA, Whyte AF, Leeman L, Caballero T. Quality of life among HAE patients in South West England (Devon and Cornwall) using HAE-QoL questionnaire designed by Foundation for Biomedical Research of la Paz University Hospital Madrid (FIBHULP). Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 4).	572 Symons 2019
573 Szilagyi 2023	Szilagyi D, Horvath HR, Andrasi N, Kempler MS, Balla Z, Farkas H. The analysis of the effect of the COVID-19 pandemic on patients with hereditary angioedema type I and type II. Scientific reports. 2023;13(1):20446.	573 Szilagyi 2023

603 Vanya 2023	Vanya M, Watt M, Shahraz S, Kosmas CE, Rhoten S, Costa-Cabral S, et al. Content validation and psychometric evaluation of the Angioedema Quality of Life Questionnaire for hereditary angioedema. Journal of patient-reported outcomes. 2023;7(1):33.	603 Vanya 2023
606 Vargas-Camano 2023	Vargas Camano ME, Buendia Lopez YO, Garces Flores H, Guzman Vazquez S. Hereditary angioedema: Patient journey approach in Mexico. Revista alergia Mexico (Tecamachalco, Puebla, Mexico : 1993). 2023;70(4):121-8.	606 Vargas-Camano 2023
609 Wadiwalla 2019	Wadiwalla SH, Kanani AS. Quality of life evaluation in Hereditary Angioedema patients on home plasma derived C1 inhibitor infusion. Journal of Allergy and Clinical Immunology. 2019;143(2 Supplement):AB115.	609 Wadiwalla 2019
617 Wedner 2023	Wedner HJ, Bernstein J, Betschel S, Manning M, Estepan DN, Fei K, et al. Effectiveness, Safety, and Patient-Reported Outcomes (PROs) in Patients With Hereditary Angioedema (HAE) From the United States and Canada Treated With Lanadelumab: 24-Month Data From the EMPOWER Study. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB131.	617 Wedner 2023
130 Busse 2022	Busse P, Zaragoza-Urdaz R, Betschel S, Wedner HJ, Brouwer E, Andriotti T, et al. Impact of lanadelumab on patient-reported outcomes in hereditary angioedema in the US and Canada: Interim findings from the EMPOWER Study. Journal of Allergy and Clinical Immunology. 2022;149(2 Supplement):AB166.	
618 Weller 2012	Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy: European Journal of Allergy and Clinical Immunology. 2012;67(10):1289-98.	618 Weller 2012
622 Weller 2017	Weller K, Maurer M, Fridman M, Supina D, Schranz J, Magerl M. Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase. Allergy and asthma proceedings. 2017;38(2):143-51.	622 Weller 2017
623 Weller 2015	Weller K, Maurer M, Magerl M, Fridman M, Supina D, Schranz J. Subcutaneous human C1-inhibitor (C1-INH) with recombinant human hyaluronidase (rHuPH20) for the prevention of angioedema attacks in patients with hereditary angioedema (HAE): health-related quality of life (HRQoL) results from a randomized, double-blind, dose-ranging, crossover study. Allergy. 2015 Sep 1;70(S101):253.	
631 Wong 2023	Wong JCY, Chiang V, Lam DLY, Lee E, Lam K, Au EYL, et al. Long-term prophylaxis for hereditary angioedema: Initial experiences with garadacimab and lanadelumab. The journal of allergy and clinical immunology Global. 2023;2(4):100166.	631 Wong 2023
632 Wong 2022	Wong JCY, Chiang V, Lam K, Tung E, Au EYL, Lau CS, et al. Prospective Study on the Efficacy and Impact of Cascade Screening and Evaluation of Hereditary	632 Wong

	Angioedema (CaSE-HAE). The journal of allergy and clinical immunology In practice. 2022;10(11):2896-903.e2.	2022
641 Zanichelli 2018	Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert R) in patients with hereditary angioedema: the SABHA study. Orphanet journal of rare diseases. 2018;13(1):51.	641 Zanichelli 2018
640 Zanichelli 2018	Zanichelli A, Azin G, Federico C, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered c1 inhibitor in patients with hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2018;73(Supplement 105):725.	
643 Zarnowski 2021	Zarnowski J, Rabe M, Kage P, Simon J-C, Treudler R. Prophylactic Treatment in Hereditary Angioedema Is Associated with Reduced Anxiety in Patients in Leipzig, Germany. International archives of allergy and immunology. 2021;182(9):819-26.	643 Zarnowski 2021
GL1 Busse 2024	Busse P, Craig TJ , Radojicic C, O'Connor M, Christiansen S, Ulloa J, Danese S, Andriotti T, Audhya P, Desai V. Real-World Impact of Treated Hereditary Angioedema Attacks on Patients' Quality of Life. ISPOR 2024. Available from: https://www.ispor.org/heor-resources/presentations-database/search	GL1 Busse 2024
U19 O'Connor 2024	O'Connor M, Busse P, Christiansen S, Radojicic C, Ulloa J, Danese S, Desai V, Andriotti T, Audhya P and Craig T. Quality of life among prophylaxis and on-demand users in hae. Allergy and Asthma Proceedings. 2024;45(3):212.	
U4 Busse 2024	Busse P, Radojicic C, O'Connor M, Craig T, Ulloa J, Danese S, Desai V, Andriotti T, Audhya P and Christiansen S. Burden of hereditary angioedema attacks in adolescents. Allergy and Asthma Proceedings. 2024;45(3):212.	
GL122 NCT04444895	ClinicalTrials NCT04444895. A Study of Long-Term Safety and Efficacy of Lanadelumab for Prevention of Acute Attacks of Non-histaminergic Angioedema With Normal C1-Inhibitor. Available from: https://clinicaltrials.gov/study/NCT04444895?term=NCT04444895&rank=1	GL122 NCT04444895
GL110 NCT02584959	ClinicalTrials NCT02584959. Study to Evaluate the Clinical Efficacy and Safety of Subcutaneously Administered C1 Esterase Inhibitor for the Prevention of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema. Available from: https://clinicaltrials.gov/study/NCT02584959?term=NCT02584959&rank=1	GL110 NCT02584959
GL87 EU-CTR 2015-002478-19	EU Clinical Trials Register. 2015-002478-19. A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002478-	

	19/results	
GL99 EU-CTR 2022-002621-98	EU Clinical Trials Register. 2022-002621-98. A Phase 3 Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2022-002621-98/results	GL99 EU-CTR 2022-002621-98
GL96 EU-CTR 2019-003921-99	EU Clinical Trials Register. 2019-003921-99. An open-label, single-arm, non-randomized phase 3 study to evaluate clinical efficacy, safety, and pharmacokinetics of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema in Japanese subjects. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003921-99/results	GL96 EU-CTR 2019-003921-99
GL86 EU-CTR 2014-002655-26	EU Clinical Trials Register. 2014-002655-26. OPuS-2 A multicentre, randomised, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX4161 for 12 weeks as an oral prophylaxis treatment for attacks of hereditary angioedema. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-002655-26/results	GL86 EU-CTR 2014-002655-26
GL85 EU-CTR 2013-002319-82	EU Clinical Trials Register. 2013-002319-82. A Phase 2a double-blind placebo-controlled 2-period crossover study to evaluate the safety and efficacy of BCX4161 as a prophylactic treatment to reduce the frequency of attacks in subjects with hereditary angioedema. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-002319-82	GL85 EU-CTR 2013-002319-82
GL7 Farkas 2023	Farkas H, Aygören- Pürsün E, Kanani A, Psarros F, Ebo D, Bara NA, Gavini F, Bent- Ennakhil N, Andresen I, Sayegh L. Real- world burden of illness in patients with hereditary angioedema (HAE) type I and II. European Journal of Allergy and Clinical Immunology - Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):.	GL7 Farkas 2023
GL9 Martinez Saguer 2023	Martinez Saguer I, Magerl M, Andriotti T, Botha J, Agmon- Levin N, Watt M, Maurer M. Quality of life during lanadelumab treatment in patients with hereditary angioedema: 24- month results from the enable study. European Journal of Allergy and Clinical Immunology - Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):26.	GL9 Martinez Saguer 2023
GL13 Watt 2023	Watt M, Simon A, Murphy R, De La Cruz M, Romanus D, Zwiener R, Sarrazola M. Burden of (HAE): Findings from a multinational patient survey in Argentina and Colombia. European Journal of Allergy and Clinical Immunology - Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):151.	GL13 Watt 2023
GL15 Arnaout	Arnaout R, Contreras- Verduzco FA, Demuth D, Jain S, Song HH, Kang HR. Real- world patient burden of hereditary angioedema (HAE) and impact on quality of life (QoL) in regions with limited HAE management options and highest unmet needs. European Journal of Allergy and Clinical Immunology - Abstracts from the	GL15 Arnaout

2023	European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):221.	2023
GL17 Tuncay 2023	Tuncay G, Can Bostan O, Kayıkcı H, Cihanbeylerden M, Damadoğlu E, Uysal Soyer O, Birben E, Karakaya G, Kalyoncu AF. The effect of tranexamic acid on disease control in hereditary angioedema with normal C1 inhibitor (type III HAE). European Journal of Allergy and Clinical Immunology - Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):333.	GL17 Tuncay 2023
GL21 Wong 2023	Wong J, Chiang V, Wong D, Lee E, Lam K, Au E, Li P. Start and success of long- term prophylaxis in hereditary (HAE) in Hong Kong. European Journal of Allergy and Clinical Immunology - Abstracts from the European Academy of Allergy and Clinical Immunology Hybrid Congress. 2023;78(S112):548.	GL21 Wong 2023
GL140 Javaud 2018	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), doi: 10.1016/j.jaip.2018.05.036.	GL140 Javaud 2018
U1 Anderson 2024	Anderson J, Soteres D, Mellor J, Connolly H, Wynne-Cattanach K, Earl L, Schultz BG and Juethner S. Physician- and patient-reported outcomes by hereditary angioedema type: Data from a real-world study. Allergy and Asthma Proceedings. 2024;45(4):247-254.	U1 Anderson 2024
U8 Castaldo 2024	Castaldo AJ, Siersbaek N, Corcoran D, Selva CN, Jervelund C, Christiansen S, Riedl MA, Zuraw BL and Busse P. Development and Validation of a US HAE-C1INH Quality of Life Instrument. Annals of allergy, asthma & immunology. 2024;doi: https://doi.org/10.1016/j.anai.2024.07.018	U8 Castaldo 2024
U9 Craig 2024	Craig TJ, Levy DS, Reshef A, Lumry WR, Martinez-Saguer I, Jacobs JS, Yang WH, Ritchie B, Aygoren-Pursun E, Keith PK, Busse P, Feuersenger H, Alexandru Bica M, Jacobs I, Pragst I and Magerl M. Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study. The Lancet Haematology. 2024;11(6):e436-e447.	U9 Craig 2024
U12 Itzler 2024	Itzler R, Lumry WR, Sears J, Braverman J, Li Y, Brennan CJ and Koch G. An international survey assessing the effects of the duration of attack-free period on health-related quality of life for patients with hereditary angioedema. Orphanet Journal of Rare Diseases. 2024;19(1):241.	U12 Itzler 2024
U18 Morioke 2024	Morioke S, Aikyo T, Tanaka A, Matsubara D, Saito R, Iwamoto K, Yamasaki C, Kogetsu A, Hamakawa N, Isono M, Yamamoto BA, Matsumura Y, Takeda T, Manabe S, Javaid MK, Barrett J, Gray N, Kaye J, Kato K and Hide M. Survey of hereditary angioedema episodes and quality of life impairment through a patient-participatory registry. Journal of Cutaneous Immunology and Allergy. 2024;7:12626.	U18 Morioke 2024
U24 Riedl 2024	Riedl MA, Tachdjian R, Lumry WR, Craig T, Karakaya G, Gelincik A, Stobiecki M, Jacobs JS, Gokmen NM, Reshef A et al. Efficacy and Safety of Donidalorsen for Hereditary Angioedema. New England Journal of Medicine. 2024;391(1):21-31.	U24 Riedl 2024

U25 Troelnikov 2024	Troelnikov A, Milburn K, Hissaria P, Thao Adriana Le T and Smith W. Hereditary angioedema prevalence and satisfaction with prophylaxis in South Australia. The World Allergy Organization journal. 2024;17(7):100918.	U25 Troelnikov 2024
629* Wolfhart 2009	Wolfhart K, Martinez-Saguer I, Rusicke E, Aygoren-Pursun E, Klingebiel T. Impact of the Frankfurt HAE therapy protocol on health-related Quality of life (HRQoL) in 50 patients with hereditary angioedema (HAE). Allergy: European Journal of Allergy and Clinical Immunology. 2009;64(S90):205.	629* Wolfhart 2009
348* Kreuz 2009	Kreuz W, Martinez-Saguer I, Rusicke E, Aygoren-Pursun 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;123(2 SUPPL. 1):S116.	
482* Ocak 2021	Ocak M, Nain E, Akarsu A, Sahiner UM, Sekerel BE, Soyer O. Health-related quality of life in children with hereditary angioedema compared with patients with histaminergic angioedema. Allergy and asthma proceedings. 2021;42(4):325-32.	482* Ocak 2021
483* Ocak 2021	Ocak M, Nain E, Akarsu A, Sahiner UM, Sekerel BE, Soyer O. Health-related quality of life in children with hereditary angioedema as compared to patients with histaminergic angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):225.	
126* Burns 2015	Burns ST. Neurofeedback in Hereditary Angioedema: A Single Case Study of Symptom Reduction. Applied psychophysiology and biofeedback. 2015;40(3):251-6.	126* Burns 2015
161* Christiansen 2015	Christiansen SC, Bygum A, Banerji A, Busse P, Li H, Lumry W, et al. Before and after, the impact of available on-demand treatment for HAE. Allergy and asthma proceedings. 2015;36(2):145-50.	161* Christiansen 2015
162* Christiansen 2023	Christiansen SC, Lopes Veronez C, Smith TD, Riedl MA, Zuraw BL. Hereditary Angioedema: Impact of COVID-19 pandemic stress upon disease related morbidity and well-being. Allergy and asthma proceedings. 2023;44(2):115-21.	162* Christiansen 2023
347* Kreuz 2009	Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Heller C, Klingebiel T. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. Transfusion. 2009;49(9):1987-95.	347* Kreuz 2009
481* Nygren	Nygren A, Nordenfelt P, Lindfors A, Mallbris L, Bjorkander J, Wahlgren C-F. Swedish children with hereditary angioedema report good overall health and quality	481* Nygren

2016	of life despite symptoms. Acta paediatrica. 2016;105(5):529-34.	2016
521* Psarros 2014	Psarros F, Koutsostathis N, Farmaki E, Speletas MG, Germenis AE. Hereditary angioedema in Greece: the first results of the greek hereditary angioedema registry. International archives of allergy and immunology. 2014;164(4):326-32.	521* Psarros 2014
GL2 Craig 2024*	Craig TJ, Busse P, Christiansen S, O'Connor M, Radojicic C, Ulloa J, Danese S, Andriotti T, Audhya P, Desai V. Real-World Impact of Treated Hereditary Angioedema Attacks on Patients' Employment and Work Productivity. ISPOR 2024. Available from: https://www.ispor.org/heor-resources/presentations-database/search	GL2 Craig 2024*
SLR34 Savarese 2018*	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.	SLR34 Savarese 2018*

* not extracted due to reporting only QoL scales not planned for extraction

Table 120 shows the publications excluded after full text review, including the reasons for exclusion.

Table 120 Publications excluded at full text reviewing, with reasons (n=161) – original review

Reference details of publications excluded	Reason for exclusion
Strassen U, Bas M, Hajdu Z, Buchberger M. Nanofiltrated C1-esterase-inhibitor in the prophylactic treatment of hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):251.	Unable to find
Bacarini LF, Vieira AL, Camargo M, Mosca T, Neves-Forte WC. [Diagnosis of hereditary angioedema after thirty years of clinical manifestations]. Diagnostico de angioedema hereditario despues de treinta anos de mani-festaciones clinicas. 2021;68(3):206-8.	Duplicate
Bacarini LF, Vieira AL, Camargo M, Mosca T, Neves-Forte WC. [Diagnosis of hereditary angioedema after thirty years of clinical manifestations]. Diagnostico de angioedema hereditario despues de treinta anos de mani-festaciones clinicas. 2021;68(3):206-8.	Duplicate
Fukunaga A, Morita E, Miyagi T, Eto K, Shimizu A, Kagami S, et al. [EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF INTRAVENOUS C1 INHIBITOR FOR LONG-TERM PROPHYLAXIS AND TREATMENT OF BREAKTHROUGH ATTACKS IN JAPANESE SUBJECTS WITH HEREDITARY ANGIOEDEMA: A PHASE 3 OPEN-LABEL STUDY]. Arerugi = [Allergy]. 2020;69(3):192-203.	Duplicate
Maurer M, Zanichelli A, Hao J, Inhaber N, Yu M, Hebert J, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. Allergy: European Journal of Allergy and Clinical Immunology. 2022;77(3):979-90.	Duplicate
Medina I, Josviack D, Berardi A, Cavallo C, Chinigo M, Chorzepa G, et al. Health related to quality life of patients with hereditary angioedema in Argentina A multicenter study. Revista Alergia Mexico. 2023;70(2):64-71.	Duplicate
Nicolas A, Launay D, Duprez C, Citerne I, Morell-Dubois S, Sobanski V, et al. [Impact of disease on daily activities, emotions and quality of life of patients with hereditary angioedema]. Impact de l'angioedeme hereditaire sur les activites de la vie quotidienne, la sphere emotionnelle et la qualite de vie des patients. 2021;42(9):608-15.	Duplicate
Sanchez MD, Cuervo J, Rave D, Clemen G, Yepes-Nunez JJ, Ortiz-Reyes B, et al. [Hereditary angioedema in Medellin (Colombia): Clinical evaluation and quality of life appraisal]. Angioedema hereditario en Medellin, Colombia: evaluacion clinica y de la calidad de vida. 2015;35(3):419-28.	Duplicate
Brix AT, Boysen HB, Weller K, Caballero T, Bygum A. Patient-reported outcome measures for angioedema: a literature review. Acta Dermato-Venereologica. 2021;101(5).	Study design

Busse PJ, Christiansen SC, Birmingham JM, Overbey JR, Banerji A, Otani IM, et al. Development of a health-related quality of life instrument for patients with hereditary angioedema living in the United States. The journal of allergy and clinical immunology In practice. 2019;7(5):1679-83.e7.	Study design
Craig T, Riedl M, Dykewicz MS, Gower RG, Baker J, Edelman FJ, Hurewitz D, Jacobs J, Kalfus I. When is prophylaxis for hereditary angioedema necessary?. Annals of Allergy, Asthma & Immunology. 2009 May 1;102(5):366-72.	Study design
Keating GM. Human C1-esterase inhibitor concentrate (Berinert). BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2009;23(6):399-406.	Study design
Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Correction to: Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. Orphanet journal of rare diseases. 2021;16(1):329.	Study design
Schmidely N, Chatelanaz C, Train C, Strub C, Delonca J, Marquet T, et al. HTA172 Value of French Framework for Early Access Programs for the HTA Appraisal in the Rare Disease Space: The Example of Lanadelumab in Patients With Hereditary Angioedema. Value in Health. 2023;26(12 Supplement):S352.	Study design
Stassek LM, Bushnell DM, McCarrier KP, Supina D. Patient experience with hereditary angioedema (HAE): a review of the literature. Quality of life research. 2015;24:80-80.	Study design
Vanya M, Watt M, Shahraz S, Kosmas CE, Rhoten S, Costa-Cabral S, et al. Correction to: Content validation and psychometric evaluation of the Angioedema Quality of Life Questionnaire for hereditary angioedema. Journal of patient-reported outcomes. 2023;7(1):53.	Study design
Banerji A. The burden of illness in patients with hereditary angioedema. Annals of Allergy, Asthma & Immunology. 2013 Nov 1;111(5):329-36.	Study design – SLR

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).	Study design – SLR
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.	Study design – SLR
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.	Study design – SLR
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.	Study design – SLR
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).	Study design – SLR
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.	Study design – SLR
Craig TJ, Cribbs K, Czado S. EE529 Characterizing Attack-Related Health Utility in Hereditary Angioedema. Value in Health. 2023 Jun 1;26(6):S156.	Study design – SLR
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.	Study design – SLR
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.	Study design – SLR
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.	Study design - SLR

Jacobson K, Soteres D, Nieto-Martinez S, Moldovan D, Martinez-Saguer I, Vardi M, et al. C1 INHIBITOR ADMINISTRATION IN PEDIATRIC PATIENTS WITH HEREDITARY ANGIOEDEMA: PATIENT COMPLIANCE WITH INTRAVENOUS THERAPY. Annals of Allergy, Asthma and Immunology. 2018;121(5 Supplement):S36.	Population
Martinez-Saguer I, Soteres D, Van Leerberghe A, Herrera EM, Devercelli G, Vardi M, et al. Improved health-related quality of life in pediatric patients with hereditary angioedema (HAE): A phase 3 study of C1 inhibitor for attack prevention. Allergy: European Journal of Allergy and Clinical Immunology. 2018;73(Supplement 105):718.	Population
Recke A, Steinmuller-Magin L, Von Bubnoff D. Recidivating angioedema in a patient with alpha-1antitrypsin (A1AT) deficiency and depressed C1 esterase inhibitor (C1INH) levels -A causal or just an occasional relationship? Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):607-8.	Population
Actrn. The influence of stress and lifestyle in hereditary angioedema. https://trialsearchwhoint/Trial2aspx?TrialID=ACTRN12621000473864. 2021.	Outcomes
Ahuja M, Dorr A, Bode E, Boulton A, Buckland M, Chee S, et al. Berotralstat for the prophylaxis of hereditary angioedema -A national survey of patient outcomes in the UK. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):413-4.	Outcomes
Anderson J, Levy DS, Lumry W, Koochaki P, Lanar S, Henry Li H. Letting the patients speak: an in-depth, qualitative research-based investigation of factors relevant to health-related quality of life in real-world patients with hereditary angioedema using subcutaneous C1 inhibitor replacement therapy. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2021;17(1):60.	Outcomes
Anderson JT, Levy DS, Lumry WR, Koochaki P, Lanar S, Li HH. Exploring the Quality of Life Benefits of Subcutaneous C1-Inhibitor (C1-INH) Replacement Therapy Using Qualitative Research Methods. Journal of Allergy and Clinical Immunology. 2019;143(2 Supplement):AB44.	Outcomes
Arce-Ayala YM, Nazario S, Ramos-Romey CJ. Burden of hereditary angioedema in the quality of life among Puerto Ricans. Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB56.	Outcomes
Arora N, Nelson B, Carpenter L, Wettenstein R, Selva C, Castaldo T, et al. Health and well-being implications of insurance coverage delays and denials for patients with hereditary angioedema. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB135.	Outcomes

Arora NS, Nelson B, Carpenter L, Wettenstein RP, Hashmi M, Selva CN, et al. Consequences of Insurance Coverage Delays and Denials for Patients With Hereditary Angioedema. The journal of allergy and clinical immunology In practice. 2023;11(8):2432-8.e1.	Outcomes
Aygoren-Pursun E, Martinez-Saguer I, Rusicke E, Klingebiel T, Kreuz W. On demand treatment and home therapy of hereditary angioedema in Germany - the Frankfurt experience. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2010;6(1):21.	Outcomes
Bacarini LF, Vieira AL, Camargo M, Mosca T, Neves-Forte WC. Diagnosis of hereditary angioedema after thirty years of clinical manifestations. Revista Alergia Mexico. 2021;68(3):206-8.	Outcomes
Badiou J, Rowe A, McGrath T, Brosz K, Dumbrille D, Bick R, et al. Real world data of Canadians living with hereditary angioedema (HAE): Attributes of new medications. Allergy, Asthma and Clinical Immunology. 2020;16(SUPPL 1).	Outcomes
Banerji A, Busse P, Christiansen SC, Li H, Lumry W, Davis-Lorton M, et al. Current state of hereditary angioedema management: a patient survey. Allergy and asthma proceedings. 2015;36(3):213-7.	Outcomes
Banerji A, Davis K, Devercelli G, Hollis K, Hunter S, Jain G. Clinical and demographic characteristics of patients with hereditary angioedema in the United States. Annals of Allergy, Asthma and Immunology. 2017;119(5 Supplement 1):S45.	Outcomes
Bara NA. First-year of short-and long-term prophylaxis with plasma derived C1-inhibitor for patients with hereditary angioedema in Romania. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):372.	Outcomes
Baynova K, Cimbollek S, Quiralte J, Lucena JM, Garcia R, Gonzalez-Quevedo T. Effectiveness of subcutaneous human C1 esterase inhibitor concentrate for the prevention of hereditary angioedema acute episodes during the COVID19 pandemic period: A case series. Allergy: European Journal of Allergy and Clinical Immunology. 2021;76(SUPPL 110):204.	Outcomes
Baynova K, Reguero M, R AV, Ochando M, Lucena JM, Garcia JR, et al. COVID-19 infection in patients with severe hereditary angioedema in long term prophylaxis with subcutaneous C1-inhibitor -A prospective study. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):412-3.	Outcomes
Baynova KZ, De Aramburu Mera T, Avila Castellano MR, Reguero Capilla M, Gonzalez-Quevedo T. Comorbidities in the spectrum of SERPING 1-related hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(SUPPL 109):465.	Outcomes

Benrajab KM, Singh G, Obah E. Hereditary angioedema presenting as irritable bowel syndrome: a case of early closure. Journal of community hospital internal medicine perspectives. 2015;5(5):29114.	Outcomes
Bernstein J, Anderson J, Manning M, Tachdjian R, Bajcic P, Rodino F, et al. PRELIMINARY RETROSPECTIVE ANALYSIS OF PATIENT OUTCOMES ASSOCIATED WITH SUBCUTANEOUS C1INH PROPHYLAXIS FOR HEREDITARY ANGIOEDEMA. Annals of Allergy, Asthma and Immunology. 2022;129(5 Supplement):S29-S30.	Outcomes
Bouillet L, Fain O, Armengol G, Aubineau M, Blanchard-Delaunay C, Dalmas M-C, et al. Long-term prophylaxis in hereditary angioedema management: Current practices in France and unmet needs. Allergy and asthma proceedings. 2022;43(5):406-12.	Outcomes
Bouillet L, Montauban V, Finck K, Jeanbat V, Bouee S. Observational study on the treatment, cost and quality of life of subjects with hereditary angioedema. Value in Health. 2011;14(7):A386.	Outcomes
Burton AE, Lindsay-Wiles I, Herron D, Owen A, Elliott J, Metcalfe A, et al. Hereditary Angioedema patient experiences of medication use and emergency care. International emergency nursing. 2023;71:101339.	Outcomes
Busse P, Caballero T, van Kooten S, Danese S, Goga L. IMPACT OF HEREDITARY ANGIOEDEMA (HAE) ATTACKS ON QUALITY OF LIFE AND ACTIVITIES OF DAILY LIVING. Annals of Allergy, Asthma and Immunology. 2022;129(5 Supplement):S26.	Outcomes
Busse P, Geng B, van Kooten S, Malloy N, Heckmann M, Ulloa J, et al. The Impact of On-demand Treatment on Quality of Life of People with HAE. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB88.	Outcomes
Buttgereit T, Vera C, Weller K, Gutsche A, Grekowitz EM, Aykanat S, et al. Lanadelumab Efficacy, Safety, and Injection Interval Extension in HAE: A Real-Life Study. The journal of allergy and clinical immunology In practice. 2021;9(10):3744-51.	Outcomes
Bygum A, Aygoren-Pursun E, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Burden of Illness in Hereditary Angioedema: A Conceptual Model. Acta dermato-venereologica. 2015;95(6):706-10.	Outcomes
Bygum A, Aygoren-Pursun E, Caballero T, Beusterien K, Gholizadeh S, Musingarimi P, et al. The hereditary angioedema burden of illness study in Europe (HAE-BOIS-Europe): background and methodology. BMC dermatology. 2012;12:4.	Outcomes

Bygum A, Caballero T, Aygo ren-Pu rsu n E, Beusterien K, Hautamaki E, Musingarimi P, et al. The hereditary angioedema burden of illness study in Europe, an innovative and comprehensive study of the patient perspective: Background and methods. Allergy: European Journal of Allergy and Clinical Immunology. 2012;67(SUPPL. 96):196.	Outcomes
Caballero T, Sala-Cunill A, Cancian M, Craig TJ, Neri S, Keith PK, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. International archives of allergy and immunology. 2013;161 Suppl 1:10-6.	Outcomes
Christiansen SC, Busse PJ, Birmingham J, Banerji A, Lumry WR, Zuraw BL. Development of a new tool for assessing health-related Quality of Life (QoL) in patients with hereditary angioedema (HAE): The United States HAE association (HAEA)-QoL. Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB51.	Outcomes
Chularojanamontri L, Kulthanan K, Tuchinda P, Rujitharanawong C, Munprom K, Pochanapan O, et al. The validity and reliability of a Thai version of the Angioedema Control Test: Which recall period is preferable? Asian Pacific journal of allergy and immunology. 2023.	Outcomes
Cicardi M, Craig T, Caballero T, Keith PK, Boccon-Gibod I, Bork K, et al. Current practice with self-administration in the management of hereditary angioedema: The results of a survey. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):613.	Outcomes
Cicardi M, Perego F, Tarricone R, Federici C. Health technology assessment of orphan drugs: The case of hereditary angioedema in Italy. International Journal of Technology Assessment in Health Care. 2017;33(Supplement 1):173-4.	Outcomes
Clifford H, Jones J, Huissoon A. From unemployment to empowerment: A patient's journey to home self-treatment for hereditary angioedema. Clinical and Experimental Immunology. 2013;174(SUPPL. 1):5.	Outcomes
Craig T, Caballero T, Keith PK, Boccon-Gibod I, Bork K, Longhurst H, et al. International practice of self-administration in the management of hereditary angioedema: Survey results and discussion from an international expert panel. Annals of Allergy, Asthma and Immunology. 2013;111(5 SUPPL. 1):A49.	Outcomes
Craig TJ, Schneider LC, MacGinnitie AJ. Plasma-derived C 1-INH for managing hereditary angioedema in pediatric patients: A systematic review. Pediatric Allergy and Immunology. 2015 Sep;26(6):537-44.	Outcomes
Dang M-TT, Ambort A, Arrey-Mensah A. Recurrent swelling and pain in the abdomen and joints in a patient with hereditary angioedema and Ehlers-Danlos syndrome. BMJ case reports. 2019;12(11).	Outcomes

Demir S, Eyice-Karabacak D, Kocaturk E, Unal D, Toprak ID, Korkmaz P, et al. Monitoring recurrent angioedema: Findings from the Turkish angioedema control test validation study. Clinical and translational allergy. 2024;14(3):e12342.	Outcomes
Dempster J. Practicalities of a reduced volume formulation of a C1-INH concentrate for the treatment of hereditary angioedema: real-life experience. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2018;14:44.	Outcomes
Diwakar L, Richter A, Huissoon A, Jolles S, El-Shanawany T. A survey to determine treatment preferences and quality of life of patients with hereditary angioedema. Journal of Clinical Immunology. 2012;32(SUPPL. 1):S143.	Outcomes
Dziewa I, Craig T. Post Marketing Safety Determination for Subcutaneous C1-Inhibitor Prophylactic Treatment in Hereditary Angioedema. Journal of Allergy and Clinical Immunology. 2020;145(2 Supplement):AB104.	Outcomes
Ebo DG, Van der Poorten MM, Van Gasse AL, Schrijvers R, Hermans C, Bartiaux M, et al. Clinical practice of hereditary angioedema in Belgium: opportunities for optimized care. Acta clinica Belgica. 2023;78(6):431-7.	Outcomes
Euctr BE. OPuS2 - A study to assess two doses of BCX4161 in the prevention of HAE attacks in patients over a 12 week period. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2014-002655-26-BE. 2015.	Outcomes
Euctr BG. A clinical trial to assess 2 different doses of BCX7353 compared to placebo as an oral treatment for the prevention of attacks in people with HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-003966-29-BG. 2018.	Outcomes
Euctr CZ. A clinical trial to assess 2 different doses of BCX7353 compared to placebo as an oral treatment for the prevention of attacks in people with HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-003966-29-CZ. 2018.	Outcomes
Euctr DE. OptIMMize-1: a Randomized, Active-controlled, Efficacy Assessor-blinded Study to Evaluate Pharmacokinetics, Safety, and Efficacy of Risankizumab in Patients From 6 to Less Than 18 Years of Age With Moderate to Severe Plaque Psoriasis. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2019-004141-32-DE. 2021.	Outcomes
Euctr GB. A clinical study to assess the efficacy and safety of Lanadelumab to prevent episodes of severe swelling in adolescents and adults. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2019-001703-20-GB. 2020.	Outcomes

Euctr GB. A placebo controlled trial of of three doses of BCX7353 to evaluate the safety and efficacy in the prevention of attacks in patients with HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2015-003923-74-GB. 2015.	Outcomes
Euctr GB. Long Term Safety Study of BCX7353 in HAE. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2017-003281-27-GB. 2017.	Outcomes
Euctr HU. A Study of the Safety and Efficacy of Subcutaneous Administration of Cinryze with Recombinant Human Hyaluronidase for the Prevention of HAE Attacks. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2012-000083-24-HU. 2012.	Outcomes
Euctr HU. BCX7353 for the prevention of HAE attacks. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2016-001272-29-HU. 2016.	Outcomes
Euctr NL. Acute treatment and prophylaxis for acquired angioedema. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2021-000720-36-NL. 2021.	Outcomes
Fain O, Du-Thanh A, Gobert D, Launay D, Inhaber N, Boudjemia K, et al. Long-term prophylaxis with lanadelumab for HAE: authorization for temporary use in France. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2022;18(1):30.	Outcomes
Fu L, Kanani A, Lacuesta G, Waserman S, Betschel S. Canadian physician survey on the medical management of hereditary angioedema. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	Outcomes
Gower RG, Busse PJ, Aygören-Pürsün E, Barakat AJ, Caballero T, Davis-Lorton M, Farkas H, Hurewitz DS, Jacobs JS, Johnston DT, Lumry W. Hereditary angioedema caused by C1-esterase inhibitor deficiency: a literature-based analysis and clinical commentary on prophylaxis treatment strategies. World Allergy Organization Journal. 2011 Dec;4:S9-21.	Outcomes
Gower R, Li HH, Levy DS, Jacobs I. Response to subcutaneous C1-esterase inhibitor (C1-INH [SC]), a prophylactic treatment for adolescents and adults with hereditary angioedema: Results from the phase 3 compact trial. Journal of Adolescent Health. 2018;62(2 Supplement 1):S5-S6.	Outcomes
Greve J. Off-label subcutaneous use of 1500 Ie C1-INH-a new approach for prophylaxis in hae? Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):451.	Outcomes
Greve J, Hoffmann TK, Hahn J. Efficacy of lanadelumab, a monoclonal antibody to plasma kallikrein, in patients with hereditary angioedema type i and ii, outside of controlled clinical trials. Laryngo- Rhino- Otologie. 2020;99(SUPPL 2):S38.	Outcomes

Grigoriadou S, Huissoon A, Kumararatne D, Hackett S, Weldon R, Hughan C. Is there a delay in the diagnosis of primary immunodeficiency (PID)? The "Is it PID?" advisory group. Clinical and Experimental Immunology. 2010;160(SUPPL. 1):8.	Outcomes
Gulbahar O, Gokmen NM, Erdogan AP, Erdogdu D, Koc ZP, Sin AZ, et al. The impact of hereditary angioedema on patients' daily life. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):252.	Outcomes
Honda D, Ohsawa I, Iwanami K, Rinno H, Tomino Y, Suzuki Y. A case of hereditary angioedema due to C1-inhibitor deficiency with recurrent abdominal pain diagnosed 40 years after the occurrence of the initial symptom. Clinical journal of gastroenterology. 2021;14(4):1175-9.	Outcomes
Hurewitz DS. Treatment of acute attacks of type III HAE with ecallantide. American Journal of Rhinology and Allergy. 2012;26(4):341.	Outcomes
Hussain T, Lang S, Dominas N. C1 esterase inhibitor for hereditary angioedema prophylaxis. Otolaryngology - Head and Neck Surgery (United States). 2016;155(Supplement 1):P266.	Outcomes
Jain G, Walter L, Reed C, O'Donnell P. An observational study to understand patient and physician communication in hereditary angioedema (HAE). Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB59.	Outcomes
Jain G, Walter L, Reed C, O'Donnell P, Troy J. How do patients and physicians communicate about hereditary angioedema in the United States? PloS one. 2021;16(12):e0260805.	Outcomes
Jean-Baptiste M, Itzler R, Prusty S, Supina D, Martin ML. The symptom experience of hereditary angioedema (HAE) patients beyond HAE attacks: literature review and clinician interviews. Orphanet journal of rare diseases. 2022;17(1):232.	Outcomes
Jean-Baptiste M, Supina D, Itzler R, Prusty S, Martin ML. Where do we need better assessment to evaluate treatment for hereditary angioedema (HAE)? Quality of Life Research. 2020;29(SUPPL 1):S144.	Outcomes
Jens G, Robin L, Susanne T, Hoffmann TK, Janina H. Efficacy of lanadelumab, a monoclonal antibody to plasma kallikrein, in patients with Hereditary Angioedema Type I and II, outside of controlled clinical trials. Laryngo- Rhino- Otologie. 2022;101(Supplement 2):S249-S50.	Outcomes
Jervelund C, Siersbaek N, Castaldo T, Selva C, Corcoran D, Riedl M, et al. Critical Analysis Reveals Methodological Flaws in a Pilot Study Using Insurance Claims Data to Assess Cost Effectiveness of Prophylaxis Therapies for the Rare Disease Hereditary Angioedema (HAE). Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB186.	Outcomes

Jolles S. Hereditary angioedema-results from a UK national audit. Allergy: European Journal of Allergy and Clinical Immunology. 2012;67(SUPPL. 96):84-5.	Outcomes
Jolles S, Williams P, Carne E, Mian H, Huissoon A, Wong G, et al. A UK national audit of hereditary and acquired angioedema. Clinical and experimental immunology. 2014;175(1):59-67.	Outcomes
Juethner S, Moran K, Sing K, Hatchell N, Earl L, Mellor-Bowman J. Frequency of HAE attacks, clinical outcomes, and quality of life for patients prescribed lanadelumab and other prophylaxis: Analysis of real-world patient data. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):153-4.	Outcomes
Kalamaha K, Fernandes H, Riedl M, Rodrigues J. SUBCUTANEOUS C1-INHIBITOR FOR LONG-TERM PROPHYLAXIS IN HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR. Annals of Allergy, Asthma and Immunology. 2018;121(5 Supplement):S89.	Outcomes
Kalra N, Craig TJ. Treatment of hereditary angioedema at the time of prodromal symptoms: International survey of physicians. Journal of Allergy and Clinical Immunology. 2014;133(2 SUPPL. 1):AB39.	Outcomes
Kaminsky L, Faybusovich P, Craig T. SUCCESSFUL USE OF LANADELUMAB IN ACQUIRED ANGIOEDEMA WITH LOW C1 ESTERASE INHIBITOR. Annals of Allergy, Asthma and Immunology. 2020;125(5 Supplement):S72.	Outcomes
Katelaris CH, Boicos K, Button PH, McCloud PI, Burton PK, Perram FA, et al. Living With Hereditary Angioedema in Australia: Findings From a National Observational Study Using Short Message Service to Monitor the Burden of Disease. The journal of allergy and clinical immunology In practice. 2023;11(8):2457-67.e1.	Outcomes
Katelaris CH, McLean-Tooke A, Nicholls K, Smith W, Perram FA, Drew N, et al. MOVING BEYOND SIMPLE CLINICAL SEVERITY SCALES FOR HEREDITARY ANGIOEDEMA: DEVELOPMENT AND PILOT TESTING OF A MULTIFACTORIAL ASSESSMENT TOOL. Internal Medicine Journal. 2022;52(Supplement 5):28.	Outcomes
Kocaturk E, Degirmentepe E, Gelincik A, Demir S, Aydin O, Baskan EB, et al. The Turkish version of the angioedema quality of life questionnaire and angioedema activity score: Cultural adaptation, assessment of reliability and validity. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):710.	Outcomes
Leibovich-Nassi I, Reshef A, Somech R, Golander H. A survey of hereditary angioedema in Israel. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	Outcomes
Levy DS, Anderson J, Chiao J. Long-term experience with subcutaneous C1-esterase inhibitor prophylactic therapy for hereditary angioedema: Case reports from an open-label extension study. Allergy and Asthma Proceedings. 2018;39(5):401.	Outcomes

Li HH, Scarupa MD. Challenges for hereditary angioedema treatment: When regular use of C1 INH concentrate can not adequately prevent attacks. Annals of Allergy, Asthma and Immunology. 2009;103(5 SUPPL. 3):A141.	Outcomes
Liu S, Zhi Y. Hereditary angioedema: A Chinese perspective. Allergy: European Journal of Allergy and Clinical Immunology. 2018;73(Supplement 105):726-7.	Outcomes
Lumry W, Craig T, Anderson J, Riedl M, Li H, Tachdjian R, et al. Patient outcomes associated with subcutaneous C1INH prophylaxis for hereditary angioedema: a retrospective analysis. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2023;19(1):105.	Outcomes
Lumry W, Davis-Lorton M, Soteres D, Earl L, Hall J, Connolly H, et al. Real-World Treatment Outcomes in Patients With Hereditary Angioedema Receiving Lanadelumab or Other Long-Term Prophylaxis. Journal of Allergy and Clinical Immunology. 2024;153(2 Supplement):AB75.	Outcomes
Magerl M, Sala-Cunill A, Weber-Chrysochoou C, Trainotti S, Mormile I, Spadaro G. Could it be hereditary angioedema?-Perspectives from different medical specialties. Clinical and translational allergy. 2023;13(9):e12297.	Outcomes
Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Klingebiel T, Kreuz W. Clinical surveillance program and management of twenty-five pediatric patients with hereditary angioedema undergoing home treatment. Allergy: European Journal of Allergy and Clinical Immunology. 2011;66(SUPPL. 94):422.	Outcomes
Martinez-Saguer I, Aygoren-Pursun E, Rusicke E, Klingebiel T, Kreuz W. Management of twenty-five pediatric patients with hereditary angioedema (HAE) undergoing home treatmentda clinical surveillance program. World Allergy Organization Journal. 2012;5(SUPPL. 2):S191.	Outcomes
Martinez-Saguer I, Rusicke E, Aygoren-Pursun E, Klingebiel T, Kreuz W. Clinical surveillance program of pediatric hereditary angioedema (HAE) patients undergoing home treatment. Allergy: European Journal of Allergy and Clinical Immunology. 2009;64(SUPPL. 90):389.	Outcomes
Medina I, Josviack D, Berardi A, Cavallo C, Chinigo M, Chorzepa G, et al. Multicenter study on health-related quality of life in patients with Hereditary Angioedema in Argentina: preliminary results. Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):518-9.	Outcomes
Merry A, Heyworth-Smith D, Kennedy C, Robertson S, James L. Quality of life (qol) assessments following the use of prophylactic c1 esterase inhibitor concentrate in patients with severe hereditary angioedema. Internal Medicine Journal. 2017;47(Supplement 5):29.	Outcomes
Morales I, Wuillemin WA, Zeerleder S, Bachmann LM, Jorg L, Ballmer-Weber B, et al. SHAECS: The Swiss Hereditary Angioedema Cohort Study. Swiss Medical Weekly. 2023;153(Supplement 270):20S.	Outcomes

Nina D, Johannes S. Hereditary angioedema - overcome the fear. Laryngo- Rhino- Otologie. 2022;101(Supplement 2):S181.	Outcomes
NI. Oral PHA-022121 for the acute treatment and prophylaxis Of angioedema attacks in Patients with Acquired C1-Inhibitor Deficiency. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=NL9397. 2021.	Outcomes
Nordenfelt P, Bjorkander J, Mallbris L, Lindfors A, Friberg S, Lofdal K, et al. Quality of life and productivity loss in patients with hereditary angioedema (HAE) in Sweden; results from a retrospective patient registry survey implemented by Sweha-Reg (a population based census of HAE in Sweden). Value in Health. 2012;15(7):A557.	Outcomes
Nordmann-Kleiner M, Trainotti S, Hahn J, Greve J. Off-label subcutaneous use of 1500 IE C1-INH for prophylaxis in HAE? A case report. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	Outcomes
Nunes FL, Ferriani MPL, Moreno AS, Langer SS, Maia LSM, Aragon DC, et al. Reduction of acute attacks in patients with hereditary angioedema (HAE) undergoing a multidisciplinary intervention program. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75(SUPPL 109):470.	Outcomes
Ohsawa I, Honda D, Hisada A, Shimamoto M, Inoshita H, Mano S, et al. Current manifestations, diagnosis and treatment of hereditary angioedema (HAE): Survey data from ninety-four physicians in Japan. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70(SUPPL. 101):257.	Outcomes
Ohsawa I, Honda D, Nagamachi S, Hisada A, Shimamoto M, Inoshita H, et al. Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2015;114(6):492-8.	Outcomes
Palasopoulou M, Tsinti G, Germenis AE, Speletas M. Radiation as a trigger of attacks in a misdiagnosed patient with hereditary angioedema and Hodgkin's disease. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	Outcomes
Paulk D, Rigell C, Wedner H. REFRACTORY LIP ANGIOEDEMA RESPONSIVE TO ICATIBANT IN A TEENAGE FEMALE WITH CHRONIC SPONTANEOUS URTICARIA. Annals of Allergy, Asthma and Immunology. 2019;123(5 Supplement):S88-S9.	Outcomes
Pierchalla G, Forster-Ruhrmann U, Magerl M, Olze H, Ellrich A, Stieber C. Causes for smell impairment in patients with hereditary angioedema. Laryngo- Rhino- Otologie. 2018;97(Supplement 2):S376.	Outcomes
Piras V, Alves F, Goncalo M. Self-administration of icatibant in acute attacks of Type I hereditary angioedema: A case report and review of hereditary angioedema. Dermatologic therapy. 2019;32(6):e13098.	Outcomes

Prior N, Caminoa M, Perez-Fernandez E, Gomez-Traseira C, Gaya F, Aabom A, et al. Hereditary angioedema: Clinical differences among countries. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):611-2.	Outcomes
Prior N, Caballero T, Gomez Traseira C, Perez E, Caminoa M, Remor E. Development of an international specific questionnaire for the assessment of health-related quality of life in adult patients with hereditary angioedema due to C1 inhibitor deficiency (IHAE-QoL): Pilot study preliminary results. Allergy: European Journal of Allergy and Clinical Immunology. 2011;66(SUPPL. 94):685.	Outcomes
Prior N, Caballero T, Gomez-Traseira C, Remor E. Multicenter study for the development of an international specific questionnaire for the assessment of health-related quality of life in adult patients with hereditary angioedema due to C1 inhibitor deficiency: Cross-cultural adaptation. Allergy: European Journal of Allergy and Clinical Immunology. 2009;64(SUPPL. 90):284.	Outcomes
Prior N, Remor E, Perez-Fernandez E, Gomez-Traseira C, Caminoa M, Gaya F, et al. Validation of the international quality of life questionnaire for hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):111.	Outcomes
Prior N, Remor E, Gomez-Traseira C, Lopez-Serrano C, Cabanas R, Contreras J, et al. Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-QoL): Spanish multi-centre research project. Health and quality of life outcomes. 2012;10:82.	Outcomes
Riedl MA, Sheridan WP, Noble LJ, Tomita D, Soteres D. Berotralstat demonstrates low hereditary angioedema (HAE) attack rates in patients switching from injectable prophylaxis. Allergy and Asthma Proceedings. 2022;43(6):566.	Outcomes
Riedl M, Sheridan W, Noble L, Tomita D, Soteres D. BEROTRALSTAT DEMONSTRATES LOW HEREDITARY ANGIOEDEMA (HAE) ATTACK RATES IN PATIENTS SWITCHING FROM INJECTABLE PROPHYLAXIS. Annals of Allergy, Asthma and Immunology. 2021;127(5 Supplement):S26-S7.	Outcomes
Robson D, Molloy G, Kimble R. Hereditary angioedema: A case series. BJOG: An International Journal of Obstetrics and Gynaecology. 2015;122(SUPPL. 2):320.	Outcomes
Rosado-Quinones AM, Zaragoza-Urdaz R. Hereditary Angioedema: An Updated Experience with Patients with Angioedema in Puerto Rico. Puerto Rico health sciences journal. 2019;38(4):248-54.	Outcomes
Saguer IM, Ettingshausen CE, Gutowski Z, Linde R. The influence of individualized treatment on the quality of life (QoL) in 100 patients with Hereditary Angioedema (HAE C1-INH). Journal of Allergy and Clinical Immunology. 2018;141(2 Supplement 1):AB51.	Outcomes

Sandberg MT, Svenssson T, Bygum A. Immigrants' perspective on living with hereditary angioedema in Denmark - A qualitative study. Allergy, Asthma and Clinical Immunology. 2019;15(Supplement 4).	Outcomes
Schranz J, Fitts D. Findings of a clinical response survey in physicians caring for patients with hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2014;69(SUPPL. 99):486.	Outcomes
Schranz J, Fitts D, King P. Findings of a clinical response survey in patients with hereditary angioedema. Allergy: European Journal of Allergy and Clinical Immunology. 2014;69(SUPPL. 99):486.	Outcomes
Soteres D, Bernstein J, Kanarek H, Mutschelknaus D, Totev T, Chen J, et al. Real-World Effectiveness of Lanadelumab in Patients With Normal C1-Inhibitor Hereditary Angioedema: A Multicenter Chart Review. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB138.	Outcomes
Soto-Molina H, Vazquez S, Vargas Camano E, Buendia O, Marin Aguilar MM. PCR180 HEREDITARY Angioedema PATIENTS Journey in Mexico a Case Series Report. Value in Health. 2023;26(6 Supplement):S346.	Outcomes
Tachdjian R, Soteres D, Anderson J, Mellor J, Connolly H, Wynne-Cattanach K, et al. Disease Burden and Physician-Reported Outcomes in Pediatric Patients With Hereditary Angioedema: Data From A Real-World Study. Journal of Allergy and Clinical Immunology. 2023;151(2 Supplement):AB142.	Outcomes
Taha O, Abi Melhem R, Taha Y, Kazemzadeh S. Healthcare disparities in a case of a 24-year old female with hereditary angioedema (HAE). Allergy: European Journal of Allergy and Clinical Immunology. 2023;78(Supplement 111):636.	Outcomes
Tallroth GA. Long-term prophylaxis of hereditary angioedema with a pasteurized C1 inhibitor concentrate. International archives of allergy and immunology. 2011;154(4):356-9.	Outcomes
Triggianese P, Raffone G, D'Antonio A, Greco E, Modica S, Bergamini A, et al. MUSCULOSKELETAL ULTRASOUND IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY: PROBING DISEASE ACTIVITY AND DAMAGE. Annals of the Rheumatic Diseases. 2023;82(Supplement 1):1152-3.	Outcomes
Umin. A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema. https://trialsearchwhoint/Trial2aspx?TrialID=JPRN-UMIN000034869. 2018.	Outcomes
Valerieva A, Krusheva B, Dimitrov V, Staevska M. Off-label intramuscular prophylactic treatment with conestat alfa (4200 l/20 mL) in HAE patient with difficult peripheral venous access. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72(Supplement 103):712.	Outcomes

Valerieva A, Krusheva B, Petkova E, Dimitrov V, Staevska M. Off-label intramuscular administration of Conestat Alfa (rhC1inh) in HAE patients: A case series. Allergy, Asthma and Clinical Immunology. 2017;13(Supplement 2).	Outcomes
Van De Graaff J, Fasano MB. A presentation of hereditary angioedema and crohn's disease. Annals of Allergy, Asthma and Immunology. 2015;115(5 SUPPL. 1):A94.	Outcomes
Von Mackensen S, Rusicke E, Cicardi M, Mykal H, Hughan C, Porebski G, et al. Health status and health-related quality of life (HRQoL) in children and adults with hereditary angioedema (HAE). Hamostaseologie. 2010;30(1):A124.	Outcomes
Wang A, Fouche A, Craig TJ. Barriers to the self-administration of medication in the treatment of hereditary angioedema (HAE). Journal of Allergy and Clinical Immunology. 2015;135(2 SUPPL. 1):AB195.	Outcomes
Wang A, Fouche A, Craig TJ. Patients perception of self-administrated medication in the treatment of hereditary angioedema. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2015;115(2):120-5.	Outcomes
Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and validation of the Angioedema Activity Score (AAS). Experimental Dermatology. 2013;22(3):e11.	Outcomes
Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development, validation, and initial results of the Angioedema Activity Score. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(9):1185-92.	Outcomes
Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. Allergy. 2016;71(8):1203-9.	Outcomes
Wiednig M. How does life change in patients with hereditary angioedema after approval of icatibant for self administration. Allergy: European Journal of Allergy and Clinical Immunology. 2013;68(SUPPL. 97):435.	Outcomes

Table 121 shows the publications excluded after full text review, including reasons for exclusion, in the updated search.

Table 121 Publications excluded at full text reviewing, with reasons (n=7) – update review

ID	Reference details of publications excluded	Reason for exclusion
U11	Guan X, Sheng Y, Liu S, He M, Chen T and Zhi Y. Epidemiology, economic, and humanistic burden of hereditary angioedema: a systematic review. Orphanet Journal of Rare Diseases. 2024;19(1):256.	SLR
U3	Busse P, Craig TJ, Radojicic C, O'Connor M, Christiansen S, Ulloa J, Danese S, Andriotti T, Audhya P and Desai V. PCR267 Real-World Impact of Treated Hereditary Angioedema Attacks on Patients' Quality of Life. Value in Health. 2024;27(S6):S346.	Duplicate
U17	Lumry W, Craig T, Anderson J, Riedl M, Henry Li H, Tachdjian R, Manning M, Bajcic P, Rodino F, Wang S and Bernstein J. Retrospective analysis of patient outcomes associated with subcutaneous c1inh prophylaxis for hereditary angioedema. Allergy and Asthma Proceedings. 2024;45(3):212-213.	Outcomes
U20	Ogata G, Nita M, Lopes L, Azevedo C, Wollinger T, Felix T, Sarti FM and P JA-RSG. P1 JAV-RARAS: Preliminary Results of a Real-Life Study through Cost-Utility Analysis in the Brazilian Unified Health System (SUS). Value in Health. 2024;27(S6):S1.	Outcomes
U21	Prada-Moreno V, Wilches-Gutierrez JD and Arias-Osorio DR. [Design and implementation of a transdisciplinary care model for patients with hereditary angioedema, in a Colombian health institution]. Diseno e implementacion de un modelo de atencion transdisciplinaria para pacientes con angioedema hereditario, en una institucion de salud colombiana. 2024;71(1): 80.	Outcomes
U22	Proskurina EV, Morozova NV and Kokushkin KA. Experience of lanadelumab usage for long-term prophylaxis of attacks in hereditary angioedema in patients of the Moscow region. Russian Journal of Allergy. 2024;21(2):254-264.	Outcomes
U23	Radojicic C, Busse P, O'Connor M, Danese S, Ulloa J, Desai V, Andriotti T, Audhya P and Christiansen S. Burden of the Untreated Attacks and Its Impact on Social, Mental and Physical Health. Value in Health. 2024;27(S6):S12.	Outcomes

A local adaption of the SLR was made for the Danish setting. Included studies are shown in Section 5.2. Studies included were the clinical trial in which the HRQoL was converted using the Danish tariff. The second study was a Swedish study used in previous

submission to different Nordic HTA-agencies including DMC. None of the other studies were assessed to be as suitable for the health economic model or as well used as the included studies. The main reason for exclusion were less relevant patient population, e.g. Iranian population. The final sample was deemed to be of high relevance for the decision problem.

I.1.4 Quality assessment and generalizability of estimates

No quality assessment was made on the two included studies.

I.1.5 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

J.1.1 Systematic search for […]

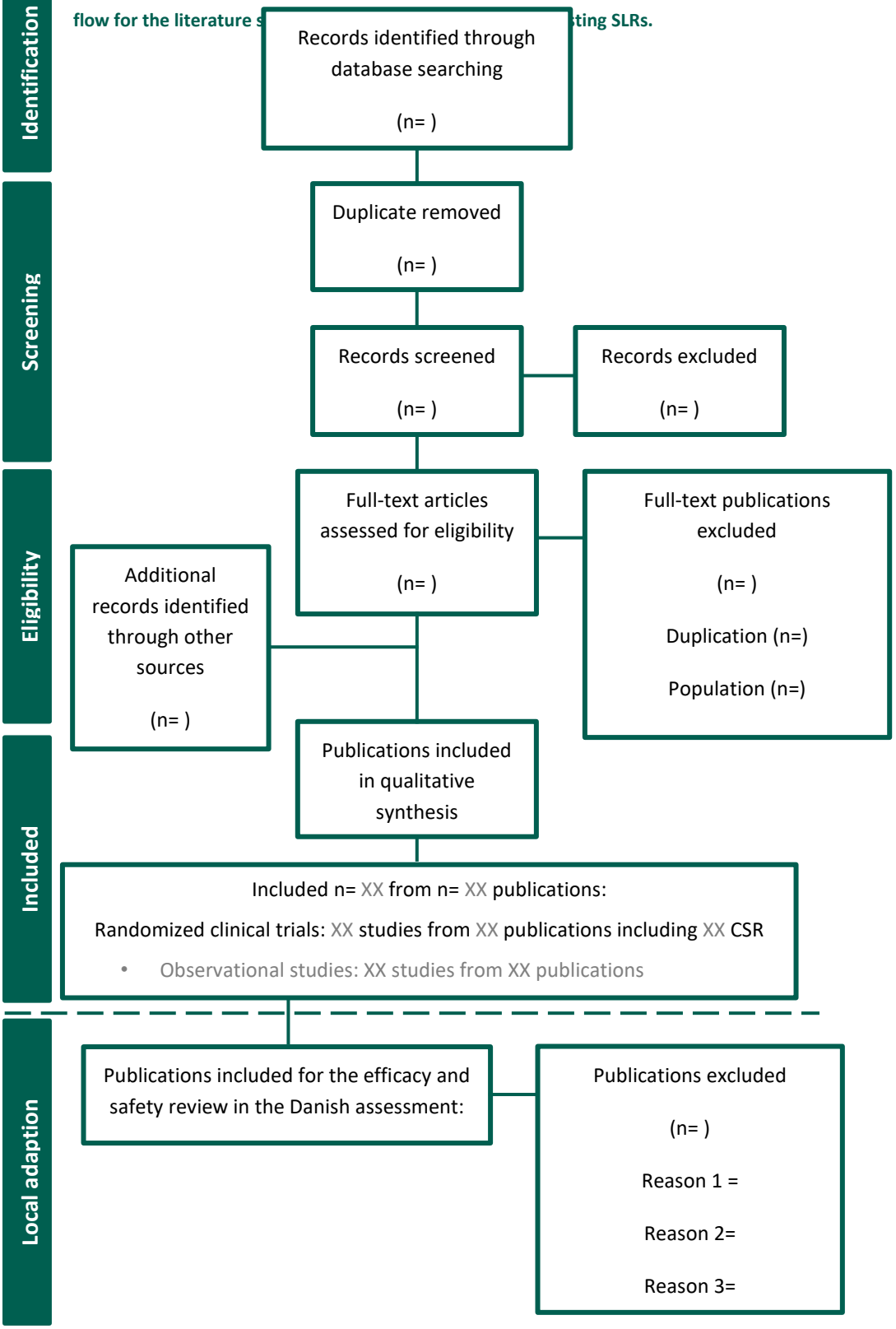
Table 122 Sources included in the search

Database	Platform	Relevant period for the search	Date of search completion
Embase			
Medline			
CENTRAL			

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature s ting SLRs.



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