12 December 2024
EMA/15345/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Andembry

International non-proprietary name: garadacimab

Procedure No. EMEA/H/C/006116/0000

Note

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

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Table of contents

1. Background information on the procedure 9
1.1. Submission of the dossier 9
1.2. Legal basis, dossier content 9
1.3. Information on paediatric requirements 9
1.4. Information relating to orphan market exclusivity 9
1.4.1. Similarity 9
1.5. Applicant's requests for consideration 10
1.5.1. Accelerated assessment 10
1.5.2. New active substance status 10
1.6. Scientific advice 10
1.7. Steps taken for the assessment of the product 10

2. Scientific discussion 13
2.1. Problem statement 13
2.1.1. Disease or condition 13
2.1.2. Epidemiology 13
2.1.3. Clinical presentation, diagnosis 13
2.1.4. Management 14
2.2. About the product 15
2.3. Type of application and aspects on development 15
2.4. Quality aspects 16
2.4.1. Introduction 16
2.4.2. Active substance 17
2.4.3. Finished medicinal product 22
2.4.4. Discussion on chemical, and pharmaceutical aspects 28
2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects 28
2.4.6. Recommendation(s) for future quality development 29
2.5. Non-clinical aspects 29
2.5.1. Pharmacology 29
2.5.2. Pharmacokinetics 30
2.5.3. Toxicology 31
2.5.4. Ecotoxicity/environmental risk assessment 38
2.5.5. Discussion on non-clinical aspects 38
2.5.6. Conclusion on the non-clinical aspects 44
2.6. Clinical aspects 44
2.6.1. Introduction 44
2.6.2. Clinical pharmacology 46
2.6.3. Discussion on clinical pharmacology 60
2.6.4. Conclusions on clinical pharmacology 66
2.6.5. Clinical efficacy 66
2.6.6. Discussion on clinical efficacy 96
2.6.7. Conclusions on the clinical efficacy 108
2.6.8. Clinical safety 109

2.6.9. Discussion on clinical safety 119
2.6.10. Conclusions on the clinical safety 126
2.7. Risk Management Plan 126
2.7.1. Safety concerns 126
2.7.2. Pharmacovigilance plan 126
2.7.3. Risk minimisation measures 128
2.7.4. Conclusion 129
2.8. Pharmacovigilance 129
2.8.1. Pharmacovigilance system 129
2.8.2. Periodic Safety Update Reports submission requirements 129
2.9. Product information 129
2.9.1. User consultation 129
2.9.2. Additional monitoring 129

3. Benefit-Risk Balance 130
3.1. Therapeutic Context 130
3.1.1. Disease or condition 130
3.1.2. Available therapies and unmet medical need 130
3.1.3. Main clinical studies 130
3.2. Favourable effects 131
3.3. Uncertainties and limitations about favourable effects 132
3.4. Unfavourable effects 132
3.5. Uncertainties and limitations about unfavourable effects 133
3.6. Effects Table 134
3.7. Benefit-risk assessment and discussion 135
3.7.1. Importance of favourable and unfavourable effects 135
3.7.2. Balance of benefits and risks 136
3.8. Conclusions 136

4. Recommendations 136

List of abbreviations

3F7	Anti-FXIIa parental antibody
AAE-C1-INH	Acquired angioedema
ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ADA	Anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AE-QoL	Angioedema quality of life
AESI	Adverse event of special interest
APS	Aseptic process simulation
aPTT	Activated partial thromboplastin time
ATS	All treated subjects
AUC	Area under the plasma concentration time curve
AUC_{0-inf}	Area under the plasma concentration-time curve extrapolated to infinity
AUC_{0-last}	Area under the plasma concentration-time curve from time of dosing up to the last measurable concentration
AUC_{0-t}	Area under the plasma concentration-time curve from time of dosing up to collection time t
AUC_{tau}	Area under the plasma concentration-time curve in 1 dosing interval
$AUC_{tau,ss}$	Area under the plasma concentration-time curve in 1 dosing interval at steady state
B2R	B2 receptor
βFXIIa	Active catalytic fragment of FXII
BK	Bradykinin
BMI	Body mass index
cHK	Cleaved high molecular weight kininogen
CHO	Chinese hamster ovary
C1-INH	C1-esterase inhibitor
C1-INH HAE	Hereditary angioedema with C1-esterase inhibitor deficiency
CCIT	Container closure integrity test
CDC	Complement-dependent cytotoxicity
CDR	Complementarity determining regions
CFU	Colony forming unit
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Systemic clearance
CL/F	Apparent systemic clearance
C_{max}	Maximum plasma concentration
C_{trough}	Trough plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
CMA	Critical material attributes
CPP	Critical process parameter
CPCS	Combination product control strategy
CPV	Continued process verification

CV	Column volumes
CTD	Common technical document
CSL312	Garadacimab
CSR	Clinical study report
DIPA	Dynamic Imaging Particle Analysis
DoE	Design of Experiment
DP	Drug product
DS	Drug substance
DSP	Downstream process
DXS	Dextran sulfate
EAACI	European Academy of Allergy and Clinical Immunology
E_0	Baseline effect
EBE	Empirical Bayes estimate
EC_{50}	Concentration achieving half-maximal effect
ECG	Electrocardiogram
EFD	Embryo-fetal development
EFF	Extended finger flange
ELISA	Enzyme-linked immunosorbent assay
EPRs	Essential Performance Requirements
EQ-5D-5L	EuroQoL-Group 5-Dimension 5-Level
ER	Exposure-response
FIH	First in human
FIX	Coagulation Factor IX
FXI	Factor XI
FXII	Factor XII
FXIIa	Activated Factor XII
FXII HAE	Hereditary angioedema with normal C1-esterase inhibitor, Factor XII mutation
FXII / PLG HAE	Hereditary angioedema with normal C1-esterase inhibitor, Factor XII or plasminogen gene mutation
Fab	Antigen-binding fragment
FBS	Foetal bovine serum
FAE	Fab-arm exchange
FMEA	Failure mode and effects analysis
GLP	Good laboratory practice
GMP	Good manufacturing practise
GPP	general process parameter
GSPR	General safety and performance requirement
HAE	Hereditary angioedema
HCP	Host cell protein
HMWK (HK)	High molecular weight kininogen
HMWS	High molecular weight species
HRP	Horseradish peroxidase
HSV	Health state utility value
IA	Interim analysis
IGART	Investigators global assessment of response to therapy
IIV	Interindividual variability
I_{max}	Maximum inhibition
INR	International normalised ratio
Ig	immunoglobulin

IP	Intraperitoneal
IV	Intravenous
IPAC	in process acceptance criteria
IPC	In-process control
ISR	Injection site reaction
ITT	Intention-to-treat
IV	Intravenous(ly)
KK	Kallikrein kinin
K	kallikrein
Ka	Association rate
Kd	Dissociation rate
KD	Equilibrium dissociation constant
kDa	Kilodalton
KPPs	Key process parameters
LD	Lactation day
LER	Low endotoxin recovery
LIVCA	Limit of *in vitro* cell age
LLOQ	Lower limit of quantification
LMWS	Low molecular weight species
mAb	Monoclonal antibody
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Affairs
MCB	Master cell bank
MMV	mouse minute virus
NCA	Noncompartmental analysis
nC1-INH HAE	Hereditary angioedema with normal C1-esterase inhibitor
NMR	Nuclear magnetic resonance
NOAEL	No observed adverse effect level
NOR	Normal operating range
NSD	Needle safety device
OL	Open label
OLE	Open label extension
PAR	Proven acceptable range
pd	Plasma derived
PD	Pharmacodynamic
PFS	Prefilled syringe
PIP	Paediatric investigational plan
PK	Pharmacokinetics
PLG	Plasminogen
POC	Proof of concept
PopPK	Population pharmacokinetics
PP	Per protocol
PT	Preferred term
PRM	primary reference material
PS80	polysorbate 80
PTM	post transitional modifications
PPCB	Post-production cell bank
PPQ	Process performance qualification
PV	process validation

POB	Percent of baseline
PopPKPD	Population pharmacokinetics and pharmacodynamics
pcVPC	Prediction-corrected visual predictive check
Q1M	Once monthly
QoL	Quality of life
q2wk	Administered every 2 weeks
q4wk	Administered every 4 weeks
QbD	Quality by design
QTPP	Quality target product profile
RCB	Research cell bank
REO	reovirus type 3
RM	reference material
RRM	research reference material
RSM	reduced scale model
RT	Room temperature
RTTE	repeat time-to-event
RVLP	retrovirus-like particles
SAD	Single ascending dose
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Standard deviation
SAE	Serious adverse event
SERPING1	Serpin family G member 1 gene
SFP	semi-finished product
SGART	Subject's global assessment of response to therapy
SmPC	Summary of product characteristics
SMQ	Standardized Medical Dictionary for Regulatory Affairs Queries
SOC	System organ class
SST	System suitability
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
TEM	transmission electron microscopy
TFF	tangential flow filtration
$t_{1/2}$	Terminal half-life
t_{max}	Time to reach maximum concentration in plasma
TI	Tolerance interval
TOR	Time out refrigeration
TPS	thermal protection system
TP	Treatment period
TQT	Thorough QT
TSQM	Treatment satisfaction for medication questionnaire
UF/DF	Ultrafiltration/diafiltration
ULOQ	Upper limit of quantification
USP	Upstream process
VAS	Visual analogue scale
V_C	Volume of the central compartment
V_P	Volume of the peripheral compartment
VPC	Visual predictive check
V_Z	Volume of distribution during the elimination phase
$V_{Z/F}$	Apparent volume of distribution during the elimination phase

WAO	World Allergy Organisation
WCB	Working cell bank
WFI	Water for injection
WPAI:GH	Work Productivity and Activity Impairment: General Health
WRM	Working reference material
XMuLV	Xenotropic murine leukaemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant CSL Behring GmbH submitted on 27 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Andembry, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2022.

Andembry was designated as an orphan medicinal product EU/3/21/2532 on 10 December 2021 in the following condition: treatment of hereditary angioedema. At the request of the applicant, the medicine was removed from the Community Register of Orphan Medicinal Products on 25 November 2024.

The applicant applied for the following indication: routine prevention of attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0048/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002726-PIP01-19-M03 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 25 November 2024. More information on the COMP's review can be found in the orphan withdrawal assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Andembry.

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance garadacimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
30 April 2020	EMEA/H/SA/4430/1/2020/III	Peter Mol and Elina Rönnemaa
16 December 2021	EMA/SA/0000069852	Fernando de Andrés Trelles and Juha Kolehmainen

The scientific advice assistance pertained to the following quality, non-clinical, and clinical aspects:

- Proposed strategy to establish the commercial shelf life for the drug product pre-filled syringe assembled with a needle safety device and in a pre-filled pen.
- Acceptability of the nonclinical package presented and agreement that no further, specific pharmacology or toxicology studies are necessary to support the registration of the product.
- Acceptability of the design of the proposed single, pivotal phase 3 study in HAE to support an indication for prophylaxis to prevent HAE attacks.
- Agreement was also sought related to the proposed primary endpoint (time-normalised number of HAE attacks) and the planned efficacy analyses to support registration for the target indication, as well as the proposed dose and dosing interval, sample size and study population, including adolescents, for the phase 3 study.
- Acceptability of the safety database including an OLE study CSL312_3002 enrolling both naïve subjects as well as rollover subjects from the previous phase 2 and phase 3 studies.
- Adequacy of the clinical pharmacology package and agreement that no further specific clinical pharmacology studies are necessary to support the registration for the proposed indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paolo Gasparini Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	27 September 2023
The procedure started on	23 November 2023
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	13 February 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	26 February 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	26 February 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	21 March 2024
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A routine GCP inspection was performed at two investigator sites (Germany and Hungary) and the sponsor in the USA. The inspections took place 21 February – 1 March, 18-21 March and 17-24 April 2024 respectively. The outcome of the inspection carried out was issued on 7 June 2024.	7 June 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	26 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	26 August 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	5 September 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	14 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	30 October 2024
The CHMP agreed on a second list of outstanding issues to be sent to the applicant on	14 November 2024
The applicant submitted the responses to the second CHMP list of outstanding issues on	18 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	27 November 2024
The CHMP, in the light of the overall data submitted and the scientific	12 December 2024

discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Andembry on	
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	12 December 2024

2. Scientific discussion

2.1. Problem statement

The claimed indication for garadacimab is: routine prevention of attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

2.1.1. Disease or condition

Hereditary angioedema (HAE) is a rare, autosomal dominant, potentially life-threatening disorder characterised by attacks of cutaneous and submucosal swelling. Most cases of HAE are caused by mutations in the serpin family G member 1 gene (SERPING1), which encodes C1-esterase inhibitor (C1-INH) protein. Mutations in SERPING1 lead to deficient (type I HAE-C1-INH with low antigenic and functional C1-INH levels, ~85% of cases) or dysfunctional (type II HAE-C1-INH with normal (or elevated) antigenic but low functional C1-INH levels, ~15% of cases) C1-INH protein and subsequent dysregulation of the kallikrein–bradykinin cascade, overproduction of bradykinin (BK) and activation of bradykinin B2 receptors. This increases vascular permeability and results in angioedema attacks. These 2 types, caused by deficiency or dysfunction of C1 INH levels, respectively, are referred collectively as C1 INH HAE. However, some patients present with a third type of HAE (HAE-nC1-INH), characterised by an absence of mutations in SERPING1 and normal C1-INH protein. Although mutations in the coagulation factor XII, angiopoietin-1, plasminogen (PLG), kininogen-1, myoferlin, and heparan sulfate-glucosamine 3-O-sulfotransferase-6 genes have been identified in some patients with HAE-nC1-INH, genetic cause is still unknown in other cases, hindering full elucidation of the pathology of this HAE subtype.

HAE is characterised by random and often unpredictable attacks of painful swelling typically affecting the extremities, genitals, bowel mucosa, face, and upper airway. If untreated, swelling is self-limiting and usually resolves spontaneously in 2 to 5 days. 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. Recurrent attacks of cutaneous angioedema (asymmetric, nonpruritic, disfiguring, and nonpitting) without urticaria or spontaneously remitting, severe abdominal symptoms (pain and swelling) or both should alert the clinician to consider hereditary angioedema. Although cutaneous and abdominal attacks are the most common feature, patients infrequently have genital swelling and, in rare cases, bladder, muscle, or joint swelling. Laryngeal episodes account for approximately 0.9% of all attacks; however, all patients are at risk for a laryngeal attack, and more than 50% have a laryngeal attack during their lifetime. The potential for life threatening laryngeal attacks is the most serious concern in HAE.

2.1.2. Epidemiology

The prevalence of HAE is estimated to 1/50,000 subjects.

2.1.3. Clinical presentation, diagnosis

Attacks in HAE are characterised by painful, non-pruritic swelling of the face, larynx, gastrointestinal tract, extremities, and/or genitals, which may last usually up to 5 days. Most patients suffer multiple attacks per year and most patients with HAE experience attacks at multiple sites. Abdominal attacks are painful and debilitating. Peripheral attacks such as those of hands or feet result in impaired

function. Laryngeal episodes account for approximately 0.9% of all attacks; however, all patients are at risk for a laryngeal attack, and more than 50% have a laryngeal attack during their lifetime.

HAE-C1-INH typically develops in childhood (mean age at onset, 8 to 12 years), and usually worsens during puberty.

HAE types I and II are phenotypically indistinguishable. Both types are characterised by low serum C4 levels from activation of the complement cascade, for which C1 inhibitor is a key regulatory protein.

The clinical appearance of HAE-nC1- INH largely resembles that of HAE-1/ 2. There is clinical evidence that bradykinin may play a major role in most types of HAE-nC1- INH, primarily in patients with HAE-FXII and HAE-PLG.

The distinction between angioedema mediated by bradykinin and angioedema mediated by mast cells or histamine is critical, with implications for morbidity, mortality, and treatment.

HAE is a serious condition associated with morbidity that has a substantial impact on day-to-day functioning for patients who suffer from uncontrolled swelling attacks due to their disease. Rapid and severe swelling in the face impairs vision and the ability to speak, eat, or breathe. Acute HAE attacks are potentially life threatening, particularly in cases of laryngeal oedema resulting in airway obstruction.

2.1.4. Management

Currently, there is no cure for HAE. Management options for HAE include on demand therapy (acute treatment) for individual attacks, long term prevention of attacks, short term prevention prior to potentially attack triggering events (i.e., medical, surgical, or dental procedures), or combinations of these therapies. According to the International WAO / EAACI HAE treatment guidelines:

- use of on demand medication should be considered for all HAE attacks, while is mandatory for attacks that affect or that may affect the upper airway

- use of long-term prophylactic treatment should take into account the patient's HAE disease activity, burden, QoL, failure to achieve control with on demand treatment, and their preferences.

In Europe, the medicinal products that are approved in adults and children and recommended for acute treatment (on-demand) of HAE attacks are intravenous C1-INH (plasma derived or recombinant) and icatibant (antagonist of the bradykinin B2 receptor).

For short-term prophylaxis the only approved treatment is intravenous pdC1-INH.

Based on international treatment guidelines, the goals of prophylactic treatment for HAE are to achieve full control of the disease burden and normalise patients' lives and thus minimise the number and severity of HAE attacks, reduce the burden of HAE symptoms, and enable patients with HAE to live a more active and productive life.

Long-term prophylaxis should be individualised and considered in all HAE-1/ 2 patients taking into consideration the disease activity, patient's quality of life, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy. According to the current WAO/EAACI HAE guideline (Maurer 2022) a goal for the LTP of HAE is "to achieve complete control of the disease and to normalise patients' lives".

While for a long time attenuated androgens (e.g. danazol) were the only treatment used to prevent attacks, the landscape of HAE long term prophylaxis has been changing, with the authorisation of new medicinal products such as C1INH ev, C1INH sc (both to be administrated every 3-4 days),

lanadelumab sc Q2W (Q4W) and as the most recent berotralstat (oral daily treatment). Both lanadelumab and berotralstat are based on blocking BK production through targeting different proteins in the kallikrein-kinin pathway. Currently, the guidelines recommend the use of androgens only as second-line long-term prophylaxis.

Antifibrinolytic agents, such as tranexamic acid, were also used, but currently are not recommended for long-term prophylaxis. Data for their efficacy are largely lacking, but some patients may find them helpful. They are primarily used where first-line prophylactic treatment options are not available and androgens are contraindicated.

For long term prophylaxis in children, there are lanadelumab (≥2 years), C1INH ev (≥6 years), C1INH sc (≥12 years), berotralstat (≥12 years).

Limitations of current prophylactic therapies include frequent breakthrough attacks, burden of venous access, high frequency administrations, and occurrence of tolerability issues.

In spite of available medicinal products for the treatment of acute attacks, HAE still is a disorder with high mortality. From the published data it appears that overall, only up to a half of the HAE patients is using the routine prophylaxis with important regional differences. The available data probably do not capture well the currently available new products use, which could also vary due to the national implementation and reimbursement differences. However, it seems to be still an unmet need for treatments that encompass better efficacy and tolerability as well as ease of administration which in return improve QoL.

2.2. About the product

Garadacimab is a fully human IgG4 lambda recombinant monoclonal antibody that binds to activated human coagulation factor XII (FXIIa and βFXIIa). FXII is the first factor activated in the contact activation pathway and initiates the inflammatory bradykinin-producing kallikrein-kinin system. The inhibition of FXIIa prevents the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks, thus blocking the cascade of events leading to an HAE attack.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the following:

The applicant has provided recent data with regard to the characteristics of HAE and the epidemiology of the disease and listed the majority of the existing methods for the long-term prophylaxis of HAE. However, the description of existing treatments is very briefly discussed and is not considered fully adequate; moreover, some options such as antifibrinolytics were not mentioned (although their role is very limited due to the low efficacy). From 2017 onwards the landscape of HAE long term prophylaxis has been changing, with the authorisation of new medicinal products such as Berinert (C1INH sc every 3-4 days, DC procedure by now authorised in 27 MS), followed by Takhzyro (lanadelumab sc Q2W (Q4W), CAP) in 2018 and Orladeyo (berotralstat oral 1 cp/die, CAP) in 2021, therefore potentially satisfying the previous unmet medical need. However, the applicant considers the unmet medical need not fully addressed and the main argument in support of this is that the approved prophylactic therapies are not sufficient to eliminate all HAE attacks in all patients. However, based on the data provided, it could not be ascertained that even garadacimab would be able to reach this goal. It is acknowledged that at present patients unable to tolerate existing treatments or those with suboptimal response to available therapies could represent the potential unmet medical need. However, the

applicant did not attempt to quantify the number of patients which could have insufficient response or are intolerant to existing treatments.

Moreover, the applicant claims the first-line indication, thus referring to a broader target population. In order to further support their arguments, the applicant reports that around one third of the patients from the garadacimab pivotal study were previously using routine prophylaxis with other products. However, only informal feedback from site investigators about reasons for enrolling for the garadacimab study is provided. Moreover, This subpopulation has not been accurately described by the applicant, the study was not designed to assess efficacy of garadacimab in treatment experienced patients and, in addition, this could represent a selection bias in the overall interpretation of the results.

From an indirect comparison of the efficacy results of garadacimab vs Takhzyro (lanadelumab, sc), Orladeyo (berotralstat, oral), Berinert (pdC1INH sc) and Cinryze (pdC1INH iv), it seems that for some efficacy endpoints garadacimab presents numerically better results. Nevertheless, when focusing on comparison between garadacimab and lanadelumab Q2wks, the difference seems more evident only for the frequency of patients attack free for the first 3 months and over the trial period, while other presented results, including the primary endpoint, are overall very similar. However, due to the lack of head-to-head trials, limitations coming from an indirect comparison should be taken into consideration and firm conclusion on the added value of garadacimab over the other available drugs, in particular lanadelumab, cannot be drawn. Moreover, safety data have not been provided and discussed, limiting the contextualisation of garadacimab among the other available treatments.

Overall, while it is agreed that further treatments with different mechanism of action and favourable efficacy and safety profile are welcome in order to implement the treatment armamentarium for a rare and potentially life threating disease like HAE, however taking all the above into consideration, the applicant’s argumentation is not considered sufficient enough to grant an accelerated assessment. Although an unmet need is recognised in a subpopulation insufficiently responder to other treatments, it is not currently considered that this need has been adequately defined/quantified, and this medicinal product cannot be considered as major therapeutic innovation. In the absence of a head-to-head comparison, it cannot be concluded that garadacimab is more effective in eliminating HAE attacks in all patients than other approved therapies.

2.4. Quality aspects

2.4.1. Introduction

The finished product (Andembry) is presented as a solution for injection containing 200 mg of garadacimab as active substance.

Other ingredients are: histidine, arginine hydrochloride, proline, polysorbate 80 and water for injection.

The product is available in two different final combination dosage forms:

- Andembry 200 mg solution for injection in pre-filled syringe (PFS) assembled with an extended finger flange and a needle safety device (NSD);

- Andembry 200 mg solution for injection in pre-filled pen (PFP).

Andembry is available as unit packs containing 1 assembled pre-filled syringe, 1 pre-filled pen and in multipacks containing 3 assembled pre-filled syringes and in multipacks containing 3 pre-filled pens.

2.4.2. Active substance

2.4.2.1. General information

The active substance, garadacimab, is a fully human IgG4 monoclonal antibody that binds to activated human coagulation factor XII (FXIIa). Garadacimab has a structure typical of monoclonal antibodies consisting of two heavy and two light chains, joined by disulfide bonds. The IgG4 heavy chain contains 456 amino acids, and the lambda light chain contains 215 amino acids. The IgG4 heavy chain constant region contains an engineered substitution to stabilise the hinge and prevent half-antibody formation. Garadacimab has a molecular weight of approximately 148.2 kDa. Garadacimab does not have any O-glycosylation sites.

Garadacimab binds to FXIIa, blocking its active site and inhibiting its enzymatic activity. It prevents the activation of prekallikrein to kallikrein and subsequent steps in the kallikrein-kinin cascade including bradykinin production, ultimately preventing episodes of oedema.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured by CSL Behring (Australia) Pty Ltd., Australia. All sites involved in manufacturing and controls of the active substance operate in accordance with EU good manufacturing practice (GMP).

Description of manufacturing process and process controls

The manufacturing process of the active substance follows a classical scheme and includes upstream cell culture production/collection and downstream purification steps. The description of manufacturing process and controls is appropriately detailed.

Briefly, during a series of sub-cultivations, the cells are expanded by using multiple steps until sufficient cells to seed the production bioreactor are reached. The cell culture fluid is harvested from the production bioreactor by filtration resulting in a clarified harvest. Primary capture of garadacimab is performed by chromatography. The resulting capture eluate pool undergoes virus inactivation and filtration, followed by further purification via additional chromatography steps. The eluate pool then undergoes a virus reduction step. Concentration and buffer exchange are performed, and the solution is concentrated to the defined target concentration.

The bulk purified protein is formulated with PS80. The resultant active substance is then filtered into single use bags. The active substance is stored frozen for further processing to the Semi-finished Product.

The active substance manufacturing scale is defined. Each individual step of the process for the manufacture of the active substance is described in detail, including a list of relevant process parameters and in-process controls with target and proven acceptable ranges. The proposed in-process controls (IPCs) are overall acceptable.

Control of materials

Compendial and non-compendial raw materials used in the manufacturing process are of non-animal origin, and the general procedures for their testing and release in order to ensure the quality and safety of the product, are described.

No raw materials of human/animal origin are used during garadacimab manufacturing beside the working cell bank (WCB) which is used as the starting material. To generate an expression construct for production of the garadacimab antibody, the nucleotide sequences encoding the variable region of the garadacimab antibody light chain and the variable region of the heavy chain were synthesised and then cloned into vectors respectively. A Chinese hamster ovary (CHO) cell line is the host cell line used to generate the garadacimab cell substrate. After final clone selection activities, the identified clone was genetically characterised to examine genomic integration, transcript, and sequence integrity.

A two-tiered cell banking system is used for CSL312 and is well described. The description of master cell bank (MCB) and WCB preparation is sufficiently detailed. The strategy for stability monitoring of MCB and WCB is presented. The MCB, WCB and cells beyond Limit of *in vitro* cell age (LIVCA) were characterised and tested in line with ICH Q5D and ICH Q5A(R2) guidelines. The results confirmed tested samples to be free from adventitious agents including bacteria, mycoplasma, fungi and viruses. Genetic consistency studies were performed on MCB and cells beyond LIVCA.

Control of critical steps and intermediates

For each of the different stages of the upstream and downstream production process, the non-critical process parameters (NCPP) and critical process parameters (CPP) are detailed according to the proposed Control Strategy.

IPC, in-process acceptance criteria (IPAC) and critical material attributes (CMA) controls for all the process manufacturing steps have also been reported.

Hold times are stated. Evaluation of the data supporting hold times is included in the dossier. Reprocessing is envisaged in the event of integrity failure of either post-filtration bag assembly or post use integrity filter test. Only a single refiltration step may be performed. This is endorsed. A Protocol for reprocessing is provided within the dossier.

The active substance is stored and shipped frozen. Evaluation of the transport validation data supporting shipping is included in the dossier.

Analytical procedures used for in-process control testing (IPC and IPAC) and validation data of the used methods have been provided. Overall, the description of all analytical methods used for in process testing have been provided as well as confirmation (validation data) that used methods are suitable for its intended purpose.

Control Strategy

The definition of the control strategy has included quality by design (QbD) elements. The totality of the pre-qualification work undertaken to assess the process parameters for the active substance commercial manufacturing process, including parameter risk assessment, process characterisation, and parameter risk mitigation, was then summarised in a process justification report including the process parameters and in-process tests to be confirmed during process performance qualification (PPQ) to consistently manufacture the active substance whilst meeting defined critical quality attributes (CQA). Critical materials assessment was included in the process justification report (PJR).

The active substance process control strategy report incorporates the information from the PJR as well as additional information from specific ancillary studies (e.g., in-process storage conditions and hold times) and facility controls relating to the manufacture of garadacimab. The active substance process

control strategy report was used to generate the active substance process performance qualification (PPQ) protocol.

The overall approach in the definition of the quality attribute (QA) criticality follows a FMEA risk assessment, taking into consideration expected impact on safety, efficacy, PK/PD and immunogenicity combined to uncertainty score, related to prior knowledge available. The criticality of process parameters results adequately assigned.

Process validation

The results presented about the active substance QC testing results, along with the validation studies of the active substance manufacturing process, demonstrate that the process consistently and reproducibly deliver a product of acceptable quality.

The process validation strategy employs a 3-stage risk-based approach to the process validation lifecycle: Stage 1, Process Design, Stage 2: Process Qualification, and Stage 3, Continued Process Verification.

The process design stage resulted in a commercial manufacturing process designed to control sources of process variability to ensure that the CQAs of the active substance are appropriately controlled throughout the product lifecycle. Process performance qualification (PPQ) was performed to verify that the commercial active substance manufacturing process, when operated within the defined ranges, performed effectively and was able to consistently produce the active substance, with the desired quality. Consecutive batches were manufactured to fulfil the PPQ with all evaluated attributes and parameters meeting the predefined acceptance criteria.

The process validation strategy is considered acceptable, and the provided data sufficiently support that the process, when operated within the defined ranges, produced active substance that consistently meets all in-process controls (IPC), in-process acceptance criteria (IPAC) and active substance release specifications. In accordance with the description of the manufacturing process, the validation exercise was performed on all process steps. All results are presented in the dossier, showing that all tested parameters met the requirements.

The applicant has provided results of the PPQ exercise for upstream and downstream active substance manufacturing process for all process parameters.

Chemical stability of in-process hold times, was performed and the outcomes are considered overall satisfactory.

Overall, the manufacturing process could be considered as validated.

For all analytical methods used in PPQ and support validation studies, description of analytical methods has been provided, as well as confirmation that used methods are suitable for their intended purpose.

Manufacturing process development

Manufacturing development history of the active substance is described in narrative and key changes introduced for manufacturing of material for the pivotal clinical study and its rationale are also presented.

No changes were made during manufacturing development to the excipients or their target concentrations used in the formulation.

Comparability studies were conducted to evaluate the impact of the process changes on the product quality attributes.

For the minor changes introduced to the garadacimab manufacturing process after early phases of clinical development a comparative quality study was performed on the active substance using batches from pre- and post-changes of the process. The results demonstrate that quality attributes of active substance batches pre- and post-change are comparable.

Overall, the process comparability can be considered acceptable. Appropriate description of analytical methods used in the comparability exercise has been provided, as well as confirmation (qualification, validation data) that used methods are suitable for its intended purpose.

The comparability exercise is supported by comparative stability data including those from accelerated or stress studies as per ICH Q5E guideline: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

Characterisation

A comprehensive set of state-of-the-art methods was applied to gain a comprehensive understanding of the physicochemical and biological properties of the product, including primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties. The description of the analytical methods used for characterisation, including confirmation (qualification, validation) that the used methods are suitable for their intended purpose, has been provided.

Characterisation of the product related variants, together with forced degradation studies, allowed to distinguish product-related substances and product-related impurities. A list of process related impurities potentially present in the active substance manufacturing process was presented and capability of the process to remove them was even satisfactorily addressed.

Toxicological risk assessment of process-related impurities in garadacimab, were also presented, as well as risk assessments for extractables and leachables, elemental impurities and nitrosamines.

Exhaustive data on the epitope/paratope of garadacimab, have been provided in accordance with the ICH guideline Q6B. Relevant information on the possible interaction of garadacimab with pro-enzyme and clinically important mutated forms is also provided.

Even if garadacimab's mechanism of action is based on the binding/inhibition of FXIIa, relevant data to confirm that garadacimab, as IgG4, does not efficiently mediate Fc-associated effector functions have been provided. Overall, the data provided are in good agreement with the reported literature evaluating interactions between human Fcγ receptors and IgG subclasses.

In summary, the characterisation is considered appropriate for this type of active substance.

2.4.2.3. Specification

The proposed active substance specification includes relevant attributes, i.e. appearance (clarity, colour), pH, identity, protein concentration, potency FXIIa enzyme inhibition assay, polysorbate 80, excipients/amino-acids (L-histidine, L-arginine, L-proline), purity and impurities (product-related impurities; process-related impurities), bioburden and bacterial endotoxins.

All selected parameters are classified as CQAs according to the proposed control strategy.

The proposed panel of methods are adequate for routine control of the active substance both at release and shelf life. They are generally in line with ICH Q6B and Ph. Eur. 2031 monoclonal antibodies for human use.

Purity and impurities (both process-related and product-related) of the active substance are properly estimated by means of a combination of methods.

Specification for charge variants is correctly included to monitor the active substance batch consistency.

FXIIa enzyme inhibition assay is considered acceptable as potency test for garadacimab antibody, whose mechanism of action being based on its ability to bind with high affinity to FXIIa, blocking its active site and inhibiting its enzymatic activity.

Monitoring of L-histidine, L-arginine, and L-proline is properly included in the garadacimab specifications, as storage stability may be compromised when the concentrations of these excipients deviate significantly from the correct concentrations.

Analytical methods

All methods are sufficiently described or alternatively (for compendial analytical procedures) the relevant reference to the European Pharmacopoeia is appropriately cited.

All non-compendial analytical procedures were validated and the results have been provided for consultation and review. The validation parameters performed and reported are overall compliant with ICH Q2(R1).

The Anti-FXIIa potency assay is adequately described.

Batch analysis

The batch analysis results are provided for active substance batches manufactured by the commercial Process for sufficient active substance batches.

All results comply with the proposed active substance commercial release specification criteria. The data provided demonstrates the consistency and uniformity of the active substance and sufficiently confirm that the process is under control.

Reference materials

The applicant presented the approach for establishment of reference standards (RS). For commercial use, a two-tiered RS system will be established. A stability protocol listing the analytical tests for monitoring stability of the reference standards, including a justification for each test, has been provided.

The protocol for preparation, calibration and replacement of the primary and secondary standard for potency assay has been provided. The overall data is considered acceptable.

Container closure

Garadacimab active substance is stored at ≤ -65°C in single use sterilised plastic bag.

The extractables and leachables risk assessment has been provided.

For the primary packaging components and functional components (bag and the stopper), specifications have been provided including testing parameters, analytical methods applied for testing, description and identification, as well as critical dimensions with drawings. With regards to analytical methods, relevant compendia references have been included where applicable, while a short description and summary of validation for non-compendial methods have also been provided.

2.4.2.4. Stability

The claimed shelf-life for the active substance stored at the long-term storage condition of < -65°C is 36 months and it is based on the 36 months real-time, long-term stability data.

The design of long-term, accelerated, and stress studies is appropriate and compliant with the relevant guidelines (ICH Q1A and ICH Q5C).

The post-approval stability protocol and stability commitment provided are adequate and in agreement with the current guidelines.

The data provided support the active substance stability at the claimed condition.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical development

The Andembry (CSL312/garadacimab) finished product is presented in two different final combination dosage forms, as summarised below:

- Andembry 200 mg solution for injection in pre-filled syringe (PFS) assembled with an extended finger flange and a needle safety device (NSD) (also referred in this report as garadacimab DP 200 mg pre-filled syringe NSD);

- Andembry 200 mg solution for injection in pre-filled pen (PFP) (also referred in this report as garadacimab DP 200 mg pre-filled pen).

Andembry is available as unit packs containing 1 assembled pre-filled syringe, 1 pre-filled pen and in multipacks containing 3 assembled pre-filled syringes and in multipacks containing 3 pre-filled pens.

Notified Body Opinions were provided to support the compliance of the device incorporated into either the pre-filled syringe or the pre-filled pen.

Both dosage forms pre-filled syringe and pre-filled pen are provided as solution for subcutaneous injection for single use only.

Garadacimab semi-finished product (SFS) 200 mg, is presented as a sterile liquid solution containing 1.2 mL garadacimab formulated active substance filled in a ready-to-use staked-in-needle pre-fillable glass syringe with rigid needle shield and syringe plunger stopper.

The garadacimab SFP 200 mg contains, besides the garadacimab active substance, PS80, L-histidine, L-arginine monohydrochloride and L-proline solved in water for injection up to 1,2 mL.

The formulation of the garadacimab SFP 200 mg is made by diluting the active substance to a nominal target concentration using a formulation buffer having the same composition as the active substance.

All excipients are generally regarded as safe for use in parenteral products and are widely used as excipients in existing pharmaceutical products containing proteins intended for parenteral administration and are compliant with the current compendial monographs.

The excipients and their concentration in the garadacimab SFP 200 mg are adequately supported by formulation studies. Key physicochemical properties include the pH and osmolality of garadacimab SFP 200mg.

The garadacimab SFP 200 mg contains no preservatives and is manufactured by using an aseptic process.

The sequence of unit operations remained unchanged throughout development of the garadacimab SFP manufacturing process.

Relatively few process changes were introduced to the SFP manufacturing process during development including increase in API concentration, change of container closure and change of manufacturing site.

Prior to commencing the pivotal Phase 3 clinical study, a comparability exercise, applying the release acceptance criteria, was undertaken to determine if garadacimab SFP 200 mg manufactured by the process used for manufacturing of the material for the pivotal clinical study remained comparable to material manufactured by the previous process. Stability studies also confirm that the finished product used for the pivotal clinical study remains stable in the glass PFS.

The development of the garadacimab SFP 200 mg manufacturing process utilised a quality by design (QbD) approach, guided by a quality target product profile (QTPP) and subsequent criticality assessment to identify the CQAs of garadacimab.

A Preliminary Risk Assessment was conducted to identify process parameters in the SFP manufacturing process that could potentially impact garadacimab CQAs. These parameters were then further assessed in process characterisation studies found, in general, adequate.

The description of the control strategy intended to be adopted for garadacimab and the CQA identification process and their criticality assessment, as well as the justification for the garadacimab SFP 200 mg manufacturing process and its control strategy, are described in the dossier.

The activities supporting the development of the manufacturing processes of the two combination products (i.e. garadacimab DP 200 mg pre-filled syringe and garadacimab DP 200 mg pre-filled pen), developed to enable subcutaneous administration, were found in general adequate.

A series of risk assessments were performed to complement the evaluation already performed for garadacimab active substance and semi-finished product (SFP), in order to identify CQAs and essential performance requirements (EPRs) related to the assembly, labelling and packaging unit operation and to derive the relevant process control for the proper functioning of the combination product garadacimab DP 200 mg pre-filled syringe and garadacimab DP 200 mg pre-filled pen.

Comparability studies have also been conducted on the final presentation level, between the SFP and the final pre-fille pen/ pre-filled syringe finished product derived from the same SFP sample. The results showed comparable CQA profiles.

2.4.3.2. Manufacture of the product and process controls

The finished product is released for commercial distribution at CSL Behring GmbH (Germany). All sites involved in manufacturing and controls of the active substance operate in accordance with EU GMP.

Garadacimab SFP 200 mg

The range of batch sizes for garadacimab SFP 200 mg manufacturing process, is defined. The consequent range of theoretical number of PFS has been also provided. A batch numbering system assuring traceability is described.

The semi-finished product (SFP) manufacturing process includes thawing and pooling the active substance, formulation of bulk, sterile filtration, and aseptic filling into prefillable syringes.

The SFP is then used either to be assembled to a pre-filled syringe presentation, or to be assembled to a pre-filled pen presentation.

No reprocessing steps are proposed within garadacimab SFP 200 mg manufacturing process.

The description of the garadacimab SFP 200 mg manufacturing process is overall acceptable and details relative to the CPP, CMA and IPC/IPAC identified are described for the different unit operations.

The finished product manufacturing process initially proposed for SFP 200mg was found deficient from the sterility assurance perspective since a sterile filtration at the Point of Filling (PoF) was missing. This was raised as a major objection during the marketing authorisation application evaluation. The applicant has incorporated a sterile filtration close to the point of filling, thus reaching a full compliance to EP 5.1.1 - Guideline EMA/CHMP/CVMP/QWP/850374/2015 - EU GMP Annex 1 requirements.

In addition, to better consolidate the proposed mitigation measure aiming to strengthen the sterility assurance/contamination control strategy, all the relevant data supporting the introduction of the sterile filtration close to the point of filling have been provided.

Concerning visual inspection activities, 100% of the filling units would undergo manual visual inspection in accordance with Ph. EU 2.9.20 method and an AQL control is performed.

With reference to the control of critical steps for garadacimab SFP 200mg, details provided can be considered overall acceptable.

Details on the "Leak tests" planned to verify the integrity of the mobile stainless-steel vessel containing the final bulk, including relevant acceptable ranges, have been provided.

The execution of the pre-use post sterilisation integrity testing (PUPSIT) IPC as well as integrity test on vent filters has been confirmed.

A Process Performance Qualification (PPQ) has been performed prospectively to verify that the commercial garadacimab SFP 200 mg manufacturing process is able to consistently produce garadacimab SFP 200mg with the desired quality attributes. The process validation exercise was found in general adequate to demonstrate the consistency of the garadacimab SFP 200mg manufacturing process.

Garadacimab DP pre-filled syringe 200 mg / Garadacimab DP pre-filled pen 200 mg

To obtain garadacimab DP pre-filled syringe 200mg, the semifinished product garadacimab SFP 200 mg is assembled with plunger rod, extended finger flange (EFF) and Needle Safety Device (NSD).

The assembly process is largely manual. All assembly steps are external attachments and are not in contact with the liquid product. After assembly, labelling and secondary packaging are performed.

The garadacimab DP 200 mg pre-filled pen manufacturing process includes the assembly of the pre-filled pen sub-assemblies (Syringe Unit and Drive Unit) with the garadacimab SFP 200mg semifinished product. The final packaging and labelling will be performed manually with pre-folded and pre-glued boxes. All assembly steps are external attachments and are not in contact with the liquid product.

None of the manufacturing steps of either garadacimab DP 200 mg pre-filled syringe or garadacimab DP 200 mg pre-filled pen manufacturing processes has been designated as critical and no CPP were identified. IPCs have been identified for both the pre-filled syringe and pre-filled pen assembling processes.

Suitable PPQ exercises were performed to confirm that the manufacturing processes for assembling the garadacimab SFP either to the pre-filled syringe subassemblies or the pre-filled pen performed effectively and were able to consistently produce garadacimab DP 200mg pre-filled syringe or garadacimab DP 200mg pre-filled pen with the desired quality.

Overall, the information and the qualification/validation data provided, adequately support that transport activities within CSL Behring's supply chain foreseen for garadacimab finished products are adequately under control.

2.4.3.3. Product specification

Specification for the applied product is set in accordance with the principles defined in ICH Q6B. Overall, the quality attributes of the product are adequately controlled.

The proposed garadacimab SFP 200 mg specification includes relevant attributes as per Ph. Eur. monographs 2031 "Monoclonal antibodies for human use" and 0520 Parenteral preparations, and ICH Q6B, appearance (clarity, colour), pH, identity, protein concentration, potency by FXIIa enzyme inhibition assay, polysorbate 80, excipients/amino-acids (L-histidine, L-arginine, L-proline), purity and product-related impurities), sterility, bacterial endotoxins, visible and subvisible particles, osmolality and extractable volume. All selected parameters are classified as CQAs according to the proposed control strategy. The proposed specification is mostly aligned with the active substance specification, with addition of parameters related to the specific dosage form (solution for injection). Process-related impurities are tested only at the active substance level, which is acceptable. The acceptance criteria apply at both release and end-of-shelf life for all tests except for the amino acids, which is tested only at release, and size variants, for which separate acceptance criteria is set at release and the end of the shelf life, which is acceptable.

Based on the Process Control Strategy and supportive stability/comparability study, the applicant states that the device assembly, labelling and packaging process have insignificant impacts on garadacimab CQAs.

Therefore, release testing on samples taken from the garadacimab SFP 200 mg are representative of the garadacimab CQAs in the assembled final garadacimab combination products and, thus, only device performance functionality testing is conducted following device assembly of the two final garadacimab combination products. The acceptance criteria for device performance functionality testing of the combination products apply to both, release and end of shelf life.

Analytical procedures

All analytical procedures used in batch release and/or stability testing of SFP are described. The description is acceptable, and the test methods are considered suitable. The analytical procedures used for device functionality performance release testing of garadacimab DP 200mg pre-filled pen and pre-filled syringe are described and detailed.

Several of the analytical procedures used for testing garadacimab SFP 200mg are the same as those used for testing the garadacimab active substance. Since the active substance and garadacimab SFP 200mg have similar excipients and protein concentrations, the validation of these analytical procedures performed using active substance was considered valid for the SFP.

The analytical methods for garadacimab DP 200 mg pre-filled syringe have been tested for repeatability and intermediate precision. All the acceptance criteria have been met.

With regard the validation of functional tests performed for garadacimab DP 200 mg pre-filled pen, all individual sample results were within the relevant Specification Limits and met the acceptance criteria, including visual inspection.

Batch analysis

Batch analysis results are provided for prefilled syringe batches and pre-filled pen batches utilizing and including SFP manufactured according to the process used for the pivotal clinical trial material. In addition, SFP batch analysis results are presented manufactured according to the final commercial process with PoF.

All results comply with the specifications in place at the time of manufacture/time of the batch release. Batches were tested with method employed at the time of release. The test results also meet the proposed commercial release specification criteria. The information is sufficient and acceptable demonstrating consistency in manufacturing.

Characterisation of Impurities

The majority of potential process- and product-related impurities are tested at the active substance stage. Garadacimab SFP 200mg has been assessed for extractables, leachables and elemental impurities, all of which are present at acceptably low levels that pose no risk to patients.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The results of testing elemental impurities after long-term storage are provided in the dossier. The levels detected are ≥ LOQ and the applicant concluded that all detectable elemental impurities remain below the applicable limits.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

Based on the information provided it is accepted that that no risk was identified on the possible presence of nitrosamine impurities in the garadacimab active substance and semifinished product.

Reference materials

Refer to the active substance section.

Container closure

Andembry 200 mg solution for injection in pre-filled syringe consists of a 1.2 mL of solution in a pre-filled glass syringe (type I glass) with a bromobutyl stopper, 27G x 1/2 5B special thin-walled (STW) staked needle, and is assembled with an extended finger flange and needle safety device.

Andembry 200 mg solution for injection in pre-filled pen consists of a 1.2 mL of solution in a pre-filled glass syringe (type I glass) with a bromobutyl stopper, 27G x 1/2 5B special thin-walled (STW) staked needle, assembled with a pen.

The applicant confirms compliance with Ph. Eur. Monographs for all the relevant container closure components. Specifications, analytical methods, technical drawings and photographs were submitted as well as the relevant certificates of compliance.

A brief description of instruction for use and the key operation steps for a correct use of the integral medicinal products is provided. The applicant confirms that the containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life.

The site of sterilisation of containers as well as the responsible site performing sterilisation of plungers is provided. In addition, information for the sterilisation method, cycle of primary package components and relevant standard conformity is presented.

Notified Body Opinions were provided to support the compliance of the device part incorporated into either the garadacimab prefilled syringe (PFS) with needle safety device (NSD) or the garadacimab pre-filled pen, to the relevant GSPRs in Annex I of the Medical Device Regulation.

2.4.3.4. Stability of the product

The applicant proposed a shelf-life of 3 years for the garadacimab SFP 200mg assembled into either pre-filled syringe or pre-filled pen when stored at 5°C±3°C.

Photostability studies were conducted but not completed on batches of garadacimab SFP. The currently available pre- and post-light exposure results of these studies shows changes in the quality of garadacimab when exposed to light. Data for the remaining study time points are yet to be obtained, however data to date show some sensitivity to light exposure already. However, the patient instructions for use for the product include a statement to avoid exposure to light.

The finished products shelf life of 3 years at 5°C±3°C as stated in the SmPC is accepted based on the real-time stability data obtained on batches manufactured before introduction of the sterile filtration step at point of filling.

The applicant has introduced PoF sterile filtration batches in the stability studies as well and has committed to notify the regulatory authority in case of any out of specification (OOS) results and to provide the confirmatory stability study results for CSL312 SFP 200mg manufactured according to sterile filtration at point of fill for annual time points (12, 24, 36 months) as they become available (recommendation).

The finished product may be stored at room temperature (up to 25°C) for a single period of up to 2 months, but not beyond the expiry date.

2.4.3.5. Adventitious agents

Adventitious agents safety evaluation

Garadacimab complies with TSE and viral safety guidelines. No animal-derived materials or materials containing substances of animal origin are used in the DS manufacturing process, apart from the CHO cells. Also, no raw materials of animal origin were used in the manufacture of MCB or WCB. FBS was used during historical derivation of cell line. However, appropriate controls were therefore included in the MCB testing. The TSE risk is adequately addressed.

MCB, WCB and cells beyond the limit of in-vitro cell age used for production have been tested for sterility, mycoplasma and for presence of viruses.

The capacity of the garadacimab manufacturing process to inactivate and/or remove deliberately spiked infectious viruses was evaluated in studies performed using a panel of adequate viruses and a qualified scale down model of the respective virus inactivation or virus reduction process steps

Chosen viruses represent specific models for viruses known / found to contaminate cell line, relevant models for viruses that could likely contaminate cells and non-specific models for the general characterisation of manufacturing process robustness in virus clearance. The approach is supported.

The laboratory scale models used in this study were qualified to mimic the production scale.

For viral inactivation studies the volume of virus added is less than 10% as requested in the CPMP/BWP/268/95 guideline. The applicant has provided respective data confirming alignment with the CPMP/BWP/268/95 guideline.

The data presented demonstrates effective reduction of a broad range of viruses. A safety factor for the removal of Retrovirus like Particles (RVLP) was calculated based on the TEM results of RVLP levels.

Overall, the safety factor for the removal of RVLP is considered acceptable.

2.4.3.6. GMO

Not applicable

2.4.4. Discussion on chemical, and pharmaceutical aspects

From the quality point of view, the medicinal product Andembry is recommended for approval as all issues are resolved.

The active substance manufacturing process is sufficiently described, and process parameters and in-process controls are stated and considered largely acceptable. The approach used for the development of the active substance manufacture control strategy has used QbD elements, and is considered overall appropriate, also considering the criticality status assignment to process parameters. With respect to the characterisation, further information on the epitope involved in the target binding and in the demonstration of absence of effector function mediated by the mAb Fc region have been provided and found adequate.

The active substance process development has been described. The comparability between the two process versions has been adequately supported by comparative stability data. The Pivotal Phase III trial has been performed using the same active substance manufacturing process as used for production of commercial material.

The data for PPQ studies are presented and overall confirm that process reproducibly deliver an active substance.

The finished product manufacturing process is typical for monoclonal antibodies, mostly properly characterised, controlled and validated. However, a major objection was identified due to the lack of a sterile filtration step as close as possible to the point of filling. To further strengthen the robustness of the garadacimab SFP 200mg manufacturing process from the sterility assurance/contamination control strategy perspective, the applicant has incorporated a sterile filtration close to the Point of Filling.

The proposed active substance and finished product specifications include parameters commonly encountered for a monoclonal antibody and the active substance and finished product presentations.

The data overall indicate that the active substance and finished product are stable at the proposed stability conditions and along the claimed shelf life. The applicant committed to provide the confirmatory stability study results for garadacimab SFP 200mg manufactured according to sterile filtration at point of fill for annual time points (12, 24, 36 months) as they become available (recommendation).

The overall viral safety of garadacimab is considered satisfactory, the data provided give sufficient assurance regarding non-viral adventitious agents (risk of contamination with animal TSE) and viral adventitious agents aspects.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to provide the confirmatory stability study results for garadacimab SFP 200mg manufactured according to sterile filtration at point of fill for annual time points (12, 24, 36 months) as they become available.

2.5. Non-clinical aspects

2.5.1. Pharmacology

2.5.1.1. Primary pharmacodynamic studies

In *in vitro* studies, the inhibitory activity of garadacimab was assessed by using contact activated plasma from human donors as well as that of patients with HAE (types I/II/III) and acquired angioedema. Garadacimab has been seen to inhibit FXIIa chromogenic activity and bradykinin generation as well as FXIIa activity in contact activated plasma from cynomolgus monkey, rabbit and mouse. Garadacimab affinity is cross reactive with mouse, rabbit and cynomolgus βFXIIa (700pM, 400pM and 19nM respectively). In all interactions tested garadacimab showed tighter affinity to both FXII zymogen and βFXIIa than the parental 3F7 mAb.

Garadacimab inhibits enzymatic activity of human plasma-derived FXIIa and FXIIa in an *in vitro* chromogenic assay at equivalent levels with IC50 of ~15 nM. Garadacimab is able to inhibit FXIIa activity in human plasma in a dose dependant manner, with similar concentrations of drug required as observed in normal plasma samples. Both garadacimab and parental 3F7 antibody showed a prolongation of aPTT clotting time in standard human plasma. However, as a result of the affinity maturation, garadacimab was more potent at prolonging aPTT in comparison to parental mAb 3F7. Cynomolgus monkey showed similar FXII activity to that of human as evident by the high OD at the 0 ug/ml CSL312 concentration.

In contrast, both mouse and rabbit showed much lower FXII activity, the lack of binding to rat FXII being likely due to lysine residues at both positions 397 and 437. Prolongation of aPTT has been shown, demonstrating the garadacimab (or the parental 3F7 antibody) pharmacological activity. No inhibition was observed in rat plasma indicating that garadacimab is not cross reactive to rat FXII.

Taken together, data demonstrate that garadacimab is a cross-species (excluding rat) FXIIa inhibitor. Furthermore, garadacimab is able to inhibit FXIIa activity in the plasma of patients affected by HAE in a dose dependent manner.

In vivo, FXIIa inhibition by garadacimab or 3F7 was accompanied by inhibition of bradykinin-mediated oedema formation in mouse models. In C1-INH-deficient mice both anti-FXII mAbs, the parental mAb 3F7 and the affinity enhanced mAb garadacimab markedly inhibited ACEI-induced increase of vascular permeability. As little as 0.1 mg/kg of the antibodies showed significant reduction in permeability, while a complete ablation of the vascular leakage was observed at doses ≥0.5 mg/kg.

In a model of Passive Cutaneous Anaphylaxis (PCA), treatment of mice with garadacimab and 3F7 led to inhibition of mast cell heparin-induced oedema, although less potently when compared to 3F7.

Overall, garadacimab was effective in attenuating the effects of FXIIa activation in two representative animal models of HAE.

2.5.1.2. Secondary pharmacodynamic studies

In vivo studies assessed the inhibition of experimental thrombosis in mice and rabbits (effect deriving from the mode of action of the compound), without increasing bleeding risk.

In a FeCl3-induced arterial occlusion mouse model, garadacimab i.v. at 2.5 mg/kg dose exhibited a strong anti-thrombotic effect. An increase in dose of garadacimab led to a concomitant increase in mean aPTT and decrease in mean FXIIa activity in the terminal mouse plasma samples, further supporting pharmacological activity of garadacimab in the treated animals, whilst no effect on PT was observed.

Garadacimab given i.v. to rabbits at 10 mg/kg, protected from FeCl3-induced arterial thrombosis, while stasis-driven venous thrombosis was unaltered in a simultaneous thrombosis model. No impact on kidney bleeding parameters was seen. In study REP-001383, 2.50 mg/kg dose of CSL312 (garadacimab) (Group 2) was tested first based on previous experience with the parental antibody 3F7 in the same thrombosis model.

Finally, treatment of mice with either 2.5 or 25 mg/kg garadacimab showed that time to haemostasis and total volume of blood loss was not significantly altered compared to isotonic saline-treated controls.

Taken together, data show that garadacimab yields antithrombotic effects in two species (mouse and rabbit) without increase in bleeding risk.

2.5.1.3. Safety pharmacology programme

In a mouse safety pharmacology study, no adverse treatment-related effects of garadacimab on respiratory parameters (e.g., respiratory rate, tidal volume and minute volume) were observed. The NOAEL was identified to be at least 100 mg/kg for the IV route and 200 mg/kg for the SC route.

The other safety pharmacology systems were assessed as part of 4-week (neurological functions) and 5- and 26-week (heart, blood pressure, pulse rate, and respiratory rate) repeat-dose toxicity studies in mice and cynomolgus monkeys, respectively. All parameters were unaffected by garadacimab treatment (see Toxicology Section).

2.5.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted.

2.5.2. Pharmacokinetics

To evaluate the pharmacokinetics (PK) of garadacimab, a single-dose PK / pharmacodynamic (PD) study with intravenous (IV) administration and a single dose study with IV and subcutaneous (SC) administration, were performed in cynomolgus monkeys. Another single-dose study following SC administration was conducted in rabbits by comparing formulations of 100 vs 170 mg/mL concentration. The content of the excipients of both formulations were identical.

Analytical Methods Validation

Validation of ELISA method for the determination of CSL312 (anti-human factor XIIa antibodies) levels in cynomolgus monkey plasma samples (Study 15060) or in mouse plasma samples (Study 15059) have been conducted. All parameters have been addressed and met the acceptance criteria, apart from the proven long-term stability, which however has no impact on the overall assessment.

Absorption

Following IV infusion to monkeys, garadacimab showed typical monoclonal antibody behaviour, with biphasic clearance curves. The beta phase was approx. 40% of total clearance, and the terminal half-life was approx. 9.7 days (mean), with neither parameter showing any significant nonlinearity over the dose range (3, 9, 27 mg/kg). Prolongation of aPTT and inhibition of FXIIa activity was observed.

In a subsequent study, single IV (0.5, 1 and 3 mg/kg) and SC (6 and 20 mg/kg) dosing to cynomolgus monkeys was evaluated. Cmax and AUC0-tlast increased with increasing doses of garadacimab for both routes. The individual t1/2 values were in the range of 147 to 581 h and between 206 and 424 h for the IV and SC administration. The bioavailability was approx. 66% (dose level: 6 mg/kg, SC). Also in this study, prolongation of aPTT and inhibition of FXIIa activity was observed.

In a single-dose Local Tolerance and PK study (described also in Toxicity Section) the PK properties of two formulations of garadacimab (100 vs 170 mg/mL) after a single SC administration at 20 mg/kg was assessed in rabbits. Maximum plasma concentrations of garadacimab were generally observed at 24 or 48 hours after dosing. The Cmax and AUC for both formulations were similar. The mean t½ of garadacimab was comparable for both formulations. No noteworthy gender differences were reported for any PK parameter.

2.5.3. Toxicology

2.5.3.1. Single dose toxicity

Single-dose toxicity studies were not performed. Instead, short-term and longer-term repeat dosing studies were performed.

2.5.3.2. Repeat dose toxicity

Repeat-dose toxicity of garadacimab was evaluated in mice (8-day and 4-week studies) and cynomolgus monkeys (8-day, 5-week, and 26-week studies) after IV and/or SC administration using doses of up to 100 mg/kg (IV) and 200 mg/kg (SC).

Pivotal studies

Mice

Following 8 days i.v or s.c. administration to CD-1 mice (study APQ0056), only elevated aPTT levels were seen at all doses tested, as reported, and are considered to be related to pharmacological action of garadacimab. The similar degree of effect suggests a maximal pharmacological response at all doses.

The 3 mg/kg i.v. dose level represents a clinical dose level resulting in inhibition of FXIIa activity, 10 mg/kg i.v. the intended maximal clinical i.v. dose, and 30 mg/kg i.v. and 100 mg/kg i.v. a 3-fold and 10-fold of the intended maximal clinical i.v. dose, respectively.

The 60 and 200 mg/kg s.c. dose levels are believed to represent at least the 3-fold and 10-fold of the maximal intended clinical dose via the s.c. route, respectively.

As the findings were considered to not be adverse, the NOAEL was considered to be 100 mg/kg/occasion for i.v. administration and 200 mg/kg/occasion for s.c. administration.

Following i.v. or s.c. garadacimab administration for 4 weeks (study APQ0061), prolongation of the activated partial thromboplastin times (aPTT) irrespective of the route of administration was consistent with the expected pharmacological response to the treatment with garadacimab.

The majority of mice receiving the 3 mg/kg dose showed treatment-related clinical signs and mortality, in addition four animals receiving 10 mg/kg/day and one female receiving 30 mg/kg had similar findings or were found dead following dosing on days 18, 22 or 29. The adverse effects observed are considered to most likely being due to an anaphylactic reaction of the mice to the repeated i.v. administration of the heterologous human protein garadacimab.

The additional investigations carried out in an attempt to elucidate the mechanism of adverse effects included assessment of a wide range of inflammatory cytokines, histopathology, immunoglobulin E, CRP, immunophenotyping of peripheral and splenic white blood cells and immunohistochemical assessment of IgM and IgG in the brain, kidney, lungs and skin (associated with clinical signs).

The mild irritation at s.c. dose sites showed complete recovery and is considered not adverse.

There were no pathological changes associated with the lower liver weights, which are also considered not adverse. As there were no other findings of toxicological significance at any other dose level tested, the NOAEL was set at 3 mg/kg/day for the i.v. group and 200 mg/kg for the s.c. one.

Monkeys

Treatment with garadacimab both IV and SC for 8 days (APQ0055) caused a clear dose-dependent prolongation of the aPTT with no associated effects on PT. For the i.v. treated animals, the aPTT prolongation peaked between 0.25 to 1 hour post dose on Day 1, gradually shortening until the next dosing on Day 8. Values did not return to baseline within this time frame and remained higher than pre-dose values on Day 1. For 60 or 200 mg/kg s.c. groups, aPTT peaked at approximately 48 hours following dosing and generally remained at this level or shortened marginally on subsequent sampling occasions. No other treatment-related effects were observed. Despite the absence of pronounced signals in the treated animals, minor findings were seen, particularly in monkey studies where statistical power is intentionally kept low due to ethical considerations. D-dimer values were reported as unaffected by treatment, however, in two male animals, #257- 200 mg/kg SC and #254- 30 mg/kg IVD-dimer values were increased 5- and 10-fold following SC and IV administration, respectively. Regarding thrombin anti-thrombin complexes, the applicant asserts, "There was no effect of treatment on Thrombin anti-thrombin complexes."; however, the raw data and study summary unmistakably reveal that pre-treatment values were not assessed for any animal, and no measurements were taken for the control group of males.

Dosing Cynomolgus monkeys i.v. and s.c. for 5 weeks (APQ0058) resulted in prolongation of the activated partial thromboplastin times (aPTT) irrespective of the route of administration, consistent with the expected pharmacological response to the treatment with garadacimab. aPTT values were higher than control and pre-treatment values 168 hours following dosing on Day 1, pre-dose on Day 36 and in recovery Week 8 (with the exception of females previously treated intravenously in Recovery Week 8) indicating a long-term effect in line with garadacimab’s TK profile.

Other effects were seen (lower body weight gain, blood glucose increase, local irritation, low thyroid and parathyroid weights) and were considered related to the treatment. However, these were mild and not associated with effects on any parameters. Certain minor changes, discernible in the raw data but not explicitly outlined in the report, should be mentioned. Specifically, the urinalysis report indicates a reduction in urine volume which was concomitant with low urinary sodium levels. Previous reports have stated that CSL312 has no impact on C3a. However, it is worth noting that the high-exposure IV group and both SC groups of male and female monkeys exhibited a more significant increase in plasma C3a over the 6 weeks of treatment compared to the control group. One potential reason for overlooking

this effect could be the substantial variability observed in certain groups. Reports have indicated that CSL312 has no impact on cytokine release; however, upon examining the raw data, it becomes apparent that a majority of readings either fell below the lower limit of quantification or were marked as "non-valid".

Therefore, the NOAEL was set to the highest dose of 100 mg/kg (i.v.) and 200 mg/kg (s.c.), respectively.

Following 26-week administration (with a 13-week interim and 8-week recovery period) with garadacimab (TH43GT), prolongation of aPTT irrespective of the route of administration was seen. This effect of the pharmacodynamics marker showed partial recovery after the cessation of treatment, whilst no impact on the platelets and prothrombin times (PT) or the maintenance of coagulation homeostasis was observed.

Partial recovery was demonstrated for the s.c. injection site changes following an 8-week recovery period with full recovery at the left intravenous injection site of females previously treated at 100 mg/kg/occasion. Animal Number 537, which was confirmed to be ADA-positive, showed similar to Control aPTT values in Week 10 confirming that, in this animal, ADAs to garadacimab interfered with the expected pharmacology.

Minor blood chemistry changes were omitted from the discussion due to the absence of a discernible dose-response relationship suggesting an association with CSL312. However, the elevated plasma phosphorus in certain groups of both male and female animals (W13) should be mentioned in light of the reduction in parathyroid weights, as a decrease in plasma phosphorus could potentially indicate parathyroid damage.

However, CSL312 consistently triggered variations in white blood cell (WBC) counts across various experiments. These immune-related changes are attributed to the immune reaction to heterologous human protein, therefore a connection between immune response and WBC alterations it is not to exclude. While direct correlation analyses were not performed, the presence of ADA, a potential proxy for the immune reaction to the drug, appears inadequate to account for the observed WBC changes. Moreover, this response does not appear to be mirrored in the release of cytokines.

There were no other findings of toxicological significance at any dose level tested (up to 100 mg/kg/occasion i.v. and 200 mg/kg/occasion s.c.).

Therefore, the NOAEL was 100 mg/kg (i.v.) and 200 mg/kg (s.c.), respectively for the interim phase, while the NOAEL for the main phase was set to 30 mg/kg (IV) and 60 mg/kg (SC) due to two animals prematurely terminated due to welfare reasons.

2.5.3.3. Genotoxicity

No genotoxicity studies have been conducted with garadacimab. As per ICH Guideline S6(R1) [ICH S6(R1), 2011], standard *in vitro* and *in vivo* genotoxicity studies are not applicable to biologics as these molecules are unlikely to interact directly with DNA or chromosomal material.

2.5.3.4. Carcinogenicity

As per standard ICH Guideline S6(R1) [ICH S6(R1), 2011], carcinogenicity studies are generally inappropriate for the evaluation of biotechnology-derived pharmaceuticals.

To assess any potential carcinogenic risk derived by the application of garadacimab a detailed carcinogenicity assessment was submitted by the applicant.

In short, an extensive investigational non-clinical programme including pharmacological, pharmacokinetic, and toxicological studies was performed to characterise the interaction between garadacimab and activated FXII as well as to identify any adverse effects of garadacimab in pharmacologically relevant animal species (cynomolgus monkey, rabbit and mouse). Garadacimab was shown to only potently antagonise FXIIa enzymatic activities, displaying 100% inhibition of FXIIa catalytic activity for both Alpha and Beta fragments meaning that zymogen FXII functions are not or negligibly impacted. In contrast, garadacimab did not significantly inhibit the other serum proteases tested, either.

There is no evidence in the literature that inhibition of activated FXII and the zymogen FXII deficiency could give evidence on any carcinogenic, neoplastic or teratogenic effect in patients.

On the contrary, there is more evidence that inflammatory responses and possible maintenance and progression of cancer could be reduced by blocking FXIIa.

A risk assessment of the carcinogenic potential of excipients in the final formulation of garadacimab concluded that L-histidine, L-arginine monohydrochloride, L-proline and polysorbate 80 are not considered carcinogenic at the exposure scenario with garadacimab.

The NOAEL for all species was considered to be 100 mg/kg for the IV route and 200 mg/kg for the SC route, i.e., the highest doses tested. No test item-related adverse events – this includes *in vivo* necropsy or histopathological examination - were observed in the non-clinical programme conducted with garadacimab, which could give evidence on any carcinogenic or neoplastic potential in patients.

2.5.3.5. Reproductive and developmental toxicity

The reproductive and developmental toxicity of garadacimab was evaluated in rabbits (male and female fertility, EFD and PPND studies) after IV and/or SC administration using doses of up to 100 mg/kg.

FEED

No maternal toxicity was noted in females, as indicated by the lack of garadacimab-related clinical observations, effects on body weight or food consumption, macroscopic observations, or effects on organ weight. No effects on mating, fecundity, or fertility indices were observed. No effects on maternal reproductive parameters or embryo survival were noted. Large number of false positive ADA results is in concordance with previous studies where ADA have been quantified. The test results cannot be interpreted as valid with this rate of unexplained false positive results - potential ADA-positive animals cannot be distinguished from false positives and in this regard the association between ADA and exposure cannot be determined.

In males, anaphylactic reactions to the human protein garadacimab were observed in a subset of animals (4/25 at a dose of 10 mg/kg and 2/25 at a dose of 30 mg/kg). Apart from this, no safety findings were seen. Again, large number of false positive ADA in concordance with previous studies, the test results cannot be interpreted as valid. There were 6 unscheduled deaths (10 mg/kg: B0101-PM6; B0101-PM12; B0103-PM24; B0125-PM27; 30 mg/kg: B0207-PM27; B0217-pairing day 2). Total mortality was as follows: CTR (0%); 10-IV (16%); 30-IV (8%); 100-IV (0%). The unscheduled deaths were determined to be unrelated to garadacimab; however, given the diversity of clinical signs, it cannot be definitively ruled out that there might be a connection between the drug and the observed clinical findings, as only animals from the treated groups were sacrificed.

EFD

In a preliminary study (MN80HQ), i.v. administration of garadacimab at dose levels of 1, 30 or 100 mg/kg/occasion to pregnant New Zealand White rabbits was well tolerated and no premature death, no sign of reaction to treatment and no treatment-related toxicologically relevant effect were observed.

Only elongation of the aPTT was seen at all dose levels. Exposure was observed only in treated groups, moreover exposure was seen in pooled fetal blood samples on Day19 mating indicating that placenta was crossed at all dose levels.

NOAEL for maternal and fetal toxicity was concluded to be 100 mg/kg/occasion, the suitable dose for use in the main embryo-fetal development study in the New Zealand White rabbit.

In the main study (VK47BJ), increase in aPTT was evident, ADA formation having no impact on the outcome or integrity of the study. Two dams treated with garadacimab at 100 mg/kg/occasion were humanely euthanised prematurely due to signs of inappetence and changes in faecal output. There was no consistency in the faecal changes of these two females (loose faeces in one and reduced faecal output in the other) or the reproductive outcome (live embryos in one case and late resorptions in the other animal). Furthermore, as stated by the applicant, rabbits are known to be sensitive to study manipulations and can show reduced food consumption/inappetence in response, whilst low food intake in pregnant rabbits is also known to cause the aborting of a litter (Cappon et al 2005).

Regarding the choice of rabbit as main species for reproductive toxicity, justification was provided by the applicant:

Although binding was also demonstrated in mouse FXIIa, mice were shown to develop immunological (i.e., anaphylactic) responses to the heterologous human proteins after repeated administration. Therefore, the results obtained by repeated administration of garadacimab over the EFD period could be affected by an immunological response and would therefore be misleading and not relevant to the human situation. Also, considering the 3Rs principle, the use of mice would not provide meaningful safety information, and the use of nonhuman primates would not be ethical in the presence of an alternative pharmacologically relevant species.

In rabbit, the transfer of maternal immunoglobulin G (IgG) and to a lower extent, albumin, occurs across the rabbit fetal yolk sac membrane from the maternal uterine lumen to the fetus.

Furthermore, human IgG injected into the maternal circulation was also transported well to the rabbit fetus, indicating that rabbit neonatal Fc receptor binds human IgG efficiently (Szikora et al, 2017). The transition of garadacimab from maternal to fetal circulation was confirmed in both the PPND and the dose-range finding EFD study in rabbits".

PPND

Administration of 10, 30, or 100 mg/kg/dose of garadacimab once every 5 days via SC injection or 100 mg/kg/dose via IV injection to pregnant New Zealand White rabbits from implantation through weaning was well tolerated. No garadacimab-related toxicity was observed.

Therefore, based upon these data, the maternal NOAEL is 100 mg/kg/dose SC / IV. In the F1 generation, the NOAEL for fetal development is 100 mg/kg/dose SC / IV. The NOAEL for developmental, neurobehavioral, and reproductive performance in the F1 generation is 100 mg/kg/dose SC / IV.

The NOAEL of 100 mg/kg SC in this study is associated with a mean AUC0-30days of 550,800 µg*h/mL and Cmax of 927 µg/mL based on LD38. The values of AUC and Cmax are approximately 53-fold and 44-fold higher, respectively, than the clinical AUC (10,300 µg*h/mL) and Cmax (21.2 µg/mL) at the recommended human dose of 200 mg once monthly. Toxicokinetics relied on results that excluded

samples positive for ADA and those suspected to be ADA-positive. However, in other studies, ADA-positive samples were included in toxicokinetic analyses, as it was determined that the presence of ADA does not impact toxicokinetics.

2.5.3.6. Toxicokinetic data

The recommended human dose of garadacimab is 200 mg once monthly. The predicted clinical steady state AUC0-30days for this dose is 10,300 µg*h/mL. The predicted clinical steady-state Cmax for this dose is 21.2 µg/mL. This value is based on population PK analysis of all subjects (N=39) treated with garadacimab at 200 mg once monthly in Study 3001.

Study ID/ species	**NOAEL (mg/kg/dose)**	**Animal AUC (µg.h/ml)**		**Cmax (µg/ml)**		**Animal: Human Exposure Multiple Based on AUC**	
		♂	♀	♂	♀	♂	♀
APQ0056 mice	200 s/c	**67077.29**	**64855.97**	**1226.99**	**1242.57**	6,5	6,3
APQ0061 mice	200 s/c	**65822.89**	**83555.41**	**1051.87**	**1637.87**	6,4	8,1
APQ0055 monkey	200 s/c	**207291.80**	**182038.82**	**1610.26**	**1527.88**	20,1	17,6
APQ0058 monkey	200 s/c	**317438.35**		**1939.73**	**2320.84**	30,8	
TH43GT monkey	60 s/c	**41726**	**44366**	**322**	**349**	4	4,3

Systemic exposure of garadacimab in mice

Study APQ0061 is a 4-week plus 8-week recovery study in mice. Systemic exposure to garadacimab via both the IV and SC routes were confirmed for all treated animals and the Cmax and AUC values increased with dose for both males and females, and for both routes of administration. Furthermore, the increase in exposure (i.e., Cmax and AUC values) was proportional to dose (in the range of 3-100 mg/kg for Day 1 and 10-100 mg/kg for Day 29) following IV (bolus) administration. There were some indications of higher plasma concentrations, and higher Cmax and AUC values for females in comparison with males after SC administration, but this was inconclusive due to the small number of animals used in this study (due to anaphylactic reactions, see Repeat Dose Toxicity Section).

Systemic exposure of garadacimab in cynomolgus monkeys

Study TH43GT is a 26-week IV/SC study in cynomolgus monkeys (once weekly dosing). The mean AUC0-168h at the NOAEL of 60 mg/kg SC was 89,385 µg*h/mL. Once weekly dosing was used in this study, while clinical garadacimab dosing is once monthly. The mean AUC values were multiplied by a ratio of 30/7 to allow for appropriate AUC comparison with the reported clinical AUC value from the 200 mg once monthly dose regimen The mean AUC0-30days and Cmax is 383,121 µg*h/mL and 686 µg/mL, respectively, at the NOAEL of 60 mg/kg SC. The AUC0- 30days at the monkey SC NOAEL is approximately 37-fold higher than the clinical AUC at the recommended human dose of 200 mg once monthly. The Cmax at the monkey SC NOAEL is approximately 32-fold higher than the clinical Cmax at the recommended human dose of 200 mg once monthly.

Systemic exposure of garadacimab in rabbits

Study 8410864 is a pre- and post-natal development study using IV or SC garadacimab every 5 days. The NOAEL in this study is 100 mg/kg SC, which is associated with a mean AUC0-30days of 550,800 µg*h/mL and Cmax of 927 µg/mL based on lactation day (LD) 38. The values of AUC and Cmax are approximately 53-fold and 44-fold higher, respectively, than the clinical AUC and Cmax at the recommended human dose of 200 mg once monthly.

ADA formation

A summary of ADA formation in the main toxicity studies is reported below:

Mice – 4 weeks

Four samples were confirmed to be positive for ADAs against CSL312. Three of these were Group 3 females (animal numbers 440, 442 and 439) and the fourth animal was a Group 6 female (animal number 488). As these findings were only seen in a few animals across the groups these results are considered to be of no toxicological significance.

One animal dosed with 100 mg/kg/occasion intravenously (No. 903) was confirmed positive for anti-drug antibody production in Recovery Week 8.

Monkeys – 5 weeks

One animal dosed with 100 mg/kg/occasion intravenously (No. 903) was confirmed positive for anti-drug antibody production in Recovery Week 8. Three other animals were also positive for antibodies however these are considered to be false positives as they include one control animal (891), and two animals (867 and 894) which tested positive on Day 8 but were negative for antibodies in Week 6 and had similar TK profiles to other animals in their group.

Monkeys – 26 weeks

Anti-drug antibody (ADA) development in some of the test item-treated animals was considered not to have any impact on the overall toxicity assessment of CSL312 in this study, since -due to the high doses used- continued (although possibly reduced) exposure was seen in all of the animals. This also included the confirmed ADA-positive premature decedent female Animal Number 537 that presented with the slightly different exposure profile and the premature decedent male Animal Number 238, which also had an atypical exposure and aPTT profile.

Rabbit FEED Study

The presence of ADA increased after repeated dosing but did not appear to have a neutralizing effect or consistently cause a reduction in observed exposure to garadacimab. Concentration results from ADA positive and ADA negative animals were generally similar at comparable doses and timepoints.

Rabbit PPND Study

Maternal ADA response was at most 44% for SC and 6.8% for IV dosing from 10 to 100 mg/kg. The lowest SC dose (10 mg/kg) appeared to have a higher incidence of maternal positive ADA induction to garadacimab compared to the other SC dose levels tested.

2.5.3.7. Local tolerance

Local tolerance of two formulations of garadacimab (100 and 170 mg/mL) was assessed after SC administration of 20 mg/kg/dose on two separate days (1 week apart), with an observation period of 11 days post the first dose.

There were neither sign of toxicity no effect on body weight in any rabbit during the observation period. Mild local irritation at any application site was apparent following administration with two garadacimab formulations. Moreover, no garadacimab-related morphological changes were seen on the treated rabbit skin following SC administrations. The toxicokinetic profiles were consistent among animals. The identification of mild local irritant effects associated with inflammatory cell infiltration aligns with previous toxicological studies, indicating minor local irritation at the IV and SC injection sites.

According to the clinical safety assessment report, injection site reactions are also found in clinical studies. This is further discussed in the clinical safety section.

2.5.3.8. Other toxicity studies

An *in vitro* tissue cross-reactivity study (APQ0057) demonstrated garadacimab-specific binding on various tissues of human and/or cynomolgus monkey origin. Importantly, staining in monkey tissues was generally predictive of staining in human tissues, confirming the cynomolgus monkey as a relevant species for toxicological studies.

2.5.4. Ecotoxicity/environmental risk assessment

The active substance garadacimab is a fully human immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) that binds to FXIIa.

In accordance with the EMA guidelines for Environmental Risk Assessment of pharmaceuticals [EMEA/CHMP/SWP/4447/00 Rev.1 - corr], ecotoxicity and environmental fate studies are not required for an active ingredient that consists of proteins, as due to their rapid and extensive degradation are considered unlikely to represent a significant risk to the environment.

2.5.5. Discussion on non-clinical aspects

Pharmacology

Primary pharmacodynamic studies

Primary pharmacology experiments initially characterised the interaction between garadacimab and FXII zymogen or its active forms, as well as the ability of garadacimab to specifically inhibit FXIIa-mediated biological activities both *in vitro* and *in vivo* using relevant animal species.

In binding affinity study, garadacimab showed a high affinity for activated form of human FXII protein (K_D for βFXIIa=0.14 nM) and low affinity to the zymogen form (55 nM). Following plasma activation with dextran sulphate, garadacimab inhibited FXIIa-mediated bradykinin generation in human, as well as FXIIa chromogenic activity in human, cynomolgus monkey, mouse and rabbit, but not in rat. Garadacimab dose-dependently inhibited FXIIa chromogenic activity in normal human donors and patients with HAE types I, II, III or acquired angioedema (C1-INH-AAE).

Both garadacimab and the parental 3F7 antibody prolonged aPTT clotting times in standard human plasma up to maximal values (240 s). As a result of the affinity maturation, garadacimab was more potent at prolonging aPTT than the parental 3F7. In DXS-activated human plasma, garadacimab completely inhibited BK formation at concentration greater than 20 µg/mL (130 nM). When compared to commercially available KKS inhibitor ecallantide (IC_{50}=548 nM), garadacimab (IC_{50}=86 nM) was approximately 6-fold more potent, but this difference might be associated with different mechanism of action between these two inhibitors. In activated cynomolgus monkey plasma, an IC_{50} value for BK

generation was higher than in human plasma. Moreover, the two-to-one stoichiometry of βFXIIa to garadacimab was observed using surface plasmon resonance (SPR) and negative stain electron microscopy (Ow et al. 2023) which is in line with the structure of typical IgG consisting of two identical binding sites (one binding site on each Fab arm). The ability of garadacimab and parental antibody 3F7 to inhibit the catalytic activity of a panel of structurally related human serine proteases was investigated *in vitro*. Garadacimab was more potent than 3F7, demonstrating 100% inhibition of FXIIa at an enzyme:antibody ratio of 1:0.5. On the other hand, neither garadacimab nor 3F7 significantly inhibited other structurally related serine proteases at enzyme to antibody ratios of up to 1:500 (corresponding to 25 nM protease:12.5 µM antibody). When using garadacimab, no IC50 (>1 µM) was reached for any protease at the highest concentration tested. Taken together, the specificity of garadacimab for human FXII was clearly confirmed.

Taking into account the calculated IC_{50} values and concentrations required for complete inhibition of FXIIa chromogenic activity or FXIIa-mediated BK formation, it could be concluded that predicted C_{max} of 21.2 µg/mL (140 nM) at the recommended human dose of 200 mg of garadacimab (pooled PopPK model for all subjects in Study 3001) should demonstrate inhibition of FXIIa activity in clinical settings.

Since garadacimab and the parental antibody 3F7 demonstrated cross-reactivity in mice, an *in vivo* efficacy was investigated in murine PSA and PCA models. When compared to control antibody, garadacimab showed statistically significant inhibition of ear skin oedema at a dose of 25 mg/kg. In addition, 3F7 demonstrated marked inhibition when administered 4 h prior to anaphylaxis induction, while the other inhibitors (icatibant, ecallantide) produced loss of efficacy likely due to their short half-lives in plasma. These results support the potential of anti-FXIIa mAbs for prophylactic use in HAE treatment.

To further demonstrate *in vivo* efficacy, inhibitory activity of garadacimab and 3F7 was assessed in murine ACEI-induced angioedema model. Garadacimab and 3F7 markedly inhibited ACEI-induced increase of vascular permeability with similar potency. Statistically significant reduction in permeability with both mAbs was demonstrated at a dose 0.1 mg/kg, while complete inhibition was achieved at doses ≥0.5 mg/kg. The observed difference in results from PSA/PCA models and ACEI-induced oedema model may be related to different degree of KKS activation between oedema models.

Considering that garadacimab and the parental antibody 3F7 effectively reduced oedema in both models, it could be concluded that FXII targeting results in decreased activity of KKS; thus providing a proof of concept for HAE treatment.

Secondary pharmacodynamic studies

Regarding the proposed mechanism of action, possible antithrombotic effects of garadacimab and effects on haemostasis were investigated with garadacimab and parental antibody 3F7.

In a simultaneous thrombosis model in rabbits, garadacimab at a dose of 10 mg/kg completely inhibited arterial thrombosis, but did not have any significant effect on venous thrombosis. In contrast to low molecular weight heparin, garadacimab did not influence physiological haemostasis, confirmed by results of bleeding measurements similar to saline control.

Another evidence of antithrombotic activity of garadacimab was demonstrated in a FeCl3-induced thrombosis model in mice. At the highest dose of 2.5 mg/kg, the maximum inhibitory response was achieved and none of the mice developed arterial occlusion. On the other hand, only partial antithrombotic effect was demonstrated following administration of low molecular weight heparin, with occlusion rate of 50%.

The potential effects of garadacimab on haemostasis were tested using a subaquatic tail tip bleeding model in mice. Either 2.5 mg/kg or 25.0 mg/kg of garadacimab did not produce statistically significant

difference in time to haemostasis or total blood loss, compared to saline control. Animals treated with garadacimab showed FXIIa activity inhibition and aPTT prolongation, while PT values were not affected.

Safety pharmacology programme

The applicant conducted a dedicated mouse safety pharmacology study to investigate potential adverse effects of garadacimab on respiratory parameters. In this GLP-compliant study, single IV or SC administration of garadacimab at doses similar or up to 10-fold higher than clinically expected produced no statistically significant or biologically relevant effects on respiratory parameters at any time point, when compared to saline control. The sensitivity and validity of the assay were confirmed by observed effects of baclofen (positive control) on respiratory endpoints. The NOAEL in this study was the highest tested dose for each route of administration (i.e. 100 mg/kg for IV and 200 mg/kg for SC).

No garadacimab-related effects on CNS were observed at different time points during the Irwin screens as part of the 4-week repeat-dose toxicity study in mice. The investigations on electrocardiography, blood pressure and respiratory rate did not demonstrate any findings following IV or SC administration of garadacimab as part of the 5-week and 26-week repeat-dose toxicity studies in cynomolgus monkeys. For detailed assessment, please refer to Toxicology part of this report.

Pharmacokinetics

The bioanalytical methods for determining plasma concentrations of garadacimab and anti-drug antibodies (ADAs) against garadacimab were adequately validated according to the requirements from ICH Q2 (R1) guideline and FDA Guidance for Industry on Analytical Procedures and Methods Validation for Drugs and Biologics.

PK profile of two variants of garadacimab (VR115-G4 and VR115 G1/2 LS) with different Fc regions was investigated following single IV administration in male cynomolgus monkeys. As expected for monoclonal antibody, both variants exhibited typical biphasic behaviour, with a relatively fast distribution phase followed by a slower elimination phase. The linearity was confirmed across the dose range tested from 3 to 27 mg/kg and no significant difference in PK parameters was observed between two variants of garadacimab. It has to be mentioned that binding affinity for human βFXIIa was also compared using these two variants. Results from *in vitro* investigation correlated with PK/PD study in monkeys, suggesting that VR115-G4 might be slightly more effective than VR115 G1/2 LS variant. Considering that main studies were conducted with VR115-G4 variant, the classification of garadacimab as IgG4 is acceptable.

PK and PD properties of garadacimab were further investigated after single IV or SC administration in cynomolgus monkeys, the relevant species based on results from *in vitro* PD and PK studies. Independently of the administered route, plasma concentrations increased with increasing doses of garadacimab, confirmed by C_{max} and AUC values. Mean $T_{1/2}$ values were in the range from 9.5 to 16.1 days for IV dosing, and 12.1 to 14.4 days for SC dosing, while bioavailability was estimated at approximately 66%.

As expected, a dose-dependent increase in aPTT and inhibition of FXIIa-mediated plasma kallikrein activity were demonstrated across all treatment groups. While increased aPTT returned to predose values until the end of the study (Day 57), PT values were unaffected by treatment with garadacimab. In line with PK characteristics, rapid and short-lived effect was measured after IV administration, while slower and sustained effect was observed in SC dosed animals.

PK profile and local tolerance of two formulations of garadacimab were evaluated following repeated SC administration in rabbits, another pharmacologically relevant species. Both formulations of garadacimab demonstrated similar concentration profile and maximum plasma concentrations were

observed approximately 24-48 hours after dosing. Comparable values were also measured for other PK parameters and no significant gender differences were observed. The mean $T_{1/2}$ was in the range from 3.5 to 3.8 days for animals dosed with batch no. 834101076, and 4.3 to 4.5 days for those treated with batch no. 8120000014.

Additional toxicokinetic analyses were included as part of the repeat-dose and reproductive toxicity studies in mice, cynomolgus monkeys and rabbits. For detailed assessment, please refer to Toxicology part of this report.

No studies on distribution, metabolism, excretion and pharmacokinetic drug interactions were conducted with garadacimab. Distribution of garadacimab in circulating blood was confirmed by volume of distribution values and no binding to plasma proteins was expected. *In vitro* tissue cross-reactivity study and investigation of placental transfer were performed to further evaluate distribution of garadacimab (see Toxicology part). According to relevant ICH S6 (R1) guideline, biotransformation and mass balance studies are not required for garadacimab. Considering that biopharmaceuticals are not metabolised via CYP 450 enzymes, pharmacokinetic drug interactions are unlikely with garadacimab.

Toxicology

The *in vivo* toxicological programme, conducted under GLP conditions, encompassed two repeat-dosing studies in mice (8-day and 4-week durations), three repeat-dosing studies in cynomolgus monkeys (8-day, 5-week, and 26-week durations), and four reproductive and developmental toxicity studies in rabbits. The latter included an embryo-fetal development (EFD) study, two fertility studies addressing both male and female fertility, and a study on prenatal and postnatal developmental (PPND) toxicity. Reproductive and developmental toxicity studies were exclusively carried out in rabbits for two primary reasons: i) rats were considered unsuitable due to their lack of pharmacological relevance (no XIIa inhibition observed in rat plasma), and mice exhibited an immunological response to repeated administration of heterologous human proteins; ii) the use of non-human primates was considered ethically unacceptable when a viable alternative model, such as rabbits, was available. Doses of up to 100 mg/kg IV and 200 mg/kg SC had no adverse treatment-related effects on safety pharmacological readouts in mice and Cynomolgus monkeys.

Repeat dose toxicity

Doses of 3 to 100 mg/kg IV and 60 to 200 mg/kg SC were well tolerated in repeat-dose toxicity studies (8-day studies in mice and cynomolgus monkeys, and a 5-week study in cynomolgus monkeys). In the 4-weeks repeat-dose toxicity study in mice, SC treatments (60 to 200 mg/kg) and the highest IV dose (100 mg/kg) were well tolerated, while lower IV doses (3 to 30 mg/kg; predominantly 3 mg/kg) revealed adverse treatment-related clinical signs and mortality after repeat dosing. These adverse effects are assessed as an immunological (i.e., anaphylactic) reaction to the human protein garadacimab, which has limited predictive value for the clinical situation. In the IV (10 to 100 mg/kg) and SC (60 to 200 mg/kg) repeat-dosing 26-weeks study in cynomolgus monkeys, two animals had to be euthanised due to animal welfare reasons (also assessed as an immunological reaction to the human protein garadacimab); whilst in remaining animals only mild local irritant treatment-related effects at injection sites were observed (also assessed as an immunological reaction to the human protein garadacimab). In the above-described studies, not fully mature mice aging 60 to 70 days and monkeys aging 27 to 31 months were used.

Taken together, data from repeat dose toxicity studies in mice up to 4 weeks and monkeys up to 26 weeks demonstrate that garadacimab is well tolerated with no findings of toxicological significance.

It is known from the literature that mice are included in toxicology studies at an age of 8-10 weeks (Annas et al, 2013; Flurkey et al, 2007), the age these were included in the repeat dose toxicity

studies APQ0056, APQ0061. The animals were 13 weeks at the end of dosing, being 21 weeks old after the 8-weeks recovery period, therefore both young and adult age were covered.

It was not the same for cynomolgus monkeys, included in repeat-dose toxicity studies at 2-years old but not reaching the adult age at the end of studies. These were indeed 3-3.3 years old, age corresponding to the prepubertal period in females and males at the end of both experimental and recovery phase, respectively (Martin, 2015). Several reasons, among which availability, costs and the lack of developmental differences in critical organ systems well documented by the literature, were presented by the applicant to support such a choice. Given also that the first HAE attacks and symptoms of types I and II are known to occur in the childhood or adolescence (Longhurst and Bork, 2006; Bork et al, 2006; Gompels et al, 2005), the age of monkeys used in repeat dose tox studies have been declared to adequately cover also the age of onset of HAE.

In light of the provided data, the applicant's justification for the choice of both young mice and monkeys is agreed, and the repeat dose toxicity studies can be considered sufficient to cover both the young and the adult populations.

Both intravenous (IV) and subcutaneous (SC) routes of administration were used, with the exception of EFD studies conducted solely via the IV route. The tested doses (3, 10, 30, and 100 mg/kg IV, and 60 and 200 mg/kg SC) were considered clinically relevant. The IV dose of 10 mg/kg mirrored the intended maximum clinical dose, while the doses of 30 and 100 mg/kg IV and 60 and 200 mg/kg SC represented 3- and 10-fold higher doses.

Moreover, a GLP ex vivo tissue cross-reactivity study was carried out on human and cynomolgus monkey tissues.

The overall toxicological programme was well-designed and provided solid evidence supporting safety of garadacimab for human use.

In vitro pharmacological studies (rep-009151, rep-21282) revealed distinct differences in plasma FXII activity among various species. Cynomolgus monkeys exhibited activities relatively similar to human, while mice demonstrated almost 3-fold lower values, and rabbits displayed almost 7-fold lower values than those in humans. Moreover, it is crucial to note that while the concentration of FXII in human and monkey plasma is approximately ~30 µg/ml, the baseline levels in rabbits (utilised in reproductive toxicology studies) appear to be ~3000–30,000-fold lower (~1-10 ng/ml).

Both mouse and cynomolgus monkey studies indicated that garadacimab administration led to immune system alterations (changes in WBC, effects on the spleen and lymph nodes, etc.). These changes were attributed to an immunological response to repeated administration of heterologous human protein and were deemed not biologically significant. The absence of a clear dose-response relationship, small effect sizes, and the interaction with sex were considered additional indicators that immunological changes were unrelated to the biological effects of the tested compound.

To analyse garadacimab's observed immune effects, the applicant conducted an additional non-GLP tolerability study, comparing garadacimab effects to an isotype control monoclonal antibody after repeated administration in mice (TOM 16-02). Despite efforts to analyse immunological effects, the study failed to replicate immunological effects with the lowest drug dose (no exposure control). Although the study reported the absence of immunological effects, which, in the context of other toxicological studies, does not conclusively prove that garadacimab lacks immune effects.

The problems with cytokine assay with most samples falling outside of the quantification range was not specific for the tolerability study (TOM 16-02) but was also observed in other studies (e.g. APQ0061, APQ0058, TH43GT, etc.) and for other tests (e.g. IgE-APQ0061; D-dimer- TH43GT, etc.). These problematic analyses were highlighted in reports for each individual study.

In all conducted repeat dose administration studies, we cannot fully exclude the possibility that immune response to CSL312 garadacimab masked important toxicological effects.

Carcinogenicity

No carcinogenic potential of the product class (inhibition of FXIIa) was previously demonstrated. The structure-activity relationship suggests no carcinogenic risk for garadacimab and its excipients. No genotoxicity for a biotechnology-derived pharmaceutical such as garadacimab is expected. No evidence of preneoplastic or neoplastic lesions could be found in repeated dose toxicity studies and long-term tissue retention of garadacimab does not occur and no local tissue reactions were observed during nonclinical studies. Thus, based on a weight of evidence approach, it is concluded that garadacimab has no carcinogenic potential when administered to patients.

Reproductive and developmental toxicity studies

The reproductive toxicity studies suggest that garadacimab administration does not lead to reproductive and developmental toxicity. However, it's crucial to consider that these studies were exclusively conducted in rabbits and should be interpreted in light of potential disparities in the biological role of FXII in rabbits, as discussed in previous comments. While human data on this matter is limited, certain reports suggest that FXII activity might be significant during pregnancy in humans (e.g., PMID: 25436153, 10.1186/s12884-020-03455-0). Therefore, potential effects should not be dismissed solely based on the presented studies demonstrating no effects in rabbits. The applicant presented a comprehensive discussion on the rabbit as appropriate species for toxicological evaluation of garadacimab. No firm conclusion can be drawn on the role of FXII in pregnancy based on the reproductive toxicity studies. Safety in pregnancy and breastfeeding has been added as missing information in the RMP and will be followed-up via routine pharmacovigilance.

Local tolerance

The local tolerance study indicated the absence of local irritation with two different garadacimab concentrations (100 vs 170 mg/mL) administration; however, an examination of raw data (histopathology) contradicts this conclusion, as mild irritation was seen. Repeated dose administration studies clearly demonstrated that garadacimab administration is linked to local irritation.

Tissue cross-reactivity was observed on various human and cynomolgus monkey tissues; however, no related safety findings were observed in cynomolgus monkey repeat-dose toxicity studies. Results from cross reactivity studies confirm that data from repeat-dose studies in cynomolgus monkeys are considered pharmacologically and toxicologically relevant. There were no safety findings of clinical relevance at any dose level tested in the cynomolgus monkey repeat-dose studies.

Cross-reactivity study was exclusively conducted using human and cynomolgus monkey tissue samples, yet the inclusion of mice and rabbits would offer crucial insights into interpreting toxicological observations from repeat-dose and reproductive toxicity studies in these species. This becomes especially crucial when considering that *in vitro* pharmacological studies have revealed distinct shapes in the inhibition curve for mouse FXIIa, along with specific binding properties. Variations in mouse and rabbit FXII binding raise the possibility of diverse tissue binding potentials in these species, potentially leading to different effects. FXII is known to have immunological effects, such as the upregulation of neutrophils, polarisation of macrophages, T-cell differentiation, etc. (e.g., 10.3389/fimmu.2019.02011; 10.1038/ncomms11626), and immune effects were observed in most toxicological studies conducted. There is no clear data indicating that the observed immune effects are exclusively mediated by the immune system's reaction to the heterologous human protein even though that is the most likely explanation, as applicant emphasises. While many cross-reactivity findings were deemed inconsequential due to cytoplasmic signals and cells protected by physiological barriers *in vivo* (e.g., the blood-brain barrier), the assessment of membrane binding was only qualitative, lacking

quantitative data, and could have been explored quantitatively by omitting the permeabilisation step. Additionally, despite differences in labelling efficiency between CSL312garadacaimab-FITC and the IgG4-FITC isotype control, no signal comparability studies were conducted. Directly comparing staining without knowledge about the relationship between signal and binding can provide biased results.

Consistency in the interpretation of findings was lacking across different studies, with changes frequently considered non-adverse and unrelated to garadacimab based on criteria such as the absence of dose-response, minimal effects, and interaction with animal sex, which was not always justified. Additionally, reporting of findings was not consistently thorough, as certain observations apparent in the raw data were not consistently emphasised in the reports.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, garadacimab is not expected to pose a risk to the environment.

2.5.6. Conclusion on the non-clinical aspects

Overall, the presented non-clinical programme provides an adequate characterisation of the PD, PK and toxicology profile of garadacimab.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
Study **3001 (pivotal)**	Completed First Subject Visit: 27 January 2021 Enrolled: 64 subjects (6 adolescents) Planned: 60 subjects (5 adolescents)	Phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel arm	Garadacimab arm: Loading dose of 400 mg garadacimab administered SC as two 200 mg injections. Subsequent 200 mg doses of garadacimab administered SC once monthly Placebo arm: Volume-matched placebo	Aged ≥ 12 years, clinically confirmed C1-INH HAE subjects (type 1 or type 2) with ≥ 3 HAE attacks during the 3 months before Screening; Experienced at least an average of 1 HAE attack per month during the

			Duration: 6 months	Run-in Period (e.g., experienced a total of at least 2 HAE attacks).
Study **3002**	Ongoing First Subject Visit: 29 March 2021 [data cut-off date: 13 February 2023 (all subjects), 22 May 2023 (adolescents only)] Enrolled: 161 subjects with HAE (10 adolescents) Planned: 150 subjects	Phase 3b, multicentre, open label	Subjects from Study 2001 or Study 3001: 200 mg garadacimab administered SC as 1 dose once monthly for a minimum of 12 doses Garadacimab-naïve subjects: Loading dose of 400 mg garadacimab administered SC as two 200 mg injections. Subsequent 200 mg doses of garadacimab administered SC once monthly for at least 11 months	As for Study 3001 (above)
Study **2001**	Completed First Subject Visit: 29 October 2018 Enrolled: 38 subjects with C1-INH HAE Planned: Up to 40 subjects with C1-INH HAE (32 randomised, 8 open label) Enrolled 3 subjects with FXII HAE and 3 subjects with PLG HAE (nC1INH-HAE)	Phase 2, multicentre, randomised, placebo controlled, parallel-arm study (TP1); open label parallel-arm study (TP2)	*C1-INH HAE* TP1 blinded: • 40 mg garadacimab IV loading dose; then 75 mg garadacimab q4wk SC • 100 mg garadacimab IV loading dose; then 200 mg garadacimab q4wk SC • 300 mg garadacimab IV loading dose; then 600 mg garadacimab q4wk SC • placebo IV loading dose; then placebo q4wk SC TP1 open label: 400 mg garadacimab q2wk SC (no loading dose) TP2: 200 mg[a] or 600 mg[b] q4wk SC	aged ≥ 18 to ≤ 65 years For subjects with C1-INH HAE (type 1 or 2): ≥ 4 HAE attacks over a consecutive 2-month period during the 3 months before Screening; occurrence of ≥ 2 HAE attacks within any consecutive 4-week period during the Run-in Period.

			FXII / PLG HAE 600 mg q4wk SC	

[a] C1-INH HAE subjects receiving 200 mg SC garadacimab q4wk during TP 2 could be uptitrated to receive 400 mg SC garadacimab q4wk at the discretion of the Investigator (per protocol).

[b] C1-INH HAE subjects receiving 600 mg SC dose of garadacimab q4wk in TP2 had their dose reduced to 200 mg SC q4wk as stipulated in Study 2001 Protocol Amendment 2.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical pharmacology PK data were obtained from 3 completed phase 1 studies (1 first-in-human study conducted in healthy subjects, 1 conducted in healthy Japanese and Caucasian subjects, and 1 conducted in healthy subjects comparing the PK following administration via the pre-filled pen [garadacimab 200 mg] with the pre-filled syringe [garadacimab 200 mg]), 1 completed phase 2 study (in subjects with HAE), and 2 phase 3 studies (in subjects with HAE).

Completed studies are as follows:

• Study 1001: A phase 1, single-centre, randomised, double-blind, placebo-controlled, single ascending dose study to investigate the safety, tolerability, and PK of IV and SC garadacimab in healthy subjects.

• Study 1003: A 2-part, phase 1, single-centre, open-label, single ascending dose study to investigate the PK, PD, safety, and tolerability of SC and IV garadacimab in healthy adult Japanese and Caucasian subjects.

• Study 1004: A phase 1, randomised, open-label, parallel-group study to compare the PK properties of garadacimab administered by SC PFS assembled to pre-filled pen to PFS assembled to NSD in healthy adult subjects.

• Study 2001: A multicentre, randomised, placebo-controlled, parallel-arm study to investigate the efficacy, PK, and safety of garadacimab in subjects with hereditary angioedema.

• Study 3001: A multicentre, double-blind, randomised, placebo-controlled, parallel-arm study to investigate the efficacy and safety of SC administration of garadacimab in the prophylactic treatment of HAE.

Ongoing studies are as follows:

• Study 3002: An open-label study to evaluate the long-term safety and efficacy of garadacimab in the prophylactic treatment of HAE.

The observed data from these studies were analysed utilizing, population pharmacokinetic (PopPK) / pharmacodynamic (PopPKPD) modelling, and exposure-response (ER) analyses and were used to characterise the PK and PD of garadacimab.

Analytical methods

Pharmacokinetic bioanalytical methods

Bioanalytical method based on enzyme-linked immunosorbent assay (ELISA) was validated for quantitation of garadacimab concentrations in human plasma.

Validation results demonstrated that the ELISA-based assay was sufficiently accurate and precise to reliably allow the determination of garadacimab in human plasma samples in pharmacokinetic studies.

Methods for PD biomarkers

For quantification of FXII enzyme-linked immunosorbent assay (ELISA) methods were verified. An in-house ELISA was developed to quantify FXII in human plasma samples.

In the verification report REP-002062, the assay showed to have acceptable accuracy and intra-assay, inter-assay and inter-operator precision. The range of the ELISA method was 0.5 – 30 ng/mL and LLOQ to be 2.5 µg/mL FXII in 100% human plasma.

Qualification results obtained in study Q1382005P2 indicate robustness and reliability of in-house ELISA method for the measurement of Factor XII in human plasma in the concentration range of 0.313 to 40.0 ng/mL. LLOQ was 3.1 µg/mL FXII in 100% human plasma.

In clinical study the performance of in-house ELISA method using for quantifying FXII plasma levels showed acceptable results.

A novel assay to monitor FXIIa-mediated kallikrein activity in human plasma samples was fit-for purpose validated. The method using a chromogenic substrate, S-2302™, to monitor the amidolytic activity generated in plasma samples upon activation of the contact system. This assay was quasi-quantitative, with no calibration standard.

In study report REP-0007322 the range of assay was considered suitable at enzymatic activities generated with spiking of 0 µg/mL to 50 µg/mL CSL312 concentration. The ULOQ derived from this range experiment based on activities in samples without CSL312 were 0.1278 ΔA_{405}nm/min. The LLOQ derived from this range experiment based on activities in samples maximally inhibited with CSL312 at 50 µg/mL was 0.0021ΔA_{405}nm/min. Precision parameters for the controls used in this validation met the revised acceptance criteria. The validation exercise has provided data to support recommendations around acceptance criteria for use in the phase 1 clinical study.

Subsequently, study reports, to evaluate the FXIIa-mediated kallikrein activity assay performance, control samples of plasma in the presence/absence of CSL312 or kallikrein were included. Moreover, HAE patient samples were tested. The quasi-quantitative range were shown to be 0.003-0.371 ΔA_{405}nm/min in report RnD-VAL-000148888 and 0.005-0.298 ΔA_{405}nm/min in study report REP-019128. Precision parameters for the controls used in these validations met the acceptance criteria and the HAE samples shown to be reliably measured within this range

In clinical study, controls of analytical method used for the evaluation of FXIIa-mediated kallikrein activity showed acceptable results.

A quasi-quantitative cleaved high molecular weight kininogen (cHK) assay for the measurement of cHK levels in human plasma samples was verified. In study report REP-002333 cHK immunoassay was shown to have acceptable intra-assay, inter-assay and inter-operator precision for the cHK spike control. Plasma samples can undergo a freeze/thaw cycle. This assay has been verified as a suitable method to analyse human clinical plasma samples for cHK.

A method was evaluated for determination of activated Prothrombin Time (aPTT) in human citrated plasma samples using the commercial activator reagent Pathromtin SL and the Behring Coagulation System XP. All predefined acceptance criteria were met in validation report REP-001673.

To evaluate the influence of Factor XIIa monoclonal antibody on the recovery of the aPTT values, garadacimab was spiked into the citrated plasma of 3 healthy donors. The predefined acceptance criterion of a recovery in the range of 80 - 120% for the influence of garadacimab on the determination of aPTT were fulfilled within the concentration range of 0.00 1 -0.009 mg/mL of

garadacimab in plasma. However, with concentrations above 0.009 mg /mL of garadacimab an influence on aPTT prolongation was shown. This interference is reflected in SmPC section 4.4.

Methods for immunogenicity

A tiered approach was used to assess the presence or absence of ADAs. Firstly, samples were analysed in a screening assay, which identifies potentially positive samples. Secondly, these potentially positive samples were tested in the presence of garadacimab (100 µg/mL) in the confirmatory assay to assess if the ADA response was specific to garadacimab. Lastly, samples confirmed as positive were assessed in a titering assay to quasi-quantitatively.

For detection of ADAs against garadacimab a bioanalytical method based on electrochemiluminescent immunoassay with an acid dissociation pre-treatment step was validated.

In all validation reports, assay cut points (CPs) were determined using plasma from 50 drug naïve healthy donors with and without drug (garadacimab). Each CP plate was divided in 2 sections, allowing the simultaneous assessment of donor samples without drug (required for screening CP) and with drug (required for confirmatory CP). The CPs were calculated according to the recommendations outlined by Shankar et al (2008).

The garadacimab ADA assay uses a garadacimab anti-idiotype antibody diluted in pooled human citrated plasma as the assay quality controls (QCs). Negative control was 100% undiluted pooled human plasma.

Precision of the assay was demonstrated in each validation reports with respect to inter-assay, intra-assay and inter-operator precision by assessing the full set of controls for each precision parameter.

The assay has been successfully validated with appropriate selectivity, drug tolerance, screening cut point, confirmatory cut point, intermediate precision, sensitivity and sample stability and is suitable for use in the clinical studies according to Guideline on Immunogenicity assessment of therapeutic proteins – EMA guidelines, 2017.

In the clinical studies, analytical method QCs results for each run were evaluated showing acceptable results. In the few runs (2 out 55) in which the QCs results were unacceptable the samples were repeated.

Evaluation and qualification of models

Population Pharmacokinetic Analysis of garadacimab in Healthy Subjects

PopPK CSL-032 was developed using data obtained with garadacimab in healthy subjects with the purpose to make dose recommendations for the Phase II study in HAE patients.

A direct response PopPKPD model described the garadacimab PK and the FXIIa-mediated kallikrein activity well. This used a 2-compartment PK model with a direct effect sigmoidal Emax model. Simulations demonstrated an increase in inhibition of FXIIa-mediated kallikrein activity with increasing concentrations of garadacimab. No covariates were determined to have a significant effect on the model. The final garadacimab PopPKPD model was evaluated by performing a prediction-corrected visual predictive check (pcVPC), for garadacimab PK and FXIIa-mediated kallikrein activity from CSL312_1001 stratified by route of administration (IV or SC) and observation type (PK or PD). The pcVPCs confirmed that the final PopPKPD model provided a good description of the data for PK. For FXIIa-mediated kallikrein activity the prediction intervals are wider than simulated PK intervals and some of the observed data fall outside the prediction intervals.

PopPKPD CSL-037 - Population Pharmacokinetic-Pharmacodynamic Analysis of garadacimab to support Phase 3 study

PopPKPD model CSL-037 was used to support dose selection for Phase 3 study 3001.

A complete PopPKPD report has been provided during the evaluation. The objectives of these analyses were to characterise garadacimab PK in a population of healthy volunteers and patients with HAE after garadacimab administration, develop a PopPK model with the purpose of providing exposure metrics for an HAE attack ER model, develop a population pharmacokinetic-pharmacodynamic (PopPKPD) model for activated Factor XII (FXIIa)-mediated kallikrein activity, assess PK and PKPD characteristics for potential doses in Phase 3 studies in patients with HAE.

The model was developed using data from healthy volunteers (Phase 1 study 1001) and patients with HAE (Phase 2 study 2001) after garadacimab administration. The dataset for the PK model development consisted of 56 subjects contributing a total of 710 garadacimab observations and 954 FXIIa-mediated kallikrein activity percent of baseline (POB) observations. These analyses adequately characterised garadacimab PK with a two-compartment PK model with first-order absorption and elimination, and FXIIa-mediated kallikrein activity POB observations by a direct effect response model. No covariate analysis was reported in the PopPK model report.

Exposure response modelling, using exposures generated from the PK model, indicated that the target daily average concentration that results in 90% relative risk reduction in HAE attack rate is ~7.8 μg/mL.

The 200 mg SC Q1M (with a 400 mg SC loading dose) was predicted to align with daily average concentrations of that approximate magnitude.

PopPKPD CSL0507F - Population Pharmacokinetic-Pharmacodynamic Modelling and Simulation of Garadacimab in Subjects with Hereditary Angioedema

The objectives of these analyses were to develop a PopPKPD model with pooled data from Studies 1001, 1003, 2001, 3001, and 3002 to evaluate the impact of specific covariates on PK and assess the need for dose adjustments for certain subgroups of patients, to evaluate the impact of specific covariates on PD and to perform simulations to confirm dose selection.

The covariate effects relating to patient status (healthy versus HAE patient), Chinese ethnicity, baseline SCR, baseline BILI and baseline ALT were fully contained within the reference range, indicating they were unlikely to have a clinically meaningful effect on CL or AUCtau,ss, while the point estimate for Japanese subjects was marginally outside of the reference range both CL or AUCtau,ss. Body weight had the largest effect on CL and AUCtau,ss; subjects with lower body weights (<70kg reference subject) had lower CL estimates and hence higher exposures (i.e., AUCtau,ss) while subjects with higher body weights (>70kg reference subject) had higher CL estimates and thus lower exposures (i.e., AUCtau,ss).

Model validation was performed using a newer data cut from Study CSL312_3002 (available on 13 February 2023) as compared to that which the model was fit. The model predictions accurately described the new data for PK, while some evidence of overprediction was present for the samples collected prior to the next dose for PD determination FXIIa-mediated kallikrein activity percent change.

Absorption

Garadacimab absorption was investigated in both healthy subjects (with IV and SC formulations) and patients with HAE. After single IV administration, garadacimab t_{max} generally occurs at the first sampling timepoint after administration. After single SC administration, garadacimab t_{max} occurs after approximately 1 week (median range: 133 to 169 hours). The final pooled PopPK model adequately

described garadacimab PK by a two-compartment PK model with first-order absorption. Final popPK/PD model estimated constant rate of absorption to be 0.00824 (L/h).

The absolute bioavailability of garadacimab was calculated by comparing the same dose levels (i.e., 1, 3, and 10 mg/kg) for IV and SC administrations separately (an intersubject comparison).

An overall comparison of pooled SC doses versus pooled IV doses estimated the bioavailability of dose-normalised AUC0-inf at 49.7% while the bioavailability determined in the PopPK analysis CSL0507F was 39.5%.

Two different garadacimab formulations were used in clinical studies on HAE patients: a 100 mg/mL formulation was used in the phase 2 Study 2001 while the to-be-marketed 170 mg/mL formulation of garadacimab was used in the phase 3 studies (Studies 3001 and 3002). The impact of formulation changes from 100 to 170 mg/mL garadacimab on the PK and safety were evaluated in a nonclinical local tolerability study in rabbits (Study 37761), where both formulations showed a similar PK profile following SC administration, and using PopPK methods, where the formulations resulted in similar garadacimab $C_{min,ss}$.

In addition, relative bioavailability of garadacimab administered SC with a pre-filled pen compared to a pre-filled syringe is supported by Study 1004, a phase 1 Study with the objective to compare the pharmacokinetic properties of garadacimab administered by subcutaneous pre-filled syringe assembled to pre-filled pen to pre-filled syringe assembled to needle safety device in healthy adult subjects. Garadacimab PK parameters were comparable for the pre-filled syringe and pre-filled pen presentations (exposure after SC administration of 200 mg garadacimab via pre-filled syringe or pre-filled pen met the criteria for bioequivalence).

Study 1004 also investigated impact of injection site on PK and resulted that garadacimab exposure was also similar after SC administration to the abdomen, thigh, or upper arm.

Distribution

Results from clinical studies after IV administration and from PopPK analysis estimated a low volume of distribution, suggesting that garadacimab was only distributed within the blood volume (V_Z ranged from 3.79 to 6.81 L after IV administration, while in the PopPK analysis, garadacimab V_C and V_P were estimated to be 2.37 L and 1.41 L, respectively).

As expected for a monoclonal antibody, the volume of distribution estimated in the population PK analysis is in the range commonly reported for mAb. Binding to plasma proteins and distribution to erythrocytes were not investigated because garadacimab is a large protein molecule.

In the proposed SmPC the applicant proposed to add apparent volume of distribution of 7.42 L which is taken form the model-predicted garadacimab pharmacokinetics in Subjects with HAE in Study 3001 after administration of garadacimab 400 mg SC loading dose (2 × 200 mg) followed by 200 mg SC Q1M, given that non-compartmental analysis has not been performed for both phase 3 studies.

Elimination

The metabolic pathway of garadacimab has not been characterised. As a human IgG4 mAb, garadacimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The NCA-derived PK of garadacimab revealed a CL of approximately 8.5 mL/h for IV administration and a CL/F of approximately 23 mL/h for SC administration and a $t_{1/2}$, similar for both routes of administration, at approximately 420 hours, comparable to the average half-life of endogenous IgG in humans (23 days).

The PopPK estimates of CL, CL/F, and $t_{1/2}$ were consistent with NCA results at 6.64 mL/h, 21.7 mL/h, and 445 hours (i.e. 19 days), respectively.

Dose proportionality and time dependencies

The garadacimab exposure (AUC0-inf and Cmax) increases after a single dose appeared dose proportional for IV administration, while for SC administration, garadacimab AUC0-inf increases appeared dose proportional and Cmax increases appeared less than dose proportional.

Garadacimab PK was evaluated as dose proportional in the dose range analysed by PopPK.

No formal assessment of accumulation has been performed for garadacimab. Garadacimab C_{trough} was consistent across multiple SC 200 mg doses.

The PopPK analysis CSL0507F predicted no appreciable accumulation after repeat garadacimab dosing following the loading dose. The simulated PK and PD profiles with and without the loading dose were generally comparable after three doses. The dosing regimen with a loading dose showed a faster achievement of steady-state PK exposures as compared to the dosing regimen without a loading dose. The PopPKPD analyses predicted that a dose regimen of garadacimab 400 mg (2 × 200 mg) SC loading dose followed by garadacimab 200 mg SC Q1M would result in consistent steady-state garadacimab exposures from the first dose.

Intra- and inter-individual variability

Based on the population PK model, the interindividual variability is moderate for clearance and volume of distribution parameters. Interindividual variability in observed serum garadacimab levels can be partly, but not entirely, attributed to differences in body weight, race and target population.

Pharmacokinetics in the target population

Two studies on the target population (Phase 2 Study 2001 and Phase 3 Study 3001) were completed while Study 3002 (Phase 3 open label) is still ongoing.
PK data did not show any influence of the disease on the garadacimab PK, since PK data on healthy subjects are consistent with PK data on target population. It is also confirmed by PopPK analysis CSL0507F, where no influence on AUCss and CL was reported in patients with HAE.

Study 3001 introduced a SC 400 mg loading dose. The PK analysis did not allow to characterise the PK profile, and the exposure reached with the loading dose, since intensive sampling was not conducted in the first hours/days after loading dose administration, but in Study 3002, to characterise the PK profile of the 400 mg loading dose, the PK parameters, C_{max}, T_{max}, and $AUC_{0\text{-}30\ days}$ were calculated for a subset of garadacimab-naïve adult subjects.

Special populations

No dedicated studies on special populations were conducted for garadacimab, except Study 1003 a phase 1 SAD Study to investigate the pharmacokinetics, pharmacodynamics, safety, and tolerability of subcutaneous and intravenous garadacimab in healthy adult Japanese and Caucasian subjects.

Differences in PK in special populations were mainly investigated through PopPK analysis.

Garadacimab (a mAb) is not primarily cleared via hepatic or renal pathways, and it is not expected that renal or hepatic function could influence garadacimab PK. No clinically relevant differences in PK have been identified in subjects with mild or moderate renal impairment, based on PopPK analysis.

Patients with hepatic impairment were not enrolled in clinical studies. Impact of hepatic impairment on garadacimab PK was investigated as part of the PopPK analysis using alanine aminotransferase and bilirubin values as a marker of hepatic function. Both of these covariates were retained on clearance in the final popPK model. However, further simulations exploring magnitude of these covariates on AUC parameter suggest no effect on PK of garadacimab.

Based on PopPK analysis CSL0507F and NCA, no influence on PK of gender, age, and ethnic factors is expected, while an influence of body weight on PK exposure was detected.

A dedicated paediatric study was not conducted. PK in paediatric patients was investigated in Phase 3 studies 3001 and 3002, where 11 adolescents (12 to ≤ 17 years) were enrolled. Garadacimab trough concentrations following SC administration of garadacimab (200 mg monthly with SC loading dose) in adolescent subjects were consistent with the adult population, apart from a greater variability than adults.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	13/173	0/173	0/173

Pharmacokinetic interaction studies

No formal DDI studies have been conducted with garadacimab. However, considering that garadacimab is a mAb and the primary elimination pathways are protein catabolism or target-mediated disposition, PK DDIs are not expected.

In the PopPKPD analysis, the use of concomitant medications (e.g., analgesic, antihistamine, antibacterials, and anti-inflammatory and antirheumatic) and rescue medications had no effect on the PK of garadacimab.

Pharmacokinetics using human biomaterials

N/A

2.6.2.2. Pharmacodynamics

Mechanism of action

Garadacimab is a 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 inhibition of FXIIa, the first factor activated in the contact system, prevents HAE attacks by blocking the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks.

Primary and Secondary pharmacology

In clinical studies, the primary pharmacodynamic action of garadacimab was assessed by measuring plasma biomarker concentrations (aPTT, FXIIa-mediated kallikrein activity, cleaved HMWK, ROTEM), plasma concentrations of FXII, and cytokines.

Two Phase 1 trials in healthy volunteers were conducted (FIH 1001 and 1003) followed by the PoC study in HAE patients, including both the C1-Esterase Inhibitor Deficiency (C1-INH, n=38) and Normal C1-esterase Inhibitor and Factor XII or Plasminogen Gene Mutation (FXII/PLG, n=6) subtype. The PoC study informed dose selection for the pivotal Phase 3 study 3001 followed by the open label extension study 3002.

Across studies, a dose-dependent inhibition of FXIIa-mediated kallikrein activity was observed following either IV or SC administration of garadacimab. After IV administration of 3 or 10 mg/kg garadacimab, near complete or complete inhibition of FXIIa-mediated kallikrein activity was observed. Inhibition was prolonged after IV administration of the 3 and 10 mg/kg garadacimab doses. After SC administration, near complete inhibition of FXIIa-mediated kallikrein activity was observed at plasma concentrations of garadacimab after SC administration at 3 or 10 mg/kg or at 600 mg. Inhibition was prolonged after SC administration of the 3 and 10 mg/kg garadacimab doses.

In Study 2001, dose-dependent inhibition of FXIIa-mediated kallikrein activity was observed across the doses administered, including 200 mg garadacimab SC. Predose samples in Study 2001 Treatment Period 2 indicated that after 4 weeks since the previous dose, garadacimab continued to inhibit FXIIa-mediated kallikrein activity at the 600 mg dose.

Table 1: Pharmacodynamics Analysis: FXIIa Mediated Kallikrein Activity (DeltaA405nm/min) Over Time Treatment Period 1 Blinded (PD Population)

Visit Statistics % of Baseline[1]	C1-INH HAE Blinded Treatment Period 1 Placebo q4wk (N=8)	 75mg CSL312 q4wk (N=9)	 200mg CSL312 q4wk (N=8)	 600mg CSL312 q4wk (N=7)
Treatment Period 1 Week 1 Day 1 0.5 Hours Post				
Number Observed	8	9	8	7
Number Missing	0	0	0	0
Mean (SD)	101.828 (16.6220)	45.881 (55.5568)	12.219 (8.0187)	4.839 (2.3297)
Median	103.125	32.323	12.641	5.344
1st Quartile, 3rd Quartile	87.773, 115.983	20.301, 47.959	4.316, 18.567	2.286, 7.216
Minimum, Maximum	76.98, 123.88	2.35, 186.36	3.57, 23.13	1.64, 7.27
Geometric Mean (Geometric SD)	100.606 (1.1825)	24.293 (3.8572)	9.569 (2.2077)	4.245 (1.8094)
Geometric Coefficient of Variation (%)	16.88	227.73	93.40	64.91
90% Geometric Confidence Interval	89.9208, 112.561	10.5214, 56.0884	5.6298, 16.2653	2.7464, 6.5620
Treatment Period 1 Week 1 Day 1 4 Hours Post				
Number Observed	0	0	0	0
Number Missing	8	9	8	7
Mean (SD)				
Median				
1st Quartile, 3rd Quartile				
Minimum, Maximum				
Geometric Mean (Geometric SD)				
Geometric Coefficient of Variation (%)				
90% Geometric Confidence Interval				

CSL Behring / CSL312_2001: /projects/csbeh239908/stats/primary/prog/tables/t_14_2_3_3_2.sas
Produced: 03MAR2022, 08:45 Page 13 of 24

[1] % of baseline: 100 * (observed value at Visit (i) / baseline value).
[2] Baseline is the most recent non-missing assessment before first dose.

Table 2: Pharmacodynamics Analysis: FXIIa Mediated Kallikrein Activity (DeltaA405nm/min) Over Time Treatment Period 1 Blinded (PD Population)

Visit Statistics % of Baseline[1]	C1-INH HAE Blinded Treatment Period 1 Placebo q4wk (N=8)	 75mg CSL312 q4wk (N=9)	 200mg CSL312 q4wk (N=8)	 600mg CSL312 q4wk (N=7)
Treatment Period 1 Week 5 Day 35				
Number Observed	8	9	8	7
Number Missing	0	0	0	0
Mean (SD)	98.285 (29.5325)	115.414 (95.4610)	81.645 (30.2793)	53.137 (36.8300)
Median	91.440	88.889	74.171	51.832
1st Quartile, 3rd Quartile	78.740, 102.230	80.147, 97.744	65.406, 89.549	16.364, 88.660
Minimum, Maximum	75.45, 166.00	38.82, 361.36	47.14, 147.76	4.10, 104.84
Geometric Mean (Geometric SD)	95.201 (1.2921)	95.231 (1.8205)	77.528 (1.3966)	36.350 (3.1361)
Geometric Coefficient of Variation (%)	26.05	65.71	34.36	164.10
90% Geometric Confidence Interval	80.1845, 113.030	65.6908, 138.0548	61.9837, 96.9697	15.7013, 84.1547
Treatment Period 1 Week 9 Day 63				
Number Observed	8	8	8	7
Number Missing	0	1	0	0
Mean (SD)	96.396 (21.9290)	82.843 (21.4439)	85.318 (31.4518)	46.719 (23.2203)
Median	91.327	81.062	77.611	54.639
1st Quartile, 3rd Quartile	81.432, 115.087	69.443, 98.419	70.053, 93.559	20.000, 66.129
Minimum, Maximum	65.63, 129.85	51.76, 113.13	47.86, 152.24	8.20, 68.06
Geometric Mean (Geometric SD)	94.203 (1.2595)	80.389 (1.3031)	80.982 (1.4009)	38.344 (2.2203)
Geometric Coefficient of Variation (%)	23.38	26.94	34.70	94.30
90% Geometric Confidence Interval	80.7157, 109.943	67.3267, 95.9859	64.6117, 101.499	21.3444, 68.8836

CSL Behring / CSL312_2001: /projects/csbeh239908/stats/primary/prog/tables/t_14_2_3_3_2.sas
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[1] % of baseline: 100 * (observed value at Visit (i) / baseline value).
[2] Baseline is the most recent non-missing assessment before first dose.

Table 3: Pharmacodynamics Analysis: FXIIa Mediated Kallikrein Activity (DeltaA405nm/min) Over Time Treatment Period 1 Blinded and Treatment Period 2 Open-Label on the Same Dose (PD Population)

Visit Statistics[4] % of Baseline[1]	C1-INH HAE Treatment Period 1 Blinded and Treatment Period 2 Open-Label Same Dose 200mg CSL312 q4wk (N=8)	 600mg CSL312 q4wk (N=7)	 Total (N=15)
Treatment Period 2 Week 17 Day 119			
Number Observed	7	7	14
Number Missing	1	0	1
Mean (SD)	112.733 (52.7321)	58.769 (21.5852)	85.751 (47.7749)
Median	109.412	59.162	82.088
1st Quartile, 3rd Quartile	85.890, 156.436	45.455, 78.286	58.015, 109.412
Minimum, Maximum	35.00, 199.25	22.13, 88.66	22.13, 199.25
Geometric Mean (Geometric SD)	100.618 (1.7384)	54.511 (1.5732)	74.059 (1.7870)
Geometric Coefficient of Variation (%)	59.81	47.74	63.31
90% Geometric Confidence Interval	67.0338, 151.0277	39.0796, 76.0358	56.2660, 97.4795

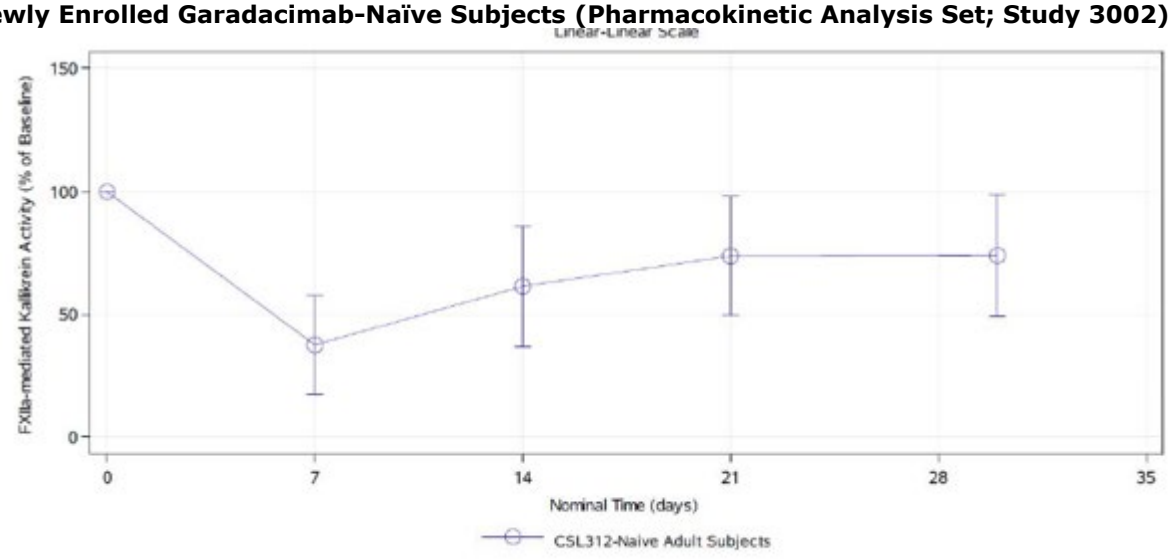
CSL Behring / CSL312_2001: /projects/csbeh239908/stats/primary/prog/tables/t_14_2_3_3_2.sas
Produced: 03MAR2022, 08:45 Page 35 of 45
[1] % of baseline: 100 * (observed value at Visit (i) / baseline value).
[2] Baseline is the most recent non-missing assessment before first dose.
[3] Only data on the same dose continuously in both treatment periods is included. Subjects with a dose decrease from 600mg to 200mg CSL312 are included until their first 200mg CSL312 dose.
[4] NE: not estimable.

In Study 1003, after a single dose of 200 mg garadacimab SC in the Japanese cohort, approximately 60% inhibition of FXIIa-mediated kallikrein activity from Baseline was observed at garadacimab Cmax concentrations followed by a return to Baseline. After a single dose of 200 mg garadacimab SC in the White cohort, approximately 40% inhibition of FXIIa-mediated kallikrein activity from Baseline was observed at garadacimab Cmax concentrations followed by a return to Baseline.

Following administration of garadacimab in Study 3001, the mean FXIIa-mediated kallikrein activity remained consistent, with approximately 20% inhibition observed at the corresponding Ctrough.

In Studies 3001 and **1**, the FXIIa-mediated kallikrein activity for adolescent subjects was similar to that of adult subjects.

Figure 1: Mean FXIIa-mediated Kallikrein Activity Percentage of Baseline Over Time for Newly Enrolled Garadacimab-Naïve Subjects (Pharmacokinetic Analysis Set; Study 3002)



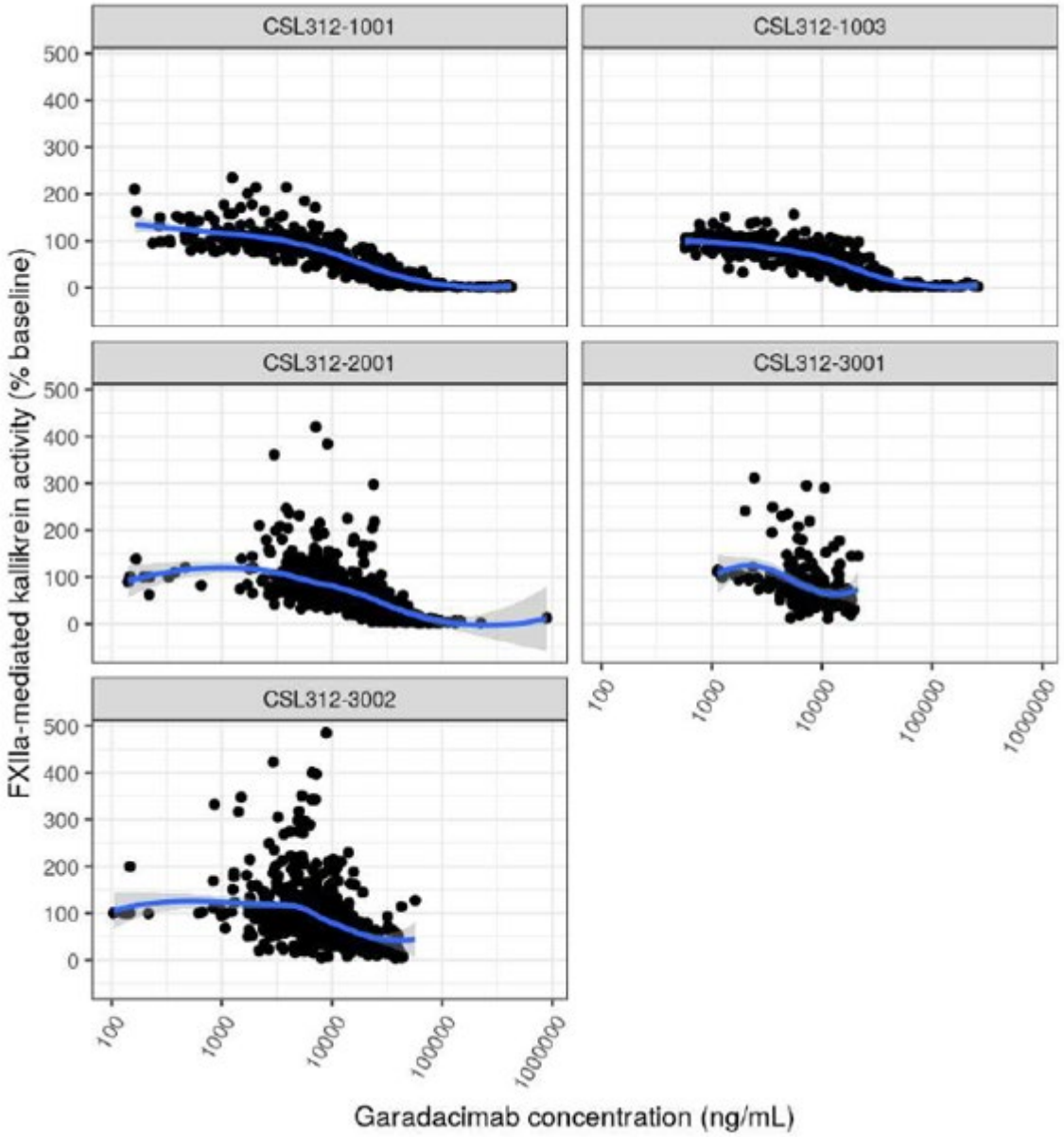
CSL312 = garadacimab; CSR = clinical study report; FXIIa = activated factor XII.

A popPKPD model for FXIIa-mediated kallikrein activity was developed with data pooled from five Phase 1, 2 and 3 studies (Study CSL312_1001, Study CSL312_1003, Study CSL312_2001, Study CSL312_3001, and Study CSL312_3002). These models described garadacimab disposition, the effect

of PK on pharmacodynamic (PD) (FXIIa-mediated kallikrein activity), and the effects of intrinsic/extrinsic factors on PK and PD.

Composite plots of FXIIa-mediated kallikrein activity POB versus time after first dose for each study and route of administration, stratified by dose group, and FXIIa-mediated kallikrein activity POB versus garadacimab concentration, stratified by study, were generated.

Figure 2: FXIIa-mediated Kallikrein activity as a percent of baseline versus garadacimab concentration; stratified by study



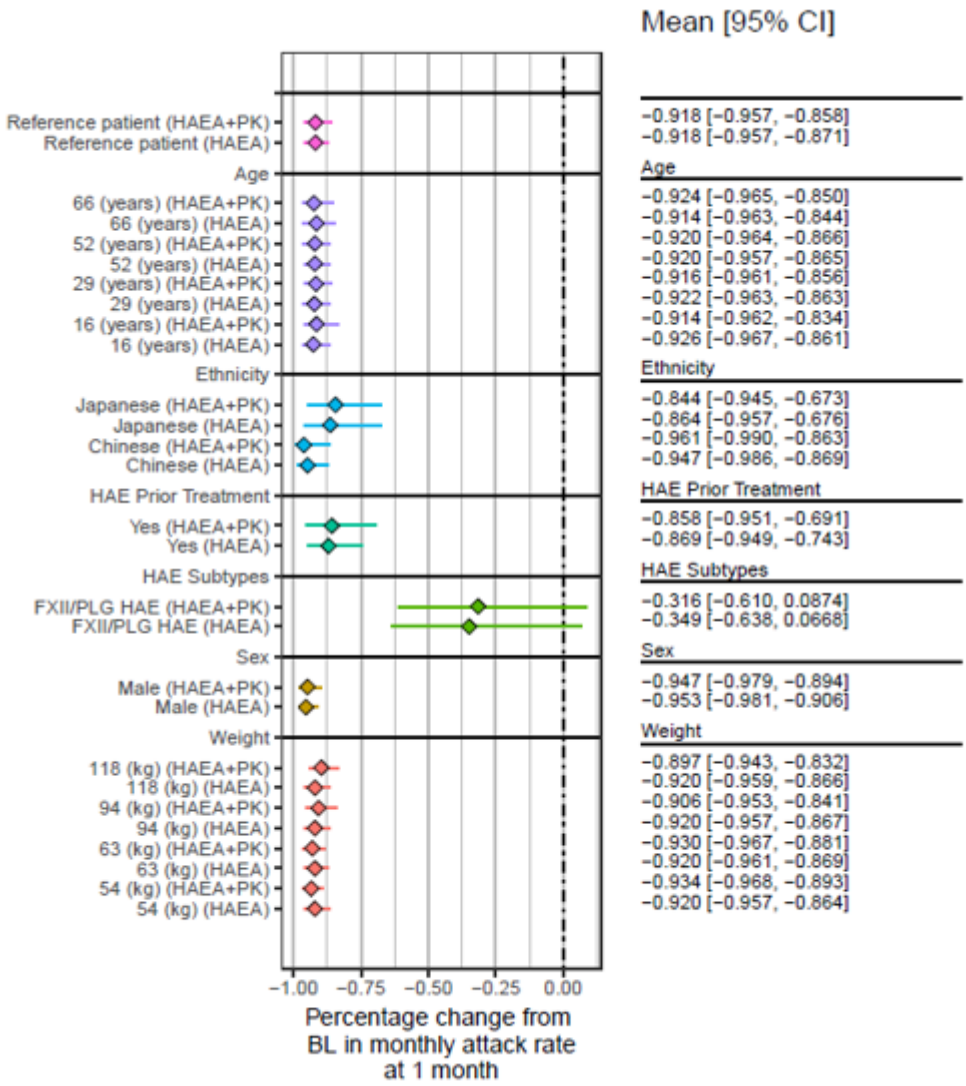
Solid black circles represent the observations. The blue lines and grey shaded areas represent the LOESS smooth lines and the associated confidence intervals through the data, respectively

An E-R model for garadacimab in preventing HAE attacks and to explore the impact of covariates and co-administered medications on efficacy in support of a 400 mg (2x200 mg) SC loading dose followed by 200 mg once monthly SC dose was developed based on data from Study CSL312_2001, Study CSL312_3001, and Study CSL312_3002.

The full analysis dataset included 177 unique subjects who received either garadacimab or placebo. Of the 177 total subjects, 165 subjects (93%) received 200 mg SC Q1M. Eighteen of the 177 total subjects dropped out, but only 3 subjects dropped out due to lack of efficacy or adverse event.

HAE attack data was modelled using a repeated time-to-event framework with a nonlinear Imax ER relationship, from subject-specific PK parameters derived from a previously developed PPK model. The ER model included age, ethnicity, sex, prior treatment, and HAE type as covariates. Among the covariates included ethnicity (non-Japanese or non-Chinese vs. Chinese vs. Japanese), HAE type (HAE type I/II vs. FXII/PLG), and prior treatment (no vs. yes) exhibited strongest influence on efficacy outcomes (Figure 3 and Figure 4).

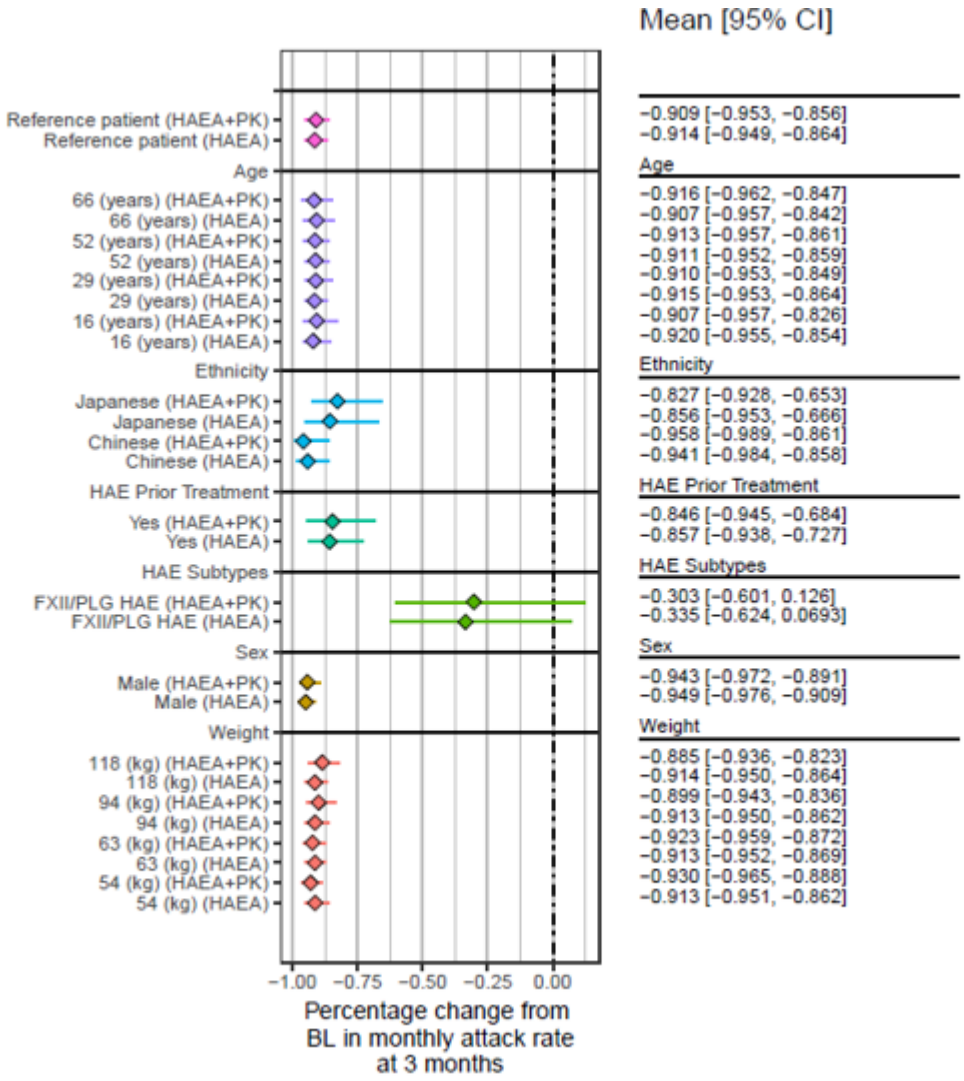
Figure 3: Forest Plots: Conditional simulations of percent change from baseline attack rate at month 1 with fixed covariate levels



Points and lines indicate the mean and 95% PI for the mean percent change from baseline attack rate.

Covariates are fixed at the indicated levels in either the HAE attack model alone (HAEA), in which case PK assumes the reference patient, or in both the HAEA and PK model. PK is simulated at steady-state with a SC 400 mg loading dose and 200 mg SC once monthly maintenance dose. Continuous covariate levels correspond to the 5th, 25th, 50th, 75th and 95th percentiles of the covariate in the analysis population

Figure 4: Forest Plots: Conditional simulations of percent change from baseline attack rate at month 3 with fixed covariate levels



Points and lines indicate the mean and 95% PI for the mean percent change from baseline attack rate.

Covariates are fixed at the indicated levels in either the HAE attack model alone (HAEA), in which case PK assumes the reference patient, or in both the HAEA and PK model. PK is simulated at steady-state with a SC 400 mg loading dose and 200 mg SC once monthly maintenance dose. Continuous covariate levels correspond to the 5th, 25th, 50th, 75th and 95th percentiles of the covariate in the analysis population

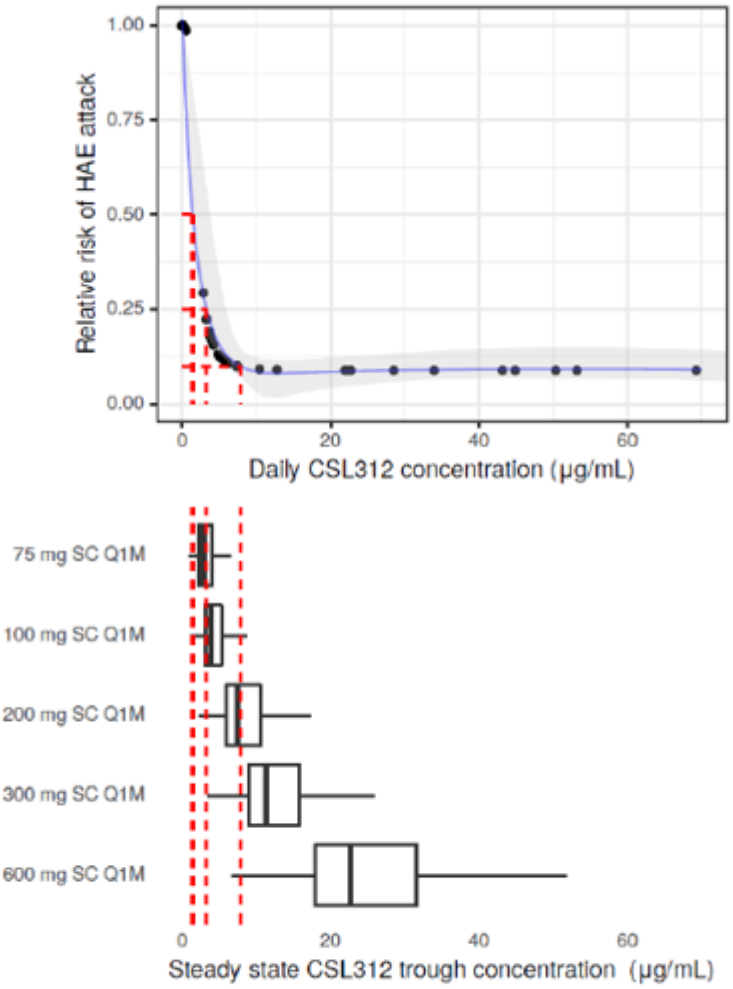
Table 4: Population Simulations: HAE Relative Risk by $AUC_{tau,ss}$ in the Adult and Adolescent Population (CSL050F-Report-ER)

$AUC_{tau,ss}$		HAE Attack Relative Risk		Responder Probability		
Percentile	Median (Minimum, Maximum) (µg•h/mL)	Mean (SD)	Median (50% PI) [90% PI]	50%	70%	90%
≤ 5%	4000 (1910, 4650)	0.136 (0.192)	0.0500 (0.0140, 0.167) [0.00255, 0.585]	0.901	0.842	0.628
5% to 25%	6250 (4650, 7490)	0.113 (0.179)	0.0355 (0.00978, 0.126) [0.00213, 0.550]	0.914	0.857	0.684
25% to 50%	8900 (7490, 10,400)	0.0875 (0.149)	0.0250 (0.00708, 0.0905) [0.00183, 0.425]	0.935	0.886	0.734
50% to 75%	12,100 (10,400, 14,500)	0.0748 (0.131)	0.0214 (0.00615, 0.0774) [0.00172, 0.348]	0.948	0.907	0.764
75% to 95%	17,300 (14,500, 23,300)	0.0565 (0.112)	0.0148 (0.00452, 0.0493) [0.00143, 0.269]	0.965	0.937	0.824
> 95%	27,200 (23,300, 73,700)	0.0443 (0.0949)	0.00953 (0.00327, 0.0353) [0.00130, 0.212]	0.964	0.952	0.873
Total	10,400 (1910, 73,700)	0.0835 (0.147)	0.0225 (0.00641, 0.0843) [0.00170, 0.406]	0.940	0.897	0.751

$AUC_{tau,ss}$ = area under the plasma concentration-time curve in 1 dosing interval at steady state; HAE = hereditary angioedema; PI = prediction interval; SD = standard deviation.

Notes: Exposure bins correspond to intervals at the 5th, 25th, 50th, 75th, and 95th percentiles of $AUC_{tau,ss}$. Within each of these exposure bins, the population-predicted mean, SD, median, 50%, and 90% PIs are provided. Population predictions of the proportion of subjects that would be classified as responders at 50%, 70%, and 90% are also included.

Figure 5: Relative Risk of an HAE Attack as a Function of Garadacimab Concentration (CSL0507F-Report-ER, Appendix 4, CSL0503H-Report)



CI = confidence interval; CSL312 = garadacimab; C_{trough} = trough plasma concentration; HAE = hereditary angioedema; IQR = interquartile range; Q1M = once monthly; SC = subcutaneous.
Notes: In the top panel, the blue line is the model prediction and the gray ribbon is the approximate 95% CI. In the bottom panel, the box plots indicate distribution of steady state garadacimab C_{trough}; the box represents the IQR, the line in the box represents the median, and the whiskers represent 1.5 × IQR. Red dash lines in both panels correspond to relative risk of HAE attacks of 0.50, 0.25, and 0.10.

TQT

No thorough QT study has been conducted for garadacimab. Garadacimab is a mAb with a low likelihood of a direct ion channel interaction. In addition, no potential proarrhythmic risks are suggested by the mechanistic considerations or based on the data from clinical and nonclinical studies.

Electrocardiograms were taken in Studies 1001, 1003, and 3001. There were no clinically relevant trends over time or differences across the garadacimab doses (across the IV and SC doses, respectively, or between the IV and SC doses) or between garadacimab and placebo for heart rate, PR duration, QRS duration, QT interval, or heart rate-corrected QT interval.

DDIs

No formal DDI studies have been conducted with garadacimab.

Genetic differences in PD response

No PD response analyses by genetic differences were provided.

Immunological events

Throughout the clinical development programme, the cumulative incidence of treatment-emergent anti-garadacimab antibodies in subjects with HAE was 2.9% (5 of 172). None of the 11 adolescent subjects tested positive for treatment-emergent anti-garadacimab antibodies. There was no apparent impact of anti-garadacimab antibodies on PK, PD, efficacy, or safety.

In general, in all clinical studies inhibition of FXIIa-mediated kallikrein activity was observed following garadacimab administration. Overall, the mean FXIIa-mediated kallikrein activity in subjects who tested positive for anti-garadacimab antibodies is similar to those that are ADA negative.

2.6.3. Discussion on clinical pharmacology

Analytical methods

Bioanalytical method based on enzyme-linked immunosorbent assay (ELISA) was validated for quantitation of garadacimab in human plasma. Validation results demonstrated that the ELISA-based assay was sufficiently accurate and precise to reliably allow the determination of garadacimab in human plasma samples in PK studies.

Multiple methods were used for PD biomarkers measurement. They are considered reliable and validated. A method was evaluated for determination of activated Prothrombin Time (aPTT) in human plasma. It was demonstrated that, with concentrations above 0.009 mg /mL of garadacimab, an influence on aPTT prolongation was shown. This interference is reflected in SmPC section 4.4.

Appropriate ADA assays have been validated successfully and is suitable for use in the clinical studies. However, despite some ADA positive results in subjects treated with garadacimab were detected, the presence of neutralizing antibodies in garadacimab-treated subjects with positive ADA results was not measured. Because of this, the clinical relevance of ADA could not be fully established. This uncertainty has been conveyed in the SmPC.

Evaluation and qualification of models

Multiple PopPK, PopPKPD and ER models were developed to characterise PK and PD and the exposure-response relationship of garadacimab. Model validation was performed using a newer data cut from Study CSL312_3002 (available on 13 February 2023). As a general comment, models were adequately developed and can be considered appropriate for the purpose.

However, it should be noted that the model predictions (both for PopPK CSL032 and PopPKPD CSL0507F) accurately described the new data for PK, while some evidence of overprediction was present in PopPKPD CSL0507F for the samples collected prior to the next dose for PD determination FXIIa-mediated kallikrein activity percent change and some of the observed data fall outside the prediction intervals in PopPK CSL032.

PopPKPD model CSL-037 was used to support dose selection for Phase 3 study 3001. A complete PopPKPD report was not initially submitted but was provided as part of D120 responses (Attachment-D120-Q90-A1). The simulations performed to establish the best dose for Phase 3 study were described in PopPK report CSL0503H-Report-PKPD-v1.0-Final, that was provided in response to D120 list of questions and is dated May 31st, 2024, but it reports the same analysis that was initially described in report CSL-037.

Exposure response modelling, using exposures generated from the PK model, indicated that the target daily average concentration that results in 90% relative risk reduction in HAE attack rate is~7.8 µg/mL

and the 200 mg SC Q1M (with a 400 mg SC loading dose) was predicted to align with daily average concentrations of that approximate magnitude.

ADME

Final popPK/PD model estimated constant rate of absorption to be 0.00824 (L/h) and it was reported in section 5.2 of the SmPC. Data on absolute bioavailability obtained by PopPK model was reported in SmPC. Although metabolism of garadacimab has not been directly studied, it has been properly reflected in the SmPC.

Special populations

In popPK model, the applicant explored covariate eGFR on PK variability of garadacimab. Simulations show that there is no effect on exposure of garadacimab in HAE patients with renal impairment.

Patients with hepatic impairment were not enrolled in clinical studies. Impact of hepatic impairment on garadacimab PK was investigated as part of the PopPK analysis using alanine aminotransferase and bilirubin values as a marker of hepatic function. Both of these covariates were retained on clearance in the final popPK model. However, further simulations exploring magnitude of these covariates on AUC parameter suggest no effect on PK of garadacimab. The information on hepatic impairment has been properly reflected in SmPC.

Effect of ethnicity on garadacimab PK was investigated in a dedicated study for Japanese population (Study 1003), in subgroup analysis of studies 3001 and 3002 and through PopPK analysis. No evidence of a clinically relevant effect of ethnicity is evident from available data, both in terms of PK and PD. However, only Asian and Caucasian populations are adequately represented, while only 4 black patients and 4 patients of other ethnicities were enrolled.

According to available data of study 3001, PK of the adolescents enrolled is similar to PK of adult subjects, apart from a greater variability than adults. A subgroup analysis, comparing PK of adolescents versus adults enrolled in study 3002 showed no clinically relevant differences in PK between adults and adolescents.

Pharmacodynamics

The pharmacological action of garadacimab was demonstrated in pre-clinical models and *in vitro* experiments and a mechanism-based PK-PD model was developed based on the non-clinical work to inform dose selection for FIH trial.

Primary and secondary pharmacology

In clinical trials conducted in healthy volunteers and patients, the mechanism of action of garadacimab was characterised through the measurement of relevant biomarkers, specifically the FXIIa-mediated kallikrein activity as indicative of primary pharmacology, in addition to aPTT, cleaved HMWK, ROTEM as measure of free FXII activity, as well as plasma concentrations of FXII, and cytokines, that characterise the drug effects deriving from the inhibitory action on FXII-dependent pathways. Consistently with the expected mode of action of the drug as derived from pre-clinical investigations, garadacimab demonstrated *in vivo* engagement of its pharmacological target as measured by inhibition of the plasmatic FXIIa-mediated kallikrein activity. A dose-dependent pharmacological effect was consistently shown throughout the clinical development programme. The *in vivo* analysis of coagulation related parameters confirmed the inhibitory action of garadacimab on the intrinsic pathway only. The pharmacodynamic of garadacimab has been reported in section 5.1 of the SmPC.

Overall, available clinical PK/PD models confirmed the primary pharmacology profile that consistently showed a dose dependent reduction in FXIIa activity. However, the relationship between FXIIa-mediated kallikrein activity over time and the occurrence of HAE attacks was not obvious, thus leaving

the identification of the therapeutic window and justification for dose selection not fully substantiated. The impossibility to characterise the exposure-response relationship in the overall population due to the epidemiology of disease and restricted number of different genetically defined disease subgroups, limits the validity of a modelling approach in the characterisation of this aspect. These limitations were overcome by the clinical evidence submitted in support of the intended indication. Indeed, the dose tested in the pivotal trial (400 mg loading dose followed by 200 mg q1M) provided evidence for a clinically relevant effect of garadacimab on HAE attack prevention as emerged from the primary efficacy analysis of study 3001 (see efficacy part), thus supporting the appropriateness of drug posology.

Genetic differences in PD response

Another aspect of uncertainty pertains to the effect of garadacimab in the totality of HAE type III–associated mutations. While mutations of FXII that are known to affect protein domains other than the catalytic site, particularly the p.Thr328Lys mutation of FXII, are not expected to impact on the binding of garadacimab to its target, the impact on drug response of different genetically defined disease subgroups cannot be fully ascertained.

As regards plasminogen mutants, the abnormal release of bradykinin that underlines HEA disease bypasses the FXII/kallikrein pathway. Therefore, the mode of action of garadacimab and/or intended dose in this subpopulation might result in an insufficient therapeutic effect. The same consideration applies to all known and unknown gene variants that fall within the category of nC1INH-HAE, for which a dysregulation of metabolic pathways other than the FXII-dependent bradykinin production underlines clinical events. Under these conditions, the pharmacological action of garadacimab could be insufficient to control HAE attacks. Based on these considerations, recommendation and precaution of use in the treatment of selected subgroups of patients have been included in the SmPC (section 4.2, 4.4 and 5.1).

In the FIH trial (1001) the selected dose ranges (0.1 - 10 mg/kg i.v. and 3-10 mg/kg s.c.) were adequately derived from the non-clinical PK-PD modelling using non-human primate data, that indicated a minimal predicted pharmacologic effect at the starting dose of 0.1 mg/kg. The clinical study provided evidence for the minimum active dose of garadacimab in healthy volunteers, based on levels of reduction in baseline FXIIa-mediated kallikrein activity relatively to placebo, and this was identified in the 3 mg/kg for both the intravenous and subcutaneous route of administration. At 3 and 10 mg dose an increase in the plasma level of FXII was also registered, which however did not seem to be dose related. The aPTT was prolonged by the 3 and 10 mg/kg in a dose-dependent manner; at 1 mg/kg there was a smaller and shorter (in duration) peak indicating a transient aPTT prolongation while no changes relatively to placebo were observable at lower doses.

In the subsequent Phase 1 study (1003), the subcutaneous administration was tested at a flat dose of 200 mg in both Japanese (Cohort-1a) and weight-matched Caucasian (Cohort-1b) healthy individuals, while a 600 mg dose was injected in Japanese individuals only (Cohort-2); the intravenous administration was tested in Japanese individuals only at the dose of 3 mg/kg and 10 mg/kg. A higher level of response was observed at 200 mg s.c. dose in Japanese individuals compared to Caucasian individuals in terms of reduction in FXIIa-mediated kallikrein activity (60% vs 40% reduction from baseline in the two populations, respectively), this inhibitory effect being more pronounced at 600 mg (near complete inhibition) with a persistence of around 30% suppression of FXIIa-mediated kallikrein activity compared to baseline levels up to the end of follow-up. The increase in FXII concentrations, previously reported in study 1001, also emerged in this population of healthy individuals. The dose-dependency of this phenomenon is unclear.

The Phase 2 study 2001 served as proof-of-concept in HAE patients receiving placebo or 75, 200 or 600 mg for the comparison of 200 mg garadacimab q4wk versus placebo and 600 mg garadacimab

q4wk versus placebo administrated via subcutaneous route, all doses preceded by an intravenous loading dose (placebo, 40, 100 or 300 mg i.v in the different groups, respectively). Both the C1-Esterase Inhibitor Deficiency (C1-INH, n=38) and Normal C1-esterase Inhibitor and Factor XII or Plasminogen Gene Mutation (FXII/PLG, n=6) disease subtypes were studied. The analysis of C1-INH subgroup showed a dose-dependent reduction in FXIIa-mediated kallikrein activity during the conduction of Part 1, with an effect that peaked at 0.5 hour post-intravenous loading to then reach a value of 67% and 11% of baseline at day 6 for the 200 and 600 mg dose respectively, which was maintained until the end of Part 1. It is quite peculiar the loss of inhibitory activity that emerged from Part 2, where even continuation of treatment at the same dose as Part 1 was associated to a return of FXIIa-mediated kallikrein activity to baseline levels in the 200 mg group and a reduced inhibitory action in the 600 mg group (around 50% of baseline). Upon request, the applicant provided an explanation on this aspect that appears to have been influenced by several factors, including the natural variability of the FXIIa-mediated kallikrein activity, limits of sensitivity and precision of the analytical method, and changes in dose as a consequence of a re-randomisation process. This is acceptable.

With regard to FXII/PLG HAE patients, they were assigned to a 600 mg dose in Part 1. The applicant did not report specific comments on this subgroup given the limited sample size. Based on the results, it appears that a reduced inhibitory effect of the 600 mg dose was reached compared to the C1-INH HAE subgroup, with a level of FXIIa-mediated kallikrein activity settled around 50% of baseline until the end of Part 1, although a slightly better performance was achieved in Part 2 (around 40% of baseline). In the pivotal trial 3001, the selected dose of 200 mg s.c. was administrated with an initial loading dose of 400 mg injected subcutaneously. The sparse sampling demonstrated an even lower level of suppression of the FXIIa-mediated kallikrein activity (below 20%) compared to the PoC study, with a value above 75% of baseline maintained throughout the study duration. This value was consistently registered in the open extension study 3002.

PopPKPD model

Development of the popPKPD model consisted of data from studies 1001, 1003, 2001, 3001 and 3002. The analysis dataset included 262 unique subjects who received either placebo or garadacimab treatment. Only 0.7% of samples were BLQ, therefore these data were excluded during model development.

The PKPD model described the inhibition of FXIIa-mediated kallikrein activity POB (percent of baseline) by garadacimab with a direct effect, sigmoidal Emax model, parameterised in terms of Emax, EC50, E0 and γ. Final model parameter estimates for fixed and random effects were estimated with reasonable precision (as judged by the CI ranges). Covariate baseline FXIIa-mediated kallikrein activity effect was retained in the final model on parameters EC50 and E0.

The 95% CI did not include the null value of zero, indicating the EC50 increased with increasing baseline FXIIa-mediated kallikrein activity. Similarly, the estimate and 95% CIs for the baseline FXIIa-mediated kallikrein activity effect on E0 (−0.262 (95% CI: −0.307, −0.271)) did not include the null value indicating that E0 decreased with increasing baseline FXIIa-mediated kallikrein activity. The magnitude of these covariate effects was further evaluated via simulations of EC50. The magnitude and direction of the baseline FXIIa-mediated kallikrein activity effect on EC50 was in agreement with the values i.e., the EC50 increased with increasing baseline FXIIa mediated kallikrein activity. However, the point estimates and 95% CIs of this effect were almost fully contained within the reference range, indicating baseline FXIIa-mediated kallikrein activity was unlikely to have a clinically meaningful effect on the EC50. However, lower limit of 95% CI is slightly below reference range (74.8%).

The final model provided a reasonable description of the FXIIa-mediated kallikrein activity POB, indicated by the goodness of fit plots.

The visual predictive check for the final population PKPD model showed simulated FXIIa-mediated kallikrein activity percent change was similar to observed FXIIa-mediated kallikrein activity percent change at the 5th, 50th, and 95th percentiles across the full time after dose and garadacimab concentration profile for each study.

New predictions conditional upon new observed dosing and the patient empirical bayes estimates from the PKPD model were generated and compared to the newly observed kallikrein percent change observations. While some evidence of overprediction was present, the majority of the data is well spread within the prediction intervals (PIs). The model was deemed appropriate to characterise the FXIIa-mediated kallikrein activity effect within the range of clinical relevance. Additionally, exposure response model was developed. However, one of the main objectives of the model were to perform simulations to confirm efficacy of a 400 mg (2x200 mg) subcutaneous (SC) loading dose followed by 200 mg once monthly SC dose and to explore covariates on HAE attack rate. Given that proposed dosage regimen was studied in phase 3 studies, exposure-response model could be considered as supportive.

Overall, exposure response model included data from studies 2001, 3001 and 3002. The primary analysis variable was the time to (repeated) HAE attack. Subjects in this patient population had multiple attacks over the duration of the studies, thus the analysis was of repeated times to event. HAE attacks were modelled using a repeated time-to-event (RTTE) framework.

Incidence of attack after treatment was comparable across ranges of observed bodyweights and other covariates (age, ethnicity, sex, prior treatment) suggesting no evidence for dose adjustments due to bodyweight or other covariates.

The probability of being a 90% responder increased from 0.628 for patients with the lowest exposure (AUCtau,ss less than the 5th percentile, 4650 µg x hour/mL) to 0.873 for those at the highest exposure (AUCtau,ss greater than the 95th percentile, 23300 µg x hour/mL). The threshold to attain a 90% reduction in relative risk corresponded to an AUCtau,ss of 7640 µg*hr/mL, a Cmax,ss of 14.5 µg/mL, and a Cmin,ss of 6.00 µg/mL. The probability of exceeding that threshold given a 200 mg once monthly dose was 0.737, 0.754, and 0.731 for AUCtau,ss, Cmax,ss, and Cmin,ss, respectively.

The PKPD model generated with the totality of clinical data, essentially confirmed the dose-dependency of the FXIIa-mediated kallikrein activity reduction induced by garadacimab. Of note, a trend was observable in the IIV random effects on EC50, E0, and γ for the ethnicity (Japanese versus non-Japanese, Chinese versus non-Chinese) and disease status (healthy volunteers versus HAE patients) covariates for the FXIIa-mediated kallikrein activity. No mechanistic explanations are hypothesised explaining these observations, that however seem to contradict the higher performance of garadacimab in Japanese versus weight-matched Caucasians that emerged in study 1003, thus suggesting that factors other than ethnicity were implicated in these results; on the contrarily, a lower degree of response could be generally reported in HAE vs healthy volunteers, although it must be considered the different sampling schedules that hampers a direct comparison across clinical trials. Importantly, no relationship was found between drug response and baseline levels of FXIIa-mediated kallikrein activity, although the variability of the measured parameter and limitation of the analytical methods must be taken into account as limiting factors of this analysis.

No major differences are appreciable between adults and adolescent as regards FXII- mediated kallikrein activity in response to treatment.

TQT study

The absence of a TQT study appears adequately substantiated by the totality of evidence currently available. The nature of the drug, mechanistic considerations, non-clinical data and ECG information collected during the clinical experimentation, are suggestive of a low risk of QT prolongation associated to garadacimab.

DDIs

No DDI studies were performed. As being a monoclonal antibody, no drug metabolism interactions with other medicines are expected for garadacimab. Currently available evidence does not indicate interference of garadacimab with drugs acting on the coagulation cascade or the bradykinin system. Considering that the binding site of garadacimab is in the catalytic domain of FXII (i.e. βFXIIa), the mutations of FXII that are known to affect protein domains other than the catalytic site, particularly the p.Thr328Lys mutation of FXII, are not expected to impact on the binding of garadacimab to its target.

Immunogenicity

Treatment with Andembry has been associated with development of low-titre treatment emergent anti-drug antibodies (ADA) in 2.9% (5/172) of treated subjects. Due to the low titre of ADA registered in these subjects, neutralizing antibodies could not be detected. Therefore, the clinical relevance of ADA could not be fully established.

Dose justification

The E-R model (CSL0507F) analysing the relationship between exposure and HAE attacks was built from studies 2001, 3001 and 3002. It was estimated that the threshold to attain a 90% relative risk reduction in HAE attack corresponded to an AUCtau,ss of 7640 µg•h/mL, a Cmax,ss of 14.5 µg/mL, and a Cmin,ss of 6.00 µg/mL. The model predicted that the majority (above 70%) of patients with HAE have exposures above the therapeutic threshold, increasing up to approximately 85% with a loading dose. Among the studied covariates, HAE type (HAE type I/II vs. FXII/PLG) exhibited the strongest influence on efficacy outcomes. Ethnicity and prior treatment were also identified as covariates of interest although it must be recognised that, in this case, deviations from mean effect, were minimal.

With regard to dose justification, the proposed posology was derived from the Phase 2 PoC study (2001) results informing the E-R model that was used to simulate HAE attack rates over garadacimab concentrations, and that formed the basis for the dose selection tested in the pivotal Phase 3 trial. The ER model CSL-0503H was initially not submitted and was provided upon request. With all the limitations derived from the few data available (dataset included 32 subjects from study 2001) that informed the model and the lack of a proper prospective validation, the model appears fit-for-purpose although its value in supporting efficacy of treatment in the totality of the population, including the different HAE subtypes, is limited. Indeed, there was a lack of relationship between the relative risk of HAE attack versus kallikrein percent of baseline.

The dose range used in the Phase 2 trial, on the other hand, was derived from a direct pharmacology analysis based on the Phase 1 data, where the key PD endpoint was the FXIIa-mediated kallikrein activity. It was hypothesised that inhibiting FXIIa-mediated kallikrein activity consistently to a particular % target inhibition was expected to provide protection from HAE attacks. However, the optimal FXIIa-mediated kallikrein inhibition able to produce the desired therapeutic effect was not pre-specified. The applicant investigated the relationship between FXIIa inhibition and HAE attacks in the Phase 2 trial 2001 but failed to provide evidence for a dose-response relationship in terms of clinical effect, considering the similar performance of the 75 mg and 200 mg dose and reduced effect of the 600 mg in controlling HAE attacks; moreover, the relationship between FXIIa-mediated kallikrein

activity over time and the occurrence of attacks was not obvious. Moreover, the model used to inform dose selection for the Phase 3 did not include Part 2 of the Phase 2 trial, with the associated variability in drug response compared to the observed effect in Part 1, at least in terms of action on FXIIa-mediated kallikrein activity, and it did not include HAE type among explored covariates, thus further limiting the knowledge around the potential implications on drug activity of FXII mutations or presence of kallikrein dysfunction other than those associated to the XII-dependent pathway.

Ultimately, the clinical observations remain the only valid support to the intended posology in spite of the failure of the modelling exercise in describing exposure-response relationships in the target population.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of garadacimab has been adequately investigated, both in healthy subjects and in target population. The mode of action of garadacimab has been sufficiently characterised, with regard to its target with consequent suppression of the FXIIa-mediated kallikrein activity. The effect appears to be dose dependent. However, no relationship has been described between the FXIIa inhibition and preventative action of garadacimab against HAE attacks. Hence, the proposed posology is mainly supported by the available clinical evidence generated in the pivotal trial.

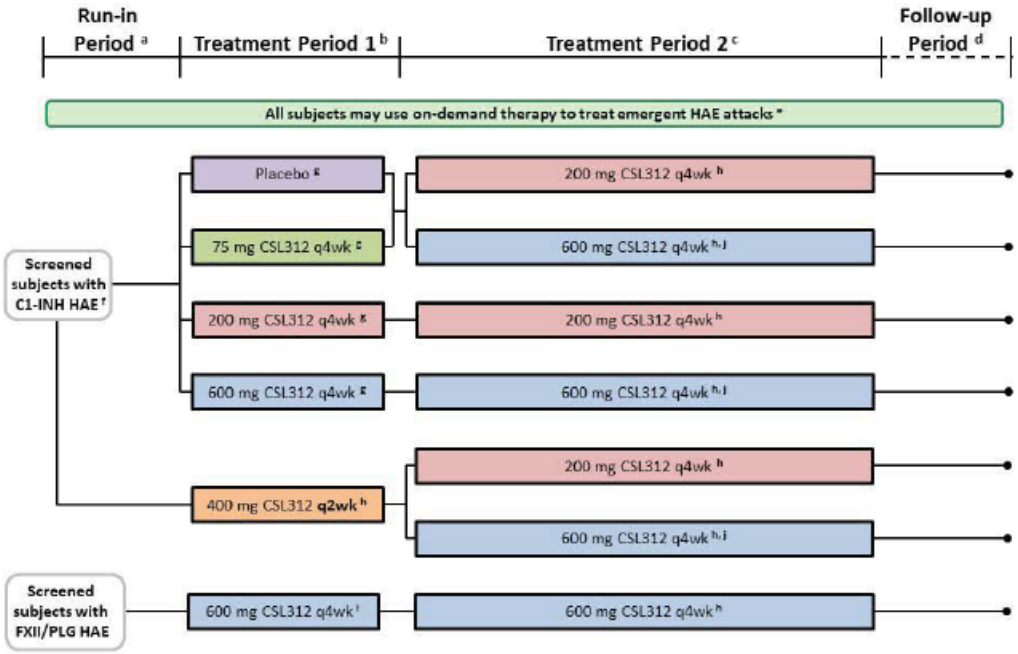
2.6.5. Clinical efficacy

Please see the Tabular overview of clinical studies in the section 2.6.1 Introduction (Clinical aspects).

2.6.5.1. Dose response study

Study 2001

This phase 2 proof-of-concept, dose-finding study was a multicentre, randomised, placebo-controlled, parallel-arm study. The primary objective was to evaluate the efficacy of garadacimab in the prevention of HAE attacks in subjects with C1-INH HAE. The secondary objectives were to further evaluate the efficacy, PK and safety and tolerability of garadacimab. Efficacy, PK / PD, QoL, and safety were evaluated further as part of the exploratory objectives in subjects with C1-INH HAE or nC1-INH HAE.



Treatment Period 1 (TP1) included a double-blind, placebo-controlled part for C1-INH subjects and had a duration of 13 weeks. TP2 was open-label and had a duration of at least 44 weeks.

32 subjects with C1-INH HAE were randomised to 1 of 4 treatment arms in a 1:1:1:1 ratio during TP1: subcutaneous garadacimab 75 mg q4wk (loading dose 40 mg IV, one week before the first dose), 200 mg q4wk (loading dose 100 mg IV), 600 mg q4wk (loading dose 300 mg IV), or placebo q4wk thereafter for 12 weeks. An additional 8 subjects received open label garadacimab 400 mg q2wk.

For FXII / PLG HAE subjects TP1 was open label (garadacimab 600 mg q4wk).

After Protocol Amendment 2 all C1-INH HAE subjects in TP2 received garadacimab 200 mg q4wk. FXII/PLG HAE subjects were to be maintained on the 600 mg q4wk SC dose.

Dose selection was based on data obtained in the phase 1 (Study 1001) and simulations that determined that fixed doses of 75 mg, 200 mg, and 600 mg administered q4wk would result in at least 75% of the patients reaching a % target inhibition of FXIIa-mediated kallikrein activity of ≥30, ≥50, and ≥90%, respectively.

Main eligibility criteria for subjects with C1-INH HAE

Subjects aged ≥18 to ≤ 65 years with a documented diagnosis of HAE (Type I or II) and ≥4 attacks over consecutive 2-months period during the 3 months before Screening and ≥2 attacks over the 4-weeks Run-in period.

Main eligibility criteria for subjects with FXII/PLG HAE:

Subjects aged ≥18 to ≤ 65 years with a documented diagnosis of FXII/PLG HAE and ≥ 1 HAE attack during the 3 months before Screening, and ≥1 attacks over the Run-in period.

The subjects should stop using C1-INH therapy, androgens, or antifibrinolytics for routine prophylaxis of attacks on the first day of the Run-in period.

Permitted therapy for HAE attacks included: treatment on-demand and pre-procedure prevention.

Primary efficacy endpoint:

Time-normalised (per month) number of HAE attacks in subjects with C1-INH HAE on treatment with garadacimab 200 mg or 600 mg q4wk compared to placebo during TP1

Secondary efficacy endpoints: number of responders (≥ 50% relative reduction in the time-normalised number of HAE attacks during TP1 compared to the Run-in Period), number of subjects who were attack-free during TP1, number of HAE attacks during TP1 (time-normalised number and percentage of mild, moderate, or severe HAE attacks), number of HAE attacks treated with on-demand HAE medication during TP1.

To test for a difference in the primary efficacy endpoint between 200 mg garadacimab q4wk or 600 mg garadacimab q4wk and placebo q4wk, pairwise comparisons were performed by testing the hypotheses using a two-sided Mann-Whitney test. To account for multiple testing, the alpha level of 5% was evenly split between the two hypotheses tested. Therefore, the 200 mg garadacimab q4wk or 600 mg garadacimab q4wk doses (in subjects with C1-INH HAE) were each evaluated against placebo at alpha = 0.025. All secondary endpoints have to be considered as descriptive in nature. To assess the impact of missing data for the primary efficacy variable an enhanced tipping-point analysis was applied to investigate the robustness of the study's conclusion to the assumed missingness pattern.

A total of 38 subjects with C1-INH HAE completed the Run-in Period and were assigned to treatment in TP1 (placebo: 8 subjects, garadacimab 75 mg q4wk: 9 subjects; 200 mg q4wk: 8 subjects; 600 mg q4wk: 7 subjects; 400 mg q2wk: 6 subjects). All subjects completed participation in TP1 and began treatment in TP2 and, of those, 36 subjects completed the study.
In TP1, 6 subjects, with either FXII HAE (3) or PLG HAE (3) received 600 mg garadacimab q4wk. 1 subject with FXII HAE discontinued TP1 due to lack of efficacy. Of the 5 subjects who completed TP1, 3 subjects completed the study after TP1, and 2 subjects completed the study after TP2.

Baseline characteristics:

While the females were 50% in the placebo arm, they varied from 25% in 200mg arm to 78% in 75mg arm. The median age of the subjects ranged from 24 years in the 600mg arm to 46 years in the 75mg arm. Type 1 C1-INH HAE patients were 87.5% in placebo and 200mg arms and 100% of subjects in 75mg and 600mg arms). The median percentage of subjects that used HAE prophylaxis before the screening ranged from 12.5% (placebo and 200mg arm) to 66.7% (75mg arm). The median number of HAE attacks before screening / start of prestudy prophylaxis ranged from 7 in 600mg arm to 15 in 75mg arm. The median Time-normalised Number of HAE Attacks per month during the Run-in Period ranged from 2.95 in 600mg arm to 6.30 in 75mg arm.

Among 6 subjects with FXII/PLG HAE, the mean (SD) age was 41.5 (7.71) years. 3 subjects had a diagnosis of FXII HAE, and 3 subjects had a diagnosis of PLG HAE. Only 1 (16.7%) subject had HAE prophylaxis during the 3 months before Screening. The mean (SD) number of HAE attacks documented during the 3 months before screening / start of prophylaxis was 5.2 (1.33) attacks.

Table 5: Time-normalised Number of HAE Attacks (Number / Month) in Subjects with C1-INH HAE, Treatment Period 1 (ITT Population)

	Placebo [c] q4wk N = 8	75 mg [c] CSL312 q4wk N = 9	200 mg [c] CSL312 q4wk N = 8	600 mg [c] CSL312 q4wk N = 7	400 mg [c] CSL312 q2wk N = 6
Number of Evaluable Subjects	8	9	8	7	6
Time-normalized Number of HAE Attacks per Month					
Mean (SD)	4.24 (1.801)	0.48 (1.057)	0.05 (0.127)	0.35 (0.407)	0.14 (0.222)
Median	4.61	0.00	0.00	0.34	0.00
Min, Max	1.40, 7.16	0.00, 3.26	0.00, 0.36	0.00, 1.05	0.00, 0.43
95% Confidence Interval	2.74, 5.75	- 0.33, 1.29	- 0.06, 0.15	- 0.02, 0.73	- 0.09, 0.38
P-value for Treatment Comparisons					
200 mg CSL312 vs Placebo [a]			< 0.001		
600 mg CSL312 vs Placebo [a]				< 0.001	
600 mg CSL312 vs 200 mg CSL312 [b]				0.082	
Percent Reduction in Time-normalized Number of HAE Attacks per Month Relative to Placebo					
Mean	–	88.68	98.94	91.68	–
Median	–	100.0	100.0	92.62	–

Secondary endpoints:

In TP1 the percentage of responders (with a ≥50% reduction in the time-normalised number of HAE attacks relative to the Run-in Period) was 9/9 (100%) responders in the 75 mg treatment arm, 8/8 (100%) responders in the 200 mg treatment arm, and 6/7 (85.7%) of responders in the 600 mg treatment arm. There were 0 responders in the placebo treatment arm. Additionally, 6/6 (100%) subjects in the open label 400 mg garadacimab q2wk treatment arm were responders.

The severity of HAE attacks was higher in subjects receiving placebo (20 severe attacks) than in subjects receiving blinded garadacimab (only 1 severe attack in the CSL312 600 mg treatment arm). All subjects receiving placebo experienced moderate HAE attacks, and 5/8 (62.5%) subjects experienced severe HAE attacks. In contrast, only 1 subject each in the 75 mg garadacimab treatment arm and the 200 mg garadacimab treatment arm and 2 subjects in the 600 mg garadacimab treatment arm experienced moderate HAE attacks.

All subjects in placebo arm had at least 1 attack treated on-demand, while the same was true for 3/9 in 75mg arm, 1/8 in 200mg arm and 2/7 in 600mg arm.

Subjects receiving garadacimab showed clinically meaningful improvements in the total score of the Angioedema Quality of Life questionnaire.
Overall, the efficacy results for Treatment Period 2 are consistent with Treatment Period.

Normal C1-INH HAE includes patients with known or unknown mutations. The safety and efficacy of garadacimab was evaluated in 6 patients with known mutations: HAE-FXII (n=3) or HAE-PLG (plasminogen) (n=3) in the phase 2 study 2001. Among the 6 subjects with nC1-INH (FXII / PLG mutations) HAE, in TP1, two of 3 subjects with FXII HAE were responders and continued to TP2. In these 2 subjects, the combined mean (SD) number of HAE attacks during both Treatment Period 1 and 2 was 0.11 (0.042) attacks per month. The remaining 4 subjects (1/3 subjects with FXII HAE and 3/3 subjects with PLG HAE) did not respond to therapy in Treatment Period 1 and, therefore, did not initiate Treatment Period 2.
All six patients (3 FXII-HAE and 3 PLG-HAE) were treated in the TP1 phase of phase 2 trial with 600 mg q4wks. This dose was selected for this subgroup in order to provide the maximum potential benefit of treatment with a target of ≥ 90% inhibition of their FXIIa-mediated kallikrein activity. Normal C1-INH HAE includes patients with known or unknown mutations. The safety and efficacy of garadacimab was evaluated in 6 patients with known mutations: HAE-FXII (n=3) or HAE-PLG (plasminogen) (n=3) in the phase 2 study 2001.

Table 6: nC1-INH HAE results

Subject	Attacks Rate Run-in	Attack Rate TP1	% attack reduction TP1	Attack Rate TP2 Duration (months)	% reduction TP2	% attack reduction in 3002 IA41
1	3.24	0.36	89%	0.05 (20.27)	99%	98.6%
2	3.2	0	100%	0.17 (17.40)	95%	100%
3	4.35	3.51	19%	NA	NA	NA
4	2.28	6.8	-189%	NA	NA	NA
5	1.45	3.17	-119%	NA	NA	NA
6	3.2	1.75	45%	NA	NA	NA

The efficacy results (only primary endpoint discussed) showed that:

- two patients with FXII-HAE were responders (and continued to TP2 with the same dose) while the third FXII-HAE patient had only a small attack rate reduction (19%) and therefore discontinued the treatment

- one patient with PLG-HAE had a reduction of 45% in attack rate but discontinued the treatment as non-responder (<50%). Two other PLG-HAE patients had instead the much higher attack rates compared to Run-in period (3-folds and 2.2 folds higher, respectively) and so they stopped garadacimab after TP1:

- one patient was being treated with tranexamic acid until 5 days prior to study entry which may have been providing at least partial control of her HAE attacks. Withdrawing this medication during the screening period may have destabilised the HAE biology allowing for more attacks to occur. [Bouillet et al 2021]. The moderate attack rates in the efficacy evaluation period (5.01 per month) and follow up period after garadacimab discontinuation (4.64 per month) were similar without meaningful improvement after garadacimab discontinuation. In addition, this subject had no severe attacks during treatment.

- one patient in the 96-day efficacy evaluation period experienced 10 (mild or moderate) HAE attacks. Symptoms of four attacks (3 mild and one moderate) resolved within 3 to 8 hours without rescue medication. This is uncharacteristic of a clinically relevant HAE attack. Additionally, further evaluation of 2 of the 10 attacks that occurred at different locations but shared the same start date and time suggests that it is a single attack.

All patients who were not already on the 200 mg q4wk (i.e. patients on 75mg q4wks, 600 mg q4wks and 400 mg q2wks) were switched to it in the TP2, with the exception of 2 FXII-HAE patients, whose dose remained at 600 mg q4wks. This decision was made because these patient's HAE disease was stable, and careful consideration was given to drawing conclusions from a limited patient population after only 12 weeks of treatment.

The 2 FXII-AE patients rolled over to study 3002 after approximately 2 years in study 2001 (after 96.7 and 109 weeks respectively) and their dose was then down-titrated to 200 mg once a month. As of the most recent data from the ongoing 3002 study (18 months FU) these subjects remain responsive to garadacimab, and their safety and tolerability continues to be favourable.

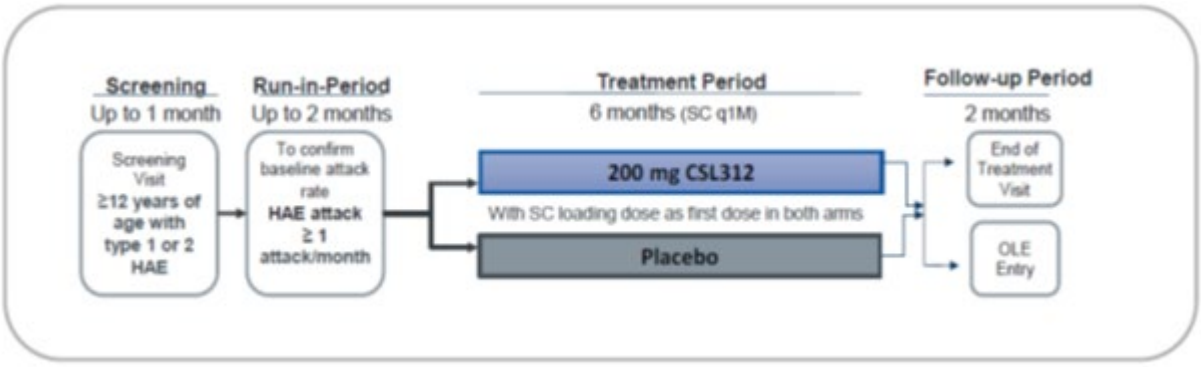
2.6.5.2. Main study

Study 3001

Methods

This phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel-arm study investigated the efficacy and safety of garadacimab in adolescent (12 to 17 years, inclusive) and adult subjects with C1-INH HAE, randomised in a 3:2 ratio to either the garadacimab active arm or the placebo arm, respectively.

Figure 6: Study Design (Study 3001 [Pivotal])



- **Study Participants**

The study was a multicentre study conducted in 7 countries (N centres): Canada (4), Germany (6), Hungary (1), Israel (1), Japan (6), Netherlands (1), and United States (9).

Main **inclusion** Criteria for the **Run-in Period**

- Males and females ≥ 12 years of age
- Diagnosed with clinically confirmed C1-INH HAE:

- Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria), and
- C1-INH antigen and / or functional activity ≤ 50% of normal as documented in the subject's medical record, and
- C4 antigen concentration below the lower limit of the reference range as documented in the subject's medical record

- Experienced ≥ 3 HAE attacks during the 3 months before Screening*

*For subjects taking any prophylactic HAE therapy during the 3 months before Screening, ≥ 3 HAE attacks may have been documented over 3 consecutive months before commencing the prophylactic therapy.

Main **inclusion** Criteria for the **Treatment Period**

1. Participated in the Run-in Period for at least 1 month with at least an average of 1 HAE attack per month during the Run-in Period (a total of at least 2 HAE attacks).
2. C1-INH functional activity and antigen, and C4 antigen concentration levels had been verified prior to randomisation.

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.
- Any preplanned major surgeries or procedures during the clinical study.
- For **adult** subjects: use of C1-INH products, androgens, antifibrinolytics, or other small molecule medications for routine prophylaxis against HAE attacks within 2 weeks prior to the Run-in Period.
- For **adolescent** subjects 12 to 17 years of age, inclusive: use of long-term prophylactic therapy for HAE before Screening.
- Use of mAb such as lanadelumab within 3 months prior to the Run-in Period.
- Use of oestrogen-containing medications with systemic absorption (e.g., oral contraceptive or hormonal replacement therapy), ACE inhibitor within 4 weeks prior to the Run-in Period, or currently receiving a therapy not permitted during the study (see below)
- Subject had any condition that in the judgment of the investigator or CSL could compromise their safety or compliance, impede successful conduct of the study, interfere with interpretation of the results, or would otherwise render the subject unsuitable for participation in the study, e.g., clinically significant bleeding due to coagulopathy, thrombotic disorder, significant illnesses, or major comorbidities.
- Female of childbearing potential or male subjects who are fertile and sexually active either not using or not willing to use an acceptable method of contraception
- Pregnancy or breastfeeding

- **Treatments**

Subjects in the garadacimab active arm received a loading dose of 400 mg SC as two 200 mg injections. Subsequent 200 mg doses of garadacimab were administered SC once a month. Subjects in

the placebo arm received a volume-matched loading dose of placebo SC as 2 injections and subsequent volume-matched doses SC once a month. Both were administered in the abdomen.

The first dose and the first 3 subsequent injections were administered by SC injection by the subject or caregiver at the study site under supervision by the investigator. Subsequent doses were self-administered with or without supervision. Compliance was assessed using the eCRF.

The 200 mg dose of garadacimab was selected based on the efficacy and safety observed in TP1 of Study 2001, PK, inhibition of FXIIa-mediated kallikrein activity, and exposure-response (E-R) modelling.

Permitted concomitant therapies: The following on-demand HAE therapies were permitted at any time during the study for the treatment of HAE attacks: plasma-derived or recombinant C1-INH, icatibant, and ecallantide. The use of medications (e.g., IV C1-INH) for the prevention of HAE attacks before any surgical procedure (e.g., IV C1-INH) was permitted at any time during the study.

Prohibited therapies: Routine (long-term) prophylaxis to prevent HAE attacks with the use of C1-INH products, androgens, antifibrinolytics, Danazol, Takhzyro or future approved medication were prohibited during the entire study, as well as ACE inhibitors and oestrogen-containing contraceptive regimens or replacement therapy with systemic absorption (e.g., oral contraceptive or hormonal replacement therapy).

- **Objectives**

The primary objective of this study was to evaluate the efficacy of SC administration of garadacimab as prophylaxis to prevent HAE attacks in subjects with HAE.

- **Outcomes/endpoints**

Primary efficacy endpoint:

- Time-normalised number of investigator-confirmed hereditary angioedema (HAE) attacks (per month and annualised) during treatment from Day 1 through Day 182 (6 months).

Secondary efficacy endpoints (hierarchical order):

- Percent reduction in monthly attack rate compared with placebo (Day 1 to 182)
- Number of attack-free subjects through Day 91
- Percentage of subjects rating therapy as "good" or better (i.e., "excellent") through the SGART at Day 182

Other secondary efficacy endpoints:

1. Reduction in the attack rate during the Treatment Period compared to the Run-in Period
2. Time-normalised number of HAE attacks requiring on-demand treatment
3. Time-normalised number of moderate and / or severe HAE attacks
4. Time-normalised number of HAE attacks at various time points (first 3-month and the second 3-month) during the treatment period
5. Subject's Global Assessment of Response to Therapy (SGART)

Exploratory efficacy endpoints: time to first attack after Day 1 and after Day 15, Subject reported outcome measures: Angioedema Quality of Life (AE-QoL), EuroQoL-Group 5-Dimension 5-Level (EQ-5D-5L), Work Productivity and Activity Impairment: General Health (WPAI:GH), Investigator's Global Assessment of Response to Therapy (IGART)

Electronic diaries were to be used to document subject-recorded data. HAE attacks that were confirmed by investigator or designate were to be used for the efficacy analyses. At each study visit (monthly) and phone contact during the Run-in Period, the subject's electronic diary entries were reviewed and confirmed the following details: location of HAE symptom(s), start / end date / time of symptom(s), dose(s) of on-demand medication(s) used, route(s) of administration of on-demand medication(s) used, type of medical assistance or intervention provided during HAE symptoms, including hospitalisation or emergency department visits, and severity of the attack.

If there has been a completely symptom-free 24-hour minimum separation between the resolution of the prior attack and the onset of next attack, this new set of symptoms would be reported as a separate single attack if the investigator confirms the HAE attack. The severity over the time that the attack develops, progresses, and resolves can range from mild to severe. The overall attack severity will reflect the maximum intensity of the attack, as assessed by the investigator. All attacks regardless of the severity should be associated with perceivable swelling and/or discomfort.

- **Sample size**

In total, 60 subjects were planned to be randomised. Forty subjects with C1-INH HAE type 1/2 completing the 6-month TP were needed for a power of approximately 90% for a two-sided Wilcoxon Test (alpha of 5%). Subjects were randomised to the Active Arm or the Placebo Arm with a ratio of 3:2 (24 and 16 subjects). The monthly attack rates were assumed to be Poisson distributed. The assumed monthly attack rates of placebo and of garadacimab (i.e. 1.3 and 0.3125 attacks/month, respectively) were used as the two means of the two Poisson distributions. The study was also aimed to randomise approximately 5 adolescents with a randomisation ratio of 3:2 (active:placebo).

- **Randomisation and Blinding (masking)**

Subjects were to be randomised using a block randomisation by means of centralised IRT to 1 of 2 treatment arms in a 3:2 ratio to either the Active Arm or to the Placebo Arm. Stratifying variables were to be age (≤ 17 years, > 17 years) and, for adults, the subject's baseline attack rate (1 to < 3 attacks/month, and ≥ 3 attacks/month).

- **Statistical methods**

Primary Efficacy Analysis

The primary endpoint was analysed using the ITT and PP Populations. The ITT population, including all subjects in the screened analysis set who were randomised, was used as the primary analysis set based on the treatment to which the subject was randomised, regardless of the treatment actually received. The PP population, including all subjects in the ITT analysis set who received at least 1 dose of investigational product and who complied with the protocol, was used as secondary analysis of primary endpoint. The primary endpoint was "time-normalized number of HAE attacks per month during treatment from Day 1 through Day 182", calculated per subject as: [the number of HAE attacks / length of subject treatment in days] * 30.4375 where the length of subject treatment was calculated as: [the date of Study Visit Day 182 or the date of study discontinuation [whatever was first]– the date of Study Visits Day 1 +1]. To test for a difference in the primary efficacy endpoint between garadacimab and placebo, a comparison of the time-normalised numbers of HAE attacks in the 6 months of the Active Arm versus Placebo Arm was performed by using a two-sided Wilcoxon Test (alpha = 5%). The time-normalised number per month and per year of HAE attacks was summarised descriptively by median and mean with corresponding 95% CIs by treatment. As a sensitivity analysis on the ITT analysis set, the time-normalised number of HAE attacks was compared for the 6 months of the Active Arm and Placebo Arm using a Poisson Regression model. The time-normalised number of HAE attacks of the Run-in Period and age as covariates and the logarithm of the length of subject

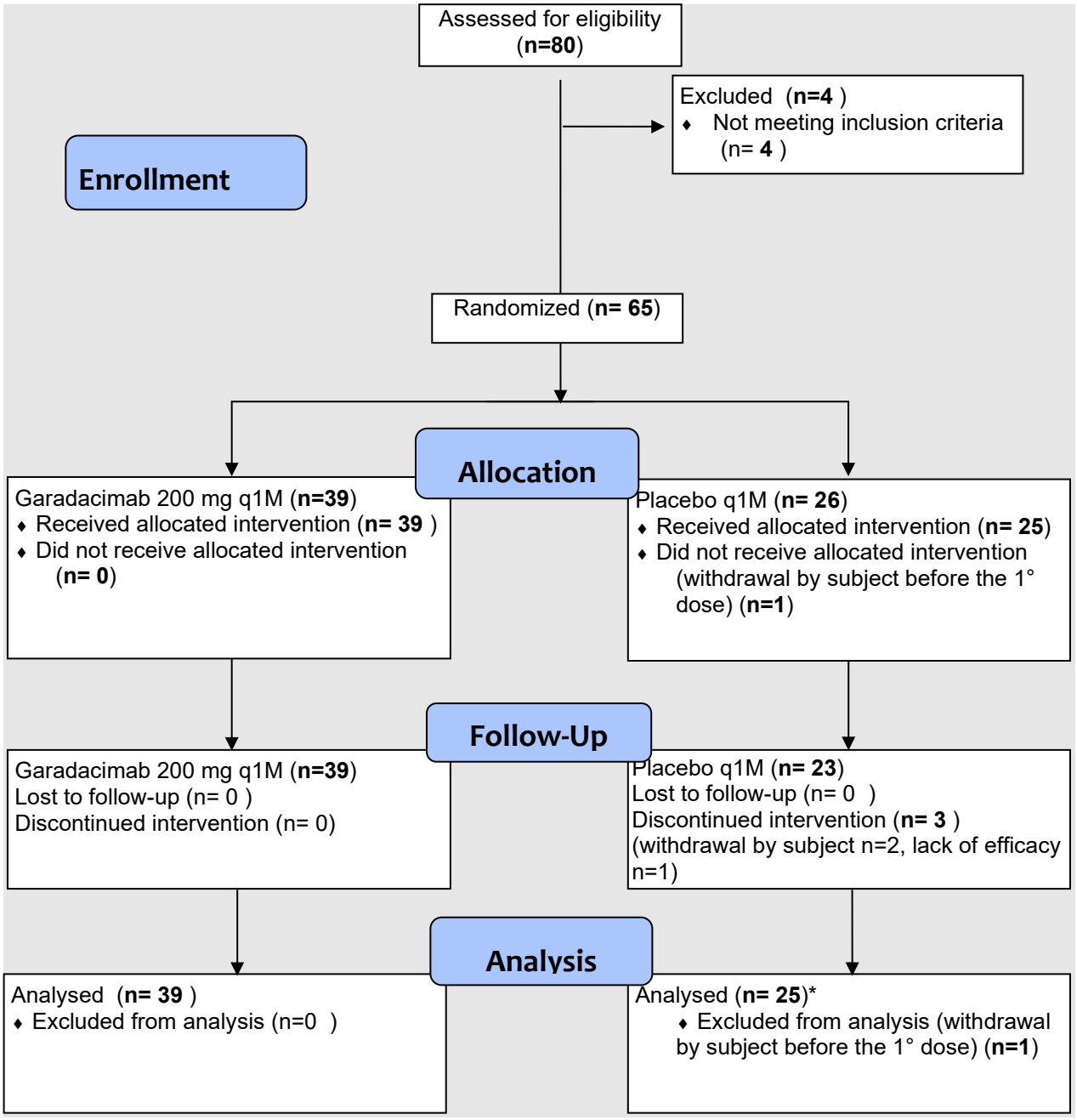
treatment as an offset variable were included. The model accounted for overdispersion. Sensitivity analyses evaluating the impact of missing values for primary outcome variable and the impact of baseline attack rate were performed on the ITT analysis set. Supplementary analysis of primary estimand was performed on subjects in the PP analysis set in order to assess the treatment effect of garadacimab during treatment from Day 1 through Day 182 while subjects were allowed to treat HAE attacks with on-demand medications but excluding subjects who do not comply with the protocol. The occurrence of an intercurrent event was considered irrelevant, in line with treatment policy strategy. No prespecified subgroup analyses were planned with exception of analyses based on stratification factors and Japanese subjects (if more than 5 subjects were enrolled).

Secondary Efficacy Analysis

The secondary efficacy endpoints were analysed using the ITT Analysis Set. To control the overall type I error rate, a hierarchical testing procedure was applied across the primary endpoint (H01) and 3 secondary efficacy endpoints according to prespecified hypotheses tested in a hierarchical order. Testing was conducted at the 2-sided 0.05 alpha level. The secondary endpoints included in the hypothesis-testing hierarchy were the percent reduction in monthly attack rate compared with placebo (Day 1 to 182) (H02), the number of attack-free subjects through Day 91 (H03), and the percentage of subjects rating therapy as "good" or better (i.e., "excellent") through the SGART at Day 182 (H04).

Results

- **Participant flow**



*ITT analysis. For PP analysis set 24 subjects were included (1 subject in the placebo arm was excluded from PP analysis set as treatment was received for < 30 days)

The Run-in failures (11 subjects) were due to: failure to meet Run-In Completion Criteria (7 subjects), AE (1 subject), lost to FU (1 subject), withdrawal by the subject (1), other (1).

Some incongruences are noted regarding the ID number error and relative narratives between the patient from placebo arm and the one from garadacimab arm (see below 'Protocol deviations'), also considering CSL312_3001_CSR Erratum_Version 1.0.

- **Recruitment**

Study period: First Subject Visit: 27 January 2021, Last Subject Visit: 07 June 2022

- **Conduct of the study**

The original protocol had no substantial amendments. Overall, there were 2 subjects that had major protocol deviations during the study, these were both during the Screening / Run-in Period:

• One subject was randomised in IRT in error (garadacimab arm). The subject should not have been randomised as the subject had only had 2 of the 3 required HAE attacks (1 HAE attack per month requirement per protocol) in order to qualify for the study as confirmed by the site. Before the subject received treatment, they experienced a 3rd HAE attack allowing them to be dosed, resulting into having a pre-dose HAE attack rate of 1 HAE attack per month. The subject was not dosed that day and subject safety was not affected. During the Blinded Data Review Meeting, the decision was made not to exclude the subject from any analyses.

• One subject in the placebo treatment arm was excluded from the ITT Analysis Set. The study centre dispensed 2 investigational medicinal product kits, but the subject did not attend the visit, then the subject withdrew consent.

Protocol minor deviations in 3 subjects (2 in CSL312 Arm and 1 in Placebo Arm) occurred as a result of the COVID-19 pandemic.

- **Baseline data**

Table 7: Demographic Characteristics – All Subjects (ITT Analysis Set)

Characteristics	CSL312 200 mg (N = 39)	Placebo (N = 25)	Total (N = 64)
Subjects: All			
Sex, n (%)			
Male	15 (38.5)	11 (44.0)	26 (40.6)
Female	24 (61.5)	14 (56.0)	38 (59.4)
Ethnicity, n (%)			
Hispanic or Latino	1 (2.6)	2 (8.0)	3 (4.7)
Not Hispanic or Latino	37 (94.9)	23 (92.0)	60 (93.8)
Not Reported	1 (2.6)	0	1 (1.6)
Race, n (%)			
Asian	4 (10.3)	2 (8.0)	6 (9.4)
Japanese	4 (10.3)	2 (8.0)	6 (9.4)
Black or African American	0	1 (4.0)	1 (1.6)
Native Hawaiian or Other Pacific Islander	1 (2.6)	0	1 (1.6)
White	33 (84.6)	22 (88.0)	55 (85.9)
Other	1 (2.6)	0	1 (1.6)
Age (Years)			
Mean (SD)	43.3 (17.45)	37.8 (12.80)	41.2 (15.92)
Median (Min, Max)	43.0 (12, 69)	38.0 (14, 62)	41.0 (12, 69)
1st Quartile, 3rd Quartile	29.0, 62.0	31.0, 45.0	30.0, 52.0
95% CI	(37.68, 48.99)	(32.56, 43.12)	(37.21, 45.16)
BMI at Screening (kg/m^2)			
Mean (SD)	27.85 (6.021)	28.37 (7.563)	28.05 (6.612)
Median (Min, Max)	27.70 (19.3, 52.7)	25.70 (18.7, 42.7)	27.25 (18.7, 52.7)
1st Quartile, 3rd Quartile	24.30, 30.90	22.70, 36.00	23.05, 31.10
95% CI	(25.902, 29.805)	(25.246, 31.490)	(26.403, 29.706)

Table 8: HAE History (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)	Total (N = 64)
HAE Type, n (%)			
C1-INH HAE Type I	34 (87.2)	22 (88.0)	56 (87.5)
C1-INH HAE Type II	5 (12.8)	3 (12.0)	8 (12.5)
History of Laryngeal Attack, n (%)			
Yes	21 (53.8)	17 (68.0)	38 (59.4)
No	18 (46.2)	8 (32.0)	26 (40.6)
Family History of HAE, n (%)			
Yes	34 (87.2)	23 (92.0)	57 (89.1)
No	5 (12.8)	2 (8.0)	7 (10.9)
Age at First Diagnosis, n %			
≤ 17 years	18 (46.2)	12 (48.0)	30 (46.9)
≤ 40 years	18 (46.2)	11 (44.0)	29 (45.3)
> 40 years	3 (7.7)	2 (8.0)	5 (7.8)
Age at First Diagnosis WITH Family History of HAE, n %			
≤ 17 years	18 (46.2)	10 (40.0)	28 (43.8)
≤ 40 years	14 (35.9)	11 (44.0)	25 (39.1)
> 40 years	2 (5.1)	2 (8.0)	4 (6.3)
Age at First Diagnosis WITHOUT Family History of HAE, n %			
≤ 17 years	0	2 (8.0)	2 (3.1)
≤ 40 years	4 (10.3)	0	4 (6.3)
> 40 years	1 (2.6)	0	1 (1.6)
HAE Prophylaxis During 3 Months Before Screening, n (%)			
Subjects With HAE Prophylaxis	14 (35.9)	7 (28.0)	21 (32.8)
Subjects Without HAE Prophylaxis	25 (64.1)	18 (72.0)	43 (67.2)

Table 9: HAE History (Intention-to-Treat Analysis Set)

Number and Percentage of Subjects[1]	CSL312 200mg (N=39)	Placebo (N=25)	Total (N=64)
Number of HAE Attacks Within 3 Months Before Screening for Subjects WITH HAE Prophylaxis During 3 Months Before Screening			
Number Observed	13	7	20
Mean (SD)	4.8 (3.70)	3.3 (1.98)	4.3 (3.23)
Median	4.0	3.0	4.0
1st Quartile, 3rd Quartile	3.0, 6.0	2.0, 5.0	3.0, 5.5
Minimum, Maximum	0, 12	0, 6	0, 12
95% Confidence Interval	(2.5, 7.0)	(1.5, 5.1)	(2.7, 5.8)
Time-normalized Number of HAE Attacks Within 3 Months Before Screening for Subjects WITH HAE Prophylaxis During 3 Months Before Screening per Month [4]			
Number Observed	13	7	20
Mean (SD)	1.6 (1.23)	1.1 (0.66)	1.4 (1.08)
Median	1.3	1.0	1.3
1st Quartile, 3rd Quartile	1.0, 2.0	0.7, 1.7	1.0, 1.8
Minimum, Maximum	0, 4	0, 2	0, 4
95% Confidence Interval	(0.8, 2.3)	(0.5, 1.7)	(0.9, 1.9)
Number of HAE Attacks Within 3 Months Before Screening for Subjects WITHOUT HAE Prophylaxis During 3 Months Before Screening			
Number Observed	25	18	43
Mean (SD)	8.6 (7.33)	9.4 (6.03)	8.9 (6.75)
Median	5.0	6.5	6.0
1st Quartile, 3rd Quartile	4.0, 10.0	4.0, 14.0	4.0, 13.0
Minimum, Maximum	3, 30	3, 22	3, 30
95% Confidence Interval	(5.6, 11.6)	(6.4, 12.4)	(6.9, 11.0)
Time-normalized Number of HAE Attacks Within 3 Months Before Screening for Subjects WITHOUT HAE Prophylaxis During 3 Months Before Screening per Month [4]			
Number Observed	25	18	43
Mean (SD)	2.9 (2.44)	3.1 (2.01)	3.0 (2.25)
Median	1.7	2.2	2.0
1st Quartile, 3rd Quartile	1.3, 3.3	1.3, 4.7	1.3, 4.3
Minimum, Maximum	1, 10	1, 7	1, 10
95% Confidence Interval	(1.9, 3.9)	(2.1, 4.1)	(2.3, 3.7)
Number of HAE Attacks During the 3 Months Before Screening or Start of HAE Prophylaxis [2]			
Number Observed	38	25	63
Mean (SD)	8.4 (6.96)	9.3 (7.01)	8.9 (6.93)
Median	5.5	6.0	6.0
1st Quartile, 3rd Quartile	4.0, 12.0	4.0, 13.0	4.0, 13.0
Minimum, Maximum	3, 30	3, 30	3, 30
95% Confidence Interval	(6.3, 10.9)	(6.4, 12.2)	(7.1, 10.6)
Time-normalized Number of HAE Attacks During the 3 Months Before Screening or Start of HAE Prophylaxis per Month [2][4]			
Number Observed	38	25	63
Mean (SD)	2.9 (2.32)	3.1 (2.34)	3.0 (2.31)
Median	1.8	2.0	2.0
1st Quartile, 3rd Quartile	1.3, 4.0	1.3, 4.3	1.3, 4.3
Minimum, Maximum	1, 10	1, 10	1, 10
95% Confidence Interval	(2.1, 3.6)	(2.1, 4.1)	(2.4, 3.5)
Primary Locations of HAE Attacks in the Last 3 Months Prior to Screening, n (%) [3]			
Cutaneous - Extremities	30 (76.9)	20 (80.0)	50 (78.1)
Abdomen	30 (76.9)	18 (72.0)	48 (75.0)
Cutaneous - Head/face/lip/neck	13 (33.3)	8 (32.0)	21 (32.8)
Genitourinary	6 (15.4)	2 (8.0)	8 (12.5)
Cutaneous - Trunk	5 (12.8)	2 (8.0)	7 (10.9)
Cutaneous - Genitourinary	2 (5.1)	4 (16.0)	6 (9.4)
Throat/Larynx/Tongue	3 (7.7)	2 (8.0)	5 (7.8)
Groin And Testicles	1 (2.6)	0	1 (1.6)
Hands	0	1 (4.0)	1 (1.6)
Peripheral	1 (2.6)	0	1 (1.6)

During the Run-in period the mean (SD) and median time-normalised number of HAE attacks per month were 3.07 (2.047) and 2.61 in garadacimab arm and 2.52 (0.944) and 2.23 in placebo arm, respectively.

Overall, 21 (32.8%) subjects were treated with **HAE prophylaxis** during the 3 months before Screening:

- 14 subjects in the CSL312 Arm received: C1-INH (6 subjects), berotralstat dihydrochloride (4 subjects), tranexamic acid (2 subjects), danazol (1 subject), and lanadelumab (1 subject);
- 7 subjects in the Placebo Arm received: berotralstat dihydrochloride (3 subjects), C1 esterase inhibitor (2 subjects), tranexamic acid (1 subject), and danazol (1 subject).

Table 10: Prior and Concomitant Medications (Safety Analysis Set)

ATC Class Level 4 Preferred Term[1]	CSL312 200mg (N=39) n (%)[2]	Placebo (N=25) n (%)[2]	Total (N=64) n (%)[2]
Any Prior or Concomitant Medication [3]	39 (100.0)	25 (100.0)	64 (100.0)
On-demand HAE Medication [4]	38 (97.4)	25 (100.0)	63 (98.4)
COMPLEMENT C1 ESTERASE INHIBITOR	30 (76.9)	20 (80.0)	50 (78.1)
ICATIBANT ACETATE	25 (64.1)	16 (64.0)	41 (64.1)
ICATIBANT	4 (10.3)	3 (12.0)	7 (10.9)
CONESTAT ALFA	1 (2.6)	2 (8.0)	3 (4.7)
EPINEPHRINE	0	3 (12.0)	3 (4.7)
ONDANSETRON	0	3 (12.0)	3 (4.7)
MORPHINE	0	2 (8.0)	2 (3.1)
PARACETAMOL	0	2 (8.0)	2 (3.1)
DEXAMETHASONE	0	1 (4.0)	1 (1.6)
DIPHENHYDRAMINE	0	1 (4.0)	1 (1.6)
FAMOTIDINE	0	1 (4.0)	1 (1.6)
IBUPROFEN	0	1 (4.0)	1 (1.6)
LORATADINE	0	1 (4.0)	1 (1.6)
OXYCODONE	0	1 (4.0)	1 (1.6)
SODIUM CHLORIDE	1 (2.6)	0	1 (1.6)
DRUGS USED IN HEREDITARY ANGIOEDEMA	38 (97.4)	25 (100.0)	63 (98.4)
COMPLEMENT C1 ESTERASE INHIBITOR	30 (76.9)	20 (80.0)	50 (78.1)
ICATIBANT ACETATE	25 (64.1)	16 (64.0)	41 (64.1)
BEROTRALSTAT DIHYDROCHLORIDE	5 (12.8)	2 (8.0)	7 (10.9)
ICATIBANT	4 (10.3)	3 (12.0)	7 (10.9)
CONESTAT ALFA	1 (2.6)	2 (8.0)	3 (4.7)
LANADELUMAB	2 (5.1)	1 (4.0)	3 (4.7)
LANADELUMAB FLYO	2 (5.1)	0	2 (3.1)
BEROTRALSTAT	0	1 (4.0)	1 (1.6)

- **Numbers analysed**

The intention-to-treat (ITT) analysis set comprised all subjects in the screened analysis set who were randomised. The ITT analysis set was to be analysed using the treatment to which the subject was randomised, regardless of the treatment actually received.
Two subjects in the Placebo Arm were not included in the ITT analysis set. Of 65 randomised subjects (39 in the garadacimab arm and 26 in the placebo arm), only 63 subjects were considered evaluable for the primary efficacy analysis: one subject was excluded since consent was withdrawn before the first study treatment administration, another subject was not considered "evaluable" since treatment period was < 30 days.

- **Outcomes and estimation**

Primary endpoint

Table 11: Primary Efficacy Analysis: Time-normalised Number of HAE Attacks Per Month During 6-month Treatment Period (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Number of Evaluable Subjects, n (%)	39 (100.0)	24 (96.0)
Number of HAE Attacks during Treatment Period	63	264
Time-normalized Number of HAE Attacks Per Month		
Mean (SD)	0.27 (0.683)	2.01 (1.341)
Median	0.00	1.35
Min, Max	0.00, 3.8	0.2, 4.4
1st Quartile, 3rd Quartile	0.00, 0.31	1.00, 3.20
95% CI	(0.05, 0.49)	(1.44, 2.57)
Two-sided Wilcoxon Test, p-value (First Hierarchical Test [H01])		< 0.001

Results from analysis of primary endpoint based on PP analysis set are the same as results from primary analysis based on ITT (the only patient with treatment period less than 30 days was also excluded from ITT analysis set).

Sensitivity Analysis of the Primary Endpoint Adjusted for Baseline Attack Rate:

Table 12: Sensitivity Analysis: Time-normalised Number of HAE Attacks Per Month During 6 months Treatment Period – Poisson Model (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Number of Evaluable Subjects	39 (100.0)	24 (96.0)
Number of HAE Attacks during Treatment Period	63	264
Poisson Model		
LS Mean time-normalized number of HAE attacks, 95% CIa	0.223 (0.1067, 0.4669)	2.068 (1.4895, 2.8724)
Standard error	0.3767	0.1675
Mean time-normalized number of HAE attacks ratio for CSL312 relative to placebo, 95% CI		0.108 (0.0477, 0.2441)
Percentage difference in the mean time-normalized number of HAE attacks for CSL312 to placebo, 95% CI		-89.211 (-95.2315, -75.5876)

Secondary efficacy endpoints (hierarchical order):

- Percent reduction in monthly attack rate compared with placebo (Day 1 to 182)

Table 13: Relative Difference in the Time-normalised Number of HAE Attacks Per Month (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Study Period: 6-Month Treatment		
Number of Evaluable Subjects, n (%)	39 (100.0)	24 (96.0)
Mean Time-normalized Number of HAE Attacks Per Month		
Mean Attack Ratio CSL312 to Placebo		0.13
Relative Difference in Means in the Time-normalized Number of HAE Attacks Per Month CSL312 to Placebo, (95%CI) [a]		-86.51 (-95.68, -57.84)
Median Time-normalized Number of HAE Attacks Per Month		
Median Attack Ratio CSL312 to Placebo		0.00
Relative Difference in Medians in the Time-normalized Number of HAE Attacks Per Month CSL312 to Placebo, (95%CI) [b]		-100.0 (ND, ND)
Two-sided Wilcoxon Test, p-value (Second Hierarchical Test [H02])		< 0.001

[a] Derived as: 100 * [(mean time-normalized number of HAE attacks for CSL312 – mean time normalized number of HAE attacks for Placebo) / mean time-normalized number of HAE attacks for Placebo].

[b] Derived as: 100 * [(median time-normalized number of HAE attacks for CSL312 – median time normalized number of HAE attacks for Placebo) / median time-normalized number of HAE attacks for Placebo].

- Number of attack-free subjects through Day 91

Table 14: Analysis of Responders (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Study Period: First 3-Month Treatment		
Number of Evaluable Subjects, n	39	24
Reduction of 100% (attack-free)	28 (71.8)	2 (8.3)
Reduction of < 100%	11 (28.2)	22 (91.7)
95% Wilson CI for Subjects with a Reduction of 100% [a]	(56.22, 83.46)	(2.32, 25.85)
Fisher Exact Test, nominal p-value (Third Hierarchical Test [H03])	< 0.001	

- Percentage of subjects rating therapy as "good" or better (i.e., "excellent") through the SGART at Day 182

Table 15: Subject Global Assessment of Response to Therapy at Day 182 (ITT Analysis Set)

	CSL312 200 mg (N = 39) n (%) [a]	Placebo (N = 25) n (%) [a]
Number observed, n	38	24
None	1 (2.6)	10 (41.7)
Poor	3 (7.9)	4 (16.7)
Fair	3 (7.9)	2 (8.3)
Good	6 (15.8)	5 (20.8)
Excellent	25 (65.8)	3 (12.5)
Good or Better	31 (81.6)	8 (33.3)
Fair or Better	34 (89.5)	10 (41.7)
Poor or Better	37 (97.4)	14 (58.3)
Chi-squared test, p-value (Fourth Hierarchical Test [H04]) [b]		< 0.001

For SGART, subjects have to respond to the following question: "Considering all of the ways HAE affects you, please rate your response to the study medication you were given to prevent HAE attacks during this treatment period".

Other secondary efficacy endpoints:

- Reduction in the attack rate during the Treatment Period compared to the Run-in Period

Table 16: Reduction in the Attack Rate During the Treatment Period Compared to the Run-in Period (ITT Analysis Set, Study 3001 [Pivotal])

	Garadacimab 200 mg (N = 39)	Placebo (N = 25)
Study Period: 6-Month Treatment		
Number of Evaluable Subjects, n	39	24
Reduction in Time-normalized Number of HAE Attacks Per Month (%) [a]		
Mean (SD)	90.67 (22.433)	20.21 (42.661)
Median (Min, Max)	100.00 (-5.8, 100.0)	8.45 (-62.4, 91.8)
1st Quartile, 3rd Quartile	89.78, 100.00	-11.76, 56.96
95% CI	(83.40, 97.94)	(2.20, 38.22)
Comparison Garadacimab vs. Placebo Two-sided Wilcoxon Test, Nominal p-value	< 0.001	
Study Period: First 3-Month Treatment		
Number of Evaluable Subjects, n	39	24
Reduction in Time-normalized Number of HAE Attacks Per Month (%) [a]		
Mean (SD)	91.10 (21.255)	18.89 (53.837)
Median (Min, Max)	100.00 (1.8, 100.0)	22.82 (-124.5, 100.0)
1st Quartile, 3rd Quartile	87.64, 100.00	-7.43, 62.73
95% CI	(84.21, 97.99)	(-3.85, 41.62)
Study Period: Second 3-Month Treatment		
Number of Evaluable Subjects, n	39	22
Reduction in Time-normalized Number of HAE Attacks Per Month (%) [a]		
Mean (SD)	90.12 (25.624)	29.87 (55.529)
Median (Min, Max)	100.00 (-35.1, 100.0)	37.89 (-133.3, 100.0)
1st Quartile, 3rd Quartile	89.49, 100.00	-13.14, 82.97
95% CI	(81.82, 98.43)	(5.25, 54.49)

Table 17: Analysis of Responders (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Study Period: 6-Month Treatment		
Number of Evaluable Subjects, n	39	24
Responders with Reduction of ≥ 50%	37 (94.9)	8 (33.3)
Non-responders with Reduction of < 50%	2 (5.1)	16 (66.7)
95% Wilson CI for the Percentage of Responders [a]	(83.11, 98.58)	(17.97, 53.29)
Reduction of ≥ 70%	36 (92.3)	4 (16.7)
Reduction of < 70%	3 (7.7)	20 (83.3)
95% Wilson CI for Subjects with a Reduction of ≥ 70% [a]	(79.68, 97.35)	(6.68, 35.85)
Reduction of ≥ 90%	29 (74.4)	2 (8.3)
Reduction of < 90%	10 (25.6)	22 (91.7)
95% Wilson CI for Subjects with a Reduction of ≥ 90% [a]	(58.92, 85.43)	(2.32, 25.85)
Reduction of 100% (attack-free)	24 (61.5)	0
Reduction of < 100%	15 (38.5)	24 (100.0)
95% Wilson Confidence Interval for Subjects with a Reduction of 100% [a]	(45.90, 75.11)	(0.00, 13.80)
Fisher Exact Test, nominal p-value	< 0.001	

- Time-normalised number of HAE attacks requiring on-demand treatment

Table 18: Time-normalised Number of HAE Attacks Per Month Requiring On-demand Treatment (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Study Period: 6-Month Treatment		
Number of Evaluable Subjects, n (%)	39 (100.0)	24 (96.0)
Number of HAE Attacks during Treatment Period, n	63	264
Number of HAE Attacks requiring on-demand treatment during Treatment Period, n (%) [a]	54 (85.7)	245 (92.8)
Time-normalized Number of HAE Attacks Requiring On-demand Treatment Per Month		
Mean (SD)	0.23 (0.663)	1.86 (1.412)
Median (Min, Max)	0.00 (0.0, 3.8)	1.35 (0.0, 4.4)
1st Quartile, 3rd Quartile	0.00, 0.17	0.67, 3.07
95% CI	(0.02, 0.45)	(1.26, 2.46)
Two-sided Wilcoxon Test, nominal p-value		< 0.001

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

Table 19: Time-normalised Number of Moderate or Severe HAE Attacks Per Month (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Study Period: 6-Month Treatment		
Number of Evaluable Subjects, n (%)	39 (100.0)	24 (96.0)
Number of HAE Attacks during Treatment Period, n	63	264
Number of Moderate or Severe HAE Attacks during Treatment Period, n (%) [a]	29 (46.0)	172 (65.2)
Time-normalized Number of Moderate or Severe HAE Attacks Per Month		
Mean (SD)	0.13 (0.296)	1.35 (1.166)
Median (Min, Max)	0.00 (0.0, 1.2)	0.83 (0.0, 4.4)
1st Quartile, 3rd Quartile	0.00, 0.16	0.52, 2.41
95% CI	(0.03, 0.22)	(0.86, 1.84)
Two-sided Wilcoxon Test, nominal p-value		< 0.001

- Time-normalised number of HAE attacks at various time points (first 3-month and the second 3-month) during the treatment period

Table 20: Time-normalised Number of HAE Attacks Per Month During the Run-in Period, First 3 months and Second 3 months of Treatment (ITT Analysis Set)

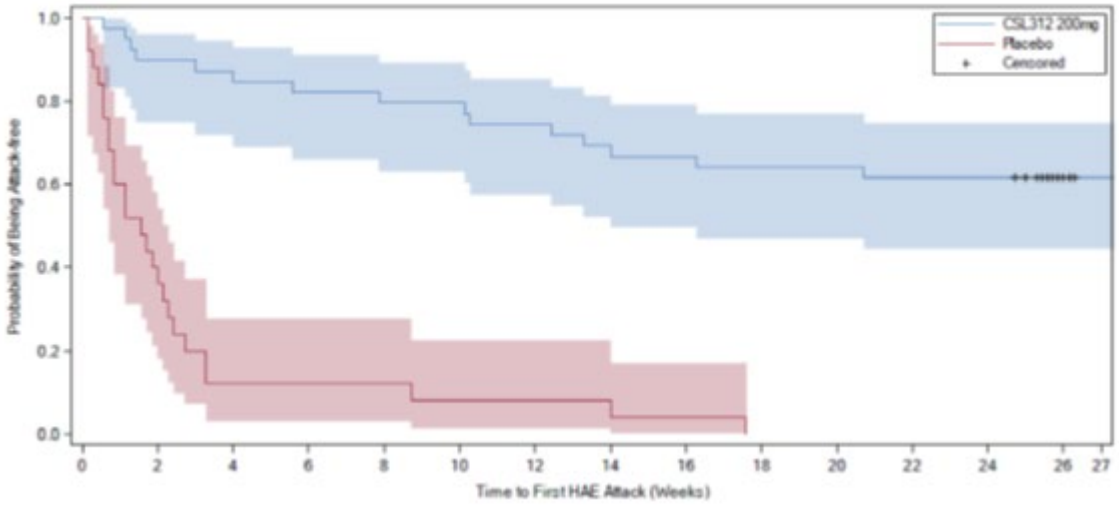
	CSL312 200 mg (N = 39)	Placebo (N = 25)
Study Period: Run-in		
Number of Evaluable Subjects, n [a]	39 (100.0)	25 (100.0)
Number of HAE Attacks during Treatment Period	149	95
Time-normalized Number of HAE Attacks Per Month		
Mean (SD)	3.07 (2.047)	2.52 (0.944)
Median (Min, Max)	2.61 (0.9, 10.1)	2.23 (1.0, 4.3)
1st Quartile, 3rd Quartile	1.79, 3.54	1.86, 3.26
95% CI	(2.41, 3.73)	(2.13, 2.91)
Study Period: First 3-Month Treatment		
Number of Evaluable Subjects, n [a]	39 (100.00)	24 (96.0)
Number of HAE Attacks during Treatment Period	31	144
Time-normalized Number of HAE Attacks Per Month		
Mean (SD)	0.26 (0.749)	1.97 (1.287)
Median (Min, Max)	0.00 (0.0, 4.4)	1.77 (0.0, 4.3)
1st Quartile, 3rd Quartile	0.00, 0.32	1.18, 2.98
95% CI	(0.02, 0.51)	(1.43, 2.51)
Two-sided Wilcoxon Test, nominal p-value		< 0.001
Study Period: Second 3-Month Treatment		
Number of Evaluable Subjects, n (%) [a]	39 (100.0)	22 (88.0)
Number of HAE Attacks during Treatment Period	32	120

- Subject's Global Assessment of Response to Therapy (SGART): Please see the Table 20 above

Exploratory efficacy endpoints:

- The time to first attack after Day 1 and after Day 15

Figure 7: Time-to-first HAE Attack After Day 1 – Kaplan-Meier Curve with 95% Confidence Interval (Safety Analysis Set, Study 3001 [Pivotal])



- For the Angioedema-QoL questionnaire, the mean scores at the end of the 6-month Treatment Period was better than those in the placebo arm for the total score and all domain scores (each nominal p-value < 0.05 for treatment effect)

Table 21: Summary AE-QoL Domains and Total Score by Study Visit (Intention-to-Treat Analysis Set)

	CSL312 200mg (N=39)		Placebo (N=25)	
Visit Domain/Total Score[1]	Actual	Change[3]	Actual	Change[3]
Visit Day 182				
Domain: Functioning [2]				
Number Observed	34	33	21	20
Mean (SD)	6.434 (16.4631)	-35.795 (23.2426)	42.262 (30.6125)	1.875 (29.6012)
Median	0.000	-37.500	43.750	-3.125
1st Quartile, 3rd Quartile	0.000, 0.000	-50.000, -18.750	12.500, 62.500	-18.750, 15.625
Minimum, Maximum	0.00, 50.00	-81.25, 12.50	0.00, 100.00	-37.50, 81.25
95% Confidence Interval	(0.690, 12.178)	(-44.037, -27.554)	(28.327, 56.197)	(-11.979, 15.729)
Domain: Fatigue/Mood [2]				
Number Observed	34	33	21	20
Mean (SD)	13.824 (18.7107)	-21.061 (22.8705)	37.857 (29.8986)	-5.750 (27.0611)
Median	5.000	-15.000	30.000	-5.000
1st Quartile, 3rd Quartile	0.000, 20.000	-30.000, -5.000	15.000, 50.000	-22.500, 2.500
Minimum, Maximum	0.00, 65.00	-80.00, 35.00	0.00, 100.00	-55.00, 80.00
95% Confidence Interval	(7.295, 20.352)	(-29.170, -12.951)	(24.247, 51.467)	(-18.415, 6.915)
Domain: Fears/Shame [2]				
Number Observed	34	33	21	20
Mean (SD)	15.319 (17.9060)	-28.030 (24.1000)	46.230 (27.3831)	-2.500 (18.6045)
Median	10.417	-29.167	33.333	-8.333
1st Quartile, 3rd Quartile	0.000, 25.000	-37.500, -8.333	25.000, 62.500	-14.583, 8.333
Minimum, Maximum	0.00, 66.67	-79.17, 20.83	4.17, 95.83	-33.33, 33.33
95% Confidence Interval	(9.071, 21.566)	(-36.576, -19.485)	(33.766, 58.695)	(-11.207, 6.207)

Visit Day 182				
Domain: Nutrition [2]				
Number Observed	34	33	21	20
Mean (SD)	6.250 (19.2791)	-16.667 (23.3157)	24.405 (34.5679)	-0.625 (16.4612)
Median	0.000	-12.500	0.000	0.000
1st Quartile, 3rd Quartile	0.000, 0.000	-25.000, 0.000	0.000, 37.500	-12.500, 12.500
Minimum, Maximum	0.00, 100.00	-62.50, 50.00	0.00, 100.00	-37.50, 25.00
95% Confidence Interval	(-0.477, 12.977)	(-24.934, -8.399)	(8.670, 40.140)	(-8.329, 7.079)
Total Score [2]				
Number Observed	34	33	21	20
Mean (SD)	11.721 (15.6241)	-26.471 (17.8943)	40.266 (24.0767)	-2.206 (19.1296)
Median	5.147	-29.412	35.294	-7.353
1st Quartile, 3rd Quartile	1.471, 16.176	-36.765, -14.706	23.529, 55.882	-15.441, 5.147
Minimum, Maximum	0.00, 61.76	-75.00, 5.88	1.47, 85.29	-25.00, 57.35
95% Confidence Interval	(6.270, 17.173)	(-32.816, -20.126)	(29.307, 51.226)	(-11.159, 6.747)

[1] AE-QoL is only answered from patients of age >= 18 years.
[2] The scores are expressed in percentage impairment (0-100%). Higher scores indicate more impairment.
[3] Change = Change from Baseline, where baseline is defined as the most recent, non-missing value prior to or on the date of the first study treatment administration (including unscheduled visits) for all assessments. Change from Baseline derived as: visit value – baseline value.

Table 22: Minimal Clinically Important Differences in Angioedema Quality of Life Scores in Subjects with C1-INH HAE (ITT Analysis Set)

	CSL312 200 mg (N = 39)	Placebo (N = 25)
Number of Evaluable Subjects	33	20
Functioning		
Subjects with MCID from Day 1 to Day 182, n (%)	30 (90.9)	10 (50.0)
Fatigue and Mood		
Subjects with MCID from Day 1 to Day 182, n (%)	24 (72.7)	9 (45.0)
Fears and Shame		
Subjects with MCID from Day 1 to Day 182, n (%)	27 (81.8)	11 (55.0)
Nutrition		
Subjects with MCID from Day 1 to Day 182, n (%)	22 (66.7)	7 (35.0)
Total Score		
Subjects with MCID from Day 1 to Day 182, n (%)	29 (87.9)	11 (55.0)

C1-INH HAE = hereditary angioedema with C1-esterase inhibitor deficiency; ITT = intention to treat; MCID = minimal clinically important difference; N = number of subjects in the ITT Analysis Set.
Notes: Angioedema Quality of Life is only answered from patients of age ≥ 18 years. A difference of at least 6 points was required to be considered a minimal clinically important difference [Weller et al, 2016].

- For the EQ-5D-5L, there was some improvement in mean HSV and VAS score in the garadacimab arm compared to placebo. Mean HSV score in the garadacimab arm increased from 0.891 at Day 1 to 0.942 at Day 182, while it remained approximately the same in the placebo arm (0.876 on Day 1 and 0.858 on Day 182). In the garadacimab arm, the mean VAS score increased from 85.784 at Day 1 to 92.342 at Day 182; in the placebo arm the mean VAS score at Day 1 was 82.625 but decreased to 75.652 by Day 182. This difference in HSV scores was primarily due to improvement in pain and discomfort in the garadacimab arm, and worse pain and discomfort scores in the placebo arm.

For the WPAI:GH there was a nominally significant improvement in mean activity impairment scores from Day 1 to Day 182 in the garadacimab arm. There were no notable changes in the placebo arm.

The most frequently reported response by investigators, measured by the IGART, at the end of treatment (Day 182) in the garadacimab treatment arm was "excellent" (31 / 39 [79.5%] subjects) or "good" (5 / 39 [12.8%] subjects), and in the placebo treatment arm was "none" (10 / 23 [43.5%] subjects). At Day 182, investigators rated 36 / 39 (92.3%) subjects' response to therapy as "good or better" in the garadacimab Arm compared to 6 / 23 (26.1%) subjects in the Placebo Arm.

- **Ancillary analyses**

No prespecified subgroup analyses were planned in Study 3001 with exception of analyses based on stratification factors and for Japanese subjects.

Table 23: Time-normalised Number of Hereditary Angioedema Attacks Per Month During 6-month Treatment Period – Japanese Subgroup (ITT Analysis Set)

	CSL312 200 mg (N = 4)	Placebo (N = 2)
Number of Evaluable Subjects, n	4	2
Number of HAE Attacks during Treatment Period	25	38
Time-normalized Number of HAE Attacks Per Month		
Mean (SD)	1.04 (1.863)	3.24 (0.177)
Median	0.17	3.24
Min, Max	0.0, 3.8	3.1, 3.4
1st Quartile, 3rd Quartile	0.00, 2.08	3.11, 3.36
95% CI	(-1.92, 4.01)	(1.65, 4.83)

Of note, 1 Japanese subject receiving garadacimab had a lower percentage reduction during the 6-month Treatment Period (14.5%), which lead to a slightly lower mean percentage reduction in HAE attacks overall for the Japanese subgroup compared to all subjects.

This subject, with HAE type 1 and, with different comorbidities in including fibromyalgia and perimenopause. Prior to enrolment, the subject was treated for HAE with tranexamic acid. During the treatment period, the subject experienced 22 mild attacks and 1 moderate attack, averaging 4 per month. A high number of on-demand medications per event were used without benefit. Both the investigator and Sponsor opinion is that the self-reported attack rate may be inflated by multiple confounding variables and no conclusion can be made regarding the efficacy of CSL312 in this subject.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical.

Table 24: Summary of Efficacy for Trial CSL312_3001

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of garadacimab in the Prophylactic Treatment of Hereditary Angioedema_		
Study identifier	CSL312_**3001** EudraCT: 2020-000570-25	
Design	Multicentre, double-blind, randomised, placebo-controlled, parallel-arm, phase 3 study to investigate the efficacy and safety of 200 mg garadacimab administered subcutaneously (SC) once a month for the prophylaxis to prevent HAE attacks in adolescent (12 to 17 years, inclusive) and adult subjects with C1-esterase inhibitor (C1-INH) HAE.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months At least 1 month and Up to 2 months None. Subjects had the option to roll over to an open label study CSL312_3002.
Hypothesis	Superiority vs placebo	

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of garadacimab in the Prophylactic Treatment of Hereditary Angioedema_			
Study identifier	CSL312_**3001** EudraCT: 2020-000570-25		
Treatments groups	placebo	SC injection monthly for 26 weeks N=25	
	garadacimab	200 mg SC injection monthly for 26 weeks N=39	
Endpoints and definitions	Primary endpoint	Time-normalised number of HAE attacks (per month) during treatment from Day 1 through Day 182 (Hierarchical Testing **H01**)	
	Secondary endpoints (key)	Percent reduction in monthly attack rate compared with placebo (Day 1 to 182) (**H02**) Number of attack-free subjects through Day 91 (**H03**) Percentage of subjects rating therapy as "good" or better (i.e., "excellent") through the SGART at Day 182 (**H04**)	
Database lock	24Jun2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT), time period: 6 months (day 182)		
Descriptive statistics and estimate variability	Treatment group	placebo	garadacimab 200 mg q1M
	Number of subjects	24	39
	Time-normalised number of HAE attacks from Day 1 to 182 mean, median 1st & 3rd quartile, min,max	2.01 1.35 1.00, 3.20 0.2, 4.4	0.27 0.00 0.00, 0.31 0.0, 3.8
	SD, 95% CI	1.341 (1.44, 2.57)	0.683 (0.05, 0.49)
Effect estimate per comparison	Primary endpoint	Comparison groups	garadacimab vs placebo
		two-sided Wilcoxon test (alpha=0.05)	garadacimab 0.00 Placebo 1.35
		95% CI	garadacimab 0.05, 0.49 Placebo 1.44, 2.57

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of garadacimab in the Prophylactic Treatment of Hereditary Angioedema				
Study identifier	CSL312_**3001** EudraCT: 2020-000570-25			
		P-value	P <0.0001	
Notes	As a **sensitivity analysis**, the time-normalised number of HAE attacks was compared for the 6 months of the Active Arm and the 6 months of the Placebo Arm using a generalised linear model (GLM) for count data assuming a Poisson distribution with the logarithm as link function and Pearson chi-square scaling of standard errors to account for potential over dispersion. The model included treatment (categorical) and the time-normalised baseline attack rate during Run-in Period (continuous) as covariates. To account for the length of subject treatment, the logarithm of the length of subject treatment was used as an offset variable. The sensitivity analysis using a Poisson Model showed the least square mean (95% CI) time-normalised number of HAE attacks per month was 0.223 (0.1067, 0.4669) attacks in the garadacimab Arm and 2.068 (1.4895, 2.8724) attacks in the Placebo Arm during the 6-month Treatment Period. There was an 89.211% reduction in the mean time-normalised number of HAE attacks in the garadacimab Arm compared to placebo. The beneficial effect of garadacimab relative to placebo in reducing the number of HAE attacks was also seen in the mean time-normalised number of HAE attacks ratio (95% CI), which was 0.108 (0.0477, 0.2441) attacks.			
Analysis description	**Secondary analysis**			
Analysis population and time point description	Intent to treat (ITT), time period: 6 months if not stated differently			
Descriptive statistics and estimate variability	Treatment group	placebo	garadacimab 200 mg q1M	
	Number of subjects	24	39	
	Relative Difference in the Time-normalised Number of HAE Attacks Per Month (Day 1 to 182) Relative Difference in Means in the Time-normalised Number of HAE Attacks Per Month garadacimab to Placebo [a] (%)	-86.51		[a] Derived as: 100 * [(mean time-normalised number of HAE attacks for garadacimab – mean time normalised number of HAE attacks for Placebo) / mean time-normalised number of HAE attacks for Placebo].
	95% CI	-95.68, -57.84		
	Number of attack-free subjects through Day 91 n (%) of subjects	2 (8.3)	28 (71.8)	

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of garadacimab in the Prophylactic Treatment of Hereditary Angioedema_				
Study identifier	CSL312_**3001** EudraCT: 2020-000570-25			
	95% Wilson CI[b]	2.32, 25.85	56.22, 83.46	[b] The 95% CI is based on Wilson's asymptotic confidence limits
	Number of subjects	24	38	
	Subject's Global Assessment of response to Therapy (SGART) at Day 182 n (%) of subjects with good or better as a response	8(33.3)	31(81.6%)	
Effect estimate per comparison	Relative Difference in the Time-normalised Number of HAE Attacks Per Month garadacimab vs placebo	Comparison groups	garadacimab vs placebo	
		two-sided Wilcoxon test	-86.51	
		95% CI	-95.68, -57.84	
		p-value (Second Hierarchical Test [H02])	P <0.0001	
	Number of attack-free subjects through Day 91	Fisher Exact Test, nominal p-value (H03)	P <0.001	
	Subject's Global Assessment of response to Therapy (SGART) n (%) of subjects with good or better as a response	Chi-squared test (H04)	P <0.001	

2.6.5.3. In vitro biomarker test for patient selection for efficacy

Not applicable

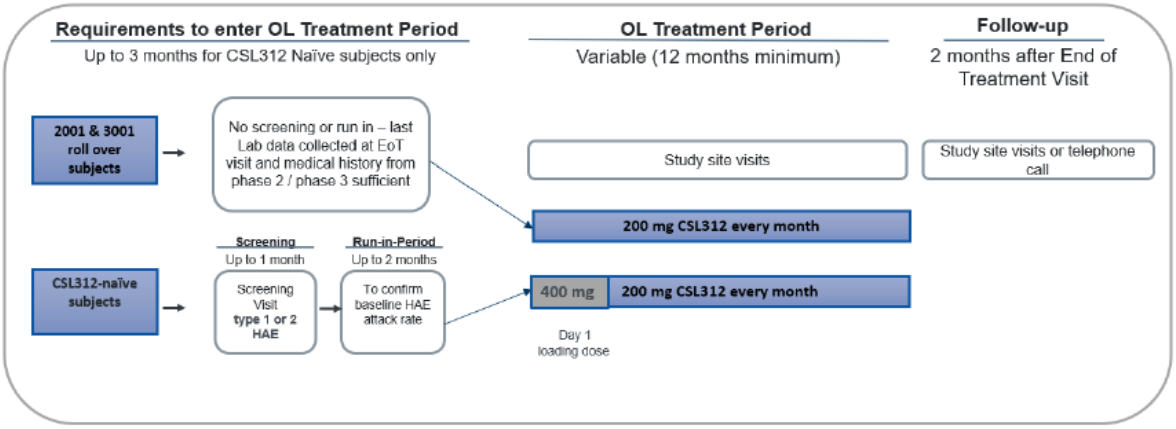
2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

The applicant presented a comparison of efficacy results across the individual clinical studies, as well as results of the pooled analysis of efficacy data from Studies 3001 (pivotal) and 3002 (ongoing open-label extension), based on the pooled analysis from Integrated Summary of Efficacy. Considering that the study 3002 is supportive (see below), the pooled data will be included after the Study 3002 data.

2.6.5.5. Supportive study

Study 3002

This is an ongoing phase 3, multicentre, open-label, single arm study that was designed for the assessment of long-term safety and efficacy of garadacimab (200 mg once a month) to prevent HAE attacks.



The primary objective of the study is to evaluate the long-term safety of SC administration of garadacimab in subjects with C1-INH HAE. The secondary objectives are to evaluate the long-term efficacy and additional assessments of long-term safety. No hypothesis testing was planned for this study. There was no primary efficacy analysis. The sample size was not based on a formal statistical sample size calculation but on the guideline E1A issued by the ICH, March 1995. The sample size of 100 subjects allowed observation of ≥ 1 AE with a probability of 3% at 95% confidence. Approximately 150 subjects) were planned to be enrolled into the study and a minimum of 100 subjects were planned to receive treatment for a minimum of 12 months.

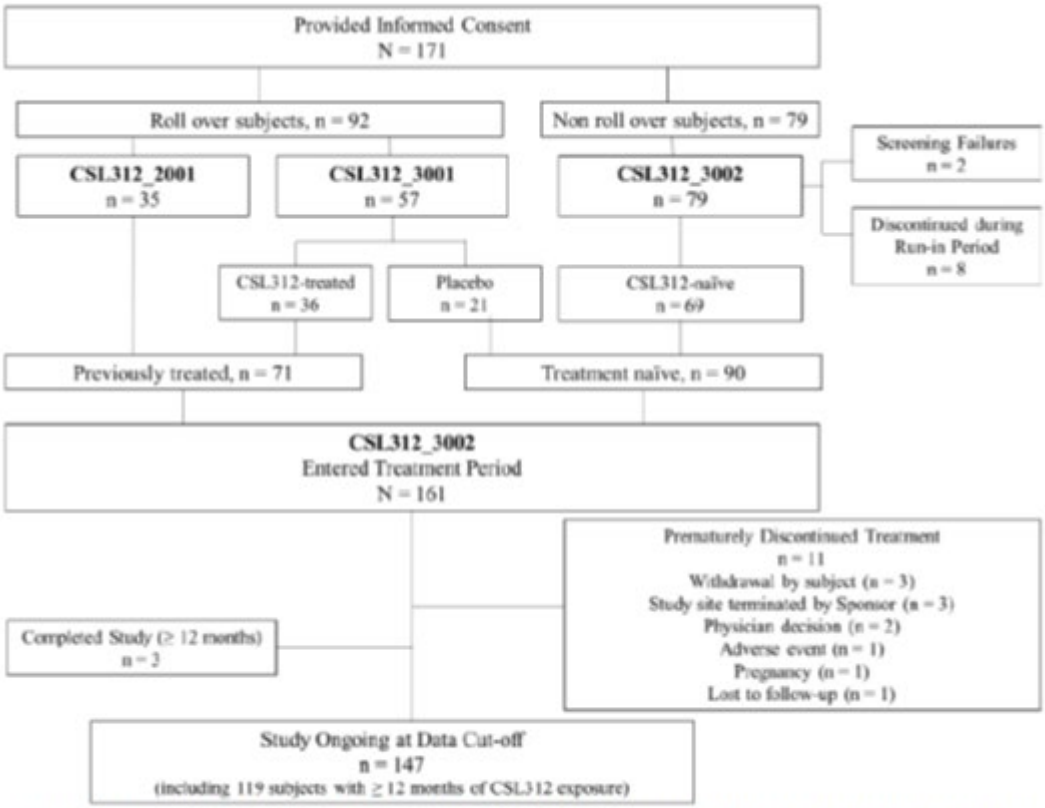
Subjects who successfully completed Studies 2001 or 3001 could rollover directly from treatment in those trials and start this study at Treatment Day 1. The eligibility criteria for newly enrolled subjects were in line with study 3001 criteria. Also, the permitted on-demand treatment and the prohibited medications were the same.

The **primary safety endpoint** was the treatment-emergent adverse events (TEAEs) for C1-INH HAE subjects.

The **secondary efficacy endpoints** of the study included: the time-normalised number of HAE attacks, the reduction in the attack rate during the Treatment Period compared to the Run-in Period, the time-normalised number of HAE attacks requiring on-demand treatment, the time-normalised number of moderate and / or severe HAE attacks, and SGART.

The IA2 was completed on all subjects, available at the data cut-off date of 13 February 2023. The IA3 of Study 3002 was completed in the adolescent subgroup when 8 / 10 adolescent subjects (80%) had ≥ 12 months of exposure to garadacimab in Study 3002 (data cut-off date of 22 May 2023).

Figure 8: Subject Disposition



Note: One subject was an adolescent (17 years of age) at the time of screening for Study CSL312_3001 but was an adult (turned 18 years of age) at the time of rolling over to Study CSL312_3002. This subject has been enrolled and analyzed as an adult in the Study 3002.

The median (range) duration of exposure to garadacimab was 1.15 years (0.3, 1.8).

From 161 subjects (IA2) treated in this study, the most of them were women (101, 62.7%), White (135, 83.9%) or Asian (22, 13.7%). The mean (SD) age was 42.3 years (range 13-73 years). There were 10 adolescents and 13 patients >65 years of age. Most of the patients had Type 1 HAE (145, 90.1%), while 14 had Type 2 (8.7%) and only 2 patients had nC1-INH (FXII HAE) as they rolled over from the study 2001. The two thirds had history of laryngeal attack and most of the patients (88.2%) had family history of HAE. There were 59 (36.6%) patients with HAE routine prophylaxis during 3 months before screening. Overall, the mean (SD) and median of HAE attacks/month during the 3 months before screening or start of prophylaxis were respectively 3.10 (2.397) and 2.33.

The mean (SD) and median time-normalised number of HAE attacks per month during the treatment period were 0.16 (0.370) attacks and 0.00 attacks, respectively.

The mean (SD) time-normalised number of HAE attacks per month and per year:

- in subjects who had previously received garadacimab while participating in Study CSL312_2001 or CSL312_3001 was 0.09 (0.285), 0.11 (0.316) per month and 1.05 (3.416), 1.29 (3.791) per year, respectively.

- in subjects who had not participated in previous garadacimab studies was 0.21 (0.414) per month and 2.57 (4.970) per year.

The mean (SD) reduction in the time-normalised number of HAE attacks during the Treatment Period compared to the Run-in Period was 94.67% (11.983).

Moreover, 158 / 161 (98.1%) subjects were responders with a reduction in attack rate ≥ 50%. The majority of subjects (96 / 161 [59.6%] subjects) were attack-free over the median exposure of 13.83 months. In subjects who received placebo in Study 3001 and rolled over to receive garadacimab in Study 3002, 11 / 21 (52.38%) subjects were attack-free during treatment with garadacimab.

The mean (SD) time-normalised number of HAE attacks requiring on-demand treatment per month during the Treatment Period was 0.14 (0.358). The mean (SD) time-normalised number of moderate and / or severe attacks per month was lower in the Treatment Period (0.11 [0.277] attacks per month) than in the Run-in Period (2.59 [2.112] attacks per month).

At the Month 12 visit SGART, 110 / 118 (93.2%) subjects (95% CI: 87.19, 96.52) recorded a response of "Good" or "Excellent" and 92 / 118 (78.0%) subjects recorded a response of "Excellent" to garadacimab treatment.
As of the IA3 data cut (22 May 2023) for the subgroup of adolescents (10 / 161 subjects), the rate of HAE attacks was similar to that observed in the overall population. The mean (SD) and median time-normalised number of HAE attacks per month was 0.08 (0.100) and 0.05 respectively. Out of the 10 HAE attacks observed in adolescent subjects in the Treatment Period, 9 (90%) were treated with on-demand treatments. The mean (SD) time-normalised number of HAE treated with on demand medication per month during the Treatment Period was 0.07 (0.103).

The applicant performed the analysis of efficacy by pooling the data from the studies 3001 and 3002.

The demographic and baseline characteristics of subjects were similar in Studies 3001 and 3002. Of the 161 subjects who entered the Treatment Period in Study 3002, 57 subjects also participated in Study 3001, which contributed to the similarities between study populations.

In pooled analysis of Studies 3001 and 3002, the mean (SD) and median time-normalised number of HAE attacks per month was 0.17 (0.40) attacks and 0.00 attacks during treatment with garadacimab, while the mean (SD) and median reduction in the time-normalised number of HAE attacks per month for the entire treatment with garadacimab compared to the Run-in Period was 94.23% (12.83) and 100%.

159 / 164 (96.95%) of subjects were responders with reductions in HAE attacks of ≥ 50% during treatment with garadacimab, over a median (range) exposure of 14.93 months (3.0, 22.3). 94 / 164 (57.32%) subjects had a reduction of 100% (attack-free) during treatment with garadacimab.

Table 25: Time-normalised Number of HAE Attacks Per Month / Year by Subgroup Age: 12 to ≤ 17 Years, > 17 Years (ITT Analysis Set, Pooled Studies 3001 [Pivotal] and 3002 [Interim Analysis 2])

> 17 Years of Age	Garadacimab (N = 153)
Number of Evaluable Subjects, n (%)	153 (100)
Number of HAE Attacks during Treatment Period	377
Time-normalized Number of HAE Attacks Per Month	
Mean (SD)	0.18 (0.41)
Median	0.00
Min, Max	0, 3
1st Quartile, 3rd Quartile	0.0, 0.1
95% CI	(0.1, 0.2)
12 to ≤ 17 Years of Age	**Garadacimab (N = 11)**
Number of Evaluable Subjects, n (%)	11 (100)
Number of HAE Attacks during Treatment Period	18
Time-normalized Number of HAE Attacks Per Month	
Mean (SD)	0.11 (0.20)
Median	0.05
Min, Max	0, 1
1st Quartile, 3rd Quartile	0.0, 0.1
95% CI	(-0.0, 0.2)

The mean (SD) and median reduction in the time-normalised number of HAE attacks per month for the entire treatment compared to the Run-in Period among adolescent subjects was 90.08% (17.85) and 95.17% during treatment with garadacimab, while among adult subjects was 94.53% (12.42) and 100%.

Table 26: Time-normalised Number of HAE Attacks Per Month / Year by Subgroup Age: ≥ 65 Years (ITT Analysis Set, Pooled Studies 3001 [Pivotal] and 3002 [Interim Analysis 2])

≥ 65 Years of Age	Garadacimab (N = 14)
Number of Evaluable Subjects, n (%)	14 (100)
Number of HAE Attacks during Treatment Period	11
Time-normalized Number of HAE Attacks Per Month	
Mean (SD)	0.06 (0.08)
Median	0.02
Min, Max	0, 0
1st Quartile, 3rd Quartile	0.0, 0.1
95% CI	(0.0, 0.1)

The mean (SD) and median reduction in the time-normalised number of HAE attacks per month for the entire treatment compared to the Run-in Period in elderly subjects was 97.27% (4.50) and 99.19% during treatment with garadacimab.

After the request, the applicant provided the updated efficacy results for the ongoing open-label, long term safety study 3002 as per the most recent data-cut on 15 June 2024. The updated efficacy results include:

- HAE attack rate (mean (95 %-CI): 0.14 (0.09, 0.20) attacks per month; median (95%-CI): 0.00 (0.00, 0.03) attacks per month

- 98.1 % of subjects had ≥ 50% reduction from Run-in in attack rate per month

- 86.3 % of subjects had ≥ 90% reduction from Run-in in attack rate per month

- 50.3 % of subjects remained attack-free through the entire study.

The results within the subgroups are also in line with the results from the phase 3 study and previous interim analysis of the OL study.

2.6.6. Discussion on clinical efficacy

To support the MAA, the applicant submitted results from the pivotal Study 3001, a phase 3 double-blind, randomised, placebo-controlled study conducted in adolescent and adult subjects with HAE to evaluate efficacy of garadacimab over placebo. Further for supporting purposes, results from completed Study 2001, a phase 2 proof-of-concept, dose-finding study, and from IA of Study 3002, an ongoing open-label, single arm study, are provided. The applicant also provided the analysis of efficacy by pooling the data from the studies 3001 and 3002.

Design and conduct of clinical studies

The pivotal Study 3001 was a phase 3, multicentre, double-blind, randomised, placebo-controlled, parallel-arm, 26-week study to investigate the efficacy and safety of garadacimab in adolescent (12 to 17 years, inclusive) and adult subjects with HAE type 1 or type 2, randomised 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. The study consisted of four parts: screening (up to 1 month), run-in (up to 2 months), treatment period (6 months) and follow-up period (2 months). The design of the pivotal study is acceptable. The participants needed to have experienced 3 or more HAE attacks in the 3 months prior to screening and 2 or more HAE attacks during the run-in period (a minimum average rate of 1 attack/month). The randomisation was stratified by age (≤ 17 years, > 17 years) and the subject's baseline attack rate (1 to < 3 attacks/month and ≥ 3 attacks/month, adults only). This is acceptable as it would ensure to have enough patients in both arms with different attack rates at baseline. In total, 64 subjects received either garadacimab (n=39) or placebo (n=25). Six adolescents were also included (4 in garadacimab and 2 in placebo arm), and this is endorsed (at least 5 adolescents required by the PIP).

The sample size of 40 subjects was statistically justified with alpha 0.05 for a two-sided Wilcoxon test and a power of 90% assuming an attack rate per month of 0.3125 and 1.3 for subjects receiving treatment and placebo, respectively. These assumed attack rates were based on the results of the phase 2 study, in which a higher attack rate was observed in the placebo arm (4,24). It was planned to randomise approximately 60 subjects and 5 adolescents to the treatment period (randomisation ratio 3:2).

The limited sample size is acceptable considering that HAE is a rare condition and is however larger than the one proposed at the time of EMA SA (EMA/CHMP/SAWP/220904/2020). The 6-month duration of placebo-controlled treatment was recommended by the SA 2020. Considering the other treatments approved for routine prophylaxis (e.g., lanadelumab, same route of administration), the study could have included an active comparator arm; this would have helped for contextualisation of results.

The study design is overall acceptable. The ITT set was used for the primary and secondary analyses although the definition of the ITT set is not completely in line with the ITT definition expected (i.e. participants less than 30 days of exposure were excluded) which is accepted.

The study included subjects ≥ 12 years of age with C1-INH HAE (type 1 or 2). The patient population was overall adequately selected during the screening and run-in period. However, the exclusion of acquired angioedema was left to the investigator's discretion, their expertise and thorough evaluation of clinical data. Although there is no final proof that acquired HAE was excluded in the two patients in the pivotal study without family history and with the age at diagnosis over 30 years (potentially onset of symptoms <30 years excluding acquired AE, information not collected), those two patients were in the garadacimab arm and had an excellent response (attack-free). Therefore, it is considered that there was no impact on study results.

The eligibility criteria in the pivotal study included ≥ 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, i.e. a subset of HAE subjects with frequent and recurrent attacks. Therefore, the applicant agreed to revise the indication to reflect that the target population is patients with recurrent attacks.

For the subjects taking any prophylactic therapy during the 3 months before screening, the minimum number of HAE attacks were to be documented over 3 consecutive months before commencing the prophylactic therapy. The applicant explained that previous using of routine prophylaxis was exclusion criterion for adolescents in the study 3001 for ethical reasons (to avoid discontinuing stable treatment during the washout and also potentially be randomised to placebo and impose risks, including the potential for life-threatening laryngeal attack). However, past use was not excluded and 3 adolescents who had previously used prophylactic HAE treatments and had independently stopped prior to screening were enrolled in study 3001 (2 adolescents) and study 3002 (1 adolescent). Therefore, also adolescents with experience of other prophylactic HAE therapy were included in the studies.

During the study on-demand HAE attack therapies (C1-INH, icatibant, ecallantide) were permitted while long-term prophylaxis with: C1-INH, androgens, antifibrinolytics, lanadelumab or future approved medication were prohibited. Also, ACE inhibitors and oestrogen-containing therapy was prohibited due to their interference with bradykinin degradation. The prior HAE on-demand treatment included C1INH (60.9% of patients), icatibant (53.1%) and conestat alfa (3.1%), well-balanced between the arms. The concomitant HAE on-demand treatment included (% subjects garadacimab vs placebo arm): icatibant (25.6% vs 60%), C1INH (20.5% vs 64%) conestat alfa (0 vs 8%); much higher portion of patients in placebo arm needed the on-demand HAE treatment during the study as compared to garadacimab arm. The prior short-term prophylaxis was used in 0% garadacimab vs 4% (1 subject) placebo arm (C1INH); no use of short-term prophylaxis was reported during the study.

Time from HAE attack onset until following on-demand treatment start (days) and number of uses per treated HAE attack were similar between the arms both during the Run-in period and during the treatment period (overall and for individual on-demand treatments).

After the treatment period, subjects had the option to participate in a phase 3b open-label study (study 3002). If not, they were followed for up to 3 months after the last dose of garadacimab.

The posology and method of administration proposed in the SmPC are consistent with those used in the study and are considered appropriate.

The primary objective of this study was to evaluate the efficacy of garadacimab over placebo in preventing HAE attacks.

The primary endpoint was the Time-normalised number of HAE attacks per month during treatment from day 1 through Day 182.

There were five secondary endpoints:

1) Time-normalised number of HAE attacks at various time points during the Treatment Period

2) The reduction in the attack rate during the Treatment Period compared to the Run-in Period

3) Subject's Global Assessment of Response to Therapy (SGART)

4) The time-normalised number of HAE attacks requiring on-demand treatment

5) The time-normalised number of moderate and / or severe HAE attacks

The key secondary endpoints were percent reduction in monthly attack rate compared with placebo (day 1 to 182) (H02); number of attack-free subjects through day 91 (H03); percentage of subjects rating therapy as "good" or better (i.e., "excellent") through the SGART at Day 182 (H04).

The endpoints of the study are accepted, and the primary endpoint adequately reflects the study objective and is considered clinically relevant. It is acknowledged that, after somehow accepting initial proposal during SA of 3-month time point, the primary analysis and duration of placebo-controlled period was extended to 6 months. After request, the applicant provided the report on validation of SGART questionnaire. Based on the analyses from this report, the SGART demonstrated significant and reliable associations with measures of clinical outcomes, clinicians' evaluations, and to a less extent with PRO measures. Of note, the validation of SGART seems to be performed only with the data from the pivotal study 3001 and therefore when chosen to be used in this study (as one of the key secondary endpoints), the score was not validated. This is not optimal but acceptable.

The primary estimand and sensitivity analysis were included. Even if the definition was not considered with adequate level of details, the treatment policy strategy and principal intercurrent events are agreed.

However, considering that in the study 3001 only one primary estimand was defined and only the treatment policy strategy was applied for all intercurrent events, the applicant was requested to perform two sensitivity analyses considering a composite strategy including the prohibited medications and non-compliance to treatment as well as descriptive analysis of prohibited medications used and of non-compliance to treatment. Only two subjects took prohibited medications (lanadelumab and C1INH for prophylaxis). The applicant confirmed the results of the primary analysis with additional analyses.

The monthly attack rates of placebo and of garadacimab, used to calculate the sample size, were assumed to be Poisson distributed. However, the two-sided Wilcoxon test used for the primary analysis is not considered optimal since it cannot include all the design features, such as the stratification factors. This was emphasised in the SA 2020 and a more appropriate method was recommended, such as the Poisson model with the HAE attack rate during the baseline (run-in) period as a covariate. The applicant justified the choice of Wilcoxon test instead of Poisson model to test the primary endpoint based on results from study CSL312_2001 showing that no baseline factors (i.e. baseline attack rate) seemed to influence the treatment effect of garadacimab. A generalised linear model for count data assuming a Poisson distribution was used as a sensitivity analysis, including the time-normalised baseline attack rate during the run-in period (which was one of the stratification factors during randomisation) as a covariate. The exclusion of age as another stratification factor in the Poisson regression model can be accepted as no difference in response between adolescent and adult patients is expected and this stratification factor was introduced to ensure that not all adolescents were included in the same treatment group. Considering the Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013) which states that the primary analysis should reflect the restriction on the randomisation implied by the stratification and that stratification variables, if not solely used for administrative reasons, should usually be included as covariates or stratification variables in the primary analysis regardless of their prognostic value, the results of the Poisson regression are considered more informative than the results based on the Wilcoxon test despite the equal distribution of the two groups of subjects based on baseline attack rate (1 to < 3 attacks/month and ≥ 3 attacks/month) in the active and placebo groups. The choice of using two different methods

to provide unadjusted and adjusted estimates cannot be fully agreed since it could have affected the robustness of results, however the results from primary analysis (Wilcoxon test) and sensitivity analysis (Poisson model) were consistent. Obviously, the choice of the Poisson model would have involved a higher number of subjects.

Missing values were only considered for subjects who discontinued within 30 days after the first study treatment administration. This approach is not acceptable because no predefined imputations were made for the withdrawals of subjects and other missing data. The applicant conducted sensitivity analysis for missing data only for the analysis of the primary endpoint based on the Wilcoxon test, which does not allow the inclusion of the stratification factors. Furthermore, the way that the primary endpoint was defined and analysed implies that HAE rate in the missing days of patients that didn't reach Day 182 would be the same as HAE rate in the non-missing days, which might not be appropriate. Following the request from the CHMP, the applicant provided sensitivity analyses for missing data for the Poisson regression model including tipping point analysis where data from missing days in discontinued subjects were imputed. There were 4 subjects who discontinued before the end of the treatment period, and all were randomised to placebo. The interpretation of the analysis provided is that none of the imputed values for discontinued subjects would have overturned the primary result.

The PP (per protocol) set was used for the supplementary analysis, excluding subjects who experienced an HAE attack caused by COVID-19 infection or other factors, who missed study drug administration due or not due to COVID-19 infection or vaccination, and subjects taking prohibited concomitant medications. It is not clear why HAE attacks due to COVID-19 infection or other reasons were excluded from the PP analysis but since only one subject was excluded from the PP set, it is assumed that this has no impact on the study results.

The choice and hierarchy of key secondary endpoints is not considered optimal and is noted that some secondary endpoints are partially overlapping and not independent from the primary endpoint, i.e. the same results are in part included in both (e.g. reduction in the attack rate during the treatment period compared to Run-in period). However, the clinically relevant endpoints are included as secondary or key secondary endpoints, and this is considered acceptable.

Some changes in the SAP were made before database lock but it is considered that these changes do not affect the validity of the study. Three analyses were added after the database was locked, and it cannot be ruled out that these were data-driven:

1. In the HAE history for the ITT and PP sets the time-normalised number of HAE attacks within 3 months before screening for subjects with and without HAE prophylaxis during 3 months before screening and the time-normalised number of HAE attacks during the 3 months before Screening or start of HAE prophylaxis were added.

2. In supplementary analyses of secondary endpoints: the summary of time-normalised number of moderate or severe attacks per month was added.

3. A sensitivity analysis of the primary endpoint adjusted for baseline attack rate was added for the first and second 3 months of treatment.

The majority of participants were female (59.4%), White (85.9%) and of Not Hispanic or Latino ethnicity (93.8%). The mean (SD) age was 41.2 (15.92), with the youngest participant being 12 and the oldest 69 years of age. The baseline characteristics were overall balanced between the arms.

Regarding HAE history, all participants in the ITT set had a biochemically confirmed diagnosis of HAE before randomisation (87.5% had a diagnosis of C1-INH HAE type I and 12.5% had C1-INH HAE type II). The minority of participants received HAE prophylaxis during the 3 months before screening (35%

in garadacimab and 28% in placebo). Among the participants who received prophylaxis, the mean number (SD) of time-normalised number of HAE attacks per month was 1.6 (1.23) in garadacimab and 1.1 (0.66) in placebo arms. Among participants who did not receive prophylaxis, the mean number (SD) of time-normalised number of HAE attacks per month was 2.9 (2.44) in garadacimab and 3.1 (2.01) in placebo arms. However, during the Run-in period the time-normalised number of HAE attacks per month was somewhat higher in the placebo compared to garadacimab arm (mean (SD) 3.07 (2.047) in placebo arm and 2.52 (0.944) in garadacimab arm). The baseline characteristics are adequately reflected in SmPC section 5.1.

The most frequent anatomical locations of HAE attacks in study participants during the 3 months before screening were cutaneous – extremities (78.1% participants), abdomen (75.0%) and cutaneous – head/face/lip/neck (32.8%). The majority of participants had a history of laryngeal attack (68% placebo vs 53.8% garadacimab arm). Overall, except for the history of laryngeal attack (which was more frequently observed in the placebo arm), the treatment arms were balanced regarding history of HAE and attacks.

The most commonly used prior and concomitant medications were drugs used for HAE; this was balanced between treatment arms.

The Study 3002 is an ongoing phase 3b multicentre, open-label, single arm study with safety as the primary objective and efficacy as the secondary objective. The study was designed to support long-term safety and efficacy of garadacimab in prevention of HAE attacks in patients who have participated in two garadacimab studies (one phase 2 and one phase 3 study) and in newly enrolled subjects. Two interim analyses were conducted (the first data cut-off for all subjects on February 13, 2023, and the second on May 22, 2023, for adolescents only). The study consists of 4 parts: screening, run-in period, treatment period (with a minimum duration of 12 months) and follow-up. The study parts, the eligibility criteria, the criteria for permitted and prohibited therapies correspond to the pivotal study. However, two subjects with HAE type III were included. Efficacy endpoints are the same as in the pivotal study, and the efficacy analyses are exploratory only.

The subjects are treated with 200 mg garadacimab SC as 1 dose once monthly for a minimum of 12 months. The eligibility criteria for newly enrolled subjects are generally in line with the study 3001. Of the 161 treated subjects (IA2), 92 subjects rolled over from previous studies (Study 2001 and Study 3001) and 69 were newly enrolled garadacimab-naïve subjects. From 92 subjects that rolled over, 35 subjects (including 2 subjects with FXII HAE) rolled over from Study 2001, and 57 subjects rolled over from Study 3001 (21 of which had received placebo previously). The number of 161 subjects who entered the treatment period and 119 (73.9%) who were exposed for at least 12 months at the cut-off date (13 February 2023) is considered a sufficient number for an extension study according to the SA 2020.

In Study 3001, 6 adolescents were enrolled and completed the study. 5 adolescent subjects rolled over to Study 3002 and 5 additional newly enrolled garadacimab-naïve adolescent subjects were enrolled directly into Study 3002.

Overall, the study population is considered representative and demographic and disease characteristics are generally in line with those of the pivotal Study 3001.

Study 2001 was a proof-of-concept, dose-finding phase 2 multicentre study that evaluated the efficacy, safety, tolerability, and PK of garadacimab across a range of doses in subjects with C1-INH HAE or nC1-INH HAE (FXII or PLG gene mutation HAE). This was a randomised, placebo-controlled, parallel-arm study during the first 13 weeks (TP1) and then open label (TP2, 44 weeks). For subjects with C1-INH HAE the inclusion criteria were 2 attacks/month, more stringent than for the study 3001.

For FXII/PLG HAE the criterion was ≥ 1 HAE attack during the 3 months before Screening, and ≥1 attacks over the Run-in period. The endpoints were overall in line with phase 3 trials.

32 subjects with C1-INH HAE who were eligible were randomised to 1 of 4 blinded treatment arms (1:1:1:1) during TP1: subcutaneous garadacimab 75 mg q4wk (loading dose 40 mg IV), 200 mg q4wk (loading dose 100 mg IV), 600 mg q4wk (loading dose 300 mg IV), or placebo q4wk thereafter for 12 weeks. Six FXII / PLG HAE subjects were treated open label with garadacimab 600 mg q4wk. Neither demographic nor baseline disease characteristics were well balanced between the controlled arms of C1-INH HAE subjects (e.g. the median time-normalised number of HAE Attacks per month during the Run-in period ranged from 2.95 in 600mg arm to 6.30 in 75mg arm). This could be due to the low number of subjects in each arm (n=7-9). However, the placebo arm and 200mg were much better balanced for most demographic and disease characteristics.

Dosing regimen

For phase 3 Study 3001 the applicant selected the 200 mg garadacimab dose, with a loading dose of 400 mg. However, it is noted that the results of the dose-finding Study 2001 are not fully consistent in terms of dose-response, with apparently lower efficacy with garadacimab 600 mg compared to 200 mg. After a request from CHMP, the applicant discussed some possible reasons for the findings of the phase 2 study in 600 mg arm and further explained the rational for the choice of 200 mg for the phase 3 study. Some other possible causes (e.g. low patient number, imbalance of baseline characteristics, etc) could have contributed.

The use of a loading dose is expected to increase exposure to the target steady-state threshold, thereby providing protection from HAE attacks (potentially life-threatening) from the first dose. While the loading dose in the phase 2 Study for 200 mg arm was 100mg IV (followed by 200mg sc after 6 days), in Study 3001 the loading dose was 400 mg sc (followed by 200 mg sc after 1 month).

While it is understood that the 200 mg sc q1M dose was chosen based on the results of phase 2 trial (study 2001) and E-R model, a mechanistic rationale for optimal % inhibition of FXIIa-mediated kallikrein activity was not provided, even if requested in the SA. Indeed, a decrease of kallikrein activity with increasing of dose was observed, and it is not clear if the fluctuations of this inhibition over time could be correlate to the occurrence of attacks. However, the dose tested in the pivotal trial (400 mg loading dose followed by 200 mg q1M) provided evidence for a clinically relevant effect of garadacimab on HAE attack prevention as emerged from the primary efficacy analysis (see data below), thus supporting the appropriateness of drug posology.

Efficacy data and additional analyses

The primary endpoint in the pivotal Study 3001 was the time-normalised number of HAE attacks during treatment from Day 1 through Day 182.

The primary endpoint analysis using two-sided Wilcoxon test showed that garadacimab 200 mg administered SC once a month resulted in a statistically significant lower mean (SD) and median time-normalised number of HAE attacks per month when compared with placebo (0.27 (0.683) / 0.0 attacks in garadacimab *vs*. 2.01 (1.341) / 1.35 attacks in placebo; $p < 0.001$). This is corroborated by the results of sensitivity analysis of the primary endpoint adjusted for baseline attack rate using the Poisson model, showing 89.211% reduction in the garadacimab arm compared to placebo (95% CI -95.2315, -75.5876). The results are also supported by the supplementary analysis of the primary endpoint in the PP analysis set.

Out of 80 screened patients with HAE, there were 4 screen failures. Out of 76 participants who entered the run-in period, 11 were excluded due to not having at least 2 HAE attacks during the run-in period. Of 65 randomised subjects (39 in the garadacimab arm and 26 in the placebo arm), only 63 subjects

were considered evaluable for the primary efficacy analysis: one subject was excluded since consent was withdrawn before first study dose, another subject was not considered "evaluable" since treatment period was < 30 days; both subjects were randomised to placebo arm. These two subjects were excluded from primary efficacy analysis of the study 3001, violating the ITT principle as defined in the protocol. Analysis of different endpoints after the multiple imputation, provided after request, can be considered overall consistent with the previous results. However, since both subjects were initially randomised to placebo arm, the sampling should have been performed within the placebo arm for both. Of the 39 randomised subjects in the garadacimab arm, 38 completed the study.

It is acknowledged that key secondary and all other endpoints support the demonstration of efficacy of garadacimab over placebo, although some endpoints are not independent. The 3 secondary efficacy endpoints evaluated by formal hierarchical testing showed:

i) a significant percentage reduction (relative difference) in the means of time-normalised number of HAE attacks for the 6-month Treatment Period of the garadacimab arm compared to placebo ($p < 0.001$, 86.51% reduction); however, it is derived from the primary efficacy result;

ii) a significantly higher number of subjects who were attack-free (had 100% reduction in HAE attacks) during the first 3 months of treatment in the garadacimab arm (71.8%) compared to placebo (8.3%) (H03: $p < 0.001$, Fisher Exact Test);

iii) a significantly higher percentage of subjects rating their response to therapy as "good" or better by the SGART at the end of the Treatment Period in the garadacimab arm (81.6%) compared to placebo (33.3%) (H04: $p < 0.001$, Chi-squared test).

The second hierarchical test (the percentage reduction in the means of the time-normalised number of HAE attacks for the 6-months in garadacimab vs placebo arm) used a two-sided Wilcoxon Test with alpha = 5%.

Other secondary outcomes (multiplicity unaccounted for) are largely overlapping and pertaining to the same efficacy measured as the hierarchically tested outcomes. These include a consistently higher percentage of responders among participants receiving garadacimab compared to participants receiving placebo, both during the initial 3 months of treatment and the last 3 months of treatment. Two participants receiving garadacimab were non-responders (one participant had a 14.5% reduction in HAE attacks in the 6-month treatment period while one participant had a 5.8% increase in HAE attacks in 6 months of treatment). The applicant clarified that the first subject was diagnosed during the study with urticaria with angioedema characterised by recurrent wheals, that could interfere with the evaluation of the response to garadacimab. Regarding the second non-responder, the comorbidities with inflammatory components are considered confounding factors and may provide additional context to the lack of response. Therefore, no definitive conclusion can be drawn regarding the efficacy of garadacimab in these two subjects. Of note, the efficacy data of the non-responders is included in the analysis.

The reduction of attack rate compared to Run-in period is of additional relevance, showing mean (SD) and median values (%) for garadacimab arm of 90.67 (22.43) and 100.00 vs placebo arm of 20.21 (42.66) and 8.45 after 6 months treatment. After request, the absolute change from baseline was provided. The mean reduction was -2.80 (SD: 2.064) and -0.50 (SD: 1.117) in garadacimab arm and placebo arm, respectively.

The time-normalised number of on-demand treated attacks was much lower than in the placebo arm (mean (SD) and median: 0.23 (0.663) and 0.00 garadacimab vs 1.86 (1.412) and 1.35 placebo arm). However, out of 63 attacks in garadacimab arm during 6 months, 54 of them (i.e. 85.7%) required on-demand treatment. Similarly, out of 264 attacks in the placebo arm during 6 months, 245 (i.e. 92.8%) required on-demand treatment. This means that the attacks that 'remain' despite prophylaxis require

on-demand treatment in almost all participants regardless of whether they received garadacimab or placebo for prophylaxis. Moreover, both the percentage and the time-normalised number of moderate or severe HAE attacks were lower with garadacimab compared to placebo. Out of 63 attacks in the garadacimab during 6 months, 29 of them (ie.46%) were moderate or severe. Out of 264 attacks during 6 months in the placebo arm, 172 (i.e. 65.2%) were moderate or severe.

The time-normalised number of attacks was similar within each arm comparing the first 3 months with the period of second three months of the study. This observation confirms both the rate consistency in the placebo arm over time but also the early efficacy in the garadacimab arm that is maintained during the further treatment within this study. The Kaplan-Meier curve of the time-to-first HAE attack after day 1 shows significant difference between the curves of two arms, that are separated already from the first week of treatment, probably due to a loading dose.

There was a greater improvement in quality of life in participants receiving garadacimab compared to participants receiving placebo, both at 31 and 182 days of treatment compared to baseline. At baseline, the total AE-QoL mean (SD) scores were 38.8 (15.1) and 43.7 (21.4) in garadacimab and placebo arms, respectively. At Day 182, the total AE-QoL mean (SD) score was 11.7 (15.6) and 40.3 (24.1) in garadacimab and placebo arms, respectively. According to a minimally clinically important difference defined as a 6-point change, these results show a clinically important improvement in participants receiving garadacimab but not in those receiving placebo.

The primary and the first 3 secondary endpoints (hierarchically tested) from the pivotal study 3001 have been included as they are clinically relevant and statistically significant. Although the analysis of the number of moderate or severe HAE attacks was a secondary endpoint and the number of HAE attacks requiring on-demand treatment and the AE-QoL score were exploratory analyses, the information on these outcomes (including the percentage of attacks that required on-demand treatment and percentage of moderate /severe attack per arm) is considered relevant for prescribers and other HCPs and have been included in section 5.1.

Analyses of other exploratory endpoints showed greater efficacy of garadacimab than placebo. Overall, 61.5% of participants receiving garadacimab were HAE attack-free from Day 1 onwards and, 64.1% after Day 14 compared to no participants in the placebo arm.

Laryngeal attacks present a significant burden for HAE patients and the effect of a new medication on laryngeal attacks is of special interest to HAE patients. However, no data was presented in the CSR regarding the occurrence of laryngeal attacks. The applicant, following CHMP's request, provided details on the laryngeal attacks. A total of 5 laryngeal attacks occurred in the garadacimab group, of which 3 occurred during the run-in phase and 2 during treatment with garadacimab. In the placebo group, 11 laryngeal attacks occurred, of which 4 occurred during the run-in phase and 7 during the treatment phase. All were treated with on-demand treatment. The time normalised number of laryngeal attacks per month during the run-in period was low (0.05 and 0.12 for the garadacimab and placebo groups, respectively). The results from the 6-month treatment period showed a slightly lower incidence in both groups (0.01 and 0.07, respectively). Although these are post-hoc analyses, it can be concluded that the incidence of laryngeal attacks during the study was low in both groups. However, it cannot be claimed that garadacimab reduces the frequency or severity of laryngeal attacks.

Overall, the efficacy analyses in the primary, hierarchically tested secondary, other secondary and exploratory analyses consistently show a superior efficacy of garadacimab compared to placebo.

According to HCPs and patient organisations, the goal of treatment is complete control of the disease, i.e. no more attacks. The reduction in the number and severity of attacks and the impact on quality of life are important efficacy information, but the most important aspect is the length of attack-free periods, as this is the obvious change in patients' daily lives. In addition, from the patient's point of

view, it may be more important to reduce the severity of the attacks than to reduce the number of attacks.

In this study, the number of HAE attacks was assessed using several endpoints: The primary and two secondary endpoints (numbers 1 and 2) measured the frequency of HAE attacks within 6 months, presented in different ways (for the 6-month period, for the first 3 months, for the second 3 months, compared to the run-in period). These endpoints are considered overlapping.

The severity of HAE attacks was assessed using two secondary endpoints time-normalised number of HAE attacks requiring on-demand treatment and time-normalised number of moderate and / or severe HAE attacks). Since the severity of attacks in the study was determined by the degree of interference in daily activities and whether the use of on-demand medication and/or medical assistance was needed, these two endpoints are not independent of each other. Therefore, the list of secondary endpoints appears redundant. In addition, there was no endpoint assessing the length of the attack free period, other than the exploratory endpoint the time to first attack after Day 1 and after Day 15 and the quality-of-life endpoints (AE-QoL, EQ-5D-5L, WPAI:GH) were tested in exploratory way without statistical significance. The angioedema quality of life questionnaire (AE-QoL) is suggested as a validated PROM (patients reported outcomes measure) for the evaluation of HAE-driven QoL impairment (The international WAO/EAACI guideline for the management of hereditary angioedema – The 2021 revision and update). The AE-QoL was only assessed in adults.

Subgroup analyses were performed for Japanese and all subjects for the primary efficacy endpoint and 2 secondary efficacy endpoints (reduction in attack rate during the treatment period, and the time-normalised number of HAE attacks requiring on-demand treatment). While the efficacy analysis from the very limited Japanese subgroup (4 subjects treated with garadacimab vs 2 subjects with placebo) seems to show results worse than results of overall study population, they seem to be driven by one patient. Due to the small number of Japanese subjects (≥ 5), no firm conclusions can be drawn on the basis of these analyses. No subgroup analysis other than the one for Japanese subjects has been presented. The analysis of primary and key secondary endpoints using statistical test that allows the inclusion of the stratification factors in the pivotal study (adolescent vs adults, baseline attack frequency) was provided after request; LS mean time-normalised number of HAE attacks seems to be consistent with the primary analysis. The applicant clarified that the 95% CIs provided in the submission for the efficacy endpoints were referred to the mean.

The majority of patients included in the study 3001 had Type 1 C1-INH HAE, however there were also 12.5% (8/64) patients with Type 2, well balanced between the arms, sufficiently reflecting the proportions of both types in the general population. The forest plot analysis was presented upon CHMP's request for the most relevant subgroups in the pivotal study including the type of HAE. The results within different subgroups did not substantially differ from overall results except in following cases:

- adolescents (while the results of adolescents in the garadacimab arm were similar with the adults, two adolescent patients on placebo had better results than respective adult arm)

- Japanese subjects had much wider CI but there were only 4 subjects in garadacimab and 2 in placebo arm, so no firm conclusion about efficacy in this subgroup could be driven.

About one third of subjects used routine prophylaxis during 3 months before screening. However, no data are provided on clinical response to the previous prophylaxis. The analysis was provided also for subgroups of the study 3001 considering previous LTP: patients naïve and treated showed similar response. The information if a subject is a non-responder to a previous prophylactic treatment was not collected during Study 3001.

In Study 3002 the mean (SD) and median time-normalised number of HAE attacks per month during the treatment period were respectively 0.16 (0.370) and 0.00 attacks for garadacimab 200 mg. The results were similar for the subjects rolled over from the study 2001 and study 3001, slightly better than for the newly enrolled subjects (mean (SD) 0.21 (0.414) attacks per month).

The mean (SD) and median reduction in the time-normalised number of HAE attacks during the Treatment Period compared to the Run-in Period was 94.67% (11.983) and 100%, respectively.

Moreover, 98.1% subjects were responders with a reduction in attack rate ≥ 50%. The majority of subjects (96 / 161 [59.6%] subjects) were attack-free over the median exposure of 13.83 months.

The mean (SD) time-normalised number of HAE attacks requiring on-demand treatment per month during the Treatment Period was 0.14 (0.358). The mean (SD) time-normalised number of moderate and / or severe attacks per month was lower in the Treatment Period (0.11 [0.277] attacks per month) than in the Run-in Period (2.59 [2.112] attacks per month).

For the subgroup of Japanese subjects (12 subjects) the time-normalised number of attacks were somewhat higher than in non-Japanese subjects (0.64 (0.693) vs 0.12 (0.303), respectively). This was the case also for reduction in number of HAE attacks/month and the number of attacks requiring on demand treatment/month. The analysis for adolescent subgroup is also provided (see below).

Overall, the results from IA2 of the ongoing OL single arm study 3002 with garadacimab seem to support the maintenance of the effect for previously treated patients and the efficacy in the treatment naive subjects.

Neither of two subjects with FXII HAE experienced HAE attacks during the 18 months of the treatment period.

Although no comparator arm is present in this OL study 3002, considering the overall very low time-normalised number of HAE attacks per month it seems that garadacimab 200 mg q4wks maintains its efficacy over time. Regarding the subgroups' results, higher HAE attack rates were observed in Asian subjects. Following CHMP's request, the applicant presented updated data of the study 3002. The efficacy results from the data cut of 15 June 2024 remain consistent and comparable with the results from previous interim analyses of this study as well as with the pivotal Study 3001.

In Study 2001, among the subjects with C1-INH HAE, in TP1, both treatments with garadacimab 200 mg and 600 mg resulted in a statistically significant lower mean time-normalised number of HAE attacks per month when compared with placebo (both with $p < 0.001$), with a mean reduction in the time-normalised number of HAE attacks of -4.19 (98.94%) with garadacimab 200 mg and -3.89 (91.68%) garadacimab with 600 mg, relative to placebo. While all patients were responders in the 75 mg and 200 mg arms vs 6/7 in 600 mg arm, there were no responders in placebo arm. Also, while no subjects treated with placebo were HAE attack-free during the efficacy evaluation period, 5/9 subjects in the 75 mg arm, 7/8 subjects in the 200 mg arm, and 3/7 subjects in the 600 mg arm were HAE attack-free.

Subjects < 18 years

Only a very limited number (4) of adolescent subjects were exposed to garadacimab in pivotal randomised, controlled Study 3001 (other 2 adolescents were in the placebo arm). These patients were included, together with other garadacimab-naïve adolescents (total of 10 adolescents) in the OL Study 3002, which is still ongoing.

Initially the data on adolescents were provided from study 3002 as IA3 data cut for the subgroup of adolescents (10/161 subjects), where the rate of HAE attacks was similar to that observed in the overall study population. The mean (SD) and median time-normalised number of HAE attacks per

month was 0.08 (0.100) and 0.05, respectively. Out of the 10 HAE attacks observed in adolescent subjects in the Treatment Period, 9 (90%) were treated with on-demand treatments. The mean (SD) time-normalised number of HAE treated with on demand medication per month during the Treatment Period was 0.07 (0.103). As of IA2 data cut off the mean (SD) percentage reduction in time-normalised number of HAE attacks was 91.49% (11.947) and the median (min, max) 95.6% (68.2, 100.0).

Although the data for adolescent subgroup from the study 3002 and from the pooled analysis (study 3001 and 3002) seems consistent with overall efficacy results and with results from adult subgroup (pooled analysis) in order to gain a clear information on the efficacy from randomised controlled setting, the applicant was asked to provide separate subgroup analysis of adolescents included in the pivotal trial 3001. Overall, while the results of adolescents in the garadacimab arm were similar with the adults, two adolescent patients on placebo had better results than respective adult arm. Of note, the baseline results for two adolescent arms were not provided; the possible baseline imbalance could explain the findings. However, the number of adolescents in the study 3001 (6 in total) is very limited and preclude any conclusion.

Considering that the pathophysiology and clinical manifestations of HAE are similar in adolescents compared to adults (similarity of disease) and, also, that the same HAE treatments, including long-term prevention, is approved for adolescents and adults, the use in adolescents is considered acceptable. In both studies there were no subjects with a body weight below 40 kg.

Taking into account the fact that the PK results in the subgroup of adolescents were consistent with the subgroup of adults, the inclusion of adolescents in the indication can be accepted despite the very limited data available. The proposed posology for adolescents is the same as that for adults.

Maintenance of effect

In the controlled setting of Study 3001 the maintenance of effect was confirmed comparing the results between the first 3 months and the second 3 months of treatment. Effect was also maintained in the ongoing OL Study 3002, in which patients needed to have at least 12 months of treatment.

To support the MAA, the applicant performed the analysis of efficacy by pooling the data from the phase 3 studies 3001 and 3002 (Integrated Summary of Efficacy). While this approach could be endorsed for more than one pivotal study, the study 3002 is considered only supportive for several reasons such as heterogeneity of study population in respect to duration and dose of previous treatment with garadacimab; descriptive nature of analyses, and number of minimum attack rate/month in subjects rolled over from Study 3001 and Study 2001.

Study population characteristics at baseline were generally comparable across the two phase 3 studies.

Albeit limitations, the result of pooled analysis supports the durability of effect observed in the individual studies. Over the median exposure of 14.93 months / 1.24 years, 57.32% of subjects were attack-free and 82.93% of subjects experienced at least a 90% attack reduction from Run-in.

n1-C1INH HAE data

The nC1INH-HAE type (HAE with normal C1-esterase inhibitor) is very rare and heterogeneous type of HAE (FXII and PLG are two most common genes involved). The proposed indication is not limited to type 1 and type 2 HAE. Considering that: a) the phase 2 study included a few patients with nC1-INH HAE type (3 with FXII HAE and 3 with PLG HAE); b) they were treated with the higher dose (600mg sc q1M) c) only 2 (FXII HAE) out of 6 responded and continued the treatment (ongoing OL phase 3 study); d) the pharmacodynamics profile of garadacimab was not characterised in this subpopulation (F XII/PLG HAE type), e) in the E-R model HAE type (HAE type I/II vs. FXII/PLG) exhibited the

strongest influence on efficacy outcomes, the applicant was requested to further substantiate the efficacy of garadacimab in this patient subgroup and the appropriateness of posology.
The applicant provided more information about the six patients with nC1INH HAE included in the studies with garadacimab and discussed some aspects of dose and efficacy results in these patients. All six patients (3 FXII-HAE and 3 PLG-HAE) were treated in the TP1 phase of phase 2 trial with 600 mg q4wks. Although the number of patients was very limited, the efficacy results (only primary endpoint discussed) are as follows:

- Among the three HAE-FXII patients enrolled, one withdrew during the second month of the treatment period due to lack of efficacy after showing a reduction in overall attack rate from 4.35 to 3.51 attacks per month and a reduction in severe attacks from 1.09 to 0.58 attacks per month. The remaining two patients completed the initial 12-week treatment period, with one demonstrating a reduction in attack rate from 3.24 to 0.36 attacks per month and the other becoming attack-free from an initial attack rate of 3.20 attacks per month. Both patients continued garadacimab for the duration of the second treatment period of 20 and 17 months, after which both patients rolled over into the phase 3 extension study and received garadacimab for an additional 18 months and remained attack free.

- three patients with HAE-PLG completed the initial 12-week treatment period and did not continue into the treatment extension period. One patient reported a decrease in their monthly overall attack rate to 1.75 and a severe attack rate to 0.35 during the treatment period, compared to 3.20 and 1.60, respectively, during the run-in period. The remaining two patients reported an increase in their monthly attack rates to 6.8 and 3.17 during the treatment period compared to 2.28 and 1.45 during the run-in period respectively. None of the reported attacks was classified as severe attack.

Overall, garadacimab dosed at 600 mg q4wk was safe and well tolerated in all 6 nC1-INH enrolled in the study. All patients who were not already on the 200 mg q4wk were switched to it in the TP2 (with the exception of 2 FXII-HAE patients whose dose remained at 600 mg q4wks) because these patients' HAE disease was stable. The 2 FXII-AE patients rolled over to study 3002 after approximately 2 years in study 2001 (after 96.7 and 109 weeks respectively) and their dose was then down-titrated to 200 mg once a month. As of the most recent data cut (16Jun23) these subjects remain responsive to garadacimab, and their safety and tolerability continues to be favourable.

Given that the clinically relevant FXII mutations associated with HAE reside in the proline-rich region of the FXII zymogen, they are not associated with the epitope residues associated with binding to the garadacimab antibody. Upon activation of FXII in patients with FXII-HAE, the βFXIIa is the same as the wildtype with the epitope remaining unchanged.

The ER model was developed (from pooled data of 2001, 3001 and 3002 studies) to characterise the relationship between PK and efficacy, in terms of risk of HAE attack. The covariate of HAE type, while exhibiting influence on efficacy outcomes, were not precisely estimated due to the low number of patients in the analysis population contributing to these effects. As such, no different thresholds were identified depending upon HAE disease subtype and other covariates.

The available data of patients with nC1INH HAE treated with garadacimab were contrasting and did not support overall extrapolation of efficacy from C1INH HAE to this HAE subtype. In phase 2 garadacimab study, while 2 out of 3 FXII HAE patients had excellent response, maintained during the following years, 2 out of 3 PLG (plasminogen) HAE patients had surprisingly a striking increase in the HAE attack rate during the three months period of treatment with garadacimab.

In vitro studies showed that aberrant plasminogen-Glu330 is activated by tissue plasminogen activator and the resulting active plasmin-Glu330 directly cleaves HMWK and LMWK to produce bradykinin. Neither FXII nor prekallikrein is involved in this bradykinin production (Dickeson, Blood 2022). Therefore, although some of the most frequent genetically characterised nC1INH HAE forms (Jones, J

Asthma Allergy 2023) involve molecules of the bradykinin cascade, plasminogen (but also kininogen 1, angiopoietin-1) act downstream of FXII/kallikrein non involving these molecules and therefore could not benefit from FXII inhibition by garadacimab.

Moreover, some nC1INH HAE forms caused by mutations described more rarely (e.g. MYOF, HSST) are not bradykinin mediated but are due to the intrinsic vascular endothelium dysfunction (DANCE consensus, Reshef, JACI 2024). Finally, the majority of patients with nC1INH are currently due to the unknown mutations.

The applicant provided a discussion on HAE-PLG pathogenic mechanism, and it is agreed that the evidence for biological plausibility of garadacimab for worsening of the condition is lacking. This partially relieves the concern for two patients with HAE-PLG, together with potential confounding factors and uncertainties, as reported in the respective narratives.

Based on the biological pathways, it is anticipated by the applicant that FXII inhibition can provide clinical benefit in those with excessive activation of the kinin-kallikrein cascade (i.e. HAE-XII) and this is what was observed in 2 of 3 HAE-FXII patients. In contrast, the biology suggests that bradykinin generation via the HAE-PLG mutation is independent of the KKS pathway meaning that FXII inhibition would likely not be effective, as observed in 2 of the 3 HAE-PLG patients, nor would it be detrimental. Therefore, there is no clear evidence that garadacimab worsens HAE disease control in either HAE-FXII or HAE-PLG and there were no increases in severe attacks.

The conclusions of the applicant regarding the potential benefit of garadacimab for some of the subcategories are not fully agreed, based on the available published data. However, the applicant acknowledged the potential for reduced efficacy or the lack of response due to the alternative metabolic pathways involved in some nC1INH-HAE forms, including HAE-PLG.

Current treatment guidelines do not differentiate between nC1-INH-HAE patients and C1-INH HAE patients but however recommend that that patients who are suspected to have HAE and have normal C1-INH levels and function are assessed for known mutations underlying HAE-nC1-INH (Maurer 2022).

Considering the evolving scientific evidence of mutations and mechanisms at the basis of nC1-INH HAE subcategories with very limited population and high unmet medical need and current data on garadacimab with no evidence of detrimental effect, it is agreed that broad indication is acceptable, and adequate information has been included in the SmPC with regard to nC1-INH HAE population (sections 4.2, 4.4 and 5.1).

2.6.7. Conclusions on the clinical efficacy

The pivotal study 3001 met its primary endpoint and the effect of the treatment is considered to be clinically relevant for patients with C1-INH HAE. The efficacy is further supported by the key secondary endpoints and other additional efficacy endpoints. Moreover, the results from the longer-term open label trial 3002 and pooled analysis support the maintenance of efficacy over time. Therefore, the CHMP considers that the available efficacy data support the following 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.*

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Of the 172 subjects who received any dose of garadacimab (≥ 75 mg garadacimab q4wk), 164 (95.3%) subjects had at least 6 months exposure and 143 (83.1%) subjects had at least 12 months exposure. Of the 166 subjects who received at least 1 dose of 200 mg garadacimab, most subjects had a cumulative exposure of ≥ 6 months (160 [96.4%]) and the majority of subjects had cumulative exposure of ≥ 12 months (142 [85.5%]).

Table 27: Exposure: Pooled Data from Study 3001 (Pivotal), Study 3002 (IA2), and Study 2001 (Safety Analysis Set)

	200 mg CSL312 (N = 166)	400 mg CSL312 (N = 3)	600 mg CSL312 (N = 24)	≥ 200 mg CSL312 (N = 172)	Placebo (N = 33)	75 mg CSL312 (N = 9)	400 mg CSL312 q2wk (N = 6)	≥ 75 mg CSL312 (N = 172)	Total (N = 176)[a]
Duration of Exposure per Subjects (Months)[b, c]									
Mean (SD)	19.00 (10.272)	14.12 (6.095)	11.29 (5.900)	20.16 (12.398)	5.00 (1.580)	3.00 (0.036)	2.79 (0.013)	20.42 (12.739)	20.89 (12.802)
Median	15.75	15.57	10.10	15.28	5.88	3.02	2.79	15.28	16.46
Min, Max	5.1, 47.4	7.4, 19.4	2.1, 25.1	2.3, 49.0	1.0, 8.0	2.9, 3.0	2.8, 2.8	2.3, 50.4	1.0, 50.4
1st Quartile, 3rd Quartile	12.91, 21.13	7.43, 19.35	7.38, 15.64	12.86, 21.62	3.09, 6.01	2.99, 3.02	2.79, 2.79	12.86, 21.62	13.27, 21.82
Total Cumulative Number of Injections[d]	3267	46	284	3597	170	36	35	3668	3838
Total Number of IV Loading Doses	8	0	13	21	8	9	0	30	38
Total Number of SC Loading Doses	108	0	0	108	25	0	0	108	133
Total Number of SC Injections	3151	46	271	3468	137	27	35	3530	3667
Total Subject-years of Exposure[e]	262.9	4	23	289	14	2	1	292.6	306.4
Total Subject-years of SC Exposure	262.7	4	22	288.6	14	2	1	292.1	305.8
Total Subject-years of SC Loading Dose Exposure	8.9	0	0	8.9	2	0	0	8.9	10.9
Cumulative Exposure of at Least, n (%)									
≥ 6 Months (ie, 182 days)	160 (96.4)	3 (100.0)	20 (83.3)	164 (95.3)	12 (36.4)	0	0	164 (95.3)	165 (93.8)
≥ 12 Months (ie, 365 days)	142 (85.5)	2 (66.7)	10 (41.7)	143 (83.1)	0	0	0	143 (83.1)	143 (81.3)

CSL312 = garadacimab; IA2 = interim analysis 2; IV = intravenous; Max = maximum; Min = minimum; N = number of subjects in the Safety Analysis Set; n = number of subjects with nonmissing value; q2wk = every 2 weeks; q4wk = every 4 weeks; SC = subcutaneous.

2.6.8.2. Adverse events

Table 28: Overall Summary of Treatment-emergent Adverse Events by Treatment: Pooled Data from Study 3001 (Pivotal), Study 3002 (IA2), and Study 2001 (Safety Analysis Set)

	200 mg garadacimab (N = 166)			Placebo (N = 33)			Total (N = 176)[a]		
	n (%)	E	RY	n (%)	E	RY	n (%)	E	RY
Any TEAE	143 (86.1)	756	2.877	21 (63.6)	66	4.843	152 (86.4)	993	3.247
Occurring Within 24 hours after any SC Dose	56 (33.7)	119	0.453	9 (27.3)	12	0.880	71 (40.3)	171	0.559
Related to Study Treatment	29 (17.5)	71	0.270	5 (15.2)	8	0.587	43 (24.4)	114	0.373

Leading to Study Discontinuation	1 (0.6)	1	0.004	0	0	0	1 (0.6)	1	0.003
TEAEs by Severity									
Mild	115 (69.3)	456	1.736	20 (60.6)	52	3.815	130 (73.9)	611	1.998
Moderate	95 (57.2)	277	1.054	9 (27.3)	14	1.027	105 (59.7)	357	1.167
Severe	13 (7.8)	20	0.076	0	0	0	15 (8.5)	22	0.072
SAEs	5 (3.0)	5	0.019	0	0	0	7 (4.0)	7	0.023
Death	0	0	0	0	0	0	0	0	0
AESIs identified by the Investigator	0	0	0	0	0	0	1 (0.6)	1	0.003

a - Total column includes subjects treated with any dose of garadacimab (75 mg, 200 mg, 400 mg, 600 mg [q4wk] or 400 mg q2wk) or placebo

Pooled Summary of Common Adverse Events (Study 3001 [Pivotal], Study 3002 (Interim Analysis 2 for All Subjects), and Study 2001)

In the pooled analysis, the most common TEAEs by SOC (≥ 20% of subjects treated with 200 mg garadacimab) observed during treatment with 200 mg garadacimab (N = 166) and during treatment with placebo (N = 33) are reported in the Table 29 below.

Table 29: Treatment-emergent Adverse Events by System Organ Classes and Preferred Terms (Reported in ≥ 10% of Subjects in Total) by Treatment: Pooled Data from Study 3001 (Pivotal), Study 3002 (IA2), and Study 2001 (Safety Analysis Set)

System Organ Class	200 mg CSL312 (N = 166)			Placebo (N = 33)			Total (N = 176)[a]		
Preferred Term	n (%)	E	RY	n (%)	E	RY	n (%)	E	RY
Any TEAE	143 (86.1)	756	2.877	21 (63.6)	66	4.843	152 (86.4)	993	3.247
Infections and infestations	104 (62.7)	247	0.940	10 (30.3)	13	0.954	115 (65.3)	293	0.958
COVID-19	59 (35.5)	61	0.232	3 (9.1)	3	0.220	63 (35.8)	65	0.213
Nasopharyngitis	30 (18.1)	44	0.167	1 (3.0)	1	0.073	32 (18.2)	50	0.163
Upper Respiratory Tract Infection	17 (10.2)	22	0.084	4 (12.1)	4	0.293	23 (13.1)	29	0.095
General disorders and administration site conditions	43 (25.9)	93	0.354	11 (33.3)	16	1.174	62 (35.2)	147	0.481
Injection Site Erythema	13 (7.8)	17	0.065	4 (12.1)	4	0.293	19 (10.8)	29	0.095
Nervous system disorders	26 (15.7)	53	0.202	5 (15.2)	5	0.367	34 (19.3)	76	0.249
Headache	19 (11.4)	37	0.141	4 (12.1)	4	0.293	26 (14.8)	52	0.170

COVID-19 = Coronavirus disease 2019; CSL312 = garadacimab; E = number of events; IA2 = interim analysis 2; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Affairs; N = number of subjects in the Safety Analysis Set; n = number of subjects with nonmissing values; q2wk = every 2 weeks; q4wk = every 4 weeks; RY = number of events / total subject-years of exposure of that treatment; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Adolescents Subgroup Analyse

As of the 3rd data cut (22 May 2023), the overall safety profile was comparable between adolescents and adults. There were no deaths, SAEs, or TEAEs leading to garadacimab discontinuation. There were no adolescent subjects assessed by the investigator as experiencing AESIs during the study. A total of 7 / 10 adolescent subjects experienced 31 TEAEs. Eight TEAEs in 4 subjects occurred within 24 hours of receiving any SC garadacimab dose. No ISRs were reported. None of the TEAEs were related to study treatment. All TEAEs were either mild (26 events in 7 subjects) or moderate (5 events in 2 subjects). The outcome of most TEAEs was reported as recovered/ resolved (25 events in 6 subjects).

The most frequently reported TEAEs (≥ 2 subjects) were in the SOCs of Infections and infestations (5 / 10 subjects, 12 events), General disorders and administration site conditions (2 / 10 subjects, 2 events), Injury, poisoning and procedural complications (2 / 10 subjects, 2 events), and Reproductive system and breast disorders (2 / 10 subjects, 2 events). The most frequently reported TEAEs (≥ 2 subjects) by PT were Nasopharyngitis (3 / 10 subjects, 6 events) and COVID-19 (3 / 10 subjects, 3 events). No anti-garadacimab antibodies were reported for the adolescent subjects.

Related TEAEs

Table 30: Related Treatment-emergent Adverse Events by System Organ Classes and Preferred Terms During Treatment with 200 mg Garadacimab or Placebo (Reported in ≥ 2 Subjects Overall): Pooled Data from Study 3001 (Pivotal), Study 3002 (IA2), and Study 2001 (Safety Analysis Set)

System Organ Class Preferred Term	200 mg CSL312 (N = 166)			Placebo (N = 33)		
	n (%)	E	RY	n (%)	E	RY
Any Related TEAE	29 (17.5)	71	0.270	5 (15.2)	8	0.587
General disorders and administration site conditions	19 (11.4)	45	0.171	5 (15.2)	8	0.587
Injection Site Erythema	13 (7.8)	17	0.065	4 (12.1)	4	0.293
Injection Site Pruritus	6 (3.6)	15	0.057	1 (3.0)	1	0.073
Injection Site Urticaria	2 (1.2)	9	0.034	0	0	0
Injection Site Bruising	2 (1.2)	2	0.008	0	0	0
Fatigue	1 (0.6)	1	0.004	1 (3.0)	3	0.220
Nervous system disorders	5 (3.0)	9	0.034	0	0	0
Headache	5 (3.0)	9	0.034	0	0	0
Gastrointestinal Disorders	3 (1.8)	4	0.015	0	0	0
Abdominal Pain	2 (1.2)	2	0.008	0	0	0

CSL312 = garadacimab; E = number of events; IA2 = interim analysis 2; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Affairs; N = number of subjects in the Safety Analysis Set; n = number of subjects with nonmissing values; q2wk = every 2 weeks; q4wk = every 4 weeks; RY = number of events / total subject-years of exposure of that treatment; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Adolescents Subgroup Analysis

None of the TEAEs were related to study treatment.

Table 31: Adverse drug reactions

MedDRA System Organ Class	ADR by MedDRA Preferred Term	200 mg Garadacimab (N = 39)		Placebo (N = 25)	
		n (%)	E	n (%)	E
General Disorders and Administration Site Conditions	Injection Site Reactions[a]	2 (5.1)	3	2 (8.0)	2

a - Injection Site Reactions include the MedDRA preferred terms: Injection Site Bruising, Injection Site Erythema, and Injection Site Pruritus

Other TEAEs judged related to study drug were headache (5 patients) and abdominal pain (2 patients).

AEs of special interest (AESIs)

AESIs (abnormal bleeding events, TEEs, severe hypersensitivity including anaphylaxis) for the pooled analysis and individual phase 2 and phase 3 studies are described below. AESI by Standardized Medical Dictionary for Regulatory Affairs Queries (SMQ) analysis was run in parallel and no safety signals were identified.

The following events were monitored during the clinical studies as AESI: abnormal bleeding events, thromboembolic events (TEE), and severe hypersensitivity including anaphylaxis.

AESIs in the SAP are defined as:

Thromboembolic events (TEE) – Standardised MedDRA Query" Embolic and thrombotic events (SMQ)" (narrow), consisting of: Embolic and thrombotic events, arterial (SMQ), Embolic and thrombotic events, venous (SMQ), Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).

Bleeding events – Standardised MedDRA Query "Haemorrhages (SMQ)" (narrow)

Severe hypersensitivity including anaphylaxis – Standardised MedDRA Query "Hypersensitivity (SMQ)" (broad), Anaphylactic reaction (SMQ) (broad), Anaphylactic/anaphylactoid shock conditions (SMQ) (broad). Here, broad scope includes narrow and broad search.

Pooled Summary (Study 3001 [Pivotal], Study 3002 (Interim Analysis 2 for All Subjects), and Study 2001)

Overall, in the pooled analysis, there was 1 AESI identified by the investigator, which was an unrelated abnormal bleeding event (Epistaxis) during treatment with 600 mg garadacimab.

In Study 3001 (pivotal) and Study 3002 (IA2 for all subjects), no subjects experienced the AESIs of abnormal bleeding events, TEEs, or severe hypersensitivity including anaphylaxis events during the studies as per the protocol. As of the IA3 data cut for Study 3002, none of the 10 adolescents had an AESI (abnormal bleeding event, TEE, or severe hypersensitivity including anaphylaxis).

2.6.8.3. Serious adverse event/deaths/other significant events

Pooled Summary of Serious Adverse Events (Study 3001 [Pivotal], Study 3002 (Interim Analysis 2 for All Subjects), and Study 2001)

Overall, in the pooled analysis, there were a low number of SAEs (4.0% [7 / 176] of subjects). Five subjects experienced SAEs during treatment with 200 mg garadacimab and 2 subjects during treatment with 600 mg garadacimab. The rate of SAEs was 0.019 events / total subject-years of exposure of that treatment during treatment with 200 mg garadacimab and 0.089 events / total subject-years of exposure of that treatment during treatment with 600 mg garadacimab.

During treatment with 200 mg garadacimab, among the 5 SAEs (Hereditary Angioedema [2 SAEs], Diverticular Perforation, COVID-19 [2 SAEs]) that occurred, none were related to study treatment. Four SAEs were severe, and 1 SAE was moderate. The outcome of all SAEs was recovered / resolved or recovered / resolved with sequelae. During treatment with 600 mg garadacimab, among the 2 SAEs (Hereditary Angioedema and Asthma) that occurred, none were related to study treatment, 1 was moderate and 1 was severe, and both had an outcome of recovered / resolved.

AEs of special interest

Overall, only one AESI of abnormal bleeding event (Epistaxis), was identified in Study 2001 and was considered unrelated by the investigator (see above).

Serious AEs

Overall, in the pooled analysis, SAEs were reported in 7 subjects, all judged as not related to study drug.

Deaths

No deaths were reported.

2.6.8.4. Laboratory findings

Pooled Summary (Study 3001 [Pivotal], Study 3002 (Interim Analysis 2 for All Subjects), and Study 2001)

In the pooled analysis, during treatment with 200 mg garadacimab (N = 166), 8 (4.8%) subjects had 21 events of clinically significant laboratory findings reported as TEAEs, and during treatment with placebo (N = 33), 2 (6.1%) subjects had 5 events. The most common events were Bacterial Test Positive (in urine) (4 subjects during treatment with 200 mg garadacimab and 1 subject during treatment with placebo), Red Blood Cells Urine Positive (2 subjects during treatment with 200 mg garadacimab and no subjects during treatment with placebo), and Urinary Tract Infection (2 subjects during treatment with 200 mg garadacimab and no subjects during treatment with placebo). All other clinically significant laboratory findings reported as TEAEs occurred in ≤ 1 subject during treatment with 200 mg garadacimab.

Haematology

In the 2 phase 3 studies (Study 3001 [pivotal] and Study 3002 [IA2 for all subjects) and 1 phase 2 study (Study 2001), there were no clinically relevant differences across treatment arms for all haematology parameters.

Biochemistry

In the 2 phase 3 studies (Study 3001 [pivotal] and Study 3002 [IA2 for all subjects) and 1 phase 2 study (Study 2001), there were no clinically relevant differences across treatment arms for all biochemistry parameters.

Coagulation

Medications that could affect the coagulation pathway were prohibited in Study 3001 (pivotal), Study 3002, and Study 2001. Prolongation of aPTT due to decreased FXIIa activity is expected with garadacimab due to its mechanism of action of inhibiting FXIIa. Overall, in the phase 2 and phase 3 studies, activated aPTT prolongations were observed in some subjects who received garadacimab (3 subjects in Study 3001, 21 subjects [including 5 subjects at Screening] in Study 3002, and 16 subjects in Study 2001). These were transient, not accompanied by abnormalities in other coagulation parameters (including prothrombin time and INR), and were not associated with abnormal bleeding events or clinical symptomatology of bleeding. The aPTT prolongations occurred within 1 to 4 days of garadacimab administration and were infrequently occurring at the 200 mg garadacimab dose. All the events of reported aPTT prolongations recovered / resolved and in most cases were single occurrences. There were no imbalances in the other coagulation parameters of INR, prothrombin time, prothrombin fragments 1 + 2, or D-dimer between the garadacimab and placebo arms.

In the pooled analysis, aPTT was within the normal range amongst the 21 subjects who rolled over from placebo in Study 3001 to 200 mg garadacimab in Study 3002 (IA2 for all subjects). The mean (SD) aPTT values were: 32.81 (13.115) seconds at 3 months; 31.08 (8.798) seconds at 6 months; and 28.89 (1.987) seconds at 12 months. The changes from baseline in aPTT among the 21 subjects who rolled over from placebo in Study 3001 to 200 mg garadacimab in Study 3002 (IA2 for all subjects) were small and not clinically relevant. The mean (SD) changes from baseline in aPTT were: 4.87 (14.189) seconds at 3 months; 3.14 (8.621) seconds at 6 months; and 1.63 (3.556) seconds at 12 months.

For Study 2001, activated partial thromboplastin time (aPTT) was considered a PD marker and not a safety laboratory parameter; and some elevations in aPTT were observed during the study. Applicant stated that elevations in aPTT were not accompanied by elevations in other coagulation parameters or TEAEs and AESI (bleeding, thromboembolic events).

For Study 3001, aPTT was planned to be summarised descriptively (both as a PD marker and a safety laboratory parameter) by scheduled visit for subjects who have been on placebo in Study 3001 and continued in Study 3002 for measured values and change from baseline. Baseline was defined as the most recent, non-missing value prior to first Placebo administration in Study 3001. Determination of the baseline value also considered unscheduled visits during the Run-in Period or Screening Period.

2.6.8.5. Safety in special populations

Age

Pooled Summary (Study 3001 [Pivotal], Study 3002 [Interim Analysis 2 for All Subjects, and Study 2001)

For the pooled analysis, TEAEs were summarised by age subgroups: 12 to ≤ 17 years of age, > 17 years of age, and ≥ 65 years of age. Please note that overall, there were a small number of subjects who were either 12 to ≤ 17 years or ≥ 65 years; therefore, comparisons between these subgroups are not suitable. However, there was no pattern in the age subgroups that indicated age had an effect on

the safety of garadacimab. There were no safety concerns observed in adolescent or elderly subjects who received garadacimab.

Elderly

In the pooled analysis, there were 13 elderly subjects ≥ 65 years of age who were treated with garadacimab (13 subjects treated with 200 mg garadacimab and 1 subject treated with 600 mg garadacimab). No elderly subjects received placebo. There were no deaths, SAEs, AESIs (abnormal bleeding events, TEEs, severe hypersensitivity including anaphylaxis), or TEAEs leading to discontinuation in elderly subjects who were treated with garadacimab.

During treatment with 200 mg garadacimab (N = 13), the majority of elderly subjects experienced TEAEs (11 [84.6%] subjects had 51 events).

Six (46.2%) subjects had 14 events that occurred within 24 hours after any SC dose of garadacimab, and 5 (38.5%) subjects had 12 events that were related to study treatment. The majority of events were mild or moderate in severity; 1 (7.7%) subject had 2 severe events; both events were not related to study treatment. Most TEAEs (34 / 51 events in 10 [76.9%] subjects) had an outcome of recovered / resolved, 11 events in 6 (46.2%) subjects had an outcome of not recovered / not resolved; the remaining events were recovering / resolving or had recovered / resolved with sequelae. The TEAEs occurred most frequently (> 3 subjects) in the SOCs of Infections and Infestations (12 / 51 events in 8 [61.5%] subjects), General Disorders and Administration Site Conditions (11 / 51 events in 4 [30.8%] subjects), and Musculoskeletal and Connective Tissue Disorders (4 / 51 events in 4 [30.8%] subjects). The most frequently reported PTs were COVID-19 (3 / 51 events in 3 [23.1%] subjects), Headache (4 / 51 events in 2 [15.4%] subjects), Injection Site Erythema (2 / 51 events in 2 [15.4%] subjects), and Gastroenteritis (2 / 51 events in 2 [15.4%] subjects); all other events occurred in ≤ 1 subject.

Garadacimab was safe and well-tolerated in elderly subjects with HAE. Safety results in the elderly subgroup were consistent with the overall subject population.

Race

Overall in the pooled analysis (N = 176; IA2 for all subjects) of subjects with HAE, 146 (83.0%) subjects were White, 24 (13.6%) subjects were Asian, 3 (1.7%) subjects were Black or African American, 1 (0.6%) subject were Native Hawaiian or Other Pacific Islander, 1 (0.6%) subject belonged to multiple racial categories, and 1 (0.6%) subject was not considered in these categories (Other). As the majority of subjects were White (> 80%), comparisons across race subgroups are not suitable. Given the under-representation of races other than White and Asian, the effect of race on safety was not evaluated.

Pooled Summary (Study 3001 [Pivotal], Study 3002 [Interim Analysis 2 for All Subjects], and Study 2001)

For the pooled analysis, TEAEs were summarised by Japanese and non-Japanese subjects. Please note that overall, there were a small number of Japanese subjects; therefore, the data should be interpreted with caution. However, there was no pattern in the Japanese and non-Japanese subgroups that indicated being of Japanese race has an effect on the safety of garadacimab. There were no safety concerns observed in the Japanese subgroup.

Use in Pregnancy and Lactation

Limited data related to the use of garadacimab in pregnant women are available.

In Study 2001, there were 2 pregnancies reported and 2 pregnancies in male subjects' female partners reported.

- A subject became pregnant while enrolled in Study 2001. The subject received garadacimab 400 mg q4wk SC during TP1 and started TP2 with garadacimab 600 mg SC on Day 85. The subject's last menstrual period was on Day 200. The subject reported being pregnant on Day 230 (confirmed by a positive human chorionic gonadotropin pregnancy test on Day 232). The subject received 10 doses of garadacimab, with the last dose administered on Day 205. The subject delivered a healthy baby, weighing 2.07 kg, at 37 weeks of gestation via vaginal delivery. There were no birth defects, congenital abnormalities, or perinatal complications.

- A subject became pregnant while enrolled in Study 2001. The subject received garadacimab 400 mg SC during TP1 and initiated TP2 with garadacimab 200 mg SC on Day 85. The subject's last menstrual period was on Day 560. The subject had a positive human chorionic gonadotropin pregnancy test on Day 682. The subject received 22 doses of garadacimab, with the last dose administered on Day 570. The estimated date of delivery was approximately 8 months after the last dose of garadacimab. Subject was known to be noncompliant with study procedures and had been asked to discontinue the study. The last Follow- up Visit occurred via phone on Day 774. No information was available on the outcome of the pregnancy.

- A subject's partner became pregnant while the subject was enrolled in Study 2001. The subject received garadacimab 400 mg SC during TP1 and initiated TP2 with garadacimab 600 mg SC first on Day 84 and then continued with garadacimab 200 mg q4wk SC starting Day 315 following Protocol Amendment 2. The subject received 29 doses of garadacimab, with the last dose administered on Day 708. The subject's partner became pregnant while the subject was receiving garadacimab 200 mg SC. The subject's partner delivered a healthy baby on Day 758, at 40 weeks of gestation via vaginal delivery. There were no birth defects, congenital abnormalities, or perinatal complications.

- A subject's partner became pregnant while the subject was enrolled in Study 2001. The subject received garadacimab 200 mg SC during TP1 and initiated TP2 with garadacimab 200 mg SC on Day 95. The subject received 29 doses of garadacimab, with the last dose administered on Day 767. The subject's partner became pregnant while the subject was receiving garadacimab 200 mg SC. The subject's partner delivered a healthy baby on Day 477, at 40 weeks of gestation via vaginal delivery. There were no birth defects, congenital abnormalities, or perinatal complications.

In **Study 3002** (IA2 for all subjects), there was 1 pregnancy reported and 4 pregnancies in male subjects' female partners reported:

- A subject became pregnant while receiving garadacimab 200 mg SC in Study 3002. The subject was a roll-over from Study 3001 and received the first dose of 200 mg garadacimab SC in Study 3002 on 03 November 2021, then received 200 mg garadacimab SC once a month until the last dose on 01 August 2022. The subject's Treatment Period exposure at the time of reporting was 302 days. The subject became pregnant while she was receiving garadacimab 200 mg SC, and she was withdrawn from the study due to pregnancy. The method of birth control used by the subject was abstinence, which was confirmed at each visit. On 15 August 2022, 1 year, 3 months and 6 days after the first dose of garadacimab and 14 days after the last dose of garadacimab, the subject was pregnant. The subject had no history of previous pregnancies. The subject's last menstrual period was on 07 July 2022. The estimated date of delivery was 13 April 2023. There were no findings from prenatal testing. The outcome of delivery is unknown. The action taken with study treatment was drug withdrawn. The subject completed participation in the study, and the End of Treatment Visit was performed on 31 August 2022 and Follow-up was on 09 November 2022.

- A subject's partner became pregnant while the subject was receiving garadacimab 200 mg SC in Study 3002. The subject was a roll-over from Study 2001 and received the first dose of 200 mg garadacimab SC in Study 3002 on 11 August 2021, then received 200 mg garadacimab SC once a month. Treatment was ongoing at the time of data cut-off (13 February 2023). The subject's

Treatment Period exposure at the time of reporting was 552 days. On an unknown date, the subject's partner experienced Spontaneous Abortion (less than 22 weeks). The date of last menstrual period is unknown. The notification of the partner's pregnancy was initially received on 29 March 2022 and was reported by a healthcare professional (physician; investigator). The event of Spontaneous Abortion at less than 22 weeks was considered not related and was considered to be coincidental.

- A subject's partner became pregnant while the subject was receiving garadacimab 200 mg SC in Study 3002. The subject was a roll-over from Study 2001 and received the first dose of 200 mg garadacimab SC in Study 3002 on 25 August 2021, then received 200 mg garadacimab SC once a month. Treatment was ongoing at the time of data cut-off (13 February 2023). The subject's Treatment Period exposure at the time of reporting was 538 days. On 21 February 2022, the subject reported his partner's pregnancy. The date of the last menstrual period was 02 August 2021. The subject's partner had no history of previous pregnancies. Maternal exposure to risk factors in relation to the current pregnancy included smoking (2012). Maternal medical history included hypothyroidism. Medications used during pregnancy were Levothyroxine 100 µg once a day and Prenatab 1 tablet once a day. There were no findings from prenatal testing. The subject's partner delivered a healthy baby on 21 April 2022, at 37.3 weeks of gestation, via caesarean section (reason: macrosomia). There were no birth defects, congenital abnormalities, or perinatal complications.

- A subject's partner became pregnant while the subject was receiving garadacimab 200 mg SC in Study 3002. The subject received a loading dose of 400 mg (two 200 mg doses) garadacimab SC on 18 January 2022, then received 200 mg garadacimab SC once a month. Treatment was ongoing at the time of the data cut-off (13 February 2023). The subject's Treatment Period exposure at the time of reporting was 392 days. The date of the subject's partner's the last menstrual period was 07 March 2022, and she had no history of previous pregnancies. Maternal risk factors in relation to the current pregnancy included smoking and environmental exposures (occupation: building supply store seller). There were no findings from prenatal testing. The delivery date was 03 December 2022. The outcome of delivery is unknown.

- A subject's partner became pregnant while the subject was receiving garadacimab 200 mg SC in Study 3002. The subject received a loading dose of 400 mg (two 200 mg doses) garadacimab SC on 06 January 2022, then received 200 mg garadacimab SC once a month. Treatment was ongoing at the time of the data cut-off 13 February 2023. The subject's Treatment Period exposure at the time of reporting was 404 days. The subject's partner last menstrual period was on07 November 2022. The estimated date of delivery was 14 August 2023. It was unknown whether there were any findings from prenatal testing. The subject's partner had a history of a previous pregnancy (Gravida 2 Para 1). No known birth defect occurred in the previous pregnancy.

No other pregnancies were reported in subjects during their participation in the garadacimab clinical studies.

No data related to the use of garadacimab in lactating women are available.

2.6.8.6. Immunological events

Overall, in the pooled analysis, the cumulative incidence of treatment-emergent anti-garadacimab antibodies after treatment with ≥ 200 mg garadacimab in subjects with HAE was 2.9% (5 / 172 subjects). No hypersensitivity reactions were observed in any of the 5 subjects.

None of the subjects who tested positive for treatment-emergent anti-garadacimab antibodies were adolescents.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No interactions of garadacimab with other medications are known. No dedicated human drug interaction studies have been conducted with garadacimab. The use of concomitant medications and rescue medications were evaluated in the population PK analysis and did not impact the PK of garadacimab.

2.6.8.8. Discontinuation due to adverse events

Pooled Summary (Study 3001 [Pivotal], Study 3002 (Interim Analysis 2 (IA2) for All Subjects), and Study 2001)

Overall, in the pooled analysis, 1 subject treated with 200 mg garadacimab experienced a TEAE of Injection Site Irritation that led to discontinuation.

In Study 3001 (pivotal), there were no AEs leading to discontinuation.

In Study 3002 (IA2 for all subjects) at the time of the data cut, 1 subject had a related TEAE of Injection Site Irritation (Reported Term: abdomen irritation at injection site) that led to discontinuation of garadacimab. This TEAE (moderate severity) had its onset within 24 hours of receiving an SC dose of garadacimab and was qualified as an ISR. Treatment with garadacimab was discontinued and the subject was withdrawn from the study due to this TEAE. The TEAE of Injection Site Irritation resolved 13 days after its onset.

One subject had a TEAE of Mood Swings (severe) that led to discontinuation of garadacimab. This subject participated in Study 3001 and rolled into the current study (Study 3002) after receiving garadacimab for 6 months. The subject had a pre-existing medical history of migraine and anxiety. Concomitant medications for anxiety included buspirone (5 mg twice daily; ongoing) and escitalopram oxalate (20 mg once daily; ongoing). The subject reported extreme irritability and difficulty managing emotions 4 days after administration of the 19th dose of garadacimab. A TEAE of Mood Swings was recorded. Approximately 2 months after the onset of this TEAE (Mood Swings), treatment with garadacimab was discontinued and the event had an outcome of resolved. This TEAE (Mood Swings) was reported as unrelated to garadacimab due the close temporal association with garadacimab administration; the underlying medical history of anxiety was identified as a contributory factor.

The subject withdrew from the study 2 days after the data cut-off date (13 February 2023; data on file: clinical database).

As of the IA3 data cut, none of the 10 adolescents had a TEAE that led to study discontinuation.

In Study 2001, TP1, there were no AEs leading to study discontinuation in subjects with C1-INH HAE or FXII / PLG HAE. In TP2, there were no AEs leading to study discontinuation in subjects with C1-INH HAE or FXII / PLG HAE. One subject with C1-INH HAE discontinued treatment during TP2 due to pregnancy. Further details on the subject who discontinued due to pregnancy are provided in Section 5.4. None of the subjects with PLG HAE started TP2 started TP2.

2.6.8.9. Post marketing experience

Garadacimab is not currently marketed in any region and no post-marketing data are available.

2.6.9. Discussion on clinical safety

The safety profile of garadacimab is mainly based on pooled safety data coming from completed phase 3 double blind Study 3001 (pivotal), ongoing phase 3b open label Study 3002 (IA2 with data cut-off 13 February 2023 for adults and IA3 with data cut-off 22 May 2023 for adolescents), and from completed phase 2 Study 2001. Study 3001 was pivotal, double-blind, randomised, placebo-controlled trial and thus provides comparative data. Study 2001 can provide only supportive (comparative and open label) data since 3001 was considered pivotal for detailed safety assessment by the applicant. An ongoing Study 3002 data provide long-term (12 months or longer) open label safety data. In principle, due to substantial differences in study designs, it is deemed inappropriate to pool Study 3001 and Study 2001. The assessment will therefore focus on individual studies' data and pooled data when appropriate. However, considering that it is difficult to assess safety profile in the individual studies because of small sample sizes, pooled data is acceptable in terms of supportive evidence.

The collection and presentation of safety data were performed at established time points, which is overall acceptable.

A total of 373 subjects were exposed to garadacimab any dose in the overall clinical development programme; of these 172 subjects have been treated with garadacimab in the phase 2 and 3 studies and 166 participants were treated with the intended dose of 200 mg garadacimab q4wk. Even if the size of treated patients appears to be rather low, it can be regarded as acceptable considering that HAE is a rare genetic disorder and a potentially life-threatening and rare disease.

Concerning exposure to study drug, of the 172 subjects who received any dose of garadacimab (≥ 75 mg garadacimab q4wk) 95.3% of subjects had at least 6 months exposure and 83.1% had at least 12 months exposure. Moreover, among 166 subjects who received at least one dose of 200 mg garadacimab, most subjects had a cumulative exposure of ≥ 6 months (160 [96.4%]) and the majority of subjects had cumulative exposure of ≥ 12 months (142 [85.5%]). For the ongoing Study 3002 at the time of respectively IA2 and IA3, ≥ 12 months of exposure to garadacimab was registered for 73.9% of overall study population and 80.0% of adolescent subjects. The relevant proportion of subjects with prolonged exposure is acknowledged considering the intended long-term use of garadacimab in the claimed indication. In addition, the applicant provided updated safety data from the Interim Analysis 4 (IA4, data-cut off 16-JUN-2023) for the ongoing study 3002 and stated that since the previously submitted data cut (13-FEB-2023), there was 1 additional unrelated Serious Adverse Event (SAE; Drug Eruption [drug reaction to dipyrone]) reported in 1 subject, and an additional related Treatment Emergent Adverse Event (TEAE; Injection Site Urticaria) which led to treatment discontinuation and study withdrawal, and 1 male subject had a new pregnancy in a female partner. Injection Site Urticaria has been added among the injection site reactions in 4.8 section of the SmPC. No new deaths or AESIs have been reported. Also, no change in the TEAE profile was reported for adolescents in the ongoing Study 3002.

The demographic characteristics seem to be overall representative of HAE patients. More than half of the subjects were female (64.2%), and almost all study participants were White (83%) of not Hispanic or Latino ethnicity, with another 13.6% identified as Asiatic. Mean age was 40.9 (SD $\pm$10.07) with 11 subjects being adolescents (12 - $\leq$17 years of age). Mean BMI was 28.29 (SD$\pm$6.6) kg/m^2. In the majority of subjects C1-INH HAE type 1 (89.2%) had been diagnosed, C1-INH HAE Type 2 (7.4%), FXII (1.7%) and PLG HAE (1.7%) were represented too. 36.9% of participants received HAE prophylaxis for 3 months before screening. More than half had a history of laryngeal attack (60.8%), suggesting a potential life-threatening disease. About one third of subjects (36.9%) were treated with HAE prophylaxis during the 3 months before screening, indicating that most subjects were naïve to treatment.

Overall, in the pooled analysis dataset (n=166) a higher rate of any TEAEs was observed with garadacimab 200 mg (86.1%) than with placebo (63.6%). However, when analysing TEAEs by exposure, the rate was lower for subjects treated with garadacimab compared to those receiving placebo (2877 vs 4843 events/subject-years of exposure). Further, only 17.5% subjects experienced related TEAEs during treatment with 200 mg garadacimab, and 5 (15.2%) subjects during treatment with placebo. The majority of TEAEs occurred within 24 hours after SC dosing of garadacimab were ISR and mild or moderate in severity. Severe TEAEs were reported in 13 (7.8%) subjects that experienced 20 events during treatment with 200 mg garadacimab (none in placebo group); 1 subject experienced a severe event of Mood Swings that was reported as unrelated to study treatment and led to discontinuation of garadacimab. The majority of TEAEs resolved during treatment with garadacimab (81.3%) or placebo (60.6%). A low number of subjects (5 subjects, 3%) experienced SAEs during treatment with 200 mg garadacimab, 2 subjects during treatment with 600 mg garadacimab and no subjects in the placebo group, all judged as unrelated. In Study 2001, no subjects with C1-INH HAE experienced SAEs during Treatment Period 1. Two subjects with C1-INH HAE experienced 2 SAEs (diverticular perforation and exacerbation of asthma) during Treatment Period 2, assessed as not related to study treatment. One subject with FXII HAE experienced 2 SAEs of Hereditary angioedema reported as severe, both resolved and were assessed as not related to investigational product. One of the SAEs was not treatment emergent as the event occurred during the Run-in Period.

In the pivotal Study 3001, one subject experienced 1 SAE of Hereditary angioedema (Reported Term: overnight stay in hospital for observation after laryngeal attack) during the study. The event was considered not related to the study treatment and had an outcome of recovered / resolved.

In study 3002 there was one reported abdominal HAE attack evaluated as severe; not related to study treatment. The subject received garadacimab on Day 95. The event was reported on Day 102 and resolved on Day 108. The dose was not changed because of this SAE.

COVID-19 was reported in 2 subjects (1 moderate, 1 severe) and both not related to study treatment. The dose of garadacimab was not changed because of these SAEs and both SAEs resolved.

No deaths occurred.

In the pooled analysis the most common AEs in 200 mg group were Infections and Infestations, more frequently reported in the treatment group compared to placebo group (104 [62.7%] subjects vs 10 [30.3%] subjects, respectively). Among infections the most common PTs were COVID-19 (35.5%), Nasopharyngitis (18.1%) and Upper respiratory tract infections (10.2%). When considering common related TEAEs the most frequent belonged to the SOC of General disorders and administration site conditions (11.4%) which however are lower than those reported for the placebo group (15.2%). The most commonly reported PTs are Injection site erythema (7.8%) and Injection site pruritus (3.6%), but also Headache (3%). Proportions of TEAEs presented as related by the applicant, according to investigators' opinion, appear to be much lower than total incidences. That is being questioned for the controlled (part of the) studies. However, the applicant clarified that the noticed differences are based on single subjects experiencing several different Injection Site reaction PTs within the same SOC.

In pivotal study 3001, most of the related TEAEs were ISRs: 1 event each of Injection Site Erythema, Injection Site Bruising, and Injection Site Pruritus in 2 [5.1%] subjects in the garadacimab arm, and 2 events of Injection Site Erythema in 2 [8.0%] subjects in the placebo arm. All TEAEs that were related to the study treatment had an outcome of recovered / resolved, except for 1 subject in the garadacimab treatment arm who experienced a mild event of Prothrombin Fragment 1.2 Increased that had an outcome of not recovered / not resolved.

The applicant considers as ADRs to be included in the label only Injection Site Reactions. However, other TEAEs judged related to study drug such as Headache (5 patients) and Abdominal pain (2

patients), have been reported. Considering the temporal relationship with garadacimab and the recovering after treatment interruption, the causality of these events with garadacimab cannot be excluded and therefore they have been included in section 4.8 of SmPC.

Also, the event of "Mood Swings" has been reassessed by the applicant and the investigator who changed the causality to not related to garadacimab. Considering all the confounding factors reported, this is considered acceptable.

The applicant does not consider the event of Prothrombin Fragment 1.2 increased which occurred in a single subject and did not reoccur during continued treatment for about 1.65 years (from the first dose in Study 3001 on 07-Oct-2021 to the last dose in study 3002 on 30-May-2023 [IA4]), to be an ADR. No clinically significant increases in other coagulation factors including activated Partial Thromboplastin Time, D-Dimer, Prothrombin Intl. Normalised Ratio, and Prothrombin Time) were noted for this subject. In the applicant's opinion, the occurrence of this isolated event can be potentially explained by the subject's underlying disease of HAE. This can be considered acceptable.

AESIs in the SAP were defined as:

AESIs include only thromboembolic events (TEE), bleeding and hypersensitivity/anaphylaxis considered SAEs, more specifically: Thromboembolic events (TEE) – Standardised MedDRA Query" Embolic and thrombotic events (SMQ)" (narrow), consisting of: Embolic and thrombotic events, arterial (SMQ), Embolic and thrombotic events, venous (SMQ), Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).

The applicant was requested to re-assess the AESI dataset after including a broader search including cases of Severe hypersensitivity including anaphylaxis and bleeding events (see above).

The applicant performed another analysis for the Study CSL312_2001 which identified additional AESIs. This is acknowledged. While the 4 cases of eczema, erythema nodosum, hand dermatitis and conjunctivitis are considered not related by the investigator, hypersensitivity is of particular importance. Events associated to severe hypersensitivity and anaphylaxis were observed: in Study 3001 were reported in 3 subjects in garadacimab 200 mg arm assessed as not related; in Study 3002 26 subjects experienced 46 events, of which in 5 subjects (12 events) were considered related.

Therefore, the applicant provided upon request the events identified by Standardised MedDRA Query "Hypersensitivity (SMQ)" (broad), Anaphylactic reaction (SMQ) (broad), Anaphylactic/anaphylactoid shock conditions (SMQ)", and has re-assessed the relatedness of those events to garadacimab and provided tabulated data. In total, there were 64 participants that experienced a total of 110 hypersensitivity/ anaphylactic events. 20 events in 12 participants were assessed as related to garadacimab administration by the investigator and were confirmed by re-assessment. However, the majority of events considered related to garadacimab treatment were confined to the local administration site, and thus, considered under the medical concepts of "injection site urticaria", "injection site erythema" and "injection site pruritus", and reported in section 4.8 of the SmPC. All other events had alternative cause or were not temporally related to the study drug administration and cannot be causally related to garadacimab with sufficient certainty. Based on the currently available data, it is agreed that current warning in SmPC section 4.4 and information in SmPC section 4.8 are sufficient. 'Severe hypersensitivity including anaphylaxis' has been included as an important potential risk in the RMP and will be followed up via routine pharmacovigilance activities.

Measure of absolute effect through the risk difference of serious adverse events and adverse events of special interest was also done. There are visible numerical differences between the placebo and garadacimab arm as was suspected per initial review. Although the numbers are small it is to be expected that some cases were not acquired only by chance, even if none were investigator related.

Concerning abnormal bleeding events, only one AESI of Epistaxis was reported for Study 2001 in a patient receiving 600 mg SC garadacimab. The event was assessed by the investigator as not related to the study drug and resolved on Day 207. Garadacimab dose was not changed, and the subject completed the study on day 786 (Extension Final Visit). Laboratory parameters including INR were in the normal range, except for clinically significant aPTT of > 160 seconds (1 day after the event), which resolved and elevated prothrombin fragments 1 + 2 at baseline (Day 1). Considering the prolongation of aPTT, a relationship between the bleeding and garadacimab cannot be completely excluded. Therefore, the applicant was requested to reassess the AESI of bleeding in this patient. It was clarified that event of Epistaxis (verbatim: nosebleed, spontaneous without any cause / trauma) occurred on Day 206 (02-Jan-2020; 3 days after the last administration of 600 mg garadacimab), was mild in severity and recovered spontaneously without any medical interventions. The subject did not experience any other adverse clinical symptoms. The event of mild Epistaxis was assessed by the investigator to be not related to the administration of garadacimab and the subject continues to be on treatment with garadacimab for more than 3 years with no further abnormal bleeding events or epistaxis. This event is not seen by the applicant as a safety concern, being epistaxis a common problem, occurring in up to 60 percent of the general population with large proportion being self-limiting with different causes, even if it is noticed that other potential causes for epistaxis have not been reported for this subject. Moreover, the applicant states that transient prolongations of aPTT upon garadacimab treatment is to be expected and is representative for target engagement of garadacimab in blocking FXII activity, with no reported bleeding events associated to these prolongations, even with co-administered anticoagulation therapy. In conclusion, considering all the above, the argumentations of the applicant that the AESI of epistaxis was correctly assessed and that transient prolongations of aPTT upon garadacimab treatment is to be expected without a close relationship with bleeding events, even with co-administered anticoagulation therapy can be followed and no amendments to the SmPC is deemed necessary at present.

Only few study drug discontinuations were recorded: 1/172 patient in pooled analysis treated with garadacimab 200 mg is reported to have experienced a TEAE of Injection Site Irritation that led to discontinuation. Moreover, one subject with C1-INH HAE in Study 2001 discontinued treatment during TP2 due to pregnancy.

In the pooled analysis, elderly subjects aged ≥ 65 years were underrepresented (only 13 subjects treated with 200 mg garadacimab and 1 subject treated with 600 mg garadacimab and no one received placebo, thus limiting the comparative assessment of safety profile in treated elderly population. Based on available data, however, the safety profile in these patients seems to be comparable to that of the overall study population with no additional safety signals, SAEs or AESI. The most frequently reported PTs were COVID-19 (3 [23.1%] subjects), Headache (2 [15.4%] subjects), Injection Site Erythema (2 [15.4%] subjects), and Gastroenteritis (2 [15.4%] subjects); all other events occurred in ≤ 1 subject. Nevertheless, it should be taken into account that theoretically this subgroup population could be at higher risk of bleeding due to the potential concurrent use of medicinal having impact on the coagulation, even if available findings seem not to suggest an increased risk of bleeding or other types of events in this population, or in patients receiving concomitant anticoagulants (see below).

Concerning intrinsic factors, analysis by sex was not carried out, as stated by the applicant that there is no clinical rational; this is endorsed. Also, no comparison across race subgroups was performed, as the majority of subjects were White (> 80%). Only safety on Japanese subgroup was provided. The majority of Japanese subjects (91.7%) experienced TEAEs and 6 (50.0%) subjects had 6 events that occurred within 24 hours after any SC dose of garadacimab. The majority were mild or moderate and not related to study drug. Only one TEAE was severe (but not related), and one was mild and considered related. TEAEs occurred most frequently in the SOC of infections and infestations. The most

frequently reported PTs (≥ 5 subjects) were Nasopharyngitis (6 / 76 events in 5 [41.7%] subjects) and COVID-19 (5 / 76 events in 5 [41.7%] subjects). No deaths, SAEs or AESIS or TEAEs leading to discontinuation were reported in Japanese subjects by the applicant.

In the overall clinical development programme, 3 pregnancies were reported (2 in study 2001 and 1 in Study 3002). Unfortunately, no information is available on the outcome of the pregnancies in two cases, while there were no birth defects, congenital abnormalities, or perinatal complications in third case. Moreover, 6 pregnancies in male subjects' female partners were reported. Among these there was one event of spontaneous abortion at less than 22 weeks that was considered not related and to be coincidental. In addition, the applicant provided updated data on 1 female pregnancy and 2 pregnancies of female partners from Study 3002. No safety issue is identified from a limited number of pregnancy cases. Therefore, considering the availability of no or very few data, no firm conclusion can be drawn on the use of garadacimab in neither pregnant nor lactating women and missing information has been included in the RMP.

The applicant provided upon request safety data (TEAEs, serious TEAEs, TEAEs by severity, TEAEs by outcome, AESIs) by subgroups weight (< 50 kg, ≥ 50 kg to <100 kg and ≥ 100 kg). The majority of subjects were in the subgroup of ≥ 50 kg to <100 kg (136), while a lower number of subjects (33) were in the subgroup ≥ 100 kg and only 3 subjects in the subgroup weight of < 50 kg. Therefore, these important differences in number of subjects per group makes difficult to make any comparison. Patients with the lowest body weight (< 50 Kg) had a total of 9 Treatment-emergent adverse events (TEAEs) in 2/3 (66.7%) of subjects, although none of these were assessed as related TEAEs. Moreover, they did not experience SAEs or severe TEAEs. It is reported only one AESI of bleeding which is considered not related. A slightly higher rate of TEAEs were observed in group ≥ 50 kg to < 100 kg (88.2%) compared to ≥ 100 kg group (78.8%) and placebo group (58.3%). However, a lower rate of SAEs was reported in ≥ 50 kg to < 100 kg (3.7%) compared to ≥ 100 kg group (6.1%) and all of these were considered not related to study drug and not led to discontinuation. In conclusion, although slight differences in frequencies of adverse events are observed among different body weight groups, overall, the safety profile seems to be similar even if firm conclusion cannot be draw considering the differences in number among weight subgroups.

For laboratory findings, the applicant presented pooled summaries of data for all treatment-emergent adverse events and there were no apparent safety concerns found. However, more long-term safety data are expected from the final analysis of Study 3002 and the non-interventional PASS. The applicant has provided a visual representation of coagulation parameters for studies 3001 and 3002. Currently the majority of the highest values in the figures provided by the applicant show similar values from pre-treatment to post-treatment. Some changes were observed in subjects for Prothrombin F 1+2 and D-dimer levels; however, clinical relevancy cannot be determined. In light of the presented results being relatively similar between study visits, this can be accepted. Numerical increases in laboratory parameters as noted above are considered not to have had a major impact on potential for bleeding since the applicant states that there are no confirmed bleeding events observed in association with a prolonged aPTT, alongside no effects on PT and INR in subjects treated with garadacimab. The change from baseline is distributed around similarly grouped values for described coagulation parameters. Among clinical laboratory evaluations the most common events were Bacterial Test Positive (in urine), Red Blood Cells Urine Positive and Urinary Tract Infection.

However, regarding the two subjects with Red Blood Cells Urine Positive the applicant stated that they are suggestive of an underlying infection based on additional events that were reported at the same time along with the event of Red Blood Cells Urine Positive. Indeed, a Bacterial test positive was reported. Moreover, for both subjects aPTT values throughout Month 18 (latest data cut for study 3002; IA4 16-JUN-2023) and other coagulation parameters indicative for bleeding (e.g., D-Dimer, Prothrombin Time, Prothrombin Intl. Normalised Ratio) did not show any clinically significant changes

in range. The event was assessed as mild and recovered within 7-8 days in both cases. Therefore, considering the confounding factors and the negativity of coagulation parameters, the conclusion of the applicant that at present Red Blood Cells Urine Positive cannot be considered as urine (microscopic / macroscopic) bleedings, can be considered acceptable. In addition, considering the lack of imbalance in the rate of events of Urinary Tract Infection between study arm and placebo and the fact that they have been assessed as not related by the investigators, there is no evidence of causality with garadacimab that would require inclusion in SmPC at this stage.

Overall, aPTT prolongations were observed in some subjects who received garadacimab (3 subjects in Study 3001, 21 subjects [including 5 subjects at Screening] in Study 3002, and 16 subjects in Study 2001). Abnormal values generally occurred within 1-4 days after garadacimab administration, were transient, and not associated to bleeding, even if an AESI of bleeding (Epistaxis) was reported in a patient with aPTT prolongation (see above).

Further, based on findings provided by the applicant from Study CSL312_1001 in healthy volunteers and Study CSL312_2001 in HAE subjects, it seems that a dose-dependent effect of aPTT was observed while due to the sparse sampling, mean duration of aPTT prolongation in the second study was not evaluated. Moreover, from the applicant's discussion the mean duration of the aPTT prolongation is not clear. It is understood that, due to the blocking effect of garadacimab on the FXII activity, the biological plausibility that the drug could interfere with the aPTT assay does exist, while the extent of PTT prolongation could be variable depending on drug exposure as well as additional parameters, such as natural variation in FXII levels, and other coagulation factors. This information has been reflected in section 4.4 of the SmPC.

Moreover, considering the uncertainties in AESIs classification and in order to better characterise the events of bleeding, the applicant presented upon request an assessment of relatedness of bleeding for all subjects who experienced a bleeding event as identified by the broader SMQ search after being treated with any dose of garadacimab (Pooled analysis, data cut-off 23-FEB-2023). In general, severity of these events was mild (one event with a severity of moderate), with most events recovered without any need for medical interventions. For most events, indicative of any abnormal bleeding episodes per SMQ search, the applicant stated some confounding factors i.e. events of trauma like falls, ongoing medical history, or concomitant medications. This is acceptable. The applicant states that no abnormal coagulation parameters were noted in association with these events. However, from Ad-hoc Listing 16.2.8.2 and 16.2.8.1 alteration of aPTT and other coagulation tests, respectively, seems to have been reported. The applicant clarified that in this pooled analysis (data cut-off 13-FEB-2023), a total of 21 subjects experienced 29 events of bleeding identified by SMQ term "Haemorrhages (SMQ)" (broad search), of which 23 were assessed as not related and only 6 were considered related to the administration of garadacimab (two cases of Injection Site Bruising which has been identified as ADR and included in the SmPC, 3 events of contusion without coagulation tests alterations and an event of Prothrombin fragment 1.2 increased.) Overall, the applicant considers that no further changes in the SmPC are warranted, and this is considered acceptable.

The majority of the events (28/29) were mild in severity and 1 was reported as moderate in severity. Moreover, the majority of events (26/29) recovered or resolved, while 3/29 events did not recover or not resolve at the time of data cut-off.

Out of the 29 events of bleeding, 5 were associated with abnormal laboratory results at time of the event. However, from the descriptions provided no evidence of a clear association between bleeding events and coagulation tests alterations could be found.

In addition, cases of increase of Prothrombin Fragment 1.2 were reported. However, the applicant specified that a total of 1/166 (0.6%) subject experienced Prothrombin Fragment 1.2 increased, after treatment with 200 mg garadacimab, which was not considered to be an ADR (see also above).

Moreover, based on the collective evidence from the HAE clinical programme, the COVID-19 study with garadacimab, preclinical studies and the literature, the applicant provided argumentations stating that there is no increased risk for patients at risk of TEEs when treated with the intended dose of 200 mg once a month. The applicant will continue to monitor all events of TEEs, through routine pharmacovigilance to ensure the safety of patients, which is considered acceptable.

It seemed that subjects treated with medications that may affect the coagulation pathway were not eligible for Study 3001 (pivotal), Study 3002, and Study 2001, and that therefore information on safety of garadacimab in these patients is missing. Nevertheless, the applicant specified that only for Study 2001 inclusion and exclusion criteria was kept conservative, while for study 3001 (pivotal) and the ongoing study 3002, patients treated with e.g., anticoagulants or antiplatelets were / are eligible to participate and were / are not excluded. Within the clinical programme for HAE, 7 subjects (as per IA4 3002) have been concomitantly receiving Aspirin prophylactically on a daily basis over several months or years, Ticagrelor and Enoxaparin without experiencing any event potentially indicative of bleeding. The same results seem to come also from CSL312_COVID-19 study where 55/58 subjects treated with garadacimab received Concomitant Medications affecting haemostasis and from non-clinical studies.

Moreover, there is no evidence from clinical trial experience suggesting that garadacimab raises any safety concerns in individuals with hepatic insufficiency or that subjects receiving garadacimab are at an increased risk of drug induced liver injury. In light of the discussion provided, the applicant considers that no precautions are warranted that would need to be informed in the SmPC or RMP in the context of use of garadacimab in patients receiving concomitant anticoagulants, or patients with hepatic insufficiency.

With regard to patients with bleeding disorders, while the phase 2 study explicitly excluded patients with history of these comorbidities, in the pivotal study 3001 and OLE study 3002 this stringent exclusion criteria was removed, and these patients were not specifically excluded. However, it is not clear if patients with these conditions have been included in the studies. However, the applicant pointed out that: i) the mechanism of action does not interfere with coagulation pathways or platelet dysfunction; ii) high-risk HAE patients receiving Aspirin, Ticagrelor, Enoxaparin have not experienced any event potentially indicative of bleeding risk with an overall cumulative exposure of up to 2 years and that HAE; ii) bleeding disorders such as haemophilia and Von Willebrand disease are very rare diseases without specific data available on prevalence of bleeding disorders in HAE population.

It is acknowledged that although this subpopulation is underrepresented in the clinical trials, there is no evidence to postulate a different safety profile at this moment in HAE patients with pre-existing bleeding disorders, including an increased risk of developing bleeding events with respect to the other HAE patients.

No hypersensitivity safety findings or other AEs related to ADA positivity were reported.

The applicant elaborated on potential clinical effects of garadacimab treatment on the various tissues, such as brain, spleen, lungs, bone marrow. *(Farfara D, et al Knockdown of circulating C1 inhibitor induces neurovascular impairment, glial cell activation, neuroinflammation, and behavioral deficits. Glia. 2019 Jul;67(7):1359-1373.)* It seems that clinical effects of garadacimab treatment on the various tissues are unlikely, but that still constitutes uncertainty.

Moreover, the implications of FXII inhibition from aspects other than coagulation and HAE have been discussed, with particular attention to any effects on the immune response, including risk for (severe) infectious disease, immunological reactions, and autoimmunity. It was concluded by the applicant that the overall scientific evidence suggests minimal risk for the development of clinically relevant immunogenicity, autoimmunity, or infection related events, thereby confirming that garadacimab is a molecule with low potential for adverse immune responses, which is agreed upon.

Assessment of paediatric data on clinical safety

Even if the number of adolescents is low, the overall safety profile in this subgroup population is similar with that observed in adults. In the adolescent population treated with garadacimab and / or placebo no deaths, SAEs, AESIs, or TEAEs leading to discontinuation were reported. One subject during treatment with 200 mg garadacimab discontinued treatment due to pregnancy. The most frequently reported PTs were Nasopharyngitis (5 / 34 events in 3 [27.3%] subjects) and COVID-19 (4 / 34 events in 4 [36.4%] subjects); all other events occurred in ≤ 1 subject. However, it was noted that bleeding events were identified via SMQ research in one adolescent. The applicant provided more information on these events of intermenstrual bleeding and urinary occult blood positive in a 15 year-old patient and concluded that these events are causally not related to garadacimab due to presence of confounding factors, in particular concomitant medications such as hormonal birth control progesterone pills (desogestrel) in the first case and underlying infection (urinal Bacterial test positive) in the second case, contributing to the occurrence of these events. Considering the concomitant medications reported by the applicant, it is agreed that firm conclusion on a potential causality between garadacimab and the above reported events cannot be drawn at this stage. Given the scarcity of safety data in adolescents and the intended lifetime use of garadacimab, long-term safety in adolescents has been added as a safety concern in the RMP and will be characterised through a non-interventional PASS.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of garadacimab, even if based on a limited population size, is considered adequately characterised and supportive support a positive benefit/risk ratio in the approved indication. However, data on long-term safety in adults and adolescents are missing and should be collected and evaluated in the non-interventional PASS.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Severe hypersensitivity including anaphylaxis
Missing information	Safety in pregnancy and breastfeeding Long-term safety in adults Long-term safety in adolescents

2.7.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				

None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Garadacimab Non-Interventional Post Authorisation Safety Study: Long Term Safety in Adults and Adolescents Planned	<u>Primary Objective:</u> To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE. <u>Endpoints:</u> 1. Incidence rate and characteristics of AEs while on treatment with garadacimab (e.g., AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents. 2. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardised growth charts for bone growth, and academic	Long-term safety in adults and Long-term safety in adolescents	Submission of feasibility assessment	April 2025 (within 3 months of EC decision)
			Protocol submission to EMA	April 2025 (within 3 months of EC decision)
			Registration in the EU PAS Register	February 2026
			Start of study	April 2026

	performance for cognitive development. Study Design and Participants: This will be a noninterventional, observational cohort study conducted with a targeted follow-up period of 4 years. The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.		Study completion	April 2034
			Final report of study results	April 2035

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Important potential risk	
Severe hypersensitivity including anaphylaxis	Routine risk communication: SmPC section 4.3 (Contraindications), 4.4 (Warnings and precautions for use) Patient Information Leaflet section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product
Missing information	
Safety in pregnancy and breastfeeding	Routine risk communication: SmPC section 4.6 (Fertility, pregnancy and lactation) Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product
Long-term safety in adults	Routine risk communication: SmPC section 4.2 (Posology and method of administration), 4.4 Special warnings and precautions for use

	Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product
Long-term safety in adolescents	Routine risk communication: SmPC section 4.8 (Paediatric population), 5.1 Pharmacodynamic properties Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.7 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Andembry (garadacimab) is included in the additional monitoring list as it contains a new active substance which was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hereditary angioedema (HAE) is a rare, autosomal dominant, potentially life-threatening disorder caused in most cases of HAE by mutations in the SERPING1 gene, which encodes C1-esterase inhibitor (C1-INH) which leads to dysregulation of the kallikrein–bradykinin cascade, overproduction of bradykinin BK and activation of bradykinin B2 receptors. This increases vascular permeability and results in angioedema attacks.

HAE is a potentially life-threatening disorder characterised by attacks of cutaneous and submucosal swelling. HAE is characterised by random and often unpredictable attacks of painful swelling typically affecting the extremities, genitals, bowel mucosa, face, and upper airway. The condition is associated with morbidity that has a substantial impact on the quality of life for patients who suffer from uncontrolled swelling attacks due to their disease. All patients are at risk for a laryngeal attack, and more than 50% have a laryngeal attack during their lifetime.

3.1.2. Available therapies and unmet medical need

While, for a long time, attenuated androgens (e.g. danazol) were the only treatment used to prevent attacks, the landscape of HAE long term prophylaxis has changed with the authorisation of new medicinal products such as C1INH, C1INH, lanadelumab and berotralstat. Antifibrinolytic agents, such as tranexamic acid, were also used, but currently are not recommended for long-term prophylaxis. Cinryze (plasma derived C1-INH concentrate, administered intravenously), Takhzyro (lanadelumab) and Orladeyo (berotralstat) are all centrally approved medicinal products in the EU. Moreover, Berinert (plasma derived C1-INH, administered subcutaneously) is approved by decentralised procedure in most of the EU member states.

According to the current WAO/EAACI HAE guideline (Maurer 2022) a goal for the long-term prevention (LTP) of HAE is "to achieve complete control of the disease and to normalize patients' lives".

While the limitations of current prophylactic therapies include breakthrough attacks (which could be life-threatening), burden of venous access, high frequency administrations, and occurrence of tolerability issues, there is still an unmet medical need for treatments that encompass better efficacy and tolerability as well as ease of administration which in return improve QoL. Garadacimab provides an alternative for patient care that is administered via SC injection with a dose regimen of administration every month.

3.1.3. Main clinical studies

The pivotal study 3001 was a phase 3, multicentre, double-blind, randomised, 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, randomised 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. In total 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).

The study 3002 is an ongoing open-label, single arm study with safety as the primary objective and efficacy as the secondary objective. The subjects are treated with 200 mg garadacimab SC as 1 dose once monthly for a minimum of 12 months. The eligibility criteria for new subjects are in line with the study 3001. Of the 161 treated subjects (IA2), 92 subjects rolled over from previous studies and 69 were newly enrolled subjects. From 92 subjects that rolled over, 35 subjects (including 2 subjects with FXII HAE) rolled over from Study 2001, and 57 subjects rolled over from Study 3001.

The study 2001 was a phase 2 proof-of-concept, dose-finding study in subjects with C1-INH HAE or nC1-INH HAE (FXII or PLG HAE). This was a randomised, placebo-controlled study for the first 13 weeks and then open label (44 weeks). For subjects with C1-INH HAE, the inclusion criterion was 2 attacks/month, higher than for the phase 3 studies. Three garadacimab dosing regimens were compared in the placebo-controlled part in 32 C1-INH HAE subjects (1:1:1:1): 75 mg q4wks, 200 mg q4wks and 600 mg q4wks. Six subjects with nC1-INH HAE were treated with 600 mg q4wks in open label arm.

3.2. Favourable effects

The pivotal 3001 study met the primary and three key secondary endpoints.

The primary efficacy endpoint was the time-normalised number of investigator-confirmed attacks of HAE (per month) in subjects treated once a month during the period from Day 1 through Day 182.

There was a statistically significant lower HAE attack rate in subjects receiving garadacimab compared to placebo (H01: $p < 0.001$, 2-sided Wilcoxon Test). The mean (SD) and median time-normalised number of HAE attacks per month during the 6-month treatment period was 0.27 (0.683) attacks and 0.0 attacks in the garadacimab arm, and 2.01 (1.341) attacks and 1.35 attacks in the placebo arm. This is corroborated by the results of sensitivity analysis of the primary endpoint adjusted for baseline attack rate using the Poisson model, showing 89.211% reduction in the garadacimab arm compared to placebo (95% CI -95.2315, -75.5876).

The key secondary efficacy endpoints were:

- Percent reduction in monthly attack rate compared with placebo (Day 1 to 182) (H02)

The percentage reduction (i.e., relative difference) in the means of time-normalised number of HAE attacks for the 6-month treatment period of the garadacimab arm compared to placebo was 86.51% ($p < 0.001$, 2-sided Wilcoxon Test).

- Number of attack-free subjects through Day 91 (H03)

The number of subjects who were attack-free (had 100% reduction in HAE attacks) during the first 3 months of treatment was 71.8% in the garadacimab arm compared to 8.3% in the placebo arm ($p < 0.001$, Fisher Exact Test).

- Percentage of subjects rating therapy as “good” or better (i.e., “excellent”) through the SGART at Day 182 (H04)

The percentage of subjects rating their response to therapy as "good" or better by the SGART at the end of the Treatment Period in the garadacimab arm was 81.6% compared to 33.3% in the placebo arm ($p < 0.001$, Chi-squared test). Concerning maintenance of effect, the preliminary results of the ongoing study 3002 indicate that for subjects previously treated with garadacimab the effect on HAE attack rate is maintained.

The open-label (OL) single arm Study 3002 showed consistent results for time-normalised number of HAE attacks per month with those of Study 3001.

With regards to the adolescent population, clinical development included 11 adolescents. The data for the adolescent subgroup from the study 3002 and from the pooled analysis (study 3001 and 3002) seems consistent with overall efficacy results and with results from adult subgroup (pooled analysis). As of the OL single arm study 3002 IA3 data cut for the subgroup of adolescents (10 / 161 subjects), the rate of HAE attacks was similar to that observed in the overall study population. The mean (SD) and median time-normalised number of HAE attacks per month was 0.08 (0.100) and 0.05, respectively.

3.3. Uncertainties and limitations about favourable effects

The proposed indication is not limited to type 1 and type 2 HAE. There are limited data available on the use of garadacimab in HAE patients with normal C1-esterase inhibitor (nC1-INH). Some subcategories of nC1-INH HAE such as HAE-PLG may not respond to treatment (e.g. reduced efficacy or lack of response) with garadacimab due to alternative pathways that do not include FXII activation. Therefore, adequate information has been added in the different sections of the SmPC including a warning in section 4.4. and recommendation in section 4.2. and data in section 5.1.

The primary analysis used a two-sided Wilcoxon test, which does not allow the inclusion of stratification factors. The CHMP in its Scientific Advice from 2020 recommended a more appropriate method, such as Poisson model, with HAE attack rate during the baseline (run-in) period included as a covariate. This was included as a sensitivity analysis and the results were consistent.

The results of secondary endpoints are overall supportive of the primary endpoint, although the choice and hierarchy of key secondary endpoints is not considered optimal (some other secondary endpoints could have been considered among key secondary endpoints), and some secondary endpoints are partially overlapping not independent from the primary endpoint.

The validation of SGART seems to be performed only with the data from the pivotal study 3001 and therefore when chosen to be used in this study (as one of the key secondary endpoints), the score was not validated. Although the approach is not optimal, this patient reported outcome measure as one of the key secondary endpoints is considered acceptable.

Although results for laryngeal attacks were provided as post-hoc analyses after request, it can be concluded that the incidence of laryngeal attacks during the study was low in both groups. However, it cannot be claimed that garadacimab reduces the frequency or severity of laryngeal attacks.

3.4. Unfavourable effects

Overall, in the pool analysis set a higher rate of TEAEs was observed with garadacimab 200 mg (86.1%) than with placebo (63.6%). Further, 17.5% subjects experienced related TEAEs during treatment with 200 mg garadacimab, and 5 (15.2%) subjects during treatment with placebo.

The majority of TEAEs occurred within 24 hours after SC dosing of garadacimab were ISR and mild or moderate in severity. Severe TEAEs were reported in 13 (7.8%) subjects that experienced 20 events during treatment with 200 mg garadacimab (none in placebo group).

SAEs were reported in 5 subjects (3%) in 200 mg garadacimab group and no subjects in the placebo group and were judged as unrelated.

In the pooled analysis the most common AEs in 200 mg group were Infections and Infestations (62.7% vs 30.3% of subjects, respectively), more frequently reported in the treatment group compared to placebo group. Among infections the most common PTs were COVID-19 (35.5%), Nasopharyngitis (18.1%) and Upper respiratory tract infections (10.2%).

When considering common related TEAEs the most frequent belonged to the SOC of General disorders and administration site conditions (11.4%) which however are lower than those reported for the placebo group (15.2%). The most commonly reported PTs are Injection site erythema (7.8%) and Injection site pruritus (3.6%), but also Headache (3%).

At first, the applicant considers as ADRs to be included in the label only Injection Site Reactions. However, other TEAEs judged related to study drug such as Headache (5 patients) and Abdominal pain (2 patients), have been reported and reflected in the SmPC, considering that a possible causality with garadacimab cannot be excluded.

Overall, aPTT prolongations were observed in some subjects who received garadacimab (3 subjects in Study 3001, 21 subjects [including 5 subjects at Screening] in Study 3002, and 16 subjects in Study 2001). Abnormal values generally occurred within 1-4 days after garadacimab administration, were transient, and not associated to bleeding.

3.5. Uncertainties and limitations about unfavourable effects

Safety database is limited in terms of size.

Further long-term safety data from the OLE Study 3002 as well as a non-interventional PASS are awaited in order to enable long-term safety characterisation for garadacimab.

There is a mechanistic plausibility to prolong aPTT, which does not seem to be associated to increased risk for severe bleedings at the moment.

Overall, aPTT prolongations were observed in some subjects who received garadacimab. Abnormal values generally occurred within 1-4 days after garadacimab administration, were transient, and not associated to bleeding. A similar phenomenon of congenital def of FXII was pointed out by the applicant, which shows similar increase in aPTT without any association with bleeding.

It is understood that, due to the blocking effect of garadacimab on the FXII activity, the biological plausibility that the drug could interfere with the aPTT assay does exist, while the extent of PTT prolongation could be variable depending on drug exposure as well as additional parameters, such as natural variation in FXII levels, and other coagulation factors. This information has been reflected in section 4.4. of the SmPC in order to inform prescribers.

The applicant reviewed the safety data in respect to the body weight as it is expected to be an important PK covariate. However, even if safety profile seems to be similar among different body weight, due to the important numeric differences among groups (e.g.: only 3 subjects in < 50 Kg weight group), no firm conclusion can be drawn.

3.6. Effects Table

Table 32: Effects Table for Andembry (garadacimab)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Time-normalised number of HAE attacks from Day 1 to 182	Garadacimab 200 mg q4wks vs placebo Mean (95% CI)	(attacks/ month)	0.27 (0.05, 0.49)	2.01 (1.44, 2.57)	P <0.001 (H01)	Study 3001
Percent (number) of subjects who were attack free from day 1 through the end of month 3	Garadacimab 200 mg q4wks vs placebo	(%)	71.8 (56.22, 83.46)	8.3 (2.32, 25.85)	P <0.001 (H03)	Study 3001
Percent reduction in time-normalised number of HAE attacks relative to placebo	Garadacimab 200 mg q4wks vs placebo	(%)	86.51 (57.84, 95.68)		P <0.001 (H02)	Study 3001
Subject's Global Assessment of response to Therapy (**SGART**)	Garadacimab 200 mg q4wks vs placebo (% of subjects with good or better as a response)	(%)	81.6%	33.3%	P <0.001 (H04)	Study 3001
Adolescents						
HAE-attacks	Garadacimab 200 mg q4wks	(attacks/ month)	0.05 (0.0, 0.2)			Pooled study 3001 and 3002 (IA3)
Unfavourable Effects						
TEAEs		%	86.1	63.6		
Related TEAEs		%	17.5	15.2		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
SAEs		%	3.0	0		
Comon related AEs by PT: Injection site erythema Injection site pruritus		% %	7.8 3.6	12.1 3		
Injection site Urticaria		%	1.2	0		
Injection site Bruising Headache Abdominal pain		% % %	1.2 3.0 1.2	0 0 0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal Study 3001 showed that garadacimab-treated HAE patients, with respect to placebo, had a statistically significant reduction in time-normalised HAE attack rate, there was an increased proportion of attack-free subjects during the first 3 months of treatment (71.8% vs 8.3%; p <0.001), and a significantly higher percentage of subjects rating their response to therapy as "good" or better by the SGART at the end of the treatment period (81.6% vs 33.3%). These findings are considered clinically relevant in the context of attack prevention in HAE, a rare and potentially life-threatening disease.

The reduction in the number of HAE attacks is a valid and clinically important endpoint. However, the goal of treatment in these patients would be total absence of attacks, which was achieved during the first 3 months of treatment in the garadacimab arm (71.8%) compared to placebo (8.3%). The severity of attacks is also an important issue for patients. Out of 63 attacks in the garadacimab arm during 6 months, 29 of them (i.e.46%) were moderate or severe. This is compared with 172 out of 264 (i.e. 65.2%) in the placebo arm. The effect of prophylactic medication on laryngeal attacks is considered to have great importance to participants. The incidence of laryngeal attacks during the study was low in both groups; however, it cannot be claimed that garadacimab reduces the frequency or severity of laryngeal attacks.

Overall efficacy of garadacimab in routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older is shown. However, some important endpoints from the patient's perspective were not hierarchically tested (e.g. AE-QoL), they were nevertheless included among the secondary/exploratory endpoints. The superiority to placebo is demonstrated.

Discussion and justification of the findings of paradoxically increased attack rate in patients with PLG HAE and discussion of the biological plausibility for a relevant effect of garadacimab in each of the

patient subcategories of nC1-INH HAE has been provided. The data on nC1-INH HAE is very limited, however current data on garadacimab do not evidence a detrimental effect. Still, there is a potential for reduced efficacy or a lack of response due to the alternative metabolic pathways involved in some nC1INH-HAE forms, including HAE-PLG. Therefore, adequate information is included in sections 4.2,4.4 and 5.1 of the SmPC.

Generally, the safety database is deemed limited in terms of size. However, given the rarity of disease, the safety database in terms of number of exposures and duration of exposure is deemed sufficient. Further long-term safety data from the OLE Study 3002 and the non-interventional PASS (FSR due in April 2035) are awaited. The most frequently reported ADRs that were ISR.

Data in adolescents is still limited but indicates similar efficacy and safety profile than in adults.

3.7.2. Balance of benefits and risks

The clinical benefit of garadacimab in the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older has been adequately shown. The assessment of the safety profile although based on limited data is considered acceptable.

The indication 'for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older' is considered justified.

The wording "routine prevention" indicates that garadacimab is intended for continuous treatment as opposed to e.g. short-term prevention at surgery. This is an established wording within this therapeutic field.

Considering the evolving scientific evidence of mutations and mechanisms at the basis of nC1-INH HAE subcategories with very limited population and high unmet medical need and current data on garadacimab with no evidence of detrimental effect, it is agreed that broad indication is acceptable, and adequate information has been included in the SmPC with regard to nC1-INH HAE population (sections 4.2, 4.4 and 5.1).

3.8. Conclusions

The overall benefit/risk balance of Andembry is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Andembry is not similar to Takhzyro within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Andembry is favourable in the following indication:

Andembry is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that garadacimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0048/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.