25 November 2024
EMA/OD/0000133460
EMADOC-1700519818-1812830
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Andembry (garadacimab)
Treatment of hereditary angioedema
EU/3/21/2532

Sponsor: CSL Behring GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Garadacimab
Other name	-
International Non-Proprietary Name	Garadacimab
Tradename	Andembry
Orphan condition	Treatment of hereditary angioedema
Sponsor's details:	CSL Behring GmbH Emil-Von-Behring-Strasse 76 Marbach 35041 Marburg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	CSL Behring GmbH
COMP opinion	5 November 2021
EC decision	10 December 2021
EC registration number	EU/3/21/2532
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Paolo Gasparini / Selma Arapovic Dzakula
Applicant	CSL Behring GmbH
Application submission	27 September 2023
Procedure start	23 November 2023
Procedure number	EMA/H/C/006116
Invented name	Andembry
Proposed therapeutic indication	ANDEMBRY is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. Further information on can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Andembry
CHMP opinion	12 December 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Enrico Costa / Maria Judit Molnar
Sponsor's report submission	14 June 2024
COMP discussion and adoption of list of questions	5-7 November 2024
Sponsor's removal request	19 November 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing garadacimab was considered justified based on preliminary clinical data showing a significant reduction in attacks in patients with the condition;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- the condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing garadacimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a significant reduction in attacks in patients with the condition which compares favourably to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing garadacimab as an orphan medicinal product for the orphan condition: treatment of hereditary angioedema".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hereditary angioedema (HAE) is a rare and severe disorder caused by genetic alterations in the regulation of the kallikrein-kinin pathway.

HAE is classified into 3 disease types; types 1 and 2 involving deficiency or dysfunction of C1-esterase inhibitor (C1-INH) levels respectively, and one type formerly known as type 3 with normal C1-INH (nC1-INH HAE) (Rosen, 1965; Bork et al, 2000). Type 1 HAE is the most common form, accounting for about 85% of HAE cases and type 2 accounts for approximately 15% of HAE cases (Zuraw, 2010). The prevalence of type 3 is currently unknown; however, it is estimated to be significantly less prevalent than types 1 and 2 HAE (Cicardi and Zanichelli, 2010; Nasr et al, 2016).

Clinically, it is characterized by unpredictable episodes of local swelling of the subcutaneous tissue throughout the body, abdominal pain attacks, and occasionally life-threatening attacks of laryngeal edema. The frequency and duration of HAE attacks are highly variable; on average, HAE attacks can occur every 1 to 2 weeks (Bork, 2016).

Garadacimab is a novel fully human IgG4/lambda recombinant monoclonal antibody which binds to the catalytic domain of activated Factor XII (FXIIa and βFXIIa) and inhibits its catalytic activity.

The approved therapeutic indication "Andembry is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older" falls within the scope of the designated orphan condition "Treatment of hereditary angioedema".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

Hereditary angioedema remains a chronically debilitating and life-threatening disease.

The sponsor discussed the life-threatening nature of the disease. The chronic nature of the HAE disease and the unpredictable incidence and severity of HAE attacks profoundly impact patients' quality of life (QoL) (Gower et al, 2011; Craig et al, 2012; Zuraw et al, 2013) and contribute to significant burden of disease. HAE negatively affects educational and professional endeavours, social activities, and mental health (Riedl, 2012). HAE detrimentally affects physical functioning, emotional well-being (ie, inducing depression and anxiety), and productivity at work or school (Lumry et al, 2010). Patients can be debilitated by their symptoms for up to 100 days per year depending on attack frequency, severity, and duration (Gower et al, 2011).

The sponsor also discussed the life-threatening nature of the condition. The potential for life-threatening laryngeal attacks is the most serious concern in HAE because of the risk of asphyxiation (Bork et al, 2003; Bernstein, 2018; Riedl, 2012). Mortality, secondary to laryngeal oedema and asphyxiation, has been reported in up to 30% of patients with previously undiagnosed HAE (Craig et al, 2009). However, the risk of mortality is greatly reduced with more appropriate diagnosis and use of available treatments (Agostoni et al, 2004).

The sponsor did not identify any significant changes in the seriousness of HAE since the orphan designation was granted in 2021. The COMP has previously accepted that the clinical course of HAE can is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia. The severe nature of HAE earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At the time of Orphan designation in 2021, the prevalence was agreed to be approximately 0.5 in 10,000 by the COMP. At that time the sponsor proposed a prevalence of 0.26 in 10,000 and they claimed that the prevalence has not been changed.

A recent systematic literature review and meta-analysis was conducted to estimate the prevalence of HAE (type 1 and 2) in Europe (Aygoren-Pursun et al., 2018). Studies included in the meta-analysis were from Spain, Norway, Denmark, Sweden, Italy and Greece. Individual estimates from these countries ranged from 0.11 to 0.16 per 10,000 persons and the overall prevalence from these countries was estimated as 0.15 per 10,000 persons (Table 1).

Table 1. Meta-analysis: population-based estimates of HAE prevalence

Country	**Spain**	**Norway**	**Denmark**	**Sweden**	**Italy**	**Greece**
Reference	Roche et al, 2005	Stray-Pedersen et al, 2000	Bygum, 2009	Nordenfelt et al, 2014	Zanichelli et al, 2015	Psarros et al, 2014
Reference population	40.5 million	4.5 million	5.5 million	9.3 million	60.8 million	10.8 million
Cases	444	67	76	146	983	116
Calculated prevalence per 10,000 persons	0.11	0.15	0.14	0.16	0.15	0.11

Source: Aygoren-Pursun et al, 2018.

One additional publication from Austria was identified that reported the prevalence of HAE (type 1 and 2) in this country as 0.16 per 10,000 which is consistent with the other published studies from Europe (Schoffl et al., 2018). Assuming the highest prevalence estimates of HAE type 1 and 2 and HAE with normal C1 inhibitor provided in the literature, the overall prevalence is estimated as 0.26 per 10,000 (0.16 per 10,000[HAE type 1 and 2] + 0.10 per 10,000 [HAE with normal C1 inhibitor]).

The COMP acknowledged the limited data published on the HAE and concluded that the prevalence is around 0.5 to be consistent with the initial orphan designation and the most recent designations.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Management options for HAE attacks include on-demand therapy (acute treatment) for individual attacks, long-term prophylaxis (routine prophylaxis), short-term prophylaxis prior to potentially attack-triggering events (e.g., medical or dental procedures), or combinations of these strategies (Maurer et al, 2022).

Consensus guidelines for the management of HAE recommend C1-inhibitors (C1-INH; both plasma derived and recombinant), icatibant, and ecallantide (not licensed in EU) as the on-demand agents of choice (Maurer et al, 2022). For short-term prophylaxis, plasma-derived C1-INH (pdC1-INH) is

recommended as first line of treatment. Long-term prophylactic treatments recommended as first line of choice include pdC1-INH (SC administered Berinert 2000 Berinert 3000 and IV administered Cinryze), SC administered monoclonal antibody to plasma kallikrein lanadelumab (Takhzyro) and orally administered plasma kallikrein inhibitor berotralstat (Orladeyo).

Other therapies, such as attenuated androgens (e.g., danazol) and tranexamic acid are approved in some European countries even though the international WAO/EAACI guidelines recommend them only as second-line treatments for prevention of HAE attacks and pre-procedural prevention in the absence of C1-INH. Danazol and other androgens are contraindicated in younger children (due to the possibility of premature closure of the epiphyses) and in pregnant or breastfeeding women.

Table 2. List of approved HAE treatments in EU

Invented name and active substance or INN	**Route of administration**	**Type of authorisation**	**Indication**	**Satisfactory method**
	On-demand treatment only			
Ruconest rhC1-INH	IV	CP	Treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with HAE due to C1 esterase inhibitor deficiency	No. Garadacimab is authorised for the treatment of routine prevention of recurrent attacks and not the acute attacks.
Firazyr icatibant	SC	CP	Symptomatic treatment of acute attacks of HAE in adults, adolescents and children aged 2 years and older, with C1-INH deficiency.	No. Garadacimab is authorised for the treatment of routine prevention of recurrent attacks and not the acute attacks.
	On-demand treatment, short-term and long-term prevention			
Berinert pdC1-INH	IV (500/1500 IU) SC (2000/3000 IU)	MRP	500/1500 IU IV: HAE type I and II treatment and pre-procedure prevention of acute episodes (all ages) 2000/3000 IU SC: prevention of recurrent HAE attacks in adolescent and adult patients with C1-INH deficiency.	Yes. There is an overlapping of the indications and more specifically the prevention of recurrent HAE attacks in adolescent and adult patients with C1-INH deficiency.
Cinryze pdC1-INH	IV	CP	Treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with HAE. Routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks of HAE, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.	Yes. There is an overlapping of the indications and more specifically the prevention of attacks in adults, and adolescents and children.
	Long-term prevention only			

Invented name and active substance or INN	**Route of administration**	**Type of authorisation**	**Indication**	**Satisfactory method**
Takhzyro Anti-kallikrein human mAb	SC	CP	Routine prevention of recurrent attacks of HAE in patients aged 2 years and older.	Yes. There is an overlapping of the indications and more specifically the routine prevention of recurrent attacks of HAE in patients aged 12 years and older.
Orladeyo Berotralstat	Oral	CP	Routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older.	Yes. There is an overlapping of the indications and more specifically the prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older.
	Long-term prevention nationally approved			
Danazol Danatrol		National FR, ES, EL	Wording of the indication variates according to the national authorisations.	No. Danatrol cover the second line treatment
Tranexamic acid		National ES, EL, CY, MT	Wording of the indication variates according to the national authorisations.	No. Tranexamic acid covers the second line treatment.

C1-INH = C1 esterase inhibitor; CP = centralized procedure; HAE = Hereditary Angioedema; IV = intravenous; pd = plasma derived; MRP = mutual recognition procedure; rh = recombinant human; SC = subcutaneous

In the absence of specific therapies for HAE-nC1-INH, it should be noted that recently approved long-term prevention treatments are approved under the general indication "HAE". The proposed indication for garadacimab is "routine prevention of recurrent attacks of HAE in patients aged 12 years and older". It should be noted that 2 patients with nC1-INH HAE were enrolled in the VANGUARD study, and that these 2 patients showed similar efficacy and had a comparable safety profile as patients with C1-INH HAE in the study.

Based on Table 2 above the COMP concluded that the IV Plasma-derived C1-inhibitor (pdC1)-INH (Cinryze), SC pdC1-INH (Berinert), lanadelumab (Takhzyro) and berotralstat (Orladeyo) are considered as satisfactory methods.

Significant benefit

The sponsor did not request protocol assistance (PA) on significant benefit.

The arguments for the significant benefit were based on the results from the pivotal study 3001. This was a phase 3, multicentre, double-blind, randomized, placebo-controlled, parallel-arm, 26 weeks study investigated the efficacy and safety of garadacimab in adolescent (12 to 17 years, inclusive) and adult subjects with HAE type 1 or type 2, randomized in a 3:2 ratio to either the garadacimab 200 mg sc q4wk active arm (with loading dose 400 mg SC) or the placebo arm, respectively. 64 subjects were treated with placebo (n=25) or garadacimab (n=39). Six subjects aged ≥12 to 18 years were included (2 in placebo arm; 4 in garadacimab arm). Study 3001 subjects were required to have had a documented attack rate of at least in average 1 attack/month (≥ 3 HAE attacks during the 3 months before Screening and at least an average of 1 HAE attack per month during the Run-in Period).

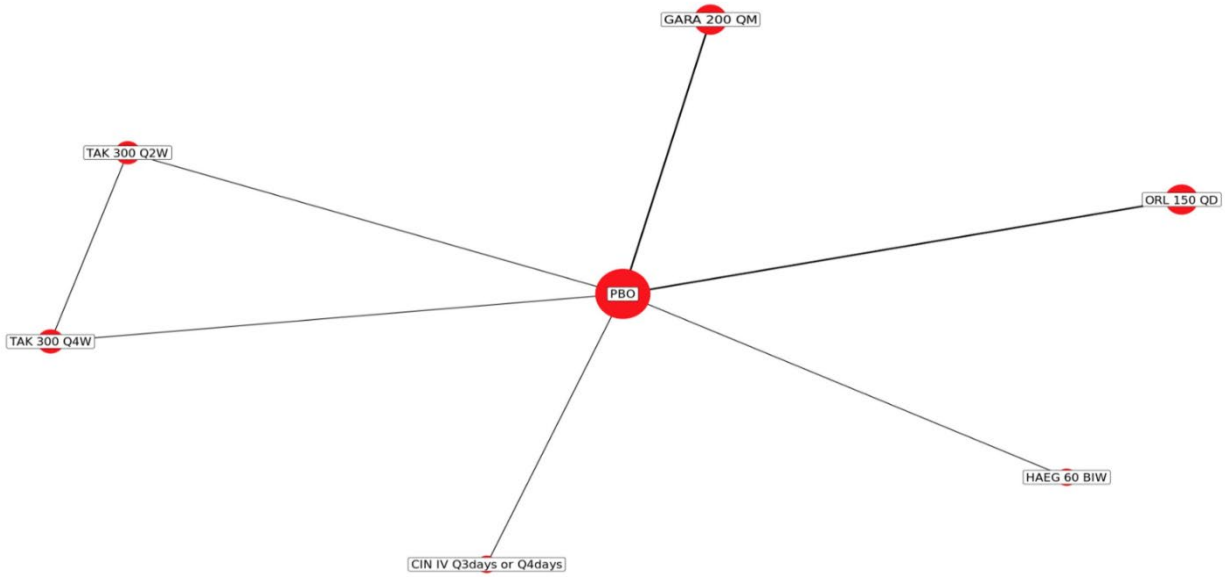
In addition to the indirect comparisons, the sponsor conducted a network meta-analysis (NMA) to estimate the comparative efficacy, safety, and impact on quality of life (QoL) of currently approved prophylactic treatments vs garadacimab. The trials included in the NMA were identified through a systematic literature review (SLR) of RCTs investigating prophylactic treatments in male or female patients (at least 12 years old) with type I or II HAE. Subsequently, a feasibility assessment was undertaken to ascertain the extent of clinical heterogeneity across the studies identified in the SLR. Trial design characteristics, patient eligibility criteria, baseline patient characteristics, outcome characteristics (i.e., definitions and methods of reporting outcomes) were all sources of clinical heterogeneity explored in the feasibility assessment.

The SLR identified 7RCTs investigating licensed doses of long-term prophylactic treatments for HAE that met the inclusion criteria, all were placebo controlled (Table 3). The network diagram is shown in Figure 1. The Cinryze trial was originally excluded as the study population did not meet the inclusion criteria, however, as it was considered helpful to provide data on all comparators, a sensitivity analysis including the CHANGE trial was conducted. The only assessed endpoint for Cinryze was time-normalized number of HAE attacks.

Table 3. Studies Included in the Network Meta- analysis (all placebo controlled)

Intervention	Study Name	Study Phase	Regimen
Garadacimab	CSL312_3001	3	garadacimab 200 mg, SC, once monthly
	CSL312_2001	2	garadacimab 200 mg, SC, once Q4W
Berinert	COMPACT	3	pdC1-INH 60 IU/kg, SC, twice weekly
Berotralstat	ApeX-2	3	berotralstat 150 mg, oral, once daily
	ApeX-J	3	berotralstat 150 mg, oral, once daily
Lanadelumab	HELP-03	3	lanadelumab 300 mg, SC, once Q2W
			lanadelumab 300 mg, SC, once Q4W
Cinryze	CHANGE	3	pdC1-INH 20 IU/kg, IV, every 3 or 4 days

Figure 1. Network diagram for studies included in NMA



Abbreviations: CIN IV Q3days or Q4days = Cinryze intravenously once every three days or once every four days;

GARA 200 QM = Garadacimab 200 mg once monthly; HAE = hereditary angioedema; HAEG 60 BIW = Haegarda 60 IU/kg twice weekly; ORL 150 QD = Orladeyo 150 mg once daily; PBO = Placebo; TAK 300 mg Q2W = Takhzyro 300 mg once every 2 weeks; TAK 300 mg Q4W = Takhzyro 300 mg once every 4 weeks.

- *Comparison of garadacimab versus pdC1-INH Berinert and Cinryze*

The sponsor claimed the significant benefit of garadacimab versus Berinert and Cinryze based on improved efficacy and major contribution to patient care (MCPC).

Improved efficacy

The comparison of efficacy across the clinical trials which was the basis for the approval of the medicinal products is presented in Table 4.

Table 4. Comparative table of efficacy – active treatment arms in phase 3 trials with Cinryze, Berinert and Garadacimab

		pdC1-INH Cinryze[1]	**pdC1-INH Berinert 2000/3000**[10]	**Garadacimab**[5]
Study name		CHANGE	COMPACT	CSL312_3001
Study design		Crossover	Crossover	Parallel
# of patients randomized to treatment		22	45	39
Dosing frequency		1000 IU every 3 or 4 days/wk	60 IU/kg every 3 or 4 days/wk	200 mg Once a month
Volume/route of administration		10 ml IV injection	8-12 ml SC injection	1.2 ml SC injection
Treatment period		12 weeks	16 weeks	6 months (182 days)
Run-in period: mean attack rate/month		N/A	4	3.07
Efficacy endpoints	**Mean HAE attack rate/month (95% CI)**	2.1 (1.5,2.97)	0.52 (0.00,1.04)	0.27 (0.05, 0.49)
	Mean reduction in attacks vs placebo	50.3% (GEE modelling, within subject)	84% (Within subject)	89%[8] (GLM)
	% of patients attack-free over entire trial period (duration)	18.2%	40%	62%
	% of patients attack-free for the first 3 months of treatment period	N/A	N/A	72%
	% of patients experiencing ≥50%, ≥70%, ≥90% reduction in monthly HAE attack rates compared to Run-in Period	50%	91%	95%
		46%	84%	92%
		18%	57%	74%
	HAE attack rate/month Rate ratio estimate vs placebo (95% CI)	0.49 (0.36, 0.68)	N/A	0.119 (0.05, 0.24)
	Time to first attack	N/A	N/A	Third quartile – 72 days
	Attack severity	N/A	17 (37.7%)	25.6%

	# of patients with moderate or severe HAE attacks, n (%)			

[1] Zuraw et al, 2010; 5 Craig et al, 2023; 8 87% is the mean reduction resulting from the primary endpoint estimates; The percent difference in the LS means from a GLM is 89%; 10 Bernstein et al, 2019 and CSR CSL830 (Annex 8).

According to the sponsor, garadacimab was numerically better on all efficacy endpoints compared to Cinryze (Table 2). Assuming a consistent attack pattern for the placebo arm, beyond 12 weeks, the efficacy inter-trial comparison favours garadacimab. The proportion of patients attack-free in the Cinryze pivotal trial was lower (18.2% during the 12-week treatment period) than the proportion of patients attack-free in the garadacimab study (62% during the 6-month treatment period). It can therefore be predicted that over a treatment period longer than 12 weeks the percentage of patients attack-free under treatment with Cinryze would decrease further.

When comparing garadacimab to Berinert 2000 and 3000, the results showed that the attack reduction vs placebo and proportion of responders (i.e., at least 50% attack reduction) were numerically comparable to garadacimab. In addition, a numerically higher proportion of garadacimab treated patients had ≥70% and ≥90% reduction in HAE attacks vs the run-in (92% and 74%, respectively) compared with Berinert (87% and 54%, respectively). Finally, a numerically higher proportion of patients treated with garadacimab were attack-free (62% during the 6-month treatment period) compared with Berinert treated patients (40% during the 16-week treatment period).

The sponsor also presented the results of the NMA. The only assessed endpoint for Cinryze was time-normalized number of HAE attacks. The pairwise comparisons of the treatment effects for plasma derived C1-INH Versus garadacimab for each endpoint are presented in Table 5.

Table 5. Pairwise Comparison of Treatment Effect of pdC1-INH vs Garadacimab

	Treatment effect	**Berinert 60 IU/kg BIW**	**Cinryze 20 IU/kg Q3D/Q4D**
Time-normalised number of HAE attacks	RR (95% credible interval)	0.67 (0.46 to 0.99)*	0.24 (0.18 to 0.32)*
Time-normalised number of HAE attacks requiring HAE treatment	RR (95% credible interval)	0.94 (0.59 to 1.52)	N/A
Time-normalised number of moderate and/or severe attacks	RR (95% credible interval)	0.57 (0.34 to 0.95)*	N/A
Proportion of patients attack-free	HR (95% credible interval)	3.43 (0.18 to 63.97)	N/A
Treatment emergent adverse events	HR (95% credible interval)	0.73 (0.3 to 1.75)	N/A
Change from baseline in AE-QoL	Mean difference (95% credible interval)	N/A	N/A

*garadacimab demonstrates statistically significant improvement using a bayesian approach: RR <1 implies that garadacimab is better; HR >1 implies that garadacimab is better; mean difference <0 implies garadacimab is better; n/a, where data is not shown for a particular comparator, there was insufficient data publicly available to include it in the comparision
RR = rate ratio; HR = hazard ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; BIW = biweekly; QD = daily; Q3D/Q4D = every 3 or 4 days.

Based on the above results, the sponsor argued that a statistically significant superiority for garadacimab over Cinryze and Berinert on the endpoint time-normalised number of HAE attacks, which was the only assessable endpoint observed for Cinryze. The probabilities of being the best treatment were higher for garadacimab than for Berinert for the endpoints time-normalised number of HAE

attacks, time-normalised number of HAE attacks requiring on demand treatment, and proportion of patients that became attack-free.

MCPC

The sponsor also referred to a recent Real-World Evidence (RWE) survey conducted by the Hereditary Angioedema Association (HAEA) in collaboration with HAE International (HAEi) (Castaldo et al, 2021). It was reported that the use of novel prophylactic treatments (i.e. SC lanadelumab and Berinert), which provide a significant reduction in HAE attack frequency, appears to be linked to meaningful improvements in the quality of life (AE-QoL score) of patients with HAE in comparison to on-demand only use. Garadacimab-treated patients who were attack-free (62%) had a median AE-QoL total score at Day 182 of 2.9, garadacimab-treated patients who were not attack-free had an AE-QoL total score of 11.0 and patients who received placebo and consistently experienced attacks had a median AE-QoL total score of 35.3 at Day 182. However, no comparison on the AE-QoL scores is done for Berinert SC and Cinryze, as these scores are not available.

The sponsor argued that the current prophylactic treatment options have a high frequency of administration, which burdens the patients and may impact treatment compliance (Jin et al 2008). Further, the WAO guidelines state that one of the goals of treatment is to reduce the treatment burden and recommend that patients preferences should be taken into account as LTP in HAE requires a high degree of compliance (Maurer et al, 2022). Garadacimab, with its once-a-month convenient low volume SC administration that is minimally invasive, has the potential of significantly reducing this burden over the course of a life-long treatment and represents a MCPC.

Garadacimab offers a less frequent dosing schedule compared to Berinert and Cinryze. Berinert and Cinryze have a short half-life (Berinert: 32 to 47 hours; Cinryze: 48±10 hours) and thus require frequent dosing (every 3-4 days) to ensure reliable prevention of attacks. This imposes treatment burden on patients with HAE, especially with long-term use.

Furthermore, the sponsor argued that since garadacimab is administered SC, this is a more patient-friendly treatment than Cinryze, which is administered IV.

COMP discussion

The comparison of garadacimab over Cinryze and Berinert is based on indirect comparisons (naïve-side-by-side comparisons and an NMA) that do not adjust for differences in predictive factors between the populations of the underlying studies. Based on the presented data and analysis results, currently a significant benefit has not been robustly demonstrated.

The following issues are still unresolved:

a) A comparison of the baseline characteristics of the CHANGE, COMPACT and CSL312_3001 studies (including the genotypes of the patients) is missing to understand differences in disease severity. The mean HAE attack rate of the placebo arms in CHANGE and COMPACT are approximately 4, as compared to a mean HAE attack rate of 2 in the placebo arm of the CSL312_3001 study, which indicates that a healthier population was included in the CSL312_3001 study. Correspondingly, indirect comparison methods that do not account for differences in populations in prognostic factors are likely biased. The lack of information on the distributions of baseline variables prevents an assessment of the comparability regarding predictive variables and hence, the robustness of the presented analyses is not established.

b) An anchored matching adjusted indirect comparison (MAIC) should be used to compare the relevant endpoints (at least all primary and key secondary endpoints of the pivotal trial), ensuring that

the uncertainty in the effect estimates is quantified and that relevant predictive variables are used for the adjustment. Due to the differences in trial duration, the comparability of the endpoint is critical, and focus should be on endpoints that are normalised by time (e.g. average number of attacks / month).

At least, a MAIC using all the below variables should be conducted. It should be amended by sensitivity analyses exploring the robustness of the results by removing some of these variables from the set of matching variables and adding other potential effect modifiers:

HAE attack rate during run-in, mean (SD)

Weight, <75 kg, %

Age, <40 years, %

Sex, female, %

Age at onset of disease

For each MAIC comparing treatments A and C based on an AB and BC trial that uses a specific set of baseline variables for weighting, the following information should be provided:

1. Variables and method used for re-weighting

   A clear description should be provided of the variables used for re-weighting, the rational for the selection and the statistical method for calculating (i) the parameter estimates for the indirect comparison and (ii) the variance of this estimate.

2. Baseline characteristics

   A table should compare the distributions of all relevant baseline variables (used and not used for weighting) between (i) the unadjusted trial 1, (ii) the adjusted trial (iii) and the comparator trial 2, see template table below.

Table 6.

Aseline Variables	Matching variable	Trial 1 Arm A (N =)	Trial 1 Arm B (N =)	Trial 1, adjusted Arm A (ESS =)	Trial 1, adjusted Arm B (ESS =)	Trial 2 Arm B (N =)	Trial 2 Arm C (N =)
Variable 1 (continuous)	Yes	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Variable 2 (categorical) Category 1 Category 2	Yes	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)	 n (%) n (%)
Variable 3	Yes	…	…	…	…	…	…
Variable 4	Yes						
Variable 5	No						
Variable 6	No						
Variable 7	No						
Variable 8	no						

3. Distribution of weights

   The distribution of weights and re-scaled weights in trial 1 separately for the treatment arms should be presented via histograms and summary measures for the distribution (min, 25% quartile, median, mean, 75% quartile, max, standard deviation).

   Please ensure that the same bin intervals are used across different plots.

4. Effective sample size

   The table shown above should include the effective sample size (ESS) of the re-weighted treatment arms of trial 1, both as an absolute ESS and relative to the original sample size of the respective trial arm.

5. Indirect comparison effect estimates

   The estimate for the difference between treatment A and C should be reported together with the estimated standard error and 95% confidence interval.

c) The robustness of the results from the fixed effects Bayesian network meta-analysis is questionable due to several reasons:

- It is unclear which NMA model in the NMA report corresponds to the results cited by the sponsor. It is assumed, that results from fixed effects meta-analyses have been presented, which is not considered adequate given the below assessment of sources of heterogeneity. In particular, the Deviation Information Criterion is mostly lower for the random effects NMA as compared to the fixed effects NMAs. The sponsor needs to (1) clarify which NMA model corresponds to the presented results, (2) update the results presentations to also include results from random effects NMA, and (3) justify the robustness of the results.
- in Appendix 6, the description of the feasibility of the NMA concludes that: "Given the variation across retrieved definitions of HAE attack, we are unable to determine whether important differences exist and might present validity issues for ITCs."
- the heterogeneity in the placebo response, which differed between trials.
- The treatment periods differ, invalidating comparisons that are not normalized by time, in particular the endpoint of "proportion of trial participants that are attack free over the trial period", or "number of attack-free days".

d) It has not been justified that the estimated benefit establishes a significant benefit.

- <u>Comparison of garadacimab versus berotralstat</u>

The sponsor claimed the significant benefit of garadacimab versus berotralstat based on improved efficacy and MCPC.

<u>Improved efficacy</u>

The comparison of efficacy across the clinical trials which was the basis for the approval of the medicinal products is presented in Table 7.

Table 7. Comparative table of efficacy – active treatment arms in phase 3 trials with berotralstat and garadacimab

		Berotralstat **Orladeyo**[2]	**Garadacimab**[5]
Study design		Parallel	Parallel
# of patients randomized to treatment		40	39
Dosing frequency		150 mg Once a day	200 mg Once a month
Volume/route of administration		2 capsules	1.2 ml SC injection
Treatment period		24 weeks	6 months (182 days)
Run-in period: mean attack rate/month		2.95	3.07
Efficacy endpoints	**Mean HAE attack rate/month (95% CI)**	1.31 (NA)	0.27 (0.05, 0.49)
	Mean reduction in attacks vs placebo	44%[7]	89%[8] (GLM)
	% of patients attack-free over entire trial period (duration)	5%[4]	62%
	% of patients attack-free for the first 3 months of treatment period	N/A	72%
	% of patients experiencing ≥50%, ≥70%, ≥90% reduction in monthly HAE attack rates compared to Run-in Period	N/A	95%
		N/A	92%
		N/A	74%
	HAE attack rate/month **Rate ratio estimate vs placebo (95% CI)**	0.56 (0.41-0.77)	0.119 (0.05, 0.24)
	Time to first attack	N/A	Third quartile – 72 days
	Attack severity **# of patients with moderate or severe HAE attacks, n (%)**	N/A	25.6%

[2] Zuraw et al, 2021; 4 BioCryst, 2021; 5 Craig et al, 2023; 6 Estimation from Figure 1; 7 Based on a negative binomial regression model; 8 87% is the mean reduction resulting from the primary endpoint estimates; the percent difference in the LS means from a GLM is 89%.

Based on the above results the sponsor claimed that garadacimab was numerically better than berotralstat on all efficacy endpoints including the HAE attack rate per month, the attack reduction vs placebo (rate ratio) and proportion of patients attack-free. Of note, only 5% of patients treated with berotralstat (2/40) were attack-free during the 24-week treatment period in contrast to 62% for garadacimab treated patients over the 6 months treatment period.

The sponsor also presented the results of the NMA. Two phase 3 trials for Berotralstat (ApX-2 and ApX-J) as well as the phase 2 (CSL312_2001) and phase 3 trial (CSL312_3001) for garadacimab were included in the NMA. The pairwise comparisons of the treatment effects for plasma derived C1-INH and each endpoint are presented in Table 8.

Table 8. Pairwise comparison of treatment effect of garadacimab vs berotralstat

	Treatment effect	**Berotralstat 150 mg QD**
Time-normalised number of HAE attacks	RR (95% credible interval)	0.18 (0.14 to 0.24)*
Time-normalised number of HAE attacks requiring HAE treatment	RR (95% credible interval)	0.17 (0.13 to 0.23)*
Time-normalised number of moderate and/or severe attacks	RR (95% credible interval)	0.08 (0.05 to 0.12)*
Proportion of patients attack- free	HR (95% credible interval)	19.33 (0.85 to 457.6)
Treatment emergent adverse events	HR (95% credible interval)	0.92 (0.41 to 2.07)
Change from baseline in AE-QoL	Mean difference (95% credible interval)	-17.28 (-29.75 to -4.68)*

*Garadacimab demonstrates statistically significant improvement using a Bayesian approach: RR <1 implies that garadacimab is better; HR >1 implies that garadacimab is better; mean difference <0 implies garadacimab is better; N/A, Where data is not shown for a particular comparator, there was insufficient data publicly available to include it in the comparision
RR = rate ratio; HR = hazard ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; BIW = biweekly; QD = daily; Q3D/Q4D = every 3 or 4 days.

Based on the above results the sponsor argued that in comparison to berotralstat, garadacimab was numerically better with respect to all efficacy parameters. The NMA showed that garadacimab was statistically significantly superior for the endpoints time-normalised number of HAE attacks, time-normalised number of HAE attacks requiring rescue medication and change in AE-QoL.

MCPC

The clinical benefit of garadacimab over berotralstat as reflected in the improvement in AE-QoL total score and each of the domains are shown in Table 9. The observations of the side-by-side comparison of AE-QoL change from baseline scores supports garadacimab's clinically meaningful improvement in the quality of life and as such contributes to demonstrate its MCPC over berotralstat.

Table 9. ANCOVA results for change in AE-QoL least square mean scores (SE) from beginning to end of treatment period by treatment adjusted for baseline scores (ITT Population) and AE-QoL Mean change from baseline scores (SD) treatment

	Total Score	**Functioning**	**Fatigue/Mood**	**Fears/Shame**	**Nutrition**
Garadacimab[1] 200 mg Q4W (n=33)	-27.22 (2.95)	-35.74 (3.73)	-22.75 (3.68)	-29.14 (3.43)	-16.87 (3.49)
Placebo (n=20)	-0.97 (3.79)	1.78 (4.79)	-2.97 (4.74)	-0.67 (4.42)	-0.29 (4.49)
Berotralstat[2] 110 mg QD (n=41)	-12.46 (2.53)	N/A	N/A	N/A	N/A
Berotralstat 150 mg QD (n=38)	-14.59 (2.59)	N/A	N/A	N/A	N/A
Placebo (n=36)	-9.69 (2.64)	N/A	N/A	N/A	N/A

1 post hoc analysis
2 Multidisciplinary review Orladeyo, October 2018.

The sponsor also argued that garadacimab offers a less frequent dosing schedule compared to berotralstat. Berotralstat provides patient convenience for those patients who prefer oral administration; however, the efficacy in the reduction of HAE attacks is relatively modest and there are tolerability concerns associated with gastrointestinal AEs (30% incidence within first month of

treatment) (BioCryst, 2022). According to BioCryst, the 1-year retention rates are approximately 60%, meaning that 40% of patients discontinue berotralstat by 1 year of treatment (BioCryst, 2023). Additionally, the convenience of oral administration did not translate into a QoL improvement for patients, which was not statistically significant compared to placebo.

COMP discussion

The comparison of garadacimab over berotralstat is based on indirect comparisons (naïve-side-by-side comparisons and an NMA) that do not adjust for differences in predictive factors between the populations of the underlying studies. Based on the presented data and analysis results, currently a significant benefit has not been robustly demonstrated.

Currently, the following issues are still unresolved:

a) A comparison and evaluation of the baseline characteristics of the Apex-2 and CSL312_3001 studies (including the genotypes of the patients) is missing to understand differences in disease severity. The mean HAE attack rate of the placebo arms is comparable, which indicates that populations with a similar prognosis have been included. However, the lack of information on the distributions of baseline variables prevents an assessment of the comparability regarding predictive variables and hence, the robustness of the presented analyses is not established.

b) An anchored MAIC should be used to compare the relevant endpoints, ensuring that the uncertainty in the effect estimates is quantified and that relevant predictive variables are used for the adjustment. Please see above for the required reporting of a MAIC. Due to the differences in trial duration, the comparability of the endpoint is critical, and focus should be on endpoints that are normalised by time (e.g. average number of attacks / month).

c) The same comments regarding the NMA as for the comparisons against Berinert and Cinryze apply.

d) It has not been justified that the estimated benefit establishes a significant benefit.

- *Comparison of garadacimab versus lanadelumab*

The sponsor claimed the significant benefit of garadacimab versus lanadelumab based on improved efficacy and MCPC.

Improved efficacy

The comparison of efficacy across the clinical trials which was the basis for the approval of the medicinal products is presented in Table 10.

Table 10. Comparative table of efficacy – active treatment arms in phase 3 trials with lanadelumab and garadacimab

	Lanadelumab **Takhzyro**[3]		**Garadacimab**[5]
Study design	Parallel		Parallel
# of patients randomized to treatment	27	29	39
Dosing frequency	300 mg Q2W	300 mg Q4W	200 mg Once a month
Volume/route of administration	2 ml SC injection		1.2 ml SC injection
Treatment period	26 weeks (182 days)		6 months (182 days)

Run-in period: mean attack rate/month		3.5	3.7	3.07
Efficacy endpoints	**Mean HAE attack rate/month (95% CI)**	0.26 (0.14,0.45)	0.53 (0.35,0.77)	0.27 (0.05, 0.49)
	Mean reduction in attacks vs placebo	87% (GLM)	73% (GLM)	89%[8] (GLM)
	% of patients attack-free over entire trial period (duration)	44%	31%	62%
	% of patients attack-free for the first 3 months of treatment period	48%	38%	72%
	% of patients experiencing ≥50%, ≥70%, ≥90% reduction in monthly HAE attack rates compared to Run-in Period	100%	100%	95%
		88.9%	75.9%	92%
		66.7%	55.2%	74%
	HAE attack rate/month Rate ratio estimate vs placebo (95% CI)	0.13 (0.07,0.23)	0.27 (0.17,0.40)	0.119 (0.05, 0.24)
	Time to first attack	Median: [6] 59 days	Median: [6] 28 days	Third quartile – 72 days
	Attack severity # of patients with moderate or severe HAE attacks, n (%)	44%	48%	25.6%

[3] Banerji et al. 2018; 5 Craig et al, 2023; 6 Estimation from Figure2; 8 87% is the mean reduction resulting from the primFary endpoint estimates; The percent difference in the LS means from a GLM is 89%.

Based on then above results the sponsor claimed that garadacimab 200 mg Q1M was generally and consistently numerically better in comparison to lanadelumab 300 mg Q4W. In addition, garadacimab's efficacy was numerically similar to lanadelumab 300 mg Q2W in measures related to attack rate and attack rate reduction vs placebo (rate ratio). Furthermore, gradacimab was numerically better with respect to the proportion of patients who became attack-free, the time to first attack and the proportion of patients with moderate or severe attacks which are considered the most important clinically meaningful measures of disease control. Finally, garadacimab was numerically better with respect to the proportion of patients with moderate or severe attacks, and in the efficacy measures of at least 70% and at least 90% attack reduction.

The sponsor also presented the results of the NMA. One phase 3 trial for lanadelumab (HELP-03) as well as the phase 2 (CSL312_2001) and phase 3 trial (CSL312_3001) for garadacimab were included in the network meta-analysis. The pairwise comparisons of the treatment effects for plasma derived C1-INH and each endpoint are presented in Table 11.

Table 11. Pairwise Comparison of treatment effect of lanadelumab vs garadacimab

	Treatment effect	**Lanadelumab 300 mg Q2W**	**Lanadelumab 300 mg Q4W**
Time-normalised number of HAE attacks	RR (95% credible interval)	0.87 (0.58 to 1.33)	0.43 (0.30 to 0.60)*
Time-normalised	RR (95% credible interval)	0.82 (0.52 to 1.30)	0.41 (0.28 to 0.59)*

number of HAE attacks requiring HAE treatment			
Time-normalised number of moderate and/or severe attacks	RR (95% credible interval)	0.50 (0.30 to 0.85)*	0.31 (0.19 to 0.49)*
Proportion of patients attack- free	HR (95% credible interval)	1.65 (0.09 to 28.92)	2.63 (0.15 to 46.03)
Treatment emergent adverse events	HR (95% credible interval)	0.51 (0.21 to 1.27)	0.85 (0.37 to 1.96)
Change from baseline in AE-QoL	Mean difference (95% credible interval)	-7.66 (-21.34 to 6.05)	-11.6 (-25.16 to 2)

*Garadacimab demonstrates statistically significant improvement using a Bayesian approach: RR <1 implies that garadacimab is better; HR >1 implies that garadacimab is better; mean difference <0 implies garadacimab is better; N/A, Where data is not shown for a particular comparator, there was insufficient data publicly available to include it in the comparision
RR = rate ratio; HR = hazard ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; BIW = biweekly; QD = daily; Q3D/Q4D = every 3 or 4 days

Based on the above results the sponsor claimed that garadacimab was statistically significantly superior to lanadelumab Q2W for the endpoint time-normalised number of moderate and/or severe attacks and lanadelumab Q4W for the endpoints time-normalised number of HAE attacks, time-normalised number of HAE attacks requiring on demand treatment and time-normalized number of moderate and/or severe attacks. Garadacimab was numerically better to both lanadelumab Q2W and Q4W dosing regimen on all endpoints. The probabilities of being the best treatment were higher for garadacimab than for lanadelumab in both the Q2W and Q4W dosing regimens for all endpoints in the NMA.

In addition, a matched adjusted indirect comparison (MAIC) was conducted, comparing garadacimab and lanadelumab (300 mg Q2W and 300 mg Q4W), the currently most widely used long-term prophylactic treatment in the EU, in order to further estimate the differences between the treatments, reducing cross trial imbalances in patient and study characteristics based on individual patient data (IPD) from gardacimab and summary-level data (SLD) for the lanadelumab trial. By leveraging IPD, MAICs can effectively correct for some of the observed cross-trial imbalances in patient and study characteristics.

The MAICs utilised individual patient data from the garadacimab placebo controlled RCTs and summary level data from the lanadelumab placebo controlled RCT (Table 12).

Given that none of the patients achieved an attack-free status over the trial period in the placebo arms of Studies CSL312_3001 and CSL312_2001, it was inappropriate to conduct an anchored MAIC. However, since only one patient achieved an attack-free status in the placebo arm of HELP-03, this suggests that prognostic differences across trials may be minimal. Therefore, unanchored MAICs were considered for the proportion of patients being attack-free.

The base case was adjusted for the covariates that were identified as the most important by clinical experts. The covariates adjusted for were baseline HAE attack rate at run-in, body weight (<75 kg), sex, and age (<40 years). The outcome measures included (1) time-normalised number of HAE

attacks, (2) time-normalised number of HAE attacks requiring on-demand treatment, (3) time-normalised number of moderate and/or severe HAE attacks, (4) proportion of attack-free patients.

Table 12. Studies Included in the MAIC

Intervention	Study Name	Study Phase	Regimen
Garadacimab	CSL312_3001	3	garadacimab 200 mg, SC, once monthly
	CSL312_2001	2	garadacimab 200 mg, SC, once Q4W
Lanadelumab	HELP-03	3	lanadelumab 300 mg, SC, once Q2W
			lanadelumab 300 mg, SC, once Q4W

A summary of results of the analyses for garadacimab 200 mg Q1M vs lanadelumab 300 mg Q2W and lanadelumab 300 mg Q4W for each outcome is presented in Table 13.

Table 13. Summary of Results Between Garadacimab Q1M (Studies CSL312_3001, CSL312_2001) vs Lanadelumab Q2W and Lanadelumab Q4W (HELP-03)

Outcome	Treatment Effect	MAIC Results	
		Garadacimab Q1M vs Lanadelumab Q2W	Garadacimab Q1M vs Lanadelumab Q4W
Time-normalised number of HAE attacks	RR (95% CI)	0.55 (0.22, 1.37)	0.29 (0.13, 0.63)*
Time-normalised number of HAE attacks requiring on-demand treatment		0.52 (0.20, 1.35)	0.29 (0.13, 0.66)*
Time-normalised number of moderate and/or severe HAE attacks		0.25 (0.07, 0.84)*	0.15 (0.05, 0.49)*
Proportion of attack-free patients over the trial period**	HR (95% CI)	1.93 (0.92, 4.03)	3.25 (1.45, 7.29)*
AE-QoL change from baseline to day 182	MD (95% CI)	-17.38 (-33.67, -1.08)*	-21.29 (-37.39, -5.18)*
Proportion of patients achieving an MCID >/= 6 points in total score from baseline to day 182	HR (95% CI)	0.97 (0.31, 3.05)	1.52 (0.47, 4.97)

***** values indicate statistical significance in favour of garadacimab 200 mg Q1M and correspond to a two-tailed p-value <0.05.
An RR <1 or an HR >1 indicates an improved outcome for garadacimab 200 mg Q1M relative to comparator.
** Unanchored MAICs were considered for the proportion of attack-free patients.
CI = confidence interval; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; RR = rate ratio.

According to the sponsor, MAIC results showed that garadacimab provides statistically significant additional benefit compared to lanadelumab 300 mg Q2W for time-normalised number of moderate and/or severe HAE attacks and AE-QoL change from baseline to day 182 and was numerically better on all other endpoints except proportion of patients achieving an MCID >/= 6 points in total score from baseline to day 182. MAIC results for garadacimab vs lanadelumab 300 mg Q4W were statistically significant in favour of garadacimab 200 mg Q1M for all endpoints except proportion of patients achieving an MCID >/= 6 points in total score from baseline to day 182 where Garadacimab was numerically favourable.

MCPC

A recent Real-World Evidence (RWE) survey conducted by the Hereditary Angioedema Association (HAEA) in collaboration with HAE International (HAEi) (Castaldo et al, 2021) reported that the use of novel prophylactic treatments (i.e. SC lanadelumab and Berinert), which provide a significant reduction in HAE attack frequency, appears to be linked to meaningful improvements in the quality of life (AE-QoL score) of patients with HAE in comparison to on-demand only use. According to Castaldo et al, 2021, among those receiving existing prophylactic therapies (Berinert or lanadelumab) who were attack free for one month, the median AE-QoL total score was 16.2 (IQR: 6.3-33.8) whereas for those who were attack free for three months, the median AE-QoL total score was 11.8 (IQR: 2.2-31.6) (note: lower scores indicate less impairment; score ranges from 0-100). Acknowledging the limitations of data and conclusions generated from RWE studies, the survey conducted by Castaldo et al., provides additional context and insight into the attributes of prophylactic treatments that would translate into clinically relevant benefits recognized by patients.

Garadacimab-treated patients achieved a numerically higher reduction from baseline compared to lanadelumab Q2W-treated patients in the AE-QoL total score and in the domains of fatigue/mood and fears/shame. The proportion of patients achieving a Minimal Clinical Important Difference (MCID), which indicate a meaningful change to a patient, was also higher for garadacimab compared to lanadelumab Q2W for the total score and for the domains functioning, fatigue/mood and fears/shame.

Compared to lanadelumab Q4W, garadacimab's AE-QoL scores reduction from baseline was numerically better for the total scores as well as for the domains of functioning, Fatigue/Mood and Fears/Shame. The proportion of patients achieving MCID was numerically better for garadacimab for the total score and for all individual domains (Table 14).

Table 14. Comparison of percent of patients achieving MCID by domain for garadacimab 200 mg Q1M, lanadelumab 300 mg Q2W, and lanadelumab 300 mg Q4W

Domain	**Garadacimab** [1] 200 mg Q4W (N=39) **(to Day 182)**	**Lanadelumab**[2] 300 mg Q2W (N=27) **(to Day** 182)	**Lanadelumab 300 mg Q4W (N=29) (to Day 182)**
Total Score	87.9%	81%	63%
Functioning	90.9%	81%	78%
Fatigue/Mood	72.7%	54%	67%
Fears/Shame	81.8%	73%	67%
Nutrition	66.7%	65%	52%

1 post hoc analysis
2 Lumry et al. 2021

Consistent with the literature, the impact of the large percentage of subjects being attack free who were treated with garadacimab are observed together with an improvement in the AE-QoL which was greater than with marketed prophylactic treatments including SC lanadelumab and Berinert. Garadacimab-treated patients who were attack-free (62%) had a median AE-QoL total score at Day 182 of 2.9, garadacimab-treated patients who were not attack-free had an AE-QoL total score of 11.0 and patients who received placebo and consistently experienced attacks had a median AE-QoL total score of 35.3 at Day 182.

The clinical benefit of garadacimab over lanadelumab as reflected in the improvement in AE-QoL total score and each of the domains are shown in Table 15.

Table 15. ANCOVA results for change in AE-QoL least square mean scores (SE) from beginning to end of treatment period by treatment adjusted for baseline scores (ITT Population) and AE-QoL mean change from baseline scores (SD) treatment for garadacimab, lanadelumab and placebo

	Total Score	**Functioning**	**Fatigue/Mood**	**Fears/Shame**	**Nutrition**
Garadacimab[1] 200 mg Q4W (n=33)	-27.22 (2.95)	-35.74 (3.73)	-22.75 (3.68)	-29.14 (3.43)	-16.87 (3.49)
Placebo (n=20)	-0.97 (3.79)	1.78 (4.79)	-2.97 (4.74)	-0.67 (4.42)	-0.29 (4.49)
Lanadelumab[3] 300 mg Q4W (n=29)	-17.38 (18.67)	-24.29 (22.67)	-13.66 (23.22)	-16.3 (23.71)	-13.34 (22.32)
Lanadelumab 300 mg Q2W (n=27)	-21.29 (18.35)	-35.97 (22.29)	-15.78 (22.79)	-17.59 (23.29)	-18.03 (22.01)
Placebo (n=41)	-4.72 (18.75)	-5.42 (22.72)	-1.79 (23.25)	-9.00 (24.02)	0.51 (22.5)

1 post hoc analysis
3 lumry et al. 2021

Furthermore, the sponsor claimed that garadacimab offers a less frequent dosing schedule compared to lanadelumab Q2W. Recent database analyses in the UK and Germany revealed that nearly 50% of patients are using the Q4W lanadelumab regimen (Dorr, 2023; Martinez-Saguer et al, 2022 prescription data analysis). This highlights the importance of treatment convenience for patients with HAE, potentially leading them to prioritize a less frequent dosing regimen over optimal efficacy. In comparison to ladadelumab Q2W dosing, Q4W lanadelumab has a less favourable efficacy profile. Assuming a 50-year lifespan of living with HAE, in comparison to Q2W dosing, Q1M dosing will result in 700 fewer injection days. From the HAE patient perspective, this equates to nearly 2 additional years without the stress and challenges associated with treating their HAE, including the possibility of experiencing injection site reactions. Once monthly dosing offers HAE patients maximum flexibility and convenience in their HAE treatment. In addition, the recommended starting dose for lanadelumab is 300 mg Q2W, with the option of Q4W dosing for patients who are stably attack free on treatment, as indicated in the SmPC. This may introduce a period of uncertainty for patients as they navigate finding the optimal dosing regimen, potentially adding to the burden of treatment.

COMP conclusion

The comparison of garadacimab over lanadelumab is based on indirect comparisons (naïve-side-by-side comparisons, an NMA and a MAIC) that do not adjust for differences in predictive factors between the populations of the underlying studies. Based on the presented data and analysis results, currently a significant benefit has not been robustly demonstrated with the methodologies used so far.

Currently, the following issues are still unresolved:

a) A comparison of the baseline characteristics of the Help-03 and CSL312_3001 studies (including the genotypes of the patients) is missing to understand differences in disease severity. While the mean HAE attack rates / months are similar, there is a difference in the proportion of patients with a moderate or severe attack, indicating a potential difference between the populations. The lack of information on the distributions of baseline variables prevents an assessment of the comparability

regarding predictive variables and hence, the unbiasedness and robustness of the presented analyses is not established.

b) The above required information for the reporting of anchored MAICs should be provided for the conducted anchored and unanchored MAICs for the comparisons against lanadelumab, in particular e.g. table 5 in annex 7 is not sufficiently describing the distribution of relevant baseline characteristics and does not include variables not used in any of the matching approaches.

c) The same comments regarding the NMA as for the comparisons against Berinert and Cinryze apply.

d) It has not been justified that the estimated benefit establishes a significant benefit.

4. COMP list of issues

Significant benefit

1. A comparison and evaluation of the baseline characteristics (including the genotypes of the patients) in placebo arm and treated populations of the CHANGE, COMPACT, Apex-2, Help-03 and CSL312_3001 studies are missing to understand differences in disease severity. Furthermore, the lack of information on the distributions of baseline variables prevents an assessment of the comparability regarding predictive variables and hence, the robustness of the presented analyses is not established.

2. An anchored MAIC should be used to compare the relevant endpoints, ensuring that the uncertainty in the effect estimates is quantified and that relevant predictive variables are used for the adjustment (please see in the report for the details regarding the required reporting of a MAIC). Due to the differences in trial duration, the comparability of the endpoint is critical, and the sponsor should emphasize on the endpoints which are normalised by time (e.g. average number of attacks/month).