Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Andembry

Active ingredient: garadacimab

Sponsor: CSL Behring (Australia) Pty Ltd

June 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-Drug Antibodies
AE	Adverse event
AE-QoL	Angioedema Quality of Life
AESI	Adverse event of special interest
AI	Autoinjector
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASCIA	Australasian Society of Clinical Immunology and Allergy
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve extrapolated to infinity
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
C1-INH	C1-esterase inhibitor
C1-INH HAE	Hereditary angioedema with C1-esterase inhibitor deficiency
CER	Clinical evaluation report
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CL	Systemic clearance
CL/F	Apparent systemic clearance
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
C_{trough}	Trough plasma concentration
DLP	Data lock point
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency

Abbreviation	Meaning
ER	Exposure-response
EU	European Union
FDA	United States Food and Drug Administration
FXII	Factor XII
FXII/PLG HAE	Hereditary angioedema with normal C1-esterase inhibitor and factor XII or plasminogen gene mutation
FXIIa	Activated Factor XII
HAE	Hereditary angioedema
ICH S6 (R1).	Preclinical safety evaluation of biotechnology-derived pharmaceuticals - Scientific guideline
IgG4	A subclass of immunoglobulins (IgG)
IRT	Interactive response technology
ISR	Injection site reaction
ITT	Intention-to-treat
IV	Intravenous
mAb	Monoclonal antibody
nC1-INH	Normal C1-esterase inhibitor
NOAEL	No observed adverse effects level
NSD	Needle safety device
PD	Pharmacodynamics
PFS	Pre-filled syringe
PI	Product Information
PK	Pharmacokinetics
PLG	Plasminogen
PopPk	Population pharmacokinetics
PP	Per-protocol
PSUR	Periodic safety update report
PT	Preferred term
QoL	Quality of life
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous

Abbreviation	Meaning
SD	Standard deviation
SE	Standard error
SGART	Subject's Global Assessment of Response to Therapy
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum concentration
TSQM	Treatment Satisfaction for Medication Questionnaire
USA	United States of America
WAO	World Allergy Organisation

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Andembry
Active ingredient:	garadacimab
Decision:	Approved
Date of decision:	9 January 2025
Date of entry onto ARTG:	14 January 2025
ARTG numbers:	428253 - Andembry garadacimab 200 mg solution for injection in pre-filled syringe with needle safety device 443611 - Andembry garadacimab 200 mg solution for injection in pre-filled pen
, *Black Triangle Scheme*	Yes
for the current submission:	*The PI and CMI for Andembry must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.*
Sponsor's name and address:	CSL Behring (Australia) Pty Ltd 189–209 Camp Road Broadmeadows Victoria 3047
Dose form:	200 mg of garadacimab in 1.2 ml solution for injection
Containers:	Andembry (garadacimab) 200 mg solution for injection in: -pre-filled syringe with needle safety device, -pre-filled pen (auto-injector).
Pack sizes:	Single packs - 1 pre-filled pen or 1 assembled pre-filled syringe. Multipacks - 3 pre-filled pens or 3 assembled pre-filled syringes.
Approved therapeutic use for the current submission:	*Andembry is indicated for routine prevention of recurrent hereditary angioedema (HAE) attacks in patients aged 12 years and older with C1-INH HAE (C1-esterase inhibitor deficiency or dysfunction).*
Route of administration:	subcutaneous (SC) injection.
Dosage:	Initial loading dose of 400 mg (SC injection- two 200 mg injections) on the first day of treatment, followed by monthly 200 mg doses. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category:	Category B1. There are limited data from the use of Andembry in pregnant women. A risk to the pregnant woman or developing foetus cannot be excluded. A decision should be made whether to initiate or discontinue treatment with Andembry, taking into account the risk/benefit of therapy. Monoclonal antibodies such as garadacimab are transported across the placenta mainly during the third trimester of pregnancy; therefore, potential effects on a foetus are likely to be greater during the third trimester of pregnancy. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by CSL Behring Australia to register Andembry (garadacimab) 200 mg in 1.2 ml of solution for injection, in pre-filled pen (auto-injector) or pre-filled syringe (with needle safety device) for the following proposed indication:

> *Andembry is indicated for routine prevention of hereditary angioedema (HAE) attacks in adult and paediatric patients (aged 12 years and older).*

The original proprietary product name was Gofyxii, which was changed to Andembry during the evaluation process.

Disease or condition

Hereditary angioedema (HAE) is a rare genetic disorder characterised by episodes of swelling (oedema) in various parts of the body, most commonly affecting the skin, gastrointestinal tract, and upper respiratory tract. HAE is classified into three types, with types 1 and 2 accounting for the majority of cases. Type 1 is due to a deficiency of C1-inhibitor (C1-INH), while type 2 involves dysfunctional C1-INH. Both types are caused by mutations in the SERPING1 gene, leading to excessive production of bradykinin, which increases vascular permeability and results in angioedema attacks. Inheritance is typically autosomal dominant, but about 25% of cases arise from new mutations.

Type 3 HAE, now referred to as HAE with normal C1-INH levels (nC1-INH HAE), is extremely rare and its underlying mechanisms are not well understood. This type includes various subtypes based on different genetic mutations, such as those affecting FXII and plasminogen. The prevalence of C1-INH HAE is estimated at 1 in 50,000 people, with no significant differences across ethnicities or sexes. Diagnosis is based on clinical suspicion and laboratory tests measuring C1-INH function and levels, as well as C4 levels.

Clinically, HAE manifests through recurrent, localized swelling episodes, which can be triggered by factors like stress, infection, trauma, and hormonal changes. These episodes are self-limiting but can significantly impact daily life due to their unpredictability and severity. Symptoms can

range from non-pruritic, non-pitting oedema of the skin to severe abdominal pain and potentially life-threatening upper airway swelling. The unpredictable nature of attacks and their potential severity pose a significant burden on patients, affecting their daily activities and quality of life.

Current treatment options

There is currently no cure for hereditary angioedema (HAE). Treatment strategies focus on managing acute attacks to reduce their severity and duration, using short-term prophylaxis to handle anticipated triggers, and implementing long-term prophylactic therapy to prevent attacks and lessen the disease burden. The Australasian Society of Clinical Immunology and Allergy (ASCIA) and the World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guidelines primarily address HAE types 1 and 2, with limited discussion on HAE type 3.

In Australia, on-demand treatments for acute HAE attacks include C1-esterase inhibitors like Berinert IV and the bradykinin B2 receptor antagonist icatibant. Although the plasma kallikrein inhibitor ecallantide is approved for acute treatment in the USA, it is not registered in Australia. For long-term prophylaxis, the WAO/EAACI guidelines recommend plasma-derived C1-inhibitors, the anti-plasma kallikrein monoclonal antibody lanadelumab, and the plasma kallikrein inhibitor berotralstat. In Australia, Berinert SC and lanadelumab (Takhzyro) are approved for long-term prophylaxis and can be self-administered by patients or caregivers.

These therapeutic options aim to manage the unpredictable and potentially severe nature of HAE attacks, which can significantly impact patients' daily lives. By reducing the frequency and severity of attacks, these treatments help improve the quality of life for individuals living with HAE.

Clinical rationale

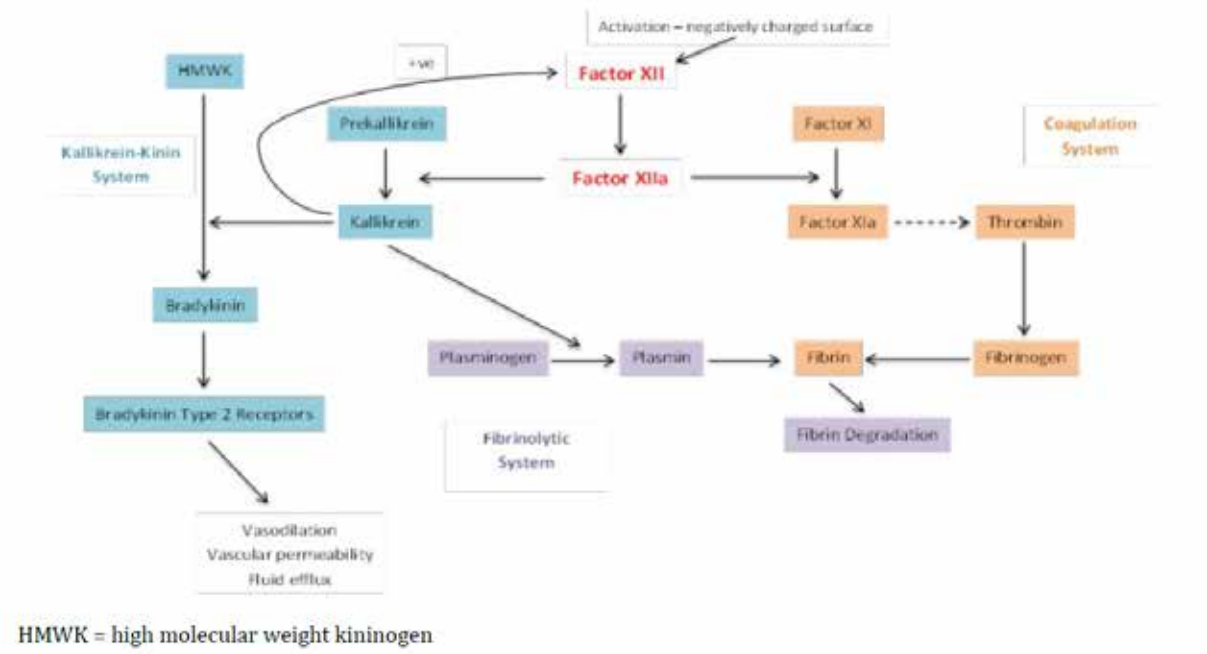
There are several approved therapies for prophylaxis as well as treatment of acute attacks. However, these prophylactic therapies do not eliminate all HAE attacks as the majority of patients still experience attacks. Limitations of current prophylactic therapies include frequent breakthrough attacks (high disease activity with some patients still experiencing life threatening laryngeal attacks), burden of venous access, and/or high frequency of intravenous (IV) infusions or SC injections, and occurrence of tolerability issues. Therefore, there is a medical need for alternative therapies.

Garadacimab potentially offers a new well-tolerated and reliable treatment option with a novel mechanism of action for the prophylactic prevention of C1-INH HAE and potential treatment option for patients with nC1-INH HAE, specifically with FXII mutation. No targeted treatment is available for the nC1-INH HAE population. Furthermore, garadacimab also provides convenience with a single-dose regimen and monthly administration with an autoinjector or needle safety device.

Garadacimab is a novel fully human IgG4/lambda recombinant monoclonal antibody, which binds to the catalytic domain of the plasma protein FXIIa and potently inhibits its catalytic activity. Factor XII is the principal initiator of the plasma contact system, a protease cascade involving the proteins FXII, Factor XI (FXI), plasma prekallikrein, and the nonenzymatic cofactor high molecular weight kininogen (see Figure 1 below). FXIIa triggers fibrin formation through activation of FXI and also leads to the production of the inflammatory mediator bradykinin through the kallikrein-kinin pathway. Thus, activated forms of FXII have proinflammatory and procoagulant activities.

Bradykinin production is increased during acute HAE attacks and is the mediator of swelling in HAE. Acute and prophylactic treatments for HAE are based on blocking bradykinin production through targeting different proteins in the kallikrein-kinin pathway. As a potential first-in-class treatment, garadacimab provides inhibition of FXIIa, thus preventing the activation of prekallikrein to kallikrein and the generation of bradykinin.

Figure 1: Factor XII and its role in the coagulation, fibrinolytic, and kallikrein-kinin systems



Regulatory status

Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes. Orphan drug designation was granted by the TGA on 25 September 2023.

International regulatory status

At the time the TGA considered this submission, similar submissions had been considered by other regulatory agencies, including Medicines and Healthcare products Regulatory Agency (UK - MHRA), Health Canada (HC), the European Medicines Agency (EMA), Food and Drug Administration (US-FDA) and Swissmedic (SMC).

This submission was evaluated as part of the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium with work-sharing between the TGA and Medicines and Healthcare products Regulatory Agency (UK - MHRA), Health Canada (HC), and Swissmedic (SMC). Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

The same technical dataset was submitted to each ACCESS agency, with some differences in the Canadian dossier in line with regional regulatory requirements. The sponsor states the dossier is based on the EU marketing authorisation dossier. Further, the US application contained the

same technical dataset as the EU dossier, except for some differences relating to device data to meet regional regulatory requirements.

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Submission PM-2023-05358-1-2

Description	Date
Designation (Orphan)	25 September 2023
Submission dossier accepted and first round evaluation commenced	2 January 2024
First round evaluation completed	15 May 2024
Sponsor provides responses on questions raised in first round evaluation	15 July 2024
Second round evaluation completed	8 October 2024
Delegate's[1] Overall benefit-risk assessment and request for Advisory Committee advice	7 November 2024
Sponsor's pre-Advisory Committee response	19 November 2024
Advisory Committee meeting	5 December 2024
Registration decision (Outcome)	9 January 2025
Administrative activities and registration in the ARTG completed	14 January 2025
Number of working days from submission dossier acceptance to registration decision*	179

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

Quality evaluation summary

Andembry (garadacimab) is an activated coagulation Factor XII (FXIIa) inhibitor monoclonal antibody (IgG4/λ-light chain) produced by recombinant DNA technology in Chinese Hamster Ovarian (CHO) cells. Each drug product contains 200 mg of garadacimab at a nominal concentration of 170 mg/mL.

[1] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Andembry (garadacimab) has two presentations:

- Andembry (garadacimab) 200 mg solution for injection in pre-filled syringe (PFS) with needle safety device is presented as a sterile liquid solution in ready-to-use 2.25 mL staked-in needle Pre-fillable Glass Syringe. Each single-dose pre-filled syringe (PFS) contains 200 mg of garadacimab in 1.2 mL of solution.
- Andembry (garadacimab) 200 mg solution for injection in pre-filled pen (auto-injector- AI) is presented as a sterile liquid solution filled in a ready-to-use 2.25 mL staked-in-needle Pre-fillable Glass Syringe and assembled in a disposable autoinjector. Each single-dose pre-filled pen (AI) contains 200 mg of garadacimab in 1.2 mL of solution.

Based upon stability data submitted by the sponsor, the recommended shelf life and storage conditions for the drug substance are 36 months, at ≤ -65°C and protected from light. While the drug product shelf life and storage conditions are 36 months at 2-8°C.

Garadacimab is a fully human immunoglobulin G subclass 4 (G4) / lambda recombinant monoclonal antibody, 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 stabilize the hinge and prevent half-antibody formation. The molecular weight is approximately 148.2kDa.

The active ingredient was produced using recombinant DNA technology. Information about the manufacturing, storage and control facilities for the active substance has been provided in the dossier.

The overall quality of the active substance was demonstrated via adequate control of the starting material, control of critical steps and intermediates, process validation, extensive characterisation using orthogonal and state-of-the-art analytical methods, control of impurities and contaminants, generation of robust reference materials and batch analyses that covered multiple manufacturing campaigns.

The proposed quality testing approach, including the stability testing was considered acceptable. The proposed specification limits are based on batch analysis and stability study results. This approach is considered acceptable.

Stability data have been generated under real time and stressed conditions to characterise the stability profile of the active ingredient and to establish a shelf life. The real time data submitted support a shelf life of 36 months when stored at ≤ - 65°C.

The Andembry finished product manufacturing process consists of drug substance thaw and pooling, formulation of bulk prior to sterile filtration, sterile filtration, and filling of pre-fillable syringes to produce the semi-finished product. The semi-finished product is then assembled with plunger rod, Needle Safety Device and extended finger flange (PFS+NSD) or in a disposable autoinjector (PEN).

All filled syringes are visually checked, discarding those with defects. After the inspection process, the syringes are stored at 2-8°C pending further assembly and packaging. The description of the manufacturing process has been provided in sufficient detail. To ensure that the finished product meets high quality standards, its manufacturing process was developed with defined manufacturing procedures, process validations, critical process parameters, in-process parameters, batch analyses of multiple manufacturing campaigns. Finished product comparability studies were conducted in order to demonstrate that the quality of the commercial manufacturing process is comparable to the pre-change product. These were assessed and considered satisfactory.

All analytical methods used for testing of the finished product are satisfactorily described in the dossier and non-compendial methods have been validated.

The quality of this product is considered acceptable when used in accordance with the conditions defined in the product information (PI), labels, consumer medicine information and the Australian Register of Therapeutic Goods (ARTG). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. From quality perspective, compliance with Therapeutic Goods Legislations and relevant Therapeutic Goods Orders as well as consistency with relevant guidelines and the ARGPM has been demonstrated.

Nonclinical (toxicology) evaluation summary

General comments

The nonclinical evaluation was conducted through the Access Consortium work-sharing program with Swissmedic serving as the lead regulator. Overall, the TGA concurs with the major findings and conclusions of the Swissmedic Nonclinical Assessment Report as summarised below.

The data was of high quality with all pivotal safety-related studies being Good Laboratory Practice (GLP) compliant. While garadacimab is proposed as a potential first in class treatment, the TGA has previously approved a monoclonal antibody, lanadelumab (ARTG 330280), for the same indication. Garadacimab is designed to target the catalytic domain of the activated plasma protein factor XIIa (FXIIa), whereas lanadelumab inhibits proteolytic activity of active plasma kallikrein, which is immediately downstream of FXIIa.

Pharmacology

FXII is the primary initiator of the plasma contact system. Upon contact with a negatively charged surface, FXII is activated (FXIIa). FXIIa then triggers fibrin formation and production of inflammatory mediator bradykinin (BK) through the kallikrein-kinin (KK) pathway. Cleavage of FXIIa also activates the classical complement pathway.

Hereditary angioedema (HAE) is an autosomal dominant disease arising from low levels of the plasma protein C1 inhibitor (C1-INH). Deficiency of C1-INH increases activation of the classical complement pathway. Studies of patients have implicated activation of the contact system in HAE[2]. Garadacimab is proposed to specifically bind the catalytic domain of FXIIa and potently inhibit its catalytic activity, thus, attenuating HAE attacks by inhibiting the KK pathway and excessive production of BK.

Primary pharmacology

In vitro studies demonstrated that garadacimab bound activated human FXII (βFXIIa) with high affinity (KD of 0.14 nM). The garadacimab affinity to mouse, rabbit and cynomolgus monkey βFXIIa was lower (KD of 0.7 nM, 0.4 nM and 19 nM, respectively). The parental 3F7 antibody showed approximately 10- to 20-fold lower KD in human (3 nM), mouse (6 nM) and rabbit (6.6 nM). Garadacimab did not bind to rat FXIIa.

[2] Caccia S., Suffritti C. and Cicardi M. (2014) Pathophysiology of Hereditary Angioedema. Pediatr. Allergy. Immunol. Pulmonol. 27: 159–163.

Garadacimab (as well as 3F7) showed 100% inhibition of FXIIa activities without significantly inhibiting the activity of a panel of relevant activated human serine proteases (FVIIa, FIXa, FXa, and FXIa). Garadacimab was a potent inhibitor of FXIIa and βFXIIa with and IC50 of 15nM at clinically relevant concentrations[3]. The inhibitory activity of garadacimab was demonstrated *in vitro* using contact-activated plasma from healthy donors and, HAE (types I/II/III) and acquired angioedema patients. Garadacimab inhibited FXIIa activity in a concentration-dependent manner from 10 µg/mL (67.5 nM), which is within the clinically relevant range[2]. Garadacimab inhibited FXIIa activity in cynomolgus monkey, mouse and rabbit plasma, but not in rat plasma. In healthy human and monkey plasma, garadacimab was an effective KKS inhibitor, inhibiting BK formation.

In the murine 'passive cutaneous anaphylaxis (PCA)' model, a 25 mg/kg IP dose of garadacimab and 3F7 effectively inhibited mast cell heparin-induced ear skin oedema. In the 'angiotensin converting enzyme inhibitor (ACEI)-induced angioedema' mouse model, garadacimab and 3F7, at IP doses of 0.5 and 2.5 mg/kg, effectively inhibited ACEI-induced increase of vascular permeability.

The *in vitro* and *in vivo* pharmacology data broadly support the proposed pharmacology and efficacy of garadacimab.

Secondary pharmacodynamics

Potential secondary pharmacodynamic effects of FXII inhibition were examined in mouse and rabbit models, specifically, the 'thrombotic model' (ferric chloride-induced arterial thrombosis by ectopic application) and/or 'bleeding model' (tail tip and kidney bleeding), respectively.

Garadacimab, up to 2.5 mg/kg in mice, induced a strong anti-thrombotic effect and concomitant increase in mean aPTT, and a decrease in FXIIa activity. No effect on prothrombin time (PT) was observed. The observations are in-line with the anticipated pharmacological effects of garadacimab. Treatment with 2.5 or 25 mg/kg garadacimab did not have any effect on mouse haemostasis based on the 'tail-tip bleeding' model. Rabbits treated with 10 mg/kg IV garadacimab were completely protected from ferric chloride-induced arterial thrombosis, and no significant effect on venous thrombosis was reported. Similar to mice, prolongation of the aPTT was noted while the PT was unaffected.

Commensurate with these findings, primary pharmacodynamic studies reported no cross reactivity with serine proteases such as FVIIa, FIXa, FXa, and FXIa.

Safety pharmacology

While one dedicated respiratory safety pharmacology study was performed in mice, cardiovascular, central nervous and respiratory system safety pharmacology was assessed in the mouse and monkey repeat-dose toxicity studies, and the rabbit pre- and postnatal development study. No garadacimab related adverse effects on respiratory parameters (e.g., respiratory rate, tidal volume and minute volume) were observed in mice administered SC doses up to 200 mg/kg (63-fold safety margin based on C_{max})[3]. The electrocardiography examination of heart function, blood pressure, pulse rate, and respiration during the 26-week monkey study, and the neurology functions assessed during the pre- and postnatal development study revealed no safety pharmacology concerns. Based on C_{max} values of 686 µg/mL and 927 µg/mL at no observed adverse effects level (NOAEL) in the 26-week monkey repeat-dose toxicity study and rabbit pre- and postnatal development study, respectively, safety margins of at least 32- and 44-fold are determined for cardiovascular and nervous system.

[3] Clinical Cmax 21.2 µg/mL. Assuming molecular weight of 148 kDa, 15 nM equates to approximately 2.2 µg/mL (based on ng/mL = nM × molecular in kD)

Pharmacokinetics

The pharmacokinetic profile of garadacimab was assessed following single IV (0.5, 1 and 3 mg/kg) and SC (6 and 20 mg/kg) administrations to male cynomolgus monkeys. C_{max} and AUC increased with dose for both routes. Following SC administration, the T_{max} ranged from 3 to 4 days, which is broadly comparable to the 6 days in patients. The $t_{½}$ ranged from 6.1 to 24.2 days for IV, and 8.6 to 17.7 days for SC administration. These values were comparable to the clinical $t_{½}$ of 19 days following SC administration. In the 26-week monkey study, C_{max} and AUC increased dose-proportionally in both sexes with no sex-related differences. Following SC administration, toxicokinetic data showed signs of accumulation over 13 and 26 weeks.

In rabbits, T_{max} was generally observed 1 to 2 days post-dosing via the SC route and the t½ ranged from 2 to 6 days. These values were slightly lower *cf*. patient T_{max} values. The C_{max} and AUC in rabbit also increased in a dose-proportional manner.

In the mouse repeat dose toxicity study, the C_{max} and AUC increased with increasing dose in both sexes. The $t_{½}$ ranged from 5 to 7 days when administered via the SC route.

No distribution, metabolism or excretion studies were conducted; this is consistent with guidelines for a product of this nature[4]. A tissue cross reactivity study was, however, conducted with multiple monkey and human tissues. Specific staining in monkey tissues was generally comparable of staining in human tissues confirming cynomolgus monkey as a relevant species for toxicological studies.

While garadacimab induced production of anti-drug antibodies (ADA) in all species (mouse, rabbit and monkey), no major impact on garadacimab serum concentrations was observed. The pharmacokinetic profiles in mouse, rabbit and monkey are therefore sufficiently similar to that of humans to allow them to serve as appropriate models.

Pharmacokinetic drug interactions

No dedicated pharmacodynamic drug interactions studies were submitted for evaluation.

Toxicity

Acute toxicity

No single-dose toxicity studies were conducted. Immediate/acute effects after a single dose garadacimab were evaluated in the repeat-dose toxicity studies, which indicated a low order of acute toxicity.

Repeat-dose toxicity

Repeat-dose toxicity of garadacimab was evaluated in mice (8 day and 4-week studies) and monkeys (8 day, and 5-and 26-week studies) following IV and/or SC administration with doses of up to 100 mg/kg (IV) and 200 mg/kg (SC), respectively. The pivotal studies were GLP compliant. The 4-week mouse study encompassed a regimen of nine doses (twice weekly), and the 5- and 26-week monkey studies included a regimen of once weekly doses. All dosing regimens were more frequent than the proposed clinical frequency and used the clinical route of administration (*cf*. loading dose). The 4-week mouse study resulted in an AUC based safety margin of 69-fold the clinical exposure (200 mg/kg/BIW, SC), and the 26-week monkey study resulted in a safety margin of 37-fold the clinical exposure (60 mg/kg/weekly SC. Plasma exposure did not appear to be significantly affected by the presence of ADAs.

[4] ICH S6 (R1) — Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

In mice, treatment-related anaphylaxis-induced mortality and clinical signs were observed following IV administration at all 3 doses. With the exception of anaphylaxis, no other clinical signs were noted in the IV administered group. No garadacimab related toxicity was reported in the SC administered treatment group. In the 26-week monkey study, treatment related immunogenic adverse reactions led to the euthanasia of two animals: a female in the 200 mg/kg/weekly SC group, and a male in the 100 mg/kg/weekly IV group. The immunogenic adverse effects notwithstanding, garadacimab was well tolerated. Thus, no garadacimab related organ toxicities were identified in any of the repeat dose toxicity studies. The observed immunogenic responses are likely to be of limited clinical relevance given that garadacimab is a humanised monoclinal antibody.

Genotoxicity

Since Garadacimab is a monoclonal antibody, no genotoxicity is anticipated. Therefore, genotoxicity studies were not performed in line with ICH S6 (R1).

Carcinogenicity

No carcinogenicity studies were performed in accordance with ICH S6 (R1). A weight of evidence approach revealed no carcinogenic potential based on (1) available nonclinical data, (2) an analysis of risk associated with the mechanism of action (based on published scientific literature), and (3) an evaluation of any carcinogenic risk of garadacimab excipients.

Reproductive and developmental toxicity

The sponsor submitted a suite of reproductive development studies which included fertility and early embryonic development, embryofetal development and pre- and post-natal studies in rabbits. The studies were designed in accordance with the relevant guideline[4] at doses up to 100 mg/kg (once every 3 days for fertility, early embryonic and embryofetal studies, and once every 5 days for pre- and postnatal study). The routes of administration were IV and/or SC (pre- and post-natal study).

At doses up to 100 mg/kg, no effect on male or female fertility was noted. Furthermore, no test article related effects were observed in the early embryofetal development study up to the highest dose (83to 103-fold the maximum clinical exposure).

No adverse effects on embryofetal development were observed at doses up to 100 mg/kg (104-fold maximum clinical exposure). The study also reported no maternal toxicity at any of the tested doses.

In the rabbit pre- and postnatal developmental study, subcutaneous administration of garadacimab every 5 days revealed no garadacimab-related effects up to 100 mg/kg (53-fold maximum clinical exposure).

No dedicated placental transfer studies were conducted with garadacimab. However, following subcutaneous dosing in the embryofetal development and pre- and postnatal development studies, garadacimab was measured in pooled foetal blood samples indicating placental transfer.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1. This category is appropriate based on lack of animal findings.

Local tolerance

Local tolerance related to garadacimab was evaluated in rabbit after SC administration (170 mg/mL), as well as in all repeat-dose toxicity studies conducted in mice and cynomolgus

monkeys (102 mg/mL). No garadacimab related changes were noted at the injection sites in rabbit; a mild irritant effect was noted in monkeys after 27 SC doses. However, while the concentration used in rabbit was comparable to the manufacturing target for nominal protein concentration of 170 mg/mL, the concentration in the monkey study was lower. Overall, garadacimab demonstrated low irritant potential in animals and thus, the potential for local intolerance limited in humans.

Antigenicity

No dedicated antigenicity studies were conducted. Treatment-related antibody formation also did not appear to significantly impact garadacimab serum concentrations nor the toxicity profile. While garadacimab is a humanised antibody and the risk of a hypersensitivity reaction is low, given its derivation, the potential for hypersensitivity in patients with pre-existing cross-reactive antibodies remains plausible.

Immunotoxicity

Immunotoxicity and immunocompetence was assessed in the repeat-dose toxicity studies in mice and monkeys. Complement activation (C3a), cytokines, immunophenotyping or C-reactive protein (CRP) analysis, as well as pathological examination of lymphoid organs revealed no garadacimab related adverse effects of toxicological significance, with the exception of the ADA-associated immunological reaction.

Impurities

The proposed specifications for impurities in the drug substance have been adequately qualified.

Paediatric use

No juvenile toxicity studies were conducted with garadacimab. The paediatric investigation plan (PIP) agreed by EMA indicated nonclinical studies with garadacimab demonstrated an adequate safety profile and support clinical studies, including adolescents and children. This is in general concordance with the nonclinical findings of the current submission.

Recommendations following the nonclinical evaluation

- The data are adequate and support the safety of garadacimab.
- TGA concurs with the major findings and conclusions of the Swissmedic Nonclinical Assessment Report.
- There are no nonclinical objections to the registration of Andembry (garadacimab- and formerly Gofyxii) for the proposed indication.
- The draft Product Information document should be amended as directed.

Clinical evaluation summary

Pharmacology

Pharmacokinetics (PK)

The clinical pharmacokinetic (PK) data are limited due to the small number of patients, with only adult subjects included in the Phase 1 and Phase 2 studies. Adolescent PK data for garadacimab is restricted to 10 patients aged 17 or younger from Phase 3 Study 3002. To

address the limited clinical data, the sponsor submitted several pharmacometric analyses to better describe garadacimab's PK and inform dosing.

Study 1001, a first-in-human study, focused primarily on safety and secondarily on PK endpoints. It involved 48 healthy subjects, with 12 male adults aged 29 to 33 receiving subcutaneous (SC) doses. Plasma concentrations peaked at approximately 5 to 7 days post-injection, with a mean half-life ranging from 18 to 20 days across SC doses. The bioavailability of SC garadacimab was estimated at 49.7% when compared to intravenous (IV) doses. However, the study had limitations, including a small number of subjects and a lack of female participants and diverse demographics. The final pooled population PK/PD analysis estimated the absolute bioavailability of SC garadacimab to be lower at 38.7%, highlighting the limitation of the data to confirm the PK profile and ensure appropriate dosing across different patient populations.

The sponsor has proposed registering two injector devices for garadacimab: the CSL312 NSD and CSL312 AI. Both devices contain the same prefilled syringe with 1.2 mL of a 170 mg/mL garadacimab solution. In Study 1004, a single SC administration of 200 mg CSL312 showed comparable pharmacokinetics for $AUC_{0\text{-}inf}$ and C_{max} between the AI and NSD devices. Although the study was open-label and not designed as a bioequivalence study, the geometric mean ratios for $AUC_{0\text{-}inf}$ and C_{max} were within the bioequivalence criteria of 0.8 to 1.25. Additionally, CSL312 exposure was similar regardless of the injection site (abdomen, thigh, or upper arm).

The PK results from Study 1004 suggest that the two injector devices are comparable, which is expected given that both devices use identical pre-filled syringes of the 200 mg garadacimab formulation. The main difference lies in the assembly of the mechanical injector device. The safety and usability of the CSL312 AI device compared to the CSL312 NSD are discussed separately in the clinical evaluation report.

Population pharmacokinetics data (PopPK)

The population pharmacokinetics (PopPK) and pharmacodynamics of garadacimab were found to align with a two-compartment pharmacokinetic model and a direct-effects sigmoidal Emax pharmacodynamic model, as supported by the submitted PopPK data.

The normalised prediction distribution errors (NPDE) plots indicate good model performance. Additionally, the visual predictive check, which compares the percentiles of predicted and observed drug concentrations, suggests a good fit for the model. Lastly, the model parameters are estimated with adequate precision.

The PopPK evaluator suggested that body weight was not found to be a significant predictor of hereditary angioedema attacks in the garadacimab exposure-response analysis. Chinese ethnicity, hereditary angioedema (HAE) status, baseline serum creatinine concentration, baseline serum bilirubin concentration and baseline serum alanine aminotransferase (ALT) activity are seen to have no impact on garadacimab clearance of $AUC_{ss\text{-}tau.}$

The pharmacometric analyses provides support for the efficacy of garadacimab at a dose of 400 mg SC (loading dose) followed by 200 mg SC monthly. Simulations from the exposure-response model suggest that 75% of patients will achieve a 90% relative risk reduction in hereditary angioedema attacks using a garadacimab dose of 400 mg SC (loading dose) followed by 200 mg SC monthly. The interquartile range of garadacimab exposure from this dosing regime is about 7500-15000 µg*h/mL (AUC_{ss_tau}), while the exposure threshold required to achieve a 90% relative risk reduction in hereditary angioedema attacks was 7640 µg*h/mL (on average).

The simulated garadacimab exposure was found to be ~30% higher adolescents than adults. The exposure-response report did not include an analysis of garadacimab safety, so it is not possible

to assess the impact of the differences in exposure between adolescents and adults on adverse drug events.

Pharmacodynamics (PD)

The limited clinical pharmacodynamic data support dose-dependent inhibition of FXIIa-mediated kallikrein activity following administration of garadacimab. The sponsor has submitted PopPK, PD and ER analyses to further predict the dose-dependent nature of this inhibition and inform choice of dosing.

The Delegate noted that Garadacimab absorption was assessed in both healthy subjects (with IV and SC formulations) and patients with HAE. However, the data are significantly limited due to small sample sizes and the inclusion of only adult subjects in early-phase studies, which restricts the generalizability of the findings. Study 1001 demonstrated acceptable PK parameters, but its conclusions are constrained by the small, non-diverse cohort, lacking female participants and broader demographic representation. Subsequent studies, particularly Study 1004, confirmed the comparability of two injector devices and garadacimab exposure was also similar after SC administration to the abdomen, thigh, or upper arm.

The clinical studies and PopPK analysis indicate that garadacimab has a low volume of distribution, suggesting it remains primarily within the blood volume. This finding aligns with expectations for a monoclonal antibody.

The clinical evaluation indicates that garadacimab exposure ($AUC_{0\text{-}inf}$ and C_{max}) after a single dose appears dose-proportional for IV administration. For SC administration, while the $AUC_{0\text{-}inf}$ increases appeared dose-proportional, the C_{max} increases were less than dose-proportional. This suggests that garadacimab's PK behave differently depending on the route of administration.

The PopPK analysis confirmed that garadacimab's PK was dose-proportional within the analysed dose range, which is consistent with expectations for a monoclonal antibody.

No accumulation is expected with monthly 200 mg SC administration of garadacimab. Steady-state is achieved after the first dose when using a regimen of a 400 mg (2 × 200 mg) SC loading dose followed by 200 mg SC every month (Q1M). Additionally, the presence of anti-drug antibodies (ADA) does not appear to impact the PK of garadacimab.

The lower estimated bioavailability for SC administration underscores the necessity for further data to validate these findings and ensure appropriate dosing across diverse patient populations. Continuous monitoring of safety and usability is essential to optimise garadacimab clinical use, given these significant limitations.

Clinical efficacy

Efficacy data were provided in the single pivotal Phase 3 Study 3001, and ongoing, open-label Phase 3b extension Study 3002.

Study 3001

The pivotal study 3001 was a double-blind, randomised, placebo-controlled multicentre study designed to evaluate the efficacy of subcutaneous (SC) administration of CSL312 as a prophylactic treatment to prevent HAE attacks. The study enrolled subjects aged 12 years and older with confirmed C1-INH HAE and a history of recurrent attacks, excluding those with HAE type 3. A total of 64 subjects were randomised, with 39 receiving CSL312 and 25 receiving a placebo. Given the rarity of the disease, the sample size is notable. Among the participants, six were adolescents (four receiving CSL312 and two receiving a placebo).

All CSL312 subjects received a loading dose of 400 mg followed by monthly doses of 200 mg. The majority of the study population had HAE type 1, with a significant proportion first diagnosed at 17 years of age or younger and having a history of laryngeal attacks. Most patients were female, with a mean age of 41.2 years. Baseline demographics and disease characteristics were similar between the CSL312 and placebo groups.

The study population for the garadacimab arm included slightly more female subjects compared to the placebo arm (61.5% versus 56%) and was slightly older, with a mean age of 43.3 years compared to 37.8 years in the placebo arm. The relatively small study population was stratified by age (adolescents vs adults) but not by gender. Most patients were White, with Asian (Japanese) subjects representing 10% in the garadacimab arm and 8% in the placebo arm. Most patients had Type 1 C1-INH HAE, with 12.5% having Type 2, balanced between the arms, reflecting the general population proportions. More than half of the subjects had a history of laryngeal attacks, with a higher proportion in the placebo arm (68%) compared to the garadacimab arm (53.8%).

While the majority of patients (89.1%) had a family history of HAE, it is unclear how many patients without a family history had disease onset after age 30. About one-third of subjects used routine prophylaxis during the three months before screening, more in the garadacimab arm (35.9%) than in the placebo arm (28%), but no data on the response to previous prophylaxis were provided. The time-normalized number of HAE attacks during the three months before screening or start of prophylaxis was balanced between the arms, although with large standard deviations.

The primary location of attacks was mainly cutaneous and abdominal, with similar proportions between the arms. The data from the run-in period confirmed the screening/pre-prophylaxis data within each arm, though the mean rates in the placebo group were slightly lower compared to screening values. The monthly rates during the run-in period were somewhat lower in the placebo arm compared to the garadacimab arm.

One of the stratification factors for adults was the baseline attack rate, ensuring inclusion of patients with different baseline rates to cover the broad target population, though baseline data by stratification group were not shown. Data on on-demand medications for HAE attacks were presented cumulatively, and data on prohibited medications were not provided. The number of subjects analysed did not follow the intention-to-treat (ITT) principle as pre-specified in the protocol, with two subjects from the placebo group excluded from the ITT analysis set. The primary endpoint calculation excluded subjects with less than 30 days of observation time, conflicting with the ITT principle and the statistical analysis plan (SAP) definition. No premature unblindings were reported.

Treatment compliance in the pivotal study 3001 was notably high, with 100% of CSL312 subjects and 88% of placebo subjects receiving all six injections during the treatment period. Overall, 60 subjects (93.8%) completed the study, and 57 subjects (89.1%) continued into the extension Study 3002.

The Delegate noted the randomisation scheme and blinding/unblinding procedures for the study 3001 were well-documented, employing a fixed-block randomization scheme controlled by centralized interactive response technology (IRT). Subjects were stratified by age and baseline attack rate, though the rationale for using baseline attack rate as a stratification factor exclusively for adults is unclear.

The study design is generally acceptable and comparable to other approved treatments for the same condition. However, the justification for selecting a single dose (200 mg SC monthly) based on Phase 2 trial results and E-R model outcomes requires further elaboration, particularly

regarding the optimal inhibition of FXIIa-mediated kallikrein activity and its correlation with attack frequency.

The implementation of a loading dose (200 mg SC) in Study 3001, supported by population PK and ER modelling, is intended to provide immediate protection from HAE attacks by rapidly achieving steady-state PK exposures. Despite this, the study design would benefit from the inclusion of an active comparator arm to better contextualize the results, especially in light of existing treatments such as lanadelumab.

The eligibility criteria are broadly acceptable, but the exclusion of adolescents using routine prophylaxis lacks sufficient justification. Additionally, the accuracy and reliability of attack documentation for subjects previously on prophylactic therapy are not clearly addressed. The indication should be refined to focus on patients with recurrent attacks, as those with rare or sporadic attacks were not included in the study, leaving their benefit-risk profile undetermined. Furthermore, while acquired angioedema due to C1-INH deficiency was an exclusion criterion, the methodology for excluding this condition in all enrolled patients requires justification.

The primary endpoint, the time-normalised number of HAE attacks per month, showed a statistically significant reduction in the CSL312 group compared to the placebo group (0.27 vs. 2.01, $p < 0.001$). The supplementary analysis in the PP Analysis Set and sensitivity analysis using a Poisson model were consistent with the primary analysis.

There was a statistically significant reduction of 86.51% in the relative difference in the means of time-normalised number of HAE attacks per month in the CSL312 arm compared to the placebo arm ($p < 0.001$). Additionally, a significantly higher proportion of subjects in the CSL312 arm were attack-free during the first three months of treatment compared to the placebo group (71.8% vs. 8.3%, $p < 0.001$).

While the Subject's Global Assessment of Response to Therapy (SGART) was a secondary endpoint tested as part of the hierarchical testing procedure, the Angioedema Quality of Life (AE-QoL) assessment, considered an exploratory endpoint, is of greater clinical relevance. This is because AE-QoL is a validated tool for assessing the impact of angioedema on patients' quality of life.

During the treatment period, 94.9% of CSL312 subjects were responders, experiencing a ≥ 50% reduction in time-normalised HAE attacks compared to the run-in period. In contrast, 33.3% of placebo subjects were responders. Notably, 61.5% of CSL312 subjects were attack-free during the six-month treatment period, compared to none in the placebo group. Additionally, there were reductions in the mean time-normalised number of moderate to severe HAE attacks per month and the number of attacks requiring on-demand treatments in the CSL312 group compared to placebo. These secondary endpoints, while not distinct from the primary endpoint, are considered clinically meaningful benefits for CSL312.

Exploratory analyses of AE-QoL data were favourable for CSL312, with a higher proportion of subjects in the CSL312 arm achieving a minimal clinically important difference (≥ 6-point change) in the total score (87.9% vs. 55%) from Day 1 to Day 182 of the study. Pre-specified subgroup analyses for the primary and two secondary endpoints were conducted for Japanese subjects only (n = 6). However, efficacy data for adolescent subjects were not presented.

The Delegate noted the primary endpoint for the garadacimab study is acceptable and aligns with the primary endpoints (PEPs) used in Phase 3 studies of other products approved for routine prophylaxis of HAE attacks.

A significant issue is that the primary endpoint was not calculated for subjects with less than 30 days of observation time during the treatment period. This approach is not consistent with the ITT principle and contradicts the ITT definition proposed in the SAP, which states that all

randomized subjects should be included in the primary analysis set based on their randomized treatment, regardless of the treatment received.

The primary analysis using a two-sided Wilcoxon test demonstrated that garadacimab 200 mg administered subcutaneously once a month significantly reduced the time-normalized number of HAE attacks per month compared to placebo ($p < 0.001$). This finding is supported by a sensitivity analysis of the primary endpoint, adjusted for baseline attack rate using the Poisson model (should have been preferred method), which showed an 89.211% reduction in the garadacimab arm compared to placebo (95% CI: -95.2315, -75.5876). This method aligns with those used for other approved HAE treatments, such as lanadelumab.

Out of 65 randomized subjects (39 in the garadacimab arm and 26 in the placebo arm), only 63 were considered evaluable for the primary efficacy analysis. One subject was excluded for withdrawing consent before the first study treatment administration, and another was excluded because their treatment period was less than 30 days (29 days); both subjects were in the placebo arm. This approach is not fully consistent with the ITT principle.

The secondary endpoints further support the efficacy of garadacimab over placebo, although some endpoints are not independent. Garadacimab showed better results in terms of the rate of responders (defined as a reduction of at least 50%) and the rate of attack-free patients after three months of treatment. Considering slight differences in baseline attack rates, the reduction in attack rate compared to the Run-in period is particularly relevant, with mean (SD) and median values for the garadacimab arm at 90.67 (22.43) and 100.00%, versus 20.21 (42.66) and 8.45% for the placebo arm after six months of treatment.

The percentage of attacks requiring on-demand treatment was slightly lower in the garadacimab group, and the time-normalized number of on-demand treated attacks was significantly lower than in the placebo arm (mean (SD) and median: 0.23 (0.663) and 0.00 for garadacimab vs. 1.86 (1.412) and 1.35 for placebo). Additionally, both the percentage and the time-normalized number of moderate or severe HAE attacks were lower with garadacimab compared to placebo.

The time-normalised number of attacks remained consistent within each arm when comparing the first three months to the second three months of the study, indicating both the rate consistency in the placebo arm and the early efficacy of garadacimab, which was maintained throughout the treatment period. The Kaplan-Meier curve for time-to-first HAE attack after day 1 shows a significant difference between the two arms, with separation occurring from the first week of treatment.

No subgroup analysis other than for Japanese subjects has been presented. Although the use of prohibited concomitant medication was considered an intercurrent event, the relevant data were not provided.

Study 3002

Study 3002 is an ongoing, open-label, single-arm study designed to assess the long-term safety of CSL312 for the prophylaxis of HAE, with efficacy as a secondary objective. At the time of the interim analysis (IA2), the median duration of the efficacy evaluation period was 13.83 months. Due to the open-label, single-arm design and heterogeneous study population, limited conclusions regarding efficacy can be drawn. However, the study included 36 of the 38 subjects who completed the CSL312 arm of Study 3001. As of the IA2 data cut-off, the mean time-normalised number of HAE attacks per month for these subjects was 0.11, suggesting the maintenance of the CSL312 treatment effect observed during the 26-week treatment period of the pivotal study.

The study also included 10 adolescent subjects, five of whom rolled over from Study 3001. At IA2, the mean time-normalised number of HAE attacks per month for adolescents was 0.09, with

a mean percentage reduction in attacks of 91.49% compared to the run-in period. Subjects with nC1-INH HAE were excluded from Study 3001, but six subjects with FXII/PLG HAE were included in Phase 2 Study 2001. The dosage regimen used in these subjects did not align with the proposed registration dosage for CSL312. Four of the six subjects with FXII/PLG HAE were non-responders in Study 2001. The two FXII HAE subjects who were responders rolled over into Study 3002 and did not experience HAE attacks as of the IA2 data cut-off. Overall, the data are insufficient to support the efficacy of CSL312 in subjects with nC1-INH HAE.

The Delegate noted the results indicate that garadacimab maintains its effect in previously treated patients and shows efficacy in treatment-naïve subjects. However, due to the open-label design and descriptive nature of Study 3002, its results are considered supportive rather than definitive. The pooled analysis of Studies 3001 and 3002 supports the durability of garadacimab's effect observed in individual studies, despite some limitations.

Clinical safety

The main safety data for CSL312 200 mg were provided in the pivotal Phase 3 randomised double-blind, placebo-controlled Study 3001 and the ongoing single-arm, open-label extension Study 3002. In Study 3001, the median duration of exposure to study treatment was comparable for CSL312 and placebo treatment arms (0.498 and 0.496 years, respectively). Median exposure to CSL312 was 13.83 months in Study 3002, with 119 (73.9%) subjects having ≥ 12 months of exposure as of the data cut-off for IA2.

In Study 3001, a comparable proportion of subjects in each treatment arm experienced at least one treatment-emergent adverse event (TEAE) (64.1% CSL312, 60.0% placebo). The most common TEAEs were upper respiratory tract infection, headache, and nasopharyngitis. One unrelated severe serious adverse event (SAE) of hereditary angioedema occurred in a CSL312 subject. In Study 3002, TEAEs were experienced by 83.9% of subjects, most commonly COVID-19, nasopharyngitis, influenza, and injection site erythema. Severe TEAEs were reported for 5.6% of subjects with no trends in the types of events. The incidence of SAEs was low (1.9%) with no events related to CSL312.

Injection site reactions (ISRs) were reported for 5.1% of CSL312 subjects and 12.0% of placebo subjects in Study 3001. In Study 3002, 11.8% of subjects experienced ISRs. ISRs were the most common treatment related TEAEs in both studies, with injection site erythema being the most frequent. Most ISRs were mild, and only one subject discontinued CSL312 in Study 3002 due to a moderate ISR. No severe or serious ISRs were reported. The pooled analysis for CSL312 200 mg showed consistent safety data, with no increase in the frequency of TEAEs, treatment related TEAEs, severe AEs, or SAEs for subjects with longer-term exposure.

In Study 3001, potential adverse events of special interest (AESI) included abnormal bleeding events, thromboembolic events (TEE) and severe hypersensitivity including anaphylaxis. No subjects experienced AESIs during the study. In Study 3002, 16.1% of subjects experienced potential AESI in the hypersensitivity / anaphylaxis category, with 3.1% related to treatment. Bleeding events were reported in 6.2% of subjects, none related to study treatment. No thromboembolic events were reported in either study. There were no deaths or TEAEs leading to discontinuation in Study 3001, and two subjects discontinued due to TEAEs in Study 3002.

The sponsor proposes to register garadacimab 200 mg for use as a prefilled syringe (PFS) with a needle safety device (NSD) and as an autoinjector. The CSL312 NSD was used in Studies 3001 and 3002, with subjects initially self-administering under supervision and later at home following training. No use errors or device malfunctions were reported in Study 3001, and one device malfunction was reported in Study 3002. In Phase 1 Study 1004, injection site related

TEAEs were higher for the autoinjector group compared to the NSD group. There were no user-testing or human factor data provided for the proposed autoinjector.

The Delegate noted no deaths were reported, and the number of SAEs was low, with all assessed as unrelated to the treatment. There was only one AESI related to abnormal bleeding, which was also deemed unrelated. The most common TEAEs were injection site reactions, classified as adverse drug reactions (ADRs).

However, uncertainties remain regarding the total number of bleeding events (both micro and macro bleeding) that should be classified as AESIs. There is a mechanistic plausibility for garadacimab to prolong activated partial thromboplastin time (aPTT), although this effect is not currently known to be dose-dependent and does not seem to be associated with an increased risk of severe bleeding. Concerns have been raised to better clarify these aspects and to understand the potential risks associated with garadacimab treatment, particularly in patients taking concomitant medications that may impact coagulation.

Risk management plan evaluation summary

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 2. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 2: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	-	-	-	-
Important potential risks	Severe hypersensitivity including anaphylaxis	ü*		ü†	
Missing information	Safety in pregnancy and lactation	ü		ü †	

*Follow-up questionnaires
† CMI package insert (PI to be included)

RMP evaluator recommendations regarding conditions of registration

The Andembry EU-Risk Management Plan (RMP) version 0.3 (dated 16 May 2024, DLP 16 June 2023), with Australia Specific Annex (version 1.1, dated 14 June 2024), included with submission PM-2023-05358-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and Andembry as a new biological entity should be included in the Black Triangle Scheme. The following wording is recommended for the condition of registration:

- Andembry (garadacimab) is to be included in the Black Triangle Scheme. The PI and CMI for Andembry must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis - Delegate's considerations

The sponsor has submitted a Type A application for Andembry to be used for routine prevention of recurrent hereditary angioedema (HAE) attacks in adult and paediatric patients (aged 12 years and older).

Hereditary angioedema (HAE) is a rare, autosomal dominant condition primarily caused by mutations in the SERPING1 gene, leading to a deficiency in C1-esterase inhibitor (C1-INH). This deficiency disrupts the kallikrein-bradykinin cascade, resulting in excessive bradykinin production, which increases vascular permeability and triggers unpredictable and painful swelling attacks. These attacks can affect various body parts, including the extremities, face, and airway, posing significant risks, particularly laryngeal attacks, which occur in over 50% of patients during their lifetime.

Garadacimab is a fully human IgG4 lambda recombinant monoclonal antibody that targets activated coagulation factor XII (FXIIa), aiming to inhibit the inflammatory bradykinin-producing pathway. By preventing the activation of prekallikrein to kallikrein, garadacimab seeks to reduce bradykinin generation and, consequently, the frequency of HAE attacks. It is administered subcutaneously and has received orphan designation for the treatment of HAE.

HAE has no cure, but various therapeutic strategies are available to manage the condition. These include treatments for acute attacks to lessen their severity and duration, short-term prophylaxis to mitigate the risk of attacks triggered by specific events, and long-term prophylactic therapy aimed at preventing attacks altogether.

On demand treatment options registered in Australia for acute attacks include C1-esterase inhibitors (e.g. Berinert IV) and the bradykinin B2 receptor antagonist icatibant. The plasma kallikrein inhibitor ecallantide is approved in the USA for acute treatment of HAE however is not registered in Australia.

The WAO/EAACI recommend use of plasma-derived C1-inhibitors, the anti-plasma kallikrein monoclonal antibody lanadelumab and the plasma kallikrein inhibitor berotralstat as first-line prophylaxis. Berinert SC (CSL Behring) and lanadelumab (Takhzyro, Takeda Pharmaceuticals Australia Pty Ltd) are approved by the TGA for use as long-term prophylaxis for patients with HAE with C1 esterase inhibitor deficiency. Both products are administered by subcutaneous injection and may be self-administered by the patient/caregiver. Berotralstat is not registered in Australia.

The proposed indication is not in line with already approved routine preventive therapies (lanadelumab) but the inclusion of adolescents is considered acceptable in the light of existing scientific and therapeutic knowledge. Clinical pharmacology data supporting the submission included 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 AI with the NSD, 1 completed phase 2 study (in subjects with HAE), and 2 phase 3 studies (in subjects with HAE). Overall PK has been

adequately characterised, both in healthy subjects and in target population without posing any substantial issues.

Although some subjects treated with garadacimab tested positive for anti-drug antibodies (ADA), the study did not measure the presence of neutralizing antibodies in these individuals. Consequently, the clinical relevance of the ADA findings remains uncertain. Further research on neutralizing antibodies is needed to clarify their impact on treatment outcomes.

Overall, the submitted PopPK, PopPKPD and ER models were adequately developed and are considered appropriate for their intended use. There is no effect on exposure of garadacimab in HAE patients with renal impairment and hepatic impairment. No evidence of a clinically relevant effect of ethnicity is evident from available data, both in terms of PK and PD.

Formal PK studies in the elderly or adolescent populations were not conducted. The effect of age was investigated using PopPKPD and ER analysis of pooled study data.

The PK of garadacimab in adolescents aged 12 to 17 years aligns with that of the adult population. Since the pathophysiology and clinical manifestations of HAE are similar in both adolescents and adults, treatment approaches, including long-term management, are comparable for these age groups. Additionally, when considering body size, the distribution of therapeutic proteins is not expected to differ significantly between adults and adolescents. Therefore, given the similarities in disease characteristics and the population pharmacokinetic modelling indicating that age does not affect the PK of garadacimab, no dose adjustments are necessary for patients aged 12 years and older.

Body weight was identified as an important covariate in the PopPK model for subjects aged ≥ 12 years; however, based on the ER analysis, no difference in monthly attack rate among subjects treated with garadacimab was observed across the weight range. Therefore, this difference is not considered to be clinically relevant, and no dose adjustments are recommended based on weight.

No drug-drug interaction (DDI) studies were performed. However, as a monoclonal antibody, it is not expected to have interactions related to drug metabolism with other medications.

Garadacimab's mode of action has been well- characterised, particularly regarding its ability to engage its target and suppress FXIIa-mediated kallikrein activity, with effects that appear to be dose-dependent. However, there is currently no established link between FXIIa inhibition and the drug's effectiveness in preventing HAE attacks. As a result, the sponsor has derived recommended dosing regimen from the clinical evidence obtained from the pivotal trials. It's also important to note that garadacimab's pharmacological effects may not be adequate for controlling HAE attacks in patients with genetic variants that influence metabolic pathways beyond FXII-mediated bradykinin production. Therefore, physicians should be informed to be cautious when treating specific patient subgroups.

The pivotal Study 3001 (a phase 3, multicentre, double-blind, randomized, placebo-controlled, parallel-arm, 26-week study) met its primary endpoint and the effect of the treatment is clinically relevant for HAE patients with C1 esterase inhibitor deficiency. It was further supported by the results from key secondary endpoints (the percentage reduction in the means of the time-normalized number of HAE attacks for the 6-months, the number of subjects who do not experience a HAE attack in the first 3 months, the percent of subjects with good or excellent responses to the SGART at the end of Treatment Period, Day 182) and other additional efficacy endpoints provided. Moreover, results from the longer-term open-label trial 3002 and pooled analyses indicate that the efficacy of the treatment is maintained over time.

The available data of patients with nC1INH HAE treated with garadacimab showed conflicting evidence and do 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. The Advisory Committee on Medicines (ACM) advice will be sought on this issue.

Even though the results of adolescents in the garadacimab arm were similar with the adults, the number of adolescents in the Study 3001 (6 in total) is very limited and preclude any definite conclusion.

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. However, s31 response demonstrated significant and reliable associations with measures of clinical outcomes, clinicians' evaluations, and to a less extent with PRO measures.

Patients with clinically significant bleeding issues, such as those with coagulopathy, thrombotic disorders, or major comorbidities, were excluded from the study. However, in the clinical trials, garadacimab was administered to HAE patients who were also taking medications like aspirin, ticagrelor, and enoxaparin, with no reported bleeding events. Additionally, in a COVID-19 study, 55 out of 58 patients treated with garadacimab were on haemostatic-affecting medications, and there was no significant difference in bleeding events compared to those receiving a placebo. Nonetheless, this subgroup will be closely monitored in the post-marketing phase to ensure ongoing safety.

Study 3002 is an ongoing phase 3b multicentre, open-label, single-arm trial primarily focused on assessing the long-term safety of garadacimab, with efficacy as a secondary objective. This study aims to evaluate the safety and effectiveness of garadacimab in preventing HAE attacks in patients who have previously participated in two earlier studies (one phase 2 and one phase 3) as well as in newly enrolled participants.

Two interim analyses have been conducted to date: the first data cut-off for all subjects was on February 13, 2023, and the second, focusing specifically on adolescents, occurred on May 22, 2023. This ongoing study is crucial for understanding the long-term implications of garadacimab treatment in HAE management. Additionally, 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.

The safety profile of garadacimab, while based on a limited data set, appears to be adequately characterised. Notably, there have been no reported deaths and only a few serious adverse events (SAEs), with just one case of abnormal bleeding classified as an adverse event of special interest (AESI), all deemed unrelated to the treatment. Long-term safety data from the open-label Study 3002 are still pending.

Garadacimab is administered subcutaneously, and the most common TEAEs are injection site reactions, which are categorised as adverse drug reactions (ADRs). There is a plausible mechanism for prolonged activated partial thromboplastin time (aPTT), but this does not currently appear to correlate with an increased risk of severe bleeding. However, some uncertainties regarding bleeding events remain. Importantly, there is no current evidence suggesting that garadacimab poses additional risks for patients with pre-existing bleeding disorders.

Outcome

The efficacy of garadacimab for the claimed indication [with C1-INH HAE (C1-esterase inhibitor deficiency or dysfunction)] has been demonstrated, showing superiority over placebo.

Treatment significantly reduced the rate of HAE attacks and increased the number of attack-free patients, indicating a clinically meaningful benefit. The safety profile appears generally favourable; however, there are important considerations regarding the target population and specific safety concerns, particularly related to its impact on the coagulation system.

Additionally, the manufacturing process for the CSL312 200 mg has some unresolved sterile filtration step to improve sterility assurance, further supporting documentation are needed to address the quality concerns raised. As a result, some uncertainties remain at this stage of the decision process.

Advisory Committee on Medicines considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following. The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Andembry is indicated for routine prevention of recurrent hereditary angioedema (HAE) attacks in adult and adolescent patients (aged 12 years and older)*

Specific advice to the delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. *Should the indication, if recommended, be modified to the "Andembry is indicated for routine prevention of recurrent hereditary angioedema (HAE) attacks in adult and paediatric patients (aged 12 years and older) with C1-INH HAE (C1-esterase inhibitor deficiency or dysfunction)"*

a. ***Does the ACM agree not to restrict the treatment to the adult population even though number of adolescent subjects in the Phase 3 studies were small?***

b. ***Should we restrict the indication to C1-esterase inhibitor deficiency or dysfunction only?***

The ACM advised that the indication not be limited to adult patients, and that the indication should reflect the use of garadacimab in the 3001 Study. The ACM acknowledged that despite the small number of adolescents in the trial population, the PK, efficacy and safety data are consistent with the respective data for adults and supportive of the use of garadacimab in adolescent populations. Additionally, the ACM noted that the comparable drug lanadelumab is approved for adolescents, and the equivalent pivotal trials had small numbers of adolescent participants.

The ACM discussed the inclusion of trial participants with Type III HAE in the 3001 Study, and the implications of their inclusion in the indication. Comparable products have historically excluded Type III HAE from their trial populations. The ACM noted that the data available for efficacy in Type III HAE is limited, but overall, were comfortable with its inclusion in the indication when the genetic defect would be expected to affect the kallikrein pathway.

2. Does the ACM have concerns over the use of garadacimab in patients with history of clinically significant bleeding due to coagulopathy, thrombotic disorders or with concomitant anticoagulant use?

The ACM discussed the known impact of garadacimab on coagulation parameters. The ACM acknowledged that patients particularly predisposed to bleeding or clotting disorders may be at greater theoretical risk of major bleeding with garadacimab, but it is unclear if this translates to

clinical risk. In the absence of sufficient data, the ACM advised that risks associated with garadacimab in patients with bleeding or clotting disorders, or concomitant anticoagulant use, would be well managed by experienced clinicians likely to prescribe garadacimab. Additionally, the ACM advised that the PI should appropriately reflect these risks.

3. *Does the ACM consider that the safety of garadacimab in the proposed new indication is sufficiently well characterised and communicated in the PI?*

The ACM held the opinion that despite the small numbers in the trial population, the safety data presented no concerns, and the risks present were sufficiently articulated in the PI and the proposed indication.

4. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM noted that use of the term 'paediatric' in the indication could lead to inadvertent inappropriate prescribing. The ACM advised replacing 'paediatric' with 'adolescent' to reduce this risk and be more specific.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Andembry is indicated for routine prevention of recurrent hereditary angioedema (HAE) attacks in adult and adolescent patients (aged 12 years and older).*

Regulatory decision (outcome)

Based on a review of quality, safety, and efficacy, the TGA decided to register Andembry (garadacimab) 200 mg solution for injection in pre-filled syringe with needle safety device, or pre-filled pen (auto-injector), indicated for:

> *Andembry is indicated for routine prevention of recurrent hereditary angioedema (HAE) attacks in patients aged 12 years and older with C1-INH HAE (C1-esterase inhibitor deficiency or dysfunction).*

Specific conditions of registration

- Andembry (garadacimab) is to be included in the Black Triangle Scheme. The PI and CMI for Andembry must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Andembry EU-Risk Management Plan (RMP) version 0.3 (dated 16 May 2024, DLP 16 June 2023), with Australian Specific Annex version 1.1 (dated 14 June 2024), included with submission PM-2023-05358-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier, who is the recipient of the approval, and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such

reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months.

If the sponsor wishes, the six-monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #