Report on the Deliberation Results

February 3, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Andembry S.C. Injection 200 mg Pens
Non-proprietary Name	Garadacimab (Genetical Recombination) (JAN*)
Applicant	CSL Behring K.K.
Date of Application	February 26, 2024

Results of Deliberation

In its meeting held on January 30, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is classified as a biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

** Japanese Accepted Name (modified INN)*

Review Report

January 9, 2025
Pharmaceuticals and Medical Devices Agency

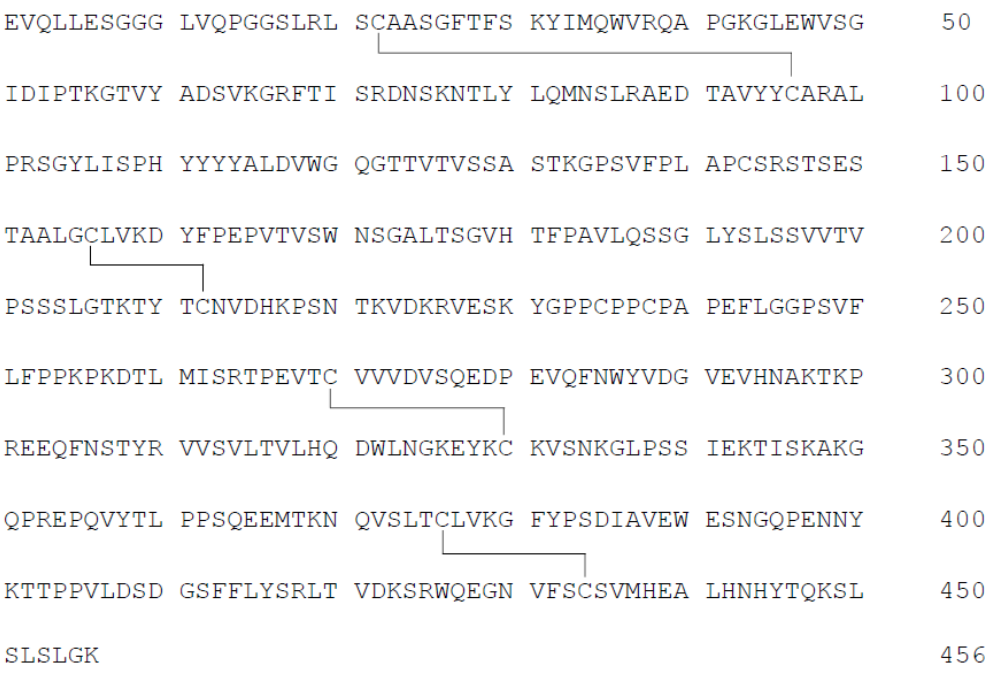
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Andembry S.C. Injection 200 mg Pens
Non-proprietary Name	Garadacimab (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	February 26, 2024
Dosage Form/Strength	Injection: Each syringe contains 200 mg of garadacimab (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Garadacimab is a recombinant anti-activated blood coagulation factor XII (FXIIa) monoclonal antibody derived from human IgG4, whose amino acid residue in the H-chain is substituted at 1 position (S237P). Garadacimab is produced in CHO cells. Garadacimab is a glycoprotein (molecular weight: ca.149,000) composed of 2 H-chains (γ4-chains) consisting of 456 amino acid residues each and 2 L-chains (λ-chains) consisting of 215 amino acid residues each.

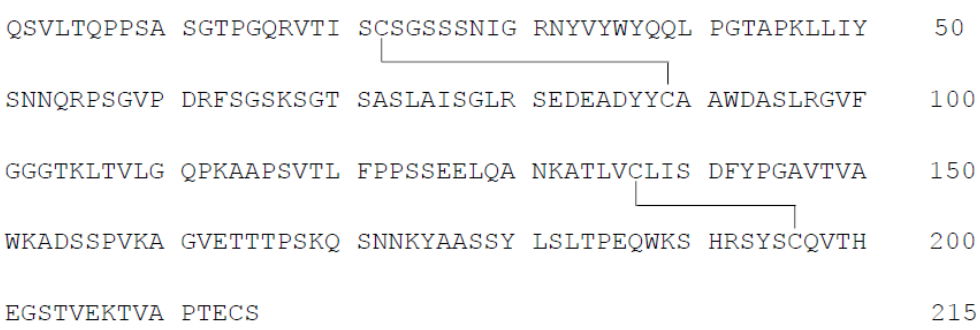
Structure

Amino acid sequence:

H-chain



L-chain



Intra-chain disulfide bonds: solid lines in the figure

Inter-chain disulfide bonds: H-chain C143–L-chain C214, H-chain C235–H-chain C235, and H-chain C238–H-chain C238

Pyroglutamic acids, partial: H-chain E1 and L-chain Q1

Glycosylation site: H-chain N306

Partial processing: H-chain K456

Main proposed carbohydrate structure

Gal, Galactose; GlcNAc, *N*-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula: $C_{6470}H_{10004}N_{1724}O_{2022}S_{42}$ (protein moiety, 4 chains)
(H-chain) $C_{2238}H_{3455}N_{589}O_{685}S_{16}$
(L-chain) $C_{997}H_{1551}N_{273}O_{326}S_5$
Molecular weight: Ca. 149,000

Items Warranting Special Mention None
Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prophylaxis of acute attacks of hereditary angioedema, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

The safety, etc. of the product in clinical practice should be further investigated in post-marketing surveillance.

Indication

Prophylaxis of acute attacks of hereditary angioedema

Dosage and Administration

The usual dosage for adults and children aged 12 years or older is 400 mg of garadacimab (genetical recombination) administered subcutaneously as the initial dose, followed by doses of 200 mg administered subcutaneously once a month.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 23, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Andembry S.C. Injection 200 mg Pens
Non-proprietary Name	Garadacimab (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	February 26, 2024
Dosage Form/Strength	Injection: Each syringe contains 200 mg of garadacimab (genetical recombination).
Proposed Indication	Long-term prophylaxis of attacks of hereditary angioedema
Proposed Dosage and Administration	The usual dosage for adults and children aged 12 years or older is 400 mg of garadacimab (genetical recombination) administered subcutaneously as the initial dose, followed by doses of 200 mg administered subcutaneously once a month.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The active ingredient of Andembry S.C. Injection 200 mg Pens is garadacimab (genetical recombination) (hereinafter referred to as garadacimab). Garadacimab is a recombinant human IgG4/λ monoclonal antibody that inhibits activated blood coagulation factor XII (FXIIa) and was discovered by CSL Limited (Australia).

Hereditary angioedema (HAE) is a designated intractable disease under the category of "primary immunodeficiency syndrome" (Designation No. 65, Ministerial Notification No. 393 of the Ministry of Health, Labour and Welfare dated October 21, 2014). It is a congenital disease that presents with repeated sudden angioedema attacks (HAE attacks) involving various areas of the body including the skin, larynx, and gastrointestinal tract. HAE is caused by a genetic abnormality of complement C1-esterase inhibitor (C1-INH) and is classified into the following types: HAE Type 1 and HAE Type 2 associated with C1-INH deficiency and dysfunction (C1-INH HAE), respectively, and HAE Type 3, which is associated with normal blood concentration and function of C1-INH, i.e., no C1-INH abnormalities. For HAE Type 3 (nC1-INH HAE), mutations in non-C1-INH genes (coagulation factor XII [*FXII*], plasminogen [*PLG*] gene, etc.) have been identified. The prevalence of C1-INH HAE (HAE Type 1 and HAE Type 2) is reported to be 1 in 50,000 people, and of these, HAE Type 1 accounts for approximately 85%, and HAE Type 2 for approximately 15% ("Guideline for hereditary angioedema (HAE) by the Japanese Association for Complement Research: The 2023 revision and update (*Journal of the Japanese Association for Complement Research*. 2023;60:103-131)" [hereinafter referred to as "Japanese guideline"]). On the other hand, the prevalence of nC1-INH HAE (HAE Type 3) is unknown (*Allergy Asthma Proc*. 2024;45:147-157).

Bradykinin is considered to be a key inflammatory mediator that causes HAE attacks. In C1-INH HAE (HAE Type 1 and HAE Type 2), C1-INH deficiency or dysfunction activates the kallikrein-kinin pathway excessively to produce bradykinin, which increases vascular permeability, resulting in angioedema as a clinical manifestation. Although information on the pathophysiology of nC1-INH HAE (HAE Type 3) is limited, there are reports suggesting that certain gene mutations may cause bradykinin-mediated angioedema (*J Clin Invest*. 2015;125:3132-3146, Japanese guideline).

HAE impacts life prognosis because it adversely affects physical function, mental health, etc. In particular, edema of the larynx may result in death due to suffocation. Therefore, appropriate treatment is needed for HAE (Japanese guideline). The treatment of HAE is roughly divided into two types: treatment at the onset of attacks and the prophylaxis of attacks. In Japan, the following drugs have been approved: icatibant acetate formulation (bradykinin B2 receptor antagonist) for treatment at the onset of HAE attacks; a human plasma-derived human C1-inactivator formulation (for intravenous injection) for treatment at the onset of HAE attacks and for the short-term prophylaxis of HAE attacks during invasive procedures; and the plasma kallikrein inhibitors berotralstat hydrochloride formulation and lanadelumab (genetical recombination) formulation, as well as a human C1-inactivator formulation (for subcutaneous injection) for the long-term prophylaxis of HAE attacks.

Upon contact with an anionic surface, the serine protease precursor FXII is activated to FXIIa, which in turn activates the blood coagulation factor XI (FXI), thereby causing fibrin formation via the intrinsic coagulation

pathway and converts prekallikrein to kallikrein thereby causing bradykinin production via the kallikrein-kinin pathway. Meanwhile, FXIIa is cleaved by kallikrein and converted to the active catalytic fragment of FXII (βFXIIa) (*Curr Opin Hematol*. 2017;24:411-418). Garadacimab binds to the catalytic domain of FXIIa and inhibits its protease activity, thereby suppressing the activation of prekallikrein to kallikrein and the production of bradykinin. The development of garadacimab was promoted with the expectation that it would prevent the acute attacks of HAE.

The clinical development of garadacimab was initiated in October 2016, and an application for marketing approval was recently filed based on the results of a global study (including Japan) and other data. As of October 2024, garadacimab has not been approved in any countries or regions.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

A Fab that specifically binds to [redacted] was selected from [redacted], and it was reconstituted into an antibody with the constant regions of the human IgG4 heavy chain and the human λ-type light chain, followed by structural optimization intended to improve the binding ability to FXIIa, etc., and a gene mutation was introduced at the hinge region of the heavy chain with the intention of ensuring a stable structure, yielding the lead antibody of garadacimab. Gene fragments, which were prepared by optimization of the base sequence, etc. of the genes encoding the lead antibody, were inserted into the expression vector to produce the gene expression construct of garadacimab. The gene expression construct was transfected into Chinese hamster ovary (CHO) cells, and the master cell bank (MCB) and working cell bank (WCB) were prepared from a clone most suitable for the manufacture of garadacimab.

The MCB, WCB, and cells cultured beyond the limit-of-*in-vitro*-cell-age (LIVCA) were subjected to characterization and purity tests in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D guidelines. As a result, genetic stability during the manufacture of garadacimab was confirmed, and none of these tests detected any viral or non-viral adventitious agents, except for endogenous retrovirus-like particles, which are commonly observed in rodent-derived cell lines.

The MCB and WCB are stored in [redacted]. The MCB [redacted], and WCB will be re-established as necessary.

2.1.2 Manufacturing process

The drug substance is manufactured through a process comprised of the following steps: expansion culture, production culture, harvesting, [redacted] chromatography, [redacted] viral inactivation, [redacted] chromatography, [redacted] chromatography, viral removal filtration, [redacted], [redacted]/filtration/filling, and testing/storage.

[redacted] viral inactivation and viral removal filtration have been defined as critical steps.

Process validation of the manufacturing process for the drug substance has been conducted on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cells, no other raw materials of biological origin, etc. are used in the manufacturing process of the drug substance.

Purity tests have been conducted on the MCB, WCB, and cells cultured beyond the LIVCA [see Section 2.1.1]. Pre-harvest unprocessed/unpurified bulk obtained on a commercial scale was subjected to bacterial endotoxin testing, microbial limit testing, mycoplasma testing, *in vitro* adventitious virus testing, minute virus of mice testing by quantitative polymerase chain reaction (qPCR), and transmission electron microscopy. None of these tests detected any viral or non-viral adventitious agents. All of these tests on the pre-harvest unprocessed/unpurified bulk, except for transmission electron microscopy, have been defined as in-process control tests.

Viral clearance testing was performed for the purification step using model viruses. The results demonstrated that the purification step has a certain level of virus clearance capacity (Table 1).

Table 1. Results of viral clearance testing

Manufacturing step	Virus reduction factor (log_{10})			
	Pseudorabies virus	Xenotropic murine leukemia virus	Minute virus of mice	Reovirus type 3
[redacted] viral inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	≥16.7	≥16.0	≥9.3	≥10.8

2.1.4 Manufacturing process development

For changes in the manufacturing process during the development of the drug substance, the comparability between pre-change and post-change drug substances has been confirmed in accordance with the ICH Q5E guideline. All phase III studies used the drug products manufactured using the drug substances manufactured by the proposed manufacturing process.

2.1.5 Characterization

2.1.5.1 Structure and characterization

The drug substance was subjected to characterization shown in Table 2.

Table 2. Characterization attributes

Primary/higher-order structure	Amino acid sequence, molecular mass, disulfide bonds, post-translational modifications ([redacted], [redacted], [redacted], [redacted], oxidation, deamidation), glycation, and higher-order structure
Physicochemical properties	Extinction coefficient, size variants, and charge variants
Carbohydrate structure	N-linked oligosaccharide profile and sialic acid
Biological properties	FXIIa binding affinity
	FcγR binding affinity (FcγRI, FcγRIIa, and FcγRIII), FcRn binding affinity, and C1q binding capacity
	FXIIa inhibitory activity, inhibition of kallikrein activation, inhibition of bradykinin production, and suppression of the blood coagulation pathway

The main investigation results of biological properties are as follows:

- Inhibition of the protease activity of FXIIa by garadacimab was confirmed based on [redacted] as the indicator.
- Inhibition of kallikrein activation by garadacimab was confirmed based on [redacted] as the indicator of the activation of prekallikrein to kallikrein using human plasma in which FXII was activated by [redacted].
- Inhibition of bradykinin production by garadacimab was confirmed by quantifying the bradykinin produced in response to kallikrein activation using human plasma with FXII that has been activated by [redacted].
- Suppression of the blood coagulation pathway was assessed by [redacted] and [redacted], and assessment confirmed that garadacimab suppresses the intrinsic coagulation pathway, but does not affect the extrinsic coagulation pathway.

2.1.5.2 Product-related substances/product-related impurities

On the basis of the results of characterization in Section 2.1.5.1, Related Substance A, Related Substance B, Related Substance C, Related Substance D, and Related Substance E were defined as product-related substances. Impurity A and Impurity B were defined as product-related impurities. Both Impurity A and Impurity B are controlled based on the specifications for the drug substance and the drug product.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, Impurity C, Impurity D, bacterial endotoxins, bioburden, Impurity E, and Impurity F were defined as process-related impurities. HCP, host cell DNA, Impurity C, and bioburden are controlled based on the specifications for the drug substance, and bacterial endotoxins are controlled based on the specifications for the drug substance and the drug product. Impurity E and Impurity D were confirmed to be adequately removed during the manufacturing process. For Impurity F, confirmation of its clearance during the manufacturing process and its control using routine tests were considered unnecessary as a result of risk assessment.

2.1.6 Control of the drug substance

The proposed specifications for the drug substance consist of content, description, identification (peptide mapping), pH, purity (size exclusion chromatography [SE-HPLC], capillary electrophoresis sodium dodecyl sulfate [CE-SDS] [[redacted]], host cell DNA, HCP, and [redacted]), [redacted], bacterial

endotoxins, microbial limit, potency (FXIIa inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of the drug substance

Table 3 shows the main stability studies of the drug substance.

Table 3. Overview of main stability studies of the drug substance

Study	Manufacturing process	No. of batches	Storage conditions	Storage period	Storage package
Long-term testing	Proposed process	1	−75°C	36 months	[redacted] with [redacted] as the contact layer
		2	−76°C/−80°C[a)]		
Accelerated testing	Proposed process	2	[redacted]°C	[redacted] months	
Stress testing	Proposed process	1	[redacted]°C	[redacted] months	
Photostability testing	Pre-application process	1	Overall illumination ≥1.2 million lux·h, and integrated near ultraviolet energy ≥200 W·h/m^2		Glass vial

a) Changed from −76°C to −80°C because the storage equipment was altered during the storage period.

In the long-term and accelerated testing, no clear changes in quality attributes were observed throughout the storage period.

In the stress testing, [redacted] tended to increase and [redacted] tended to decrease in [redacted].

Photostability testing showed that the drug substance was photolabile.

In view of the above, a shelf life of 36 months was proposed for the drug substance when stored using [redacted] with [redacted] as the contact layer at −80°C.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is an aqueous injection containing 200 mg of garadacimab per 1.2 mL in syringe (volume: 2.25 mL). Excipients contained in the drug product are L-histidine, L-arginine hydrochloride, L-proline, polysorbate 80, and water for injection. The drug product is a combination product consisting of a needled glass syringe prefilled with the drug solution and a dedicated pen-injector.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: thawing/mixing of the drug substance, [redacted], sterile filtration, sterile filling/closing, assembling, labeling/packaging/storage, and testing/storage.

[redacted], [redacted], and [redacted] have been defined as critical steps.

Process validation of the manufacturing process has been conducted on a commercial scale.

2.2.3 Manufacturing process development

For changes in the manufacturing process during the development of the drug product, the comparability between pre-change and post-change drug products has been confirmed in accordance with the ICH Q5E guideline. All phase III studies used the drug products manufactured by the proposed process were used.

2.2.4 Control of the drug product

The proposed specifications for the drug product consist of strength, description, identification (peptide mapping), osmotic pressure, pH, purity (SE-HPLC and CE-SDS [ ]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, potency (FXIIa inhibitory activity), and assay (ultraviolet-visible spectrophotometry). , , , , and have been defined as specifications for the functionality of the drug product.

2.2.5 Stability of the drug product

Table 4 shows the main stability studies of the drug product.

Table 4. Overview of main stability studies of the drug product

Study	No. of batches[a)]	Storage conditions	Storage period	Storage package
Long-term testing	3	5 ± 3°C	36 months	A glass syringe with a stainless-steel needle and a bromobutyl rubber plunger stopper
Accelerated testing	4	25 ± 2°C/60 ± 5%RH	24 months	
Stress testing	1	°C	months	
Photostability testing	1	Overall illumination ≥1.2 million lux·h, and integrated near ultraviolet energy ≥200 W·h/m^2		

a) The drug substance and the drug product were manufactured by the proposed manufacturing process.

In the long-term testing, no clear changes in quality attributes were observed throughout the storage period.

In the accelerated testing, tended to increase and tended to decrease in , tended to increase and tended to decrease in , and decreased and tended to increase in .

In the stress testing, the changes observed in accelerated testing were enhanced, and was also observed.

Photostability testing showed that the drug product was photolabile.

In view of the above, a shelf life of 36 months was proposed for the drug product when stored using a glass syringe with a stainless-steel needle and a bromobutyl rubber plunger stopper (primary packaging) in a carton at 2°C to 8°C, protected from light.

2.3 Quality control strategy

On the basis of the following investigations, control methods for quality attributes were developed by combining the in-process controls and specifications [for the control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

- Identification of critical quality attributes (CQAs):

  The following CQAs were identified based on the information obtained during the development of the drug substance and the drug product and other related information:

  CQAs of the drug substance:

  [redacted], host cell DNA, [redacted], bacterial endotoxins, bioburden, sterility, osmotic pressure, pH, description (color, clarity, appearance, and foreign insoluble matter), [redacted], viral safety, and mycoplasma

  CQAs of the drug product:

  Protein content, [redacted], bacterial endotoxins, sterility, osmotic pressure, pH, description (color, clarity, appearance, and foreign insoluble matter), insoluble particulate matter, extractable volume, [redacted], and [redacted]

- Characterization of steps

  On the basis of the risk assessment of process parameters and characterization of steps, critical process parameters that affect CQAs were identified, and acceptable control ranges for process parameters were determined.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and the drug product was controlled in an appropriate manner.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted data on the primary pharmacodynamics, in the form of results data from studies investigating the binding to FXII, FXIIa, and βFXIIa, the inhibition of FXIIa activity, the inhibition of bradykinin production, the effect on edema formation in a mouse model, etc. In addition, since FXIIa is involved in fibrin formation via the intrinsic coagulation pathway, studies on secondary pharmacodynamics were conducted to investigate the effects on thrombosis and bleeding models. The applicant submitted data on safety pharmacology, in the form of results data from studies investigating the effect of garadacimab on the respiratory system. The effect on the central nervous, cardiovascular, and respiratory systems was also investigated in repeated-dose toxicity studies in mice and monkeys [see Section 5.2]. Unless otherwise specified, pharmacodynamic parameter values are expressed using the mean or the mean ± standard deviation.

3.1 Primary pharmacodynamics

3.1.1 Binding to FXII, FXIIa, and βFXIIa (CTD 4.2.1.1.1)

Binding of garadacimab to FXII, FXIIa, and βFXIIa in various animal species was investigated by the surface plasmon resonance (SPR) method. The dissociation constants (K_D) of garadacimab for human FXII and human

βFXIIa were 55 and 0.14 nmol/L, respectively, showing that garadacimab had a higher binding affinity for βFXIIa than for FXII. Table 5 shows the binding affinity of garadacimab for FXII, FXIIa, and βFXIIa in other animal species.

Table 5. Binding affinity of garadacimab for FXII, FXIIa, and βFXIIa in various animal species (K_D: nmol/L)

	FXII	FXIIa	βFXIIa
Human	55	-	0.14
Mouse	800	0.3	0.7
Rabbit	0.3	0.1	0.4
Monkey	143	-	19

-: Not investigated.

3.1.2 Inhibition of human FXIIa (CTD 4.2.1.1.4)

The inhibitory effect of garadacimab on the protease activities of plasma-derived purified human FXIIa and βFXIIa (62.5 nmol/L for both) was investigated based on the degradation activities of the chromogenic substrates of human FXIIa and βFXIIa as the indicators. The 50% inhibitory concentration (IC_{50}) was 15 nmol/L for both.

Using human plasma, the inhibitory effect of garadacimab (0-1.0×10^3 μg/mL) on FXIIa was investigated by measuring activated partial thromboplastin time (APTT). The APTT was prolonged (≥240 seconds) compared with the control (plasma not spiked with garadacimab [APTT: 34.8 seconds]) in the concentration range investigated (garadacimab 31.3-1.0×10^3 μg/mL).

3.1.3 Inhibition of human plasma FXIIa (CTD 4.2.1.1.5)

Using diluted plasma from healthy subjects, patients with C1-INH HAE (HAE Type 1 and HAE Type 2), patients with nC1-INH HAE (HAE Type 3), including those with FXII T309K/R mutation, and patients with acquired angioedema (AAE-C1-INH), of which the FXII was activated by the addition of dextran sulfate, the inhibitory effect of garadacimab (0-30 μg/mL) on the protease activity of FXIIa was investigated based on the degradation activity of the chromogenic substrate of FXIIa as the indicator. Garadacimab inhibited the protease activity of FXIIa in a concentration-dependent manner in all diluted plasma samples and showed its maximal inhibitory effect at 10 μg/mL.

3.1.4 Inhibition of plasma FXIIa derived from various animal species (CTD 4.2.1.1.10 and CTD 4.2.1.1.11)

The inhibitory effect of garadacimab (0-30 μg/mL) on the protease activity of FXIIa in diluted plasma from humans and other animal species (mice, rabbits, and cynomolgus monkeys), in which FXII was activated by the addition of dextran sulfate, was investigated based on the degradation activity of the chromogenic substrate of FXIIa as the indicator. Garadacimab inhibited FXIIa in a concentration-dependent manner in all animal species.

The inhibitory effect of garadacimab (0-600 nmol/L) on the protease activity of FXIIa in the plasma from humans and other animal species (cynomolgus monkeys and rats), in which FXII was activated by the addition

of dextran sulfate, was investigated based on the degradation activity of the chromogenic substrate of FXIIa as the indicator. Garadacimab inhibited FXIIa activity in cynomolgus monkey plasma, as in human plasma, but did not inhibit FXIIa activity in rat plasma.

3.1.5 Specificity for human FXIIa (CTD 4.2.1.1.3 [reference data])

The inhibitory effect of garadacimab on the protease activities of FXIIa, βFXIIa, and other serine proteases (activated blood coagulation factor VII [FVIIa], activated blood coagulation factor IX [FIXa], activated blood coagulation factor X [FXa], activated blood coagulation factor XI [FXIa], kallikrein, tissue plasminogen activator [tPA], activated protein C [APC], urokinase type plasminogen activator [uPA], and plasmin), which are structurally related to FXIIa, was investigated based on the degradation activities of the chromogenic substrates of these serine proteases as the indicators. The protease activities of FXIIa and βFXIIa (25 nmol/L for each) were completely inhibited in the presence of garadacimab (12.5 nmol/L). However, the IC_{50} values of garadacimab were >1 μmol/L for all of the other serine proteases.

3.1.6 Inhibition of bradykinin production in human plasma (CTD 4.2.1.1.6)

Using human plasma in which FXII was activated by the addition of dextran sulfate, the inhibitory effect of garadacimab (0-530 nmol/L) on bradykinin production was investigated. The production of bradykinin was completely inhibited at garadacimab concentrations of >130 nmol/L, with an IC_{50} of 86 nmol/L.

3.1.7 Effects on a mouse passive anaphylaxis model (CTD 4.2.1.1.8)

An anaphylactic reaction model was established to investigate the suppressive effect of garadacimab on increased vascular permeability during an anaphylactic reaction. Anti-dinitrophenyl IgE antibody was intradermally injected to mouse ear skin, and 20 hours later, garadacimab 25 mg/kg was intraperitoneally administered. Four hours after garadacimab administration, dinitrophenyl-human serum albumin was intravenously injected to induce an anaphylactic reaction. Garadacimab suppressed the increased vascular permeability.

3.1.8 Effects on ACEi-induced edema in C1-INH-deficient mice (CTD 4.2.1.1.9)

Bradykinin-mediated edema was induced in C1-INH-deficient mice by intravenous administration of captopril, an angiotensin converting enzyme inhibitor (ACEi), at 2.5 mg/kg, 4 hours after intraperitoneal administration of garadacimab 0.1, 0.5, or 2.5 mg/kg, to investigate the suppressive effect of garadacimab on increased vascular permeability during bradykinin-mediated edema. Garadacimab suppressed the increased vascular permeability in a dose-dependent manner, and the increased vascular permeability was completely suppressed in the garadacimab 0.5 mg/kg and higher dose groups.

3.2 Secondary pharmacodynamics

3.2.1 Effect on a rabbit simultaneous thrombosis model (CTD 4.2.1.2.1)

A single intravenous dose of garadacimab 10 mg/kg or physiological saline was administered to rabbits, and 15 minutes later, thrombosis was induced by applying iron (III) chloride to the bilateral femoral arteries. Venous thrombosis was also simultaneously induced by occluding the external jugular vein. FXII is considered

to contribute to arterial thrombus formation,[1)] and arterial thrombi were observed in 4 of 5 rabbits in the physiological saline group, but arterial occlusion was not induced by the application of iron (III) chloride within the observation period (90 minutes) in the garadacimab group. FXII is not considered to contribute to venous thrombus formation,[2)] and there were no clear differences in the mean venous thrombus wet weight or thrombus score (vein)[3)] between the garadacimab and physiological saline groups, suggesting that the administration of garadacimab did not suppress venous thrombosis. During the sample collection period (180 minutes), the APTT was prolonged in the garadacimab group (504.7-600 seconds), while the PT was not affected (9.4-10.5 seconds) compared with the physiological saline group (APTT, 24.0-25.8 seconds; prothrombin time [PT], 9.2-9.4 seconds).

Using the rabbits of the above investigation of the effect of garadacimab on thrombus formation, the effects of garadacimab on hemostasis after kidney incision were investigated. There were no clear differences between the garadacimab and physiological saline groups in the mean blood loss after kidney incision (2.0 ± 1.7 mL and 3.2 ± 1.6 mL, respectively) or the time to hemostasis (3.4 ± 0.5 minutes and 4.6 ± 0.7 minutes, respectively).

3.2.2 Effect on a mouse arterial thrombosis model (CTD 4.2.1.2.2)

A single intravenous dose of garadacimab 1, 1.75, or 2.5 mg/kg or physiological saline was administered to mice, and 15 minutes later, arterial thrombosis was induced by applying iron (III) chloride to the carotid artery. During the observation period (45 minutes), a dose-dependent decrease in the percent occlusion of the carotid artery was observed in the garadacimab groups (50% in the 1 mg/kg group, 40% in the 1.75 mg/kg group, 0% in the 2.5 mg/kg group, and 70% in the physiological saline group). The APTT was prolonged in the garadacimab groups (28.9-62.4 seconds), while the PT was not affected (9.5-9.8 seconds) compared with the physiological saline group (APTT, 26.2 seconds; PT, 10.2 seconds).

3.2.3 Effect on a mouse tail-end bleeding model (CTD 4.2.1.2.3)

A single intravenous dose of garadacimab 2.5 or 25 mg/kg or physiological saline was administered to mice, and 15 minutes later, the tail end was cut. There were no clear differences between the garadacimab 2.5 mg/kg and 25 mg/kg groups and the physiological saline group in the time to hemostasis (242 ± 211 seconds, 104 ± 64 seconds, and 156 ± 167 seconds, respectively) or total blood loss (10.7 ± 5.6 μL, 12.1 ± 7.3 μL, and 14.7 ± 11.5 μL, respectively). The APTT was prolonged in the garadacimab groups (83.1 seconds in the 2.5 mg/kg group and 63.7 seconds in the 25 mg/kg group), while the PT was not affected (9.1 seconds in the 2.5 mg/kg group and 9.3 seconds in the 25 mg/kg group) compared with the physiological saline group (APTT, 27.7 seconds; PT, 9.6 seconds).

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1) There is a report suggesting that FXII contributes to thrombus enlargement based on the inhibition of the enlargement and stabilization of thrombi in FXII-deficient mice in an investigation using a mouse iron (III) chloride-induced arterial thrombosis model (*J Exp Med*. 2005;202:271-281).

2) There is a report suggesting that FXII deficiency does not affect venous thrombus formation due to congestion, given that the venous thrombus weight in FXII-deficient mice did not differ from that in wild-type mice in an investigation using a mouse model of venous thrombosis induced by congestion (*J Thromb Haemost*. 2020;18:2899-2909).

3) Visual qualitative assessment of thrombi formed in vessels as a result of venous occlusion was based on the following 4-point scale: 0, no thrombi found; 1, 1 or several small thrombi; 2, thrombus formation with incomplete occlusion; 3, occlusive thrombus formation.

3.3 Safety pharmacology (CTD 4.2.1.3.1, CTD 4.2.3.2.3, CTD 4.2.3.2.5, and CTD 4.2.3.2.6)

When a single intravenous dose of garadacimab 3, 10, 30, or 100 mg/kg or a single subcutaneous dose of garadacimab 60 or 200 mg/kg was administered to mice, there were no effects on the respiratory system (respiratory rate, tidal volume, and minute volume) associated with garadacimab administration.

Central nervous system endpoints were investigated in a 4-week repeated-dose toxicity study in mice [see Section 5.2].

When garadacimab 60 or 200 mg/kg was subcutaneously administered to mice twice a week for 4 weeks, there were no effects on the central nervous system (modified Irwin's method) associated with garadacimab administration.[4)]

Safety pharmacology endpoints were investigated in 5- and 26-week repeated-dose toxicity studies in cynomolgus monkeys [see Section 5.2]. When garadacimab 10, 30, or 100 mg/kg was intravenously administered or garadacimab 60 or 200 mg/kg was subcutaneously administered to cynomolgus monkeys once a week for 26 weeks, there were no effects on the cardiovascular system (heart rate, ECG, and blood pressure) or the respiratory system (respiratory rate) associated with garadacimab administration. Similar results were obtained in a repeated-dose toxicity study in which garadacimab 3, 10, 30, or 100 mg/kg was intravenously administered or garadacimab 60 or 200 mg/kg was subcutaneously administered to cynomolgus monkeys once a week for 5 weeks.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of garadacimab for HAE

The applicant's explanation about the mechanism of action of garadacimab for HAE:

In HAE patients, the kallikrein-kinin pathway becomes excessively activated, and the produced bradykinin induces increased vascular permeability, resulting in angioedema (Japanese guideline). FXIIa is considered to cause bradykinin production by converting prekallikrein to kallikrein. It has been reported that plasma FXIIa concentrations are increased during HAE attacks compared with symptom-free periods (*Orphanet J Rare Dis*. 2015;10:132, *Immunopharmacology*. 1996;33:361-364).

The pharmacology study results of garadacimab showed its inhibitory effects on FXIIa activity and FXIIa-mediated bradykinin production in human plasma, as well as its suppressive effects on increased vascular permeability in a mouse passive anaphylaxis model and ACEi-induced increased vascular permeability in C1-INH-deficient mice. Therefore, garadacimab can be expected to prevent HAE attacks by inhibiting FXIIa.

[4)] When garadacimab 3, 10, 30, or 100 mg/kg was intravenously administered to mice twice a week for 4 weeks, there were no effects on the central nervous system (modified Irwin's method) associated with garadacimab administration 1 hour after the initial dose. However, from the third dose onward, some animals died or became moribund, probably due to an immune reaction caused by the administration of a heterologous protein in the garadacimab 3, 10, and 30 mg/kg groups [see Section 5.2].

PMDA's view:

The submitted data have shown that garadacimab inhibits FXIIa activity, FXIIa-mediated bradykinin production, and increased vascular permeability. Therefore, garadacimab can be expected to prevent HAE attacks in humans.

3.R.2 Effect of garadacimab on the blood coagulation system

PMDA's view:

Since APTT prolongation due to garadacimab administration was observed in an *in vitro* study using human plasma and investigations using model animals [see Sections 3.1.2, 3.2.1, 3.2.2, and 3.2.3], the effect in humans should be further investigated based on the incidences of adverse events such as activated partial thromboplastin time prolonged and haemorrhage in clinical studies.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted data on absorption, in the form of results data from intravenous and subcutaneous dose studies of garadacimab using mice, rabbits, and cynomolgus monkeys. The applicant also submitted the results of a pre- and postnatal developmental (PPND) study as data on distribution. Plasma garadacimab concentrations were measured by enzyme-linked immunosorbent assay (ELISA) (lower limit of quantitation: mice [500 ng/mL], rabbits [500 ng/mL], and cynomolgus monkeys [256 ng/mL or 500 ng/mL]), and plasma anti-drug antibody (ADA) was measured by ELISA (lower limit of quantitation: mice and cynomolgus monkeys [dilution factor: 1:512]) or the biotin-drug extraction and acid dissociation (BEAD) method (detection sensitivity: rabbits [100 ng/mL]). Since garadacimab is a monoclonal antibody and is considered to be degraded into peptides and amino acids and then reused or excreted, systemic tissue distribution, metabolism, and excretion have not been investigated, except for placental transfer.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.2, CTD 4.2.2.2.3, and CTD 4.2.3.6.1)

Table 6 shows the pharmacokinetic parameters of garadacimab in cynomolgus monkeys or rabbits that received a single dose of garadacimab. The absolute bioavailability of garadacimab after subcutaneous administration in cynomolgus monkeys was approximately 66%.[5)] When 2 formulations with different active ingredient concentrations (Formulation 1 [100 mg/mL] and Formulation 2 [170 mg/mL]) were administered to rabbits, there were no clear differences in the pharmacokinetic parameters of garadacimab between the 2 formulations.

[5)] Calculated based on the AUC_{inf} after intravenous administration of garadacimab 3 mg/kg and the AUC_{inf} after subcutaneous administration of garadacimab 6 mg/kg. The absolute bioavailability after subcutaneous administration of garadacimab 20 mg/kg was not calculated because the ratio of $AUC_{last\text{-}inf}$ to AUC_{inf} exceeded 0.2.

Table 6. Pharmacokinetic parameters following a single dose of garadacimab

Animal species	Route of administration	Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max} (h)	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_d or V_z (mL/kg)[a)]
Cynomolgus monkeys	IV (drip infusion)	3	3 males	143 ± 20.1	-	14,200 ± 2,210	204 ± 26.4	0.21 ± 0.03	21.4 ± 3.3
		9	3 males	260 ± 14.7	-	37,900 ± 9,620	204 ± 43.2	0.25 ± 0.07	34.7 ± 2.0
		27	3 males	497 ± 157	-	67,700 ± 11,800	290 ± 96	0.39 ± 0.06	59.1 ± 19.9
	IV (rapid)	0.5	3 males	11.7	1.83	1,020	-	-	-
		1	3 males	27.2	0.25	5,000	386	0.21	100
		3	3 males	83.0	0.25	11,100	227	0.27	90
	SC	6	3 males	30.2	74.7	14,100	291	-	-
		20	3 males	90.7	96.0	35,100	345	-	-
Rabbits	SC	20[b)]	3 males	63.5 ± 9.8	40.0 ± 13.9	6,840 ± 1,210	83.3 ± 47.8	-	-
			3 females	76.5 ± 3.2	40.0 ± 13.9	9,380 ± 567	91.9 ± 1.25	-	-
		20[c)]	3 males	75.8 ± 6.3	40.0 ± 13.9	9,220 ± 6,650	104 ± 14.4	-	-
			3 females	80.2 ± 20.8	40.0 ± 13.9	9,410 ± 3,030	107 ± 36.7	-	-

Mean ± standard deviation or mean; -, not calculated.

a) V_d for IV (drip infusion) and V_z for IV (rapid); b) Formulation 1 (100 mg/mL); c) Formulation 2 (170 mg/mL).

4.1.2 Repeated-dose studies (toxicokinetics) (CTD 4.2.3.2.3 and CTD 4.2.3.2.6)

The toxicokinetics following repeated intravenous or subcutaneous doses of garadacimab was investigated in a 4-week repeated-dose toxicity study in mice and a 26-week repeated-dose toxicity study in cynomolgus monkeys [see Section 5.2]. Table 7 shows the pharmacokinetic parameters of garadacimab and the status of ADA development.

When repeated intravenous or subcutaneous doses of garadacimab were administered to mice twice a week, the exposure increased with increasing dose in the dose range investigated, with a tendency toward accumulation with repeated doses. There were no clear sex differences in exposure following intravenous administration. Although the exposure following subcutaneous administration tended to be higher in females than in males, no definitive conclusions were reached due to a limited number of animals. ADA development due to garadacimab administration was observed in 3 animals in the 10 mg/kg IV group and 1 animal in the 60 mg/kg SC group (Table 7), and the garadacimab exposure at ADA development in the 3 animals in the 10 mg/kg IV group was below the lower limit of quantitation.[6)]

When repeated intravenous or subcutaneous doses of garadacimab were administered to cynomolgus monkeys once a week, there were no clear sex differences in pharmacokinetics. The exposure increased dose-proportionally in the dose range investigated, with a tendency toward accumulation with repeated doses. ADA development due to garadacimab administration was observed in 1 animal each in the 30 mg/kg and 100 mg/kg IV groups and 1 animal in the 200 mg/kg SC group, and the exposure to garadacimab decreased in the 1 animal in the 200 mg/kg SC group. In 1 animal determined to be ADA-negative in the 100 mg/kg IV group, edema was observed in the subcutaneous tissue and elsewhere, and the exposure to garadacimab tended to decrease. Therefore, the applicant considered that this animal might be false-negative.

[6)] In the 1 animal in the 60 mg/kg SC group, garadacimab concentrations after confirmation of ADA development were not measured.

Table 7. Pharmacokinetic parameters following repeated doses of garadacimab

Animal species	Administration period (frequency)	Route of administration	Dose (mg/kg)	Measurement time point	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	t_{max} (h)	No. of animals with ADA development
Mice	4 weeks (twice/week)	IV	3[a)]	Day 1	Males	3/sex	54.5	843	1.00	Male: 0 Female: 0
					Females		171	1,090	1.00	
				Day 29	Males		-	-	-	
					Females		-	-	-	
			10	Day 1	Males		143	2,690	1.00	Male: 0 Female: 3
					Females		184	2,330	0.08	
				Day 29	Males		503	7,640	1.00	
					Females		304	4,780	0.08	
			30	Day 1	Males		649	9,010	0.08	Male: 0 Female: 0
					Females		796	8,970	0.08	
				Day 29	Males		1,010	21,200	6.00	
					Females		1,050	21,100	6.00	
			100	Day 1	Males		1,630	23,500	1.00	Male: 0 Female: 0
					Females		2,040	23,100	0.08	
				Day 29	Males		1,700	33,900	1.00	
					Females		2,120	32,600	1.00	
		SC	60	Day 1	Males		325	4,750	24.0	Male: 0 Female: 1
					Females		713	5,380	96.0	
				Day 29	Males		811	14,200	32.0	
					Females		877	16,600	16.0	
			200	Day 1	Males		728	11,000	72.0	Male: 0 Female: 0
					Females		988	16,900	16.0	
				Day 29	Males		1,050	19,400	24.0	
					Females		1,640	29,600	24.0	
Cynomolgus monkeys	26 weeks (once/week)	IV	10	Week 1	Males	4/sex	264 ± 31.0	4,840 ± 437	0.25 ± 0.00	Male: 0 Female: 0
					Females		158 ± 13.5	2,540 ± 156	0.25 ± 0.00	
				Week 14	Males		290 ± 40.0	5,360 ± 621	0.25 ± 0.00	
					Females		323 ± 86.1	6,220 ± 1,670	0.25 ± 0.00	
				Week 27	Males		347 ± 56.7	6,870 ± 961	1.44 ± 2.38	
					Females		370 ± 35.1	7,360 ± 767	0.25 ± 0.00	
			30	Week 1	Males		618 ± 64.9	11,600 ± 837	1.44 ± 2.38	Male: 0 Female: 1
					Females		540 ± 48.0	9,072 ± 644	0.25 ± 0.00	
				Week 14	Males		827 ± 184	16,100 ± 4,230	0.25 ± 0.00	
					Females		951 ± 58.1	17,300 ± 1,030	0.25 ± 0.00	
				Week 27	Males		1,000 ± 168	17,300 ± 4,170	0.25 ± 0.00	
					Females		1,020 ± 75.9	19,900 ± 2,210	0.25 ± 0.00	
			100	Week 1	Males	8/sex	2,290 ± 194	39,700 ± 3,330	0.25 ± 0.00	Male: 1[b)] Female: 0
					Females		2,000 ± 259	36,500 ± 7,090	0.84 ± 1.68	
				Week 14	Males		2,860 ± 297	52,500 ± 6,860	0.25 ± 0.00	
					Females		2,820 ± 103	50,500 ± 2,240	0.25 ± 0.00	
				Week 27	Males	5	3,010 ± 254	58,300 ± 5,070	0.25 ± 0.00	
					Females	6	3,090 ± 207	56,300 ± 2,200	0.25 ± 0.00	

Animal species	Administration period (frequency)	Route of administration	Dose (mg/kg)	Measurement time point	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)	t_{max} (h)	No. of animals with ADA development
		SC	60	Week 1	Males	4/sex	322 ± 50.0	4,220 ± 1,040	38.0 ± 12.0	Male: 0 Female: 0
					Females		349 ± 35.4	3,890 ± 515	44.0 ± 8.00	
				Week 14	Males		639 ± 46.4	12,400 ± 1,330	28.0 ± 4.62	
					Females		732 ± 38.3	14,700 ± 1,060	26.0 ± 4.00	
				Week 27	Males		463 ± 105	9,600 ± 1,970	24.0 ± 0.0	
					Females		728 ± 49.9	15,200 ± 654	24.0 ± 0.00	
			200	Week 1	Males	8/sex	1,120 ± 91.7	13,400 ± 2,260	44.00 ± 7.41	Male: 0 Female: 1
					Females		1,070 ± 130	12,500 ± 2,200	40.0 ± 11.3	
				Week 14	Males	8	2,020 ± 225	37,200 ± 3,350	30.0 ± 3.70	
					Females	7	2,030 ± 407	37,700 ± 6,910	33.1 ± 17.5	
				Week 27	Males	6	1,640 ± 238	31,000 ± 4,020	29.3 ± 9.69	
					Females	5	1,800 ± 468	33,400 ± 8,270	27.2 ± 4.38	

Mean or mean ± standard deviation; -, not measured.

a) Pharmacokinetic evaluation on Day 29 was not conducted because the treatment with garadacimab was terminated early due to changes in clinical signs and deaths related to garadacimab administration.

b) Besides the animal determined to be ADA-positive, 1 animal was suspected to be false-negative.

4.2 Distribution

4.2.1 Placental transfer (CTD 4.2.3.5.3.1)

Toxicokinetics was investigated in a PPND study in pregnant rabbits [see Section 5.5]. Repeated subcutaneous doses of garadacimab 10, 30, or 100 mg/kg, or repeated intravenous doses of garadacimab 100 mg/kg were administered at 5-day intervals from Gestation Day 7 to Gestation Day 27, and the percentages of fetal-to-maternal plasma garadacimab concentration on Gestation Day 29, excluding ADA-positive animals, were calculated to be 76.6%, 136.6%, 40.8%, and 101.4%, respectively, which suggested that garadacimab was transferred to fetuses via the placenta. The rates of ADA development in the garadacimab groups of 10 mg/kg SC, 30 mg/kg SC, 100 mg/kg SC, and 100 mg/kg IV were 43.6% (17 of 39 dams), 16.7% (7 of 42 dams), 11.1% (5 of 45 dams), and 6.8% (3 of 44 dams), respectively, in dams; the rates were 100% (3 of 3 fetuses), 33.3% (1 of 3 fetuses), 100% (3 of 3 fetuses), and 66.7% (2 of 3 fetuses), respectively, in fetuses. In some dams and fetuses with ADA development, the plasma garadacimab concentrations were below the lower limit of quantitation.

4.R Outline of the review conducted by PMDA

PMDA's view:

On the basis of the non-clinical pharmacokinetic study results submitted, the *in vivo* behavior of garadacimab can be understood to a certain extent. Garadacimab was found to cross the placenta in pregnant rabbits. Although no studies on the excretion of garadacimab into mother's milk have been conducted, human IgG is generally known to be transferred into milk. In view of the above information, precautions regarding the placental transfer and excretion of garadacimab into milk should be provided in the package insert.

5. Toxicology and Outline of the Review Conducted by PMDA

Toxicity studies of garadacimab consisted of repeated-dose toxicity studies, reproductive and developmental toxicity studies, a local tolerance study, and other studies (tissue cross-reactivity studies). Since garadacimab inhibits FXIIa activity in mouse, rabbit, and cynomolgus monkey plasma [see Sections 3.1.1 and 3.1.4], the repeated-dose toxicity studies of garadacimab were conducted using mice and cynomolgus monkeys, and the reproductive and developmental toxicity studies were conducted using rabbits.[7)]

5.1 Single-dose toxicity

The results of the initial dose in repeated-dose toxicity studies in mice and cynomolgus monkeys [see Section 5.2] were used to evaluate the acute toxicity and approximate lethal dose of garadacimab for intravenous and subcutaneous administration. In mice, dead or moribund animals, which suggested the involvement of an immune response to the administered heterologous protein, were observed following repeated doses in the 3, 10, and 30 mg/kg/dose IV groups, but there were no deaths in the 100 mg/kg/dose IV group [see Section 5.2]. No acute symptoms were observed after the initial dose in either animal species. In view of these, the approximate lethal dose was determined to be >100 mg/kg for intravenous administration and >200 mg/kg for subcutaneous administration, regardless of the animal species.

5.2 Repeated-dose toxicity

Four-week repeated intravenous and subcutaneous dose toxicity studies in mice were conducted (Table 8). APTT prolongation was observed after intravenous or subcutaneous administration of garadacimab, which was determined to be a change associated with FXIIa inhibition by garadacimab. The main toxicity findings were dead or moribund animals in the 3, 10, and 30 mg/kg/dose IV groups, and these animals showed flattened posture, hunched posture, and partial eyelid closure associated with skin swelling, abnormal breathing, and worsening of clinical signs. Decreased liver weight observed after intravenous or subcutaneous administration was considered to be of low toxicological significance because there were no related histopathological changes. Skin inflammation, increased lymphocyte/eosinophil counts, and enlargement of the axillary or inguinal lymph nodes observed after subcutaneous administration were considered to be changes associated with local irritation or inflammation due to garadacimab. In view of the above, the no observed adverse effect level (NOAEL) for systemic effects was determined to be <3 mg/kg/dose for intravenous administration and 200 mg/kg/dose for subcutaneous administration.

The mechanism of development of the toxicity findings observed in the dead or moribund mice after intravenous administration of garadacimab was investigated. Although the mechanism was not clarified, the involvement of an immune response to the administered heterologous protein was suggested based on the following: (a) abnormal findings in the observation of clinical signs were similar to anaphylactic reactions (*J Allergy Clin Immunol*. 2007;120:506-515) and were only observed following repeated doses; (b) the groups with these findings included animals with ADAs detected in blood; and (c) anaphylaxis was also observed in

[7)] Since mice that received repeated doses of garadacimab were shown to develop a strong immune response to the administered heterologous protein [see Section 5.2], only rabbits were selected as the animal species for the reproductive and developmental toxicity studies.

the control group that received a human isotype control monoclonal antibody. Therefore, these findings were considered unlikely to be relevant to humans.

Table 8. Summary of the repeated-dose toxicity studies in mice

Test system	Route of administration	Administration period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached data CTD
Male and female mice (CD-1)	IV	4 weeks (twice/week) + 8-week recovery	0,[a) b)] 3, 10, 30, and 100	[Moribund sacrifices or deaths[c)]] (3,[d)] 13 males and 1 female; 10, 1 male and 3 females; 30, 1 female) Swelling of the muzzle/hindlimbs/ forelimbs, redness of the limbs/snout, decreased activity, piloerection, shallow breathing, bradypnea, flattened posture, hunched posture, and partial eyelid closure [Surviving animals] ≥10: Increased APTT (males and females); decreased liver weight (males) ≥30: Decreased liver weight (females) 10: Blood ADA positive (females) 3: Increased APTT (males and females) Reversibility: Reversible	<3	4.2.3.2.3
	SC		0,[a) b)] 60, and 200	≥60: Increased APTT, increased lymphocyte count, enlargement of the axillary lymph nodes, and subcutaneous inflammatory cell filtration (males and females); enlargement of the inguinal lymph nodes (males); increased eosinophil count (females) 200: Decreased liver weight and increased lymphocyte cellularity in the axillary/inguinal lymph nodes (males and females); enlargement of the inguinal lymph nodes (females) 60: Blood ADA positive (females)	200	
Male and female mice (CD-1)	IV	4 weeks (twice/week)	0,[a)] 3, and 3 + pyrilamine,[e)] MAb[f)]	3: Decreased activity, edema, and decreased body temperature (males) 3 + pyrilamine: Transiently decreased activity and decreased body temperature (males) MAb: Decreased activity and decreased body temperature (males)	-[g)]	4.2.3.2.1 Reference

a) Vehicle: 0.9% physiological saline.
b) The control group was common to intravenous and subcutaneous administration. The vehicle was intravenously and subcutaneously administered.
c) Sum of dead animals in the toxicity evaluation, recovery, and satellite groups.
d) In the 3 mg/kg group, all animals were euthanized after administration on Day 11 or 15.
e) The histamine H_1 receptor antagonist pyrilamine 2.5 mg/kg/dose was intravenously administered 30 minutes before intravenous administration of garadacimab 3 mg/kg/dose.
f) Human isotype control monoclonal antibody (MAb) 3 mg/kg/dose was intravenously administered.
g) The NOAEL was not investigated.

Five- and 26-week repeated intravenous and subcutaneous dose toxicity studies in cynomolgus monkeys were conducted (Table 9). APTT prolongation was observed after intravenous or subcutaneous administration of garadacimab, which was determined to be a change associated with FXIIa inhibition by garadacimab. As the main toxicity findings, moribund sacrifices associated with worsening of clinical signs were observed in high-dose IV and SC groups. These animals showed edema of the subcutaneous tissue, inflammatory cell infiltration into organs and tissues of the whole body, necrosis and regeneration of skeletal muscle fibers, and ADA production in blood. The toxicity findings observed in the moribund sacrifices were considered unlikely to be

relevant to humans because the involvement of an immune response to the administered heterologous protein was suggested based on the incidences of these findings. Other findings observed after intravenous or subcutaneous administration, including decreased weight gain, increased blood glucose, decreased blood ALT, increased blood potassium, and decreased thyroid and parathyroid weights, were considered to be of low toxicological significance because there were no related abnormal findings, or based on the severity of the abnormality. Inflammatory changes at the administration site after subcutaneous administration were considered to be changes associated with local irritation by garadacimab.

In view of the above, the NOAEL in the 26-week repeated-dose toxicity study was determined to be 30 mg/kg/week for intravenous administration and 60 mg/kg/week for subcutaneous administration. When repeated subcutaneous doses of garadacimab were administered at the NOAEL (60 mg/kg/week) in the 26-week repeated-dose toxicity study, the $AUC_{0\text{-}168h}$ of garadacimab at Week 14 was 89,400 μg·h/mL (the mean of males and females), which was approximately 8.7-fold the clinical exposure in humans[8)] ($AUC_{tau,ss}$: 10,300 μg·h/mL).

Table 9. Summary of the repeated-dose toxicity studies in cynomolgus monkeys

Test system	Route of administration	Administration period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/week)	Attached data CTD
Male and female cynomolgus monkeys	IV	5 weeks (once/week) + 8-week recovery	0,[a) b)] 3, 10, 30, and 100	≥3: Increased APTT and decreased weight gain (males and females) ≥10: Decreased thyroid/parathyroid weights (males) 3: Blood ADA positive (males and females) After the end of the recovery period 100: Blood ADA positive (females)	100	4.2.3.2.5
	SC		0,[a) b)] 60, and 200	≥60: Increased APTT, decreased weight gain, and subcutaneous inflammatory cell infiltration at the administration site (males and females); subcutaneous hemorrhage at the administration site (females) 200: Inflammatory cell infiltration in the dermis (males and females); increased blood glucose, subcutaneous hemorrhage at the administration site, and epidermal ulceration (males) Reversibility: Reversible	200	

8) $AUC_{tau,ss}$ at steady state when garadacimab 200 mg (400 mg as the initial dose only) was subcutaneously administered once a month to patients with C1-INH HAE (HAE Type 1 or Type 2) in Study 3001 (estimated based on a population pharmacokinetic analysis model [see Section 6.2.3]).

Test system	Route of administration	Administration period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/week)	Attached data CTD
Male and female cynomolgus monkeys	IV	26 weeks (once/week) + 8-week recovery	0,[a) b)] 10, 30, and 100	[Moribund sacrifices] (100: 1 male) Swelling of the abdomen/muzzle, subcutaneous fluid retention, edema of the fatty tissue/pancreas/salivary gland/ skin/subcutaneous tissue, thickening of the duodenum/jejunum, red coloration of the jejunal mucosa, and inflammatory cell infiltration in the heart/kidney/ esophagus/mandibular and sublingual salivary glands [Surviving animals] ≥10: Increased APTT (males and females); increased blood potassium (females) 100: Decreased blood ALT and blood ADA positive (males); subcutaneous hemorrhage/inflammatory cell infiltration around the saphenous vein at the administration site, and inflammatory cell infiltration in the dermis around the saphenous vein at the administration site (females) 30: Blood ADA positive (females) Reversibility: Reversible	30	4.2.3.2.6
	SC		0,[a) b)] 60, and 200	[Moribund sacrifices] (200: 1 female) Swelling of the neck/shoulder area, impaired vocalization, wheezing on breathing, pyrexia, dark red coloration of the lung, pale coloration/dark coloration/enlargement of the kidney, deformed gallbladder, enlargement of the mandibular lymph nodes, partial elevation of the skeletal muscle, dark red coloration of the skin at the administration site, thyroid cyst, edema of the submandibular gland, necrosis/ regeneration of skeletal muscle fibers, plasmacytosis of the mandibular lymph nodes, inflammatory cell infiltration in the submandibular/sublingual gland, subcutaneous inflammatory cell infiltration in the skin at the administration site, increased germinal centers in the axillary lymph nodes, thymic atrophy, alveolar bleeding of the lung, subcutaneous bleeding/ inflammatory cell infiltration, and blood ADA positive [Surviving animals] ≥60: Increased APTT, and subcutaneous bleeding/inflammatory cell infiltration/ lymphocyte aggregation at the administration site (males); decreased blood ALT (males); increased blood potassium (females) 200: Blood ADA positive (females); subcutaneous lymphocyte aggregation at the administration site (females) Reversibility: Reversible	60	

a) 0.9% physiological saline.
b) The control group was common to intravenous and subcutaneous administration. The vehicle was intravenously or subcutaneously administered.

5.3 Genotoxicity

Garadacimab is a monoclonal antibody, and is considered to neither pass through the nuclear envelope or mitochondrial membrane nor directly interact with DNA or other nuclear chromosomal materials. Therefore, garadacimab is unlikely to be genotoxic, and no genotoxicity studies have been conducted.

5.4 Carcinogenicity

No carcinogenicity studies of garadacimab have been conducted. In view of the following points, the applicant explained that the inhibition of FXIIa by garadacimab is unlikely to increase the risk of tumor development:

- FXII (FXIIa) reportedly promotes inflammation and cell proliferation (*Front Immunol*. 2019;10:2011, *Res Pract Thromb Haemost*. 2019;3:599-606, etc.); however, no reports suggesting the involvement of FXIIa inhibition or FXII deficiency in carcinogenesis or its promotion exist at present.
- Although APTT prolongation was observed in a phenotype analysis in FXII-knockout mice ($FXII^{-/-}$), these mice could survive for ≥12 months and had no macroscopic or histopathological changes, compared with wild-type mice (*Thromb Haemost*. 2004;92:503-508).
- In repeated-dose toxicity studies of garadacimab, no changes suggestive of preneoplastic or proliferative lesions were observed [see Section 5.2].

5.5 Reproductive and developmental toxicity

Studies of fertility and early embryonic development to implantation (fertility and early embryonic development [FEED] studies) by intravenous administration, a study of embryo-fetal development (EFD study) by intravenous administration, and a study of effects on pre- and postnatal development, including maternal function (PPND study) by subcutaneous and intravenous administration were conducted in rabbits (Table 10).

In the FEED study in females, an increased number of implantation sites was observed in the 10 and 100 mg/kg/dose groups, and decreased pre-implantation loss in the 10 mg/kg/dose group. However, the changes were mild, did not show dose-dependency but were within the range of historical data, and had no effects on fertility or early embryonic development. Therefore, these findings were considered to be of low toxicological significance, and the NOAEL for general toxicity and fertility in females was determined to be 100 mg/kg/dose. When repeated intravenous doses of garadacimab were administered at the NOAEL from before mating throughout gestation, the $AUC_{0\text{-}72h}$ of garadacimab on Gestation Day 7 was 85,200 μg·h/mL, which was approximately 8.3-fold the clinical exposure in humans ($AUC_{tau,ss}$: 10,300 μg·h/mL).

In the FEED study in males, dead or moribund-sacrificed animals were observed in the garadacimab groups. It was inferred that these findings were likely associated with the immune response to the administered heterologous protein based on positive blood ADA in these animals and the incidences of toxicity findings. There were no effects on fertility or early embryonic development, and the NOAEL for general toxicity and fertility in males was determined to be 100 mg/kg/dose. When repeated intravenous doses of garadacimab were administered at the NOAEL before mating, the $AUC_{0\text{-}72h}$ of garadacimab on Gestation Day 27 was 106,000 μg·h/mL, which was approximately 10.3-fold the clinical exposure in humans ($AUC_{tau,ss}$: 10,300 μg·h/mL).

In the EFD study, no toxicity findings were observed, and the NOAEL for dams and embryo-fetal development was determined to be 100 mg/kg/dose. When repeated intravenous doses of garadacimab were administered at the NOAEL during gestation, the $AUC_{0\text{-}72h}$ of garadacimab on Day 18 was 107,000 μg·h/mL, which was approximately 10.4-fold the clinical exposure in humans ($AUC_{tau,ss}$: 10,300 μg·h/mL).

In the PPND study, there were no effects on the fertility of dams or the development/growth/neurological behavior/fertility of offspring, and the NOAEL for dams and offspring was determined to be 100 mg/kg/dose for both subcutaneous and intravenous administration. When repeated subcutaneous doses of garadacimab were administered at the NOAEL during gestation and lactation, the $AUC_{0\text{-}120h}$ of garadacimab on Lactation Day 38 was 91,800 μg·h/mL, which was approximately 8.9-fold the clinical exposure in humans ($AUC_{tau.ss}$: 10,300 μg·h/mL).

Table 10. Summary of the reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached data CTD
FEED	Female rabbits (NZW)	IV	14 days before mating to Gestation Day 7 (once/3 days)	0,[a] 10, 30, and 100	Parental animals ≥10: APTT prolongation and blood ADA positive Fertility 10: Increased number of implantation sites and decreased pre-implantation loss 100: Increased number of implantation sites Early embryonic development None	General toxicity in parental animals: 100 Female fertility: 100 Early embryonic development: 100	4.2.3.5.1.1
	Male rabbits (NZW)	IV	28 days before mating to 8 days after the end of the mating period (once/3 days)	0,[a] 10, 30, and 100	[Deaths or moribund sacrifices] (10, 4 animals; 3, 2 animals) Emaciation, decreased activity, paleness, pale gingiva, dyspnea, abnormal breathing, dilated pupil, eyelid closure, tremor, vocalization, side position, discoloration/ swelling/yellow granular contents of the penis, small size/decreased contents/atrophy of the prostate/ seminal vesicles, abnormal morphology/softening/white coloration of the testis, dilatation of the rete testis, decreased feces, decreased body weight/food consumption, and blood ADA positive [Surviving animals] General toxicity in parental animals ≥10: APTT prolongation and blood ADA positive Fertility None	General toxicity in parental animals: 100 Female fertility: 100 Male fertility: 100	4.2.3.5.1.2

Study	Test system	Route of administration	Administration period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached data CTD
EFD	Female rabbits (NZW)	IV	Gestation Days 6-18 (once/3 days) Caesarean section: Gestation Day 29	0,[a] 10, 30, and 100	[Deaths or moribund sacrifices] (100, 2 animals) Emaciation, soft feces, fur staining with feces, decreased water consumption, decreased/no food consumption, decreased fecal volume, red/pink staining of the cage tray (delivery of fetus), and late resorption [Surviving animals] <u>General toxicity in maternal animals</u> ≥10: APTT prolongation <u>Embryo-fetal development</u> None	Maternal animals: 100 Embryo-fetal development: 100	4.2.3.5.2.2
PPND	Female rabbits (NZW)	SC	Gestation Day 7 to 38 after delivery (once/5 days)	SC: 0,[a] 10, 30, and 100	<u>General toxicity in maternal animals</u> ≥10: APTT prolongation <u>Development of F1 offspring</u> None <u>Growth/neurological behavior/fertility of F1 offspring</u> None	Maternal animals: 100 Development of F1 offspring: 100 Growth/ neurological behavior/ fertility of F1 offspring: 100	4.2.3.5.3.1
		IV		IV: 100	<u>General toxicity in maternal animals</u> None <u>Development of F1 offspring</u> None <u>Growth/neurological behavior/fertility of F1 offspring</u> None	Maternal animals: 100 Development of F1 offspring: 100 Growth/ neurological behavior/ fertility of F1 offspring: 100	

a) 0.9% physiological saline

5.6 Local tolerance

A local tolerance study in rabbits was conducted using 2 formulations with different active ingredient concentrations (Formulation 1 [100 mg/mL] and Formulation 2 [170 mg/mL]). Neither of these formulations showed skin irritation (Table 11).

The skin tolerance following repeated intravenous or subcutaneous doses of garadacimab was evaluated in repeated-dose toxicity studies in mice and cynomolgus monkeys [see Section 5.2]. In mice, dark redness was observed at the administration site of the tail vein. The change was considered to be due to the administration procedure because the incidence was similar to that in the control group. In addition, inflammatory cell infiltration increased at the subcutaneous administration site following garadacimab administration compared with the control group. This change was minimal to mild and was reversible in all cases. Therefore, the finding was considered to be a tolerable change. In cynomolgus monkeys, bleeding and inflammatory cell infiltration were observed at the subcutaneous and intravenous administration sites; however, these changes were also observed in the control group. These findings were reversible, and no dose-dependent relationships in the incidence or severity were observed. Therefore, these were considered to be changes due to the administration procedure.

As described above, inflammatory cell infiltration increased at the local administration site following repeated subcutaneous doses of garadacimab, which suggested its irritation potential. However, since this finding was minimal to mild and reversible, it was considered to be tolerable.

Table 11. Summary of the local tolerance study

Test system	Test method	Main findings	Attached data CTD
Male and female rabbits (NZW)	The local tolerance of garadacimab formulations for subcutaneous administration[a)] was evaluated by subcutaneously administering each formulation at 0[b)] or 20 mg/kg/dose twice at a 1-week interval.	None No local irritation was observed.	4.2.3.6.1

a) Two formulations with different active ingredient concentrations (Formulation 1 [100 mg/mL] and Formulation 2 [170 mg/mL]); b) 0.9% physiological saline

5.7 Other studies

5.7.1 Tissue cross-reactivity

A tissue cross-reactivity study of garadacimab was conducted using frozen tissue sections of normal human and cynomolgus monkey tissues. Cross-reactivity was observed in the tissues shown in Table 12, the tissues with positive staining in humans were the same as those in cynomolgus monkeys, except for the parathyroid gland. The applicant explained that, since there were no findings in the tissues with positive staining that may raise safety concerns in repeated-dose toxicity studies and clinical studies [see Sections 5.2 and 7.R.3], garadacimab is unlikely to raise safety concerns in humans.

Table 12. Summary of the tissue cross-reactivity study

Test system	Test method	Main findings	Attached data CTD
Normal human tissue	Frozen tissue sections were treated with garadacimab (1.25, 2.5, and 5 μg/mL), and tissue binding was evaluated by indirect immunoperoxidase staining.	Tissues with positive staining: Liver,[a)] adrenal gland, pituitary gland, lung[a)] (alveolar macrophage, alveolar epithelial cell), myocardium, cerebellum, cerebral cortex,[a)] spinal cord,[a)] peripheral nerve, optic nerve,[a)] testis, prostate gland, oviduct, endometrium, placenta, mammary gland, kidney, ureter, bladder, lymph node, spleen, thymus gland, bone marrow,[a)] blood smear, stomach, pancreas, parotid gland, and parathyroid gland	4.2.3.7.7.1
Normal cynomolgus monkey tissue[b)]		Tissues with positive staining: Liver, adrenal gland, pituitary gland, lung (alveolar macrophage, alveolar epithelial cell), cerebellum, cerebral cortex, spinal cord, peripheral nerve, testis, prostate gland, ureter, bladder, lymph node, spleen, bone marrow, pancreas, and parotid gland	

a) Tissues with strong staining.
b) Myocardium, optic nerve, oviduct, endometrium, placenta, mammary gland, kidney, thymus gland, blood smear, and stomach were not evaluated because these tissues were negative in the preliminary study (Study APQ0060).

5.7.2 Immunotoxicity

In the 4-week repeated-dose toxicity study of garadacimab in mice and 5- and 26-week repeated-dose toxicity studies in cynomolgus monkeys [see Section 5.2], Complement component C3a (C3a) (marker for complement activation), cytokines,[9)] and C-reactive protein (CRP) were measured, and immunophenotyping[10)] and macroscopic and histopathological examination of the immune system tissue were performed. The results are

9) The cytokines measured were tumor necrosis factor (TNF)-α, keratinocyte-derived chemokines (KC), interleukin (IL)-1β, IL-2, IL-4, IL-10, IFNγ, IL-5, IL-6, IL-17, and IL-12p40 in the 4-week repeated intravenous or subcutaneous dose toxicity study in mice, TNF-α, IL-2, IL-4, IL-5, IL-6, IFNγ, and G-CSF in the 5-week repeated intravenous or subcutaneous dose toxicity study in cynomolgus monkeys, and TNF-α, IL-2, IL-4, IL-5, IL-6, IFNγ, and G-CSF in the 26-week repeated intravenous or subcutaneous dose toxicity study in cynomolgus monkeys.
10) Peripheral blood and the spleen were used for mice (IV groups), and peripheral blood was used for cynomolgus monkeys.

as follows: In the immunophenotyping in mice that exhibited anaphylaxis, increases in the cell counts of peripheral blood T-lymphocytes, B-lymphocytes, neutrophils, monocytes, and NK cells were observed in female mice that received ≥3 mg/kg/dose of intravenous garadacimab, and slight increases in the proportion (%) and cell count of splenic NK cells were observed in male mice that received 10 mg/kg/dose of intravenous garadacimab. However, the evaluation results of other immunophenotyping items, C3a, cytokines, CRP, and macroscopic and histopathological examinations of the immune system tissue in mice and the evaluation results in cynomolgus monkeys showed no effects of garadacimab administration.

5.R Outline of the review conducted by PMDA

PMDA's view:

The toxicity study results did not suggest any clear safety concerns with garadacimab administration in normal animals. However, since abnormal findings associated with the immune response to a heterologous protein, including death, were observed following repeated doses of garadacimab, the safety in humans will be further examined in relation to ADA production in Section 6.R.2. In toxicity studies, although there were no findings suggestive of bleeding associated with coagulation system abnormalities considered to be caused by garadacimab administration, APTT prolongation associated with FXIIa inhibition by garadacimab was observed. Therefore, the safety in humans will be discussed based on APTT changes and the incidences of coagulation abnormality-related adverse events in clinical studies in Section 7.R.3.3.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted biopharmaceutic study data, in the form of results data from a clinical study investigating the pharmacokinetic profiles, etc. of a needle safety device (NSD) and a pen product that is the proposed commercial formulation in healthy subjects.[11)]

Plasma garadacimab concentrations were measured by ELISA (lower limit of quantitation: 1.01, 10.6, 100, or 125 ng/mL), and plasma ADA was measured by electrochemiluminescence (ECL) (detection sensitivity: 10, 20, or 50 ng/mL).

In the clinical development of garadacimab, 2 formulations with different active ingredient concentrations (Formulation 1 [100 mg/mL] and Formulation 2 [170 mg/mL]) were used.[12)] The NSD product of Formulation 2 was used in phase III studies in HAE patients (Studies 3001 and 3002), and the pen product of Formulation 2 was chosen as the proposed commercial formulation.

[11)] Study 1004. Using the NSD product or the pen product of Formulation 2, a single subcutaneous dose of garadacimab 200 mg was administered to the abdomen, thigh, or upper arm of healthy non-Japanese subjects, to investigate the pharmacokinetic parameters of garadacimab by administration site. The study confirmed that there are no clear differences in garadacimab exposure between the products used or among the administration sites.

[12)] Clinical studies conducted using each formulation: Formulation 1 was used in phase I studies (Studies 1001 and 1003 [IV groups]) and a phase II study (Study 2001); Formulation 2 was used in phase I studies (Studies 1003 [SC groups] and 1004) and phase III studies (Studies 3001 and 3002).

6.2 Clinical pharmacology

The applicant submitted evaluation data, in the form of results data from clinical studies in healthy subjects and HAE patients, and population pharmacokinetic/pharmacodynamic analyses. Unless otherwise specified, the dose of garadacimab is expressed as the amount of garadacimab itself.

6.2.1 Investigations in healthy subjects

6.2.1.1 Foreign phase I study (CTD 5.3.3.1: Study CSL312_1001 [October 2016 to September 2017])

A single intravenous dose of garadacimab 0.1, 0.3, 1, 3, or 10 mg/kg or a single subcutaneous dose of garadacimab 1, 3, or 10 mg/kg was administered to non-Japanese healthy subjects. Table 13 shows the pharmacokinetic parameters of garadacimab. The C_{max} and AUC_{inf} following a single intravenous dose of garadacimab increased dose-proportionally. The AUC_{inf} following a single subcutaneous dose of garadacimab also increased dose-proportionally, in the dose range investigated; however, the increase in C_{max} was slightly below the dose ratio. The absolute bioavailability following a single subcutaneous dose of garadacimab 1, 3, or 10 mg/kg was 63.3%, 54.3%, and 42.4%, respectively. ADA development was not observed.

Table 13. Pharmacokinetic parameters following a single dose of garadacimab

Route of administration	Treatment group (mg/kg)	N	C_{max} (µg/mL)	AUC_{inf} (µg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	Vz or Vz/F (L)	CL or CL/F (mL/h)
IV	0.1	4/group	2.73 ± 0.45	967 ± 252[a)]	3.50 [1.00, 12.0]	353 ± 64.2	4.82 ± 1.12[a)]	9.83 ± 3.19[a)]
	0.3		11.0 ± 1.69	4,350 ± 1,260	1.00 [1.00, 12.0]	490 ± 206	3.79 ± 1.23	5.64 ± 0.98
	1		32.5 ± 6.30	9,760 ± 1,940	1.03 [1.00, 6.00]	408 ± 47.5	4.04 ± 0.42	6.98 ± 1.45
	3		110 ± 27.1	32,100 ± 7,440	1.00 [1.00, 1.00]	393 ± 12.2	4.02 ± 1.10	7.05 ± 1.82
	10		410 ± 17.5	102,000 ± 24,200	1.00 [1.00, 6.02]	344 ± 116	4.22 ± 1.33	8.65 ± 2.02
SC	1		9.40 ± 2.17	6,470 ± 2,610	168 [94.5, 170]	440 ± 102	8.15 ± 1.17	13.3 ± 3.41
	3		24.7 ± 8.02	18,100 ± 7,150	133 [48.0, 170]	437 ± 94.7	8.73 ± 1.60	14.6 ± 5.00
	10		59.0 ± 20.6	42,900 ± 7,910	169 [122, 169]	470 ± 104	12.9 ± 5.69	18.5 ± 4.30

Mean ± standard deviation or median [range]; a) n = 3

6.2.1.2 Foreign phase I study (CTD 5.3.4.1: Study CSL312_1003 [October 2020 to May 2021])

A single intravenous dose of garadacimab 3 or 10 mg/kg was administered to Japanese healthy subjects, a single subcutaneous dose of garadacimab 200 mg was administered to Japanese healthy subjects and body weight-matched Caucasian healthy subjects, and a single subcutaneous dose of garadacimab 600 mg was administered to Japanese healthy subjects. Table 14 shows the pharmacokinetic parameters of garadacimab. There were no clear differences between the ethnic groups. ADA development was not observed.

Table 14. Pharmacokinetic parameters following a single dose of garadacimab

Route of administration	Population	Treatment group	N	C_{max} (µg/mL)	AUC_{inf} (µg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_z/F or V_d (L)	CL/F or CL (L/h)
IV[a)]	Japanese	3 mg/kg	4	72.5 ± 7.42	20,400 ± 2,910	4.51 [1.02, 8.00]	417 ± 37.7	6.10 ± 0.62	0.010 ± 0.002
		10 mg/kg	4	233 ± 29.9	61,100 ± 3,790	1.02 [1.02, 1.02]	449 ± 80.2	6.81 ± 0.75	0.011 ± 0.002
SC[b)]	Japanese	200 mg	12	21.2 ± 17.0	11,900 ± 5,840	169 [8.00, 171]	424 ± 72.2	12.5 ± 5.84	0.022 ± 0.014
	Caucasian	200 mg	13	15.4 ± 4.70	11,900 ± 3,610[c)]	168 [96.4, 340]	457 ± 55.7[c)]	12.1 ± 4.29[c)]	0.019 ± 0.007[c)]
	Japanese	600 mg	4	29.5 ± 4.85	21,800 ± 2,940	145 [95.8, 145]	427 ± 38.0	17.2 ± 2.55	0.028 ± 0.004

Mean ± standard deviation or median [range]; a) Formulation 1 (100 mg/mL); b)Formulation 2 (170 mg/mL); c) n = 12

6.2.2 Investigations in HAE patients

6.2.2.1 Foreign phase II study (CTD 5.3.5.1: Study CSL312_2001 [October 2018 to October 2021])

Multiple subcutaneous doses of garadacimab 75, 200, or 600 mg every 4 weeks (Q4W) were administered to non-Japanese patients with C1-INH HAE (HAE Type 1 or Type 2) aged ≥18 years, and multiple subcutaneous doses of garadacimab 600 mg Q4W were administered to non-Japanese patients with nC1-INH HAE (hereditary angioedema with normal C1-esterase inhibitor and a factor XII mutation [FXII HAE] or hereditary angioedema with normal C1-esterase inhibitor and a plasminogen gene mutation [PLG HAE]) aged ≥18 years (the corresponding dose[13)] was intravenously administered as the initial dose [see Section 7.1.1]). Table 15 shows the pharmacokinetic parameters of garadacimab after the last dose (Day 63) and the ratio of FXIIa-mediated kallikrein activity on Day 70 to baseline. The administration of garadacimab inhibited FXIIa-mediated kallikrein activity in a dose-dependent manner. The inhibition of FXIIa-mediated kallikrein activity was observed regardless of the HAE type of the patients.

Table 15. Pharmacokinetic parameters of garadacimab and the inhibition of FXIIa-mediated kallikrein activity after the last dose of multiple administration

Population	Treatment group (mg)	N	C_{max} (μg/mL)	AUC_{tau} (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_z/F (L)	CL/F (L/h)	Ratio of FXIIa-mediated kallikrein activity to baseline (%)
C1-INH HAE	75	9	10.6 ± 6.09	4,510 ± 2,420	143 [45.4, 196]	412 ± 97.0[a)]	10.6 ± 5.10[a)]	0.020 ± 0.008	110 ± 119
	200	8	15.9 ± 5.22	7,170 ± 2,410	166 [116, 218]	394 ± 85.6[a)]	17.0 ± 4.78[a)]	0.030 ± 0.008	63.5 ± 24.8
	600	7	56.4 ± 15.9	26,500 ± 8,150	166 [72.4, 188]	444 ± 44.0[b)]	17.1 ± 6.67[b)]	0.025 ± 0.008	11.8 ± 6.87
nC1-INH HAE (FXII HAE or PLG HAE)	600	6	43.0 ± 17.9[c)]	18,800 ± 8,380[c)]	146 [70.4, 334][c)]	348 ± 106[d)]	16.8 ± 7.83[d)]	0.038 ± 0.017[c)]	23.9 ± 32.1

Mean ± standard deviation or median [range]; a) n = 7; b) n = 5; c) n = 4; d) n = 3

6.2.2.2 Global phase III study (CTD 5.3.5.1: Study CSL312_3001 [January 2021 to June 2022])

Multiple subcutaneous doses of garadacimab 200 mg (400 mg as the initial dose only) were administered to patients with C1-INH HAE (HAE Type 1 or Type 2) aged ≥12 years once a month for 6 months [see Section 7.2.1]. Table 16 shows the time course of plasma garadacimab concentrations. There were no clear differences in plasma garadacimab concentration after garadacimab administration between the age groups (12-17 years/≥18 years) or between the races (Japanese/non-Japanese). The FXIIa-mediated kallikrein activity as the ratio to baseline at the trough time point after garadacimab administration remained between 76.8% ± 39.5% and 85.5% ± 38.3% from Day 31 to Day 182. The FXIIa-mediated kallikrein activity was inhibited (by appropriately 20% as the mean), even immediately before dosing during multiple subcutaneous administration of garadacimab. ADA developed in 1 subject after garadacimab administration (Day 182) in the garadacimab group.

[13)] The corresponding initial doses in the garadacimab 75, 200, and 600 mg Q4W groups were 40, 100, and 300 mg, respectively.

Table 16. Time course of plasma garadacimab concentrations (μg/mL) following multiple doses

Dosage regimen	Population		Day 31	Day 61	Day 91	Day 121	Day 151	Day 182
200 mg once a month	Overall population		10.5 ± 4.00 (39)	8.60 ± 3.91 (39)	8.39 ± 3.81 (39)	8.69 ± 3.93 (38)	8.20 ± 4.37 (39)	8.09 ± 4.28 (39)
	Age	12-17 years	11.3 ± 2.49 (4)	8.64 ± 3.43 (4)	8.36 ± 1.43 (4)	9.69 ± 2.42 (4)	7.30 ± 2.08 (4)	9.13 ± 4.97 (4)
		≥18 years	10.4 ± 4.16 (35)	8.59 ± 4.01 (35)	8.39 ± 4.01 (35)	8.58 ± 4.08 (34)	8.28 ± 4.52 (35)	7.97 ± 4.26 (35)
	Race	Japanese	10.2 ± 2.63 (4)	7.12 ± 1.50 (4)	6.27 ± 3.02 (4)	4.18 ± 1.63 (3)	6.97 ± 2.18 (4)	6.55 ± 2.15 (4)
		Non-Japanese	10.6 ± 4.16 (35)	8.77 ± 4.07 (35)	8.63 ± 3.85 (35)	9.08 ± 3.84 (35)	8.34 ± 4.56 (35)	8.26 ± 4.44 (35)

Mean ± standard deviation (N)

6.2.3 Population pharmacokinetic analyses

6.2.3.1 Population pharmacokinetic/pharmacodynamic analyses using the data of healthy subjects and HAE patients (CTD 5.3.3.5)

A population pharmacokinetic analysis (NONMEM version 7.5.0) was performed using plasma garadacimab concentration and other data (242 subjects, 2,560 time points) obtained from 5 clinical studies in healthy subjects and HAE patients.[14)] The pharmacokinetics of garadacimab was described by a 2-compartment model with first-order absorption and first-order elimination, using a base model in which clearance (CL, Q [clearance between the compartments]) and volume of distribution (V_d) (V2 [V_d of the central compartment] and V3 [V_d of the peripheral compartment]) were incorporated with allometric scaling by body weight. As a result of covariate assessment,[15)] race (Japanese/non-Japanese, Chinese/non-Chinese), health status (healthy subject/HAE patient), and serum creatinine, ALT, and bilirubin at baseline were selected as covariates for CL in the final model. Table 17 shows the results of investigating the effect of covariates using the final model. While body weight was identified as a covariate with the strongest impact on CL and $AUC_{tau,ss}$, there were no clear differences associated with different body weights in the monthly frequency of HAE attacks during the use of garadacimab [see Section 6.2.3.2]. In view of this, the applicant explained that dose adjustment according to body weight is not required because body weight difference is not clinically significant.

Table 18 shows the pharmacokinetic parameters of garadacimab following multiple subcutaneous doses of garadacimab 200 mg (400 mg as the initial dose only) once a month, estimated using the final model. There were no clear differences between Japanese and non-Japanese subjects.

A population pharmacokinetic/pharmacodynamic analysis was performed using FXIIa-mediated kallikrein activity measurement data (262 subjects, 3,163 time points) obtained from 5 clinical studies in healthy subjects and HAE patients[14)] and pharmacokinetic data consisting of the dataset used for the population pharmacokinetic analysis and data from 20 placebo-treated subjects.

Table 19 shows the steady-state pharmacokinetic parameters of garadacimab following multiple subcutaneous doses of garadacimab 200 mg (400 mg as the initial dose only) once a month in each population (all ages/ages

14) Phase I studies in healthy subjects (Studies 1001 and 1003) and clinical studies in HAE patients (a phase II study [Study 2001] and phase III studies [Studies 3001 and 3002]).

15) The following factors were investigated as covariates: age at baseline, body weight at baseline, sex, race (Japanese/non-Japanese, Asian/non-Asian, and Chinese/non-Chinese), health status (healthy subject/HAE patient), HAE type (C1-INH HAE Type 1/C1-INH HAE Type 2/nC1-INH HAE [HAE Type 3]), formulation (Formulation 1 [100 mg/mL]/Formulation 2 [170 mg/mL]), hepatic function markers at baseline (AST, ALT, and bilirubin), and renal function markers at baseline (creatinine clearance, serum creatinine, and estimated glomerular filtration rate [eGFR]). Disease-specific covariates such as FXIIa-mediated kallikrein activity at baseline were also investigated. If possible, ADA, neutralizing antibody, and rescue drugs and concomitant drugs (analgesics, antihistamines, anti-inflammatory drugs, and antirheumatic drugs) were also to be investigated.

12-17/ages ≥18) and the minimum ratio of FXIIa-mediated kallikrein activity to baseline, estimated using the final model for the pharmacokinetic/pharmacodynamic analysis.[16] There were no clear differences between the age groups of 12 to 17 years and ≥18 years in pharmacokinetics or pharmacodynamics after administration of garadacimab.

Table 17. Effect of covariates in the final model

Covariate		CL (L/h)	$AUC_{tau,ss}$ (μg·h/mL)
HAE patient		1.06 [0.96, 1.17]	0.94 [0.86, 1.04]
Japanese		1.27 [1.12, 1.43]	0.79 [0.70, 0.89]
Chinese		1.02 [0.85, 1.21]	0.98 [0.82, 1.17]
Body weight (kg)[a)]	55	0.76 [0.72, 0.80]	1.32 [1.26, 1.39]
	65	0.92 [0.91, 0.93]	1.09 [1.07, 1.11]
	75	1.08 [1.07, 1.10]	0.92 [0.91, 0.94]
	85	1.25 [1.20, 1.30]	0.80 [0.77, 0.83]
	95	1.43 [1.34, 1.51]	0.70 [0.66, 0.75]
	105	1.60 [1.47, 1.73]	0.62 [0.58, 0.68]
Serum creatinine (mg/dL)[a)]	0.6	1.01 [0.97, 1.05]	0.99 [0.95, 1.03]
	1	0.99 [0.94, 1.04]	1.01 [0.96, 1.07]
Bilirubin (μmol/L)[a)]	4	1.10 [1.05, 1.15]	0.91 [0.87, 0.95]
	13	0.94 [0.91, 0.97]	1.07 [1.04, 1.10]
ALT (U/L)[a)]	10	1.08 [1.00, 1.15]	0.93 [0.87, 1.00]
	40	0.96 [0.93, 1.00]	1.04 [1.00, 1.07]

Ratio to a typical case (healthy subject; non-Japanese; non-Chinese; body weight at baseline, 70 kg; serum creatinine, 0.75 mg/dL; ALT, 25 U/L; bilirubin, 8 μmol/L): median [95% CI].

a) The upper and lower limits in simulation were defined as 10th and 90th percentiles, respectively, of the dataset.

Table 18. Steady-state pharmacokinetic parameters of garadacimab following multiple doses, estimated using the final model

Population[a)]	N	$AUC_{tau,ss}$ (μg·h/mL)	$C_{max,ss}$ (μg/mL)	$C_{min,ss}$ (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)
Overall population	173	9,920 ± 4,470	20.5 ± 9.66	8.94 ± 4.64	140 [30.0, 185]	442 ± 120
Japanese	12	9,420 ± 2,310	20.1 ± 5.34	7.80 ± 1.90	136 [126, 170]	394 ± 61.6
Non-Japanese	161	9,960 ± 4,590	20.6 ± 9.92	9.02 ± 4.77	141 [30.0, 185]	446 ± 123

Mean ± standard deviation or median [range]; a) subjects of Studies 2001, 3001, and 3002

Table 19. Steady-state pharmacokinetic parameters of garadacimab and the inhibition of FXIIa-mediated kallikrein activity (minimum ratio) following multiple doses, estimated using the final model

Population (HAE patients)	$C_{max,ss}$ (μg/mL)	$AUC_{tau,ss}$ (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	Minimum ratio of FXIIa-mediated kallikrein activity to baseline (%)
Overall population	23.9 ± 12.9	11,900 ± 5,940	141 ± 31.4	501 ± 170	45.8 ± 28.0
Ages 12-17	27.3 ± 14.4	13,700 ± 6,670	143 ± 31.4	524 ± 173	40.7 ± 27.0
Ages ≥18	20.5 ± 10.0	10,100 ± 4,400	140 ± 31.4	478 ± 163	50.9 ± 28.2

Mean ± standard deviation

6.2.3.2 Exposure-response analysis (CTD 5.3.3.5)

An exposure-response analysis was performed using the results of clinical studies in HAE patients (Studies 2001, 3001, and 3002). The threshold value of each pharmacokinetic parameter for a 90% reduction in the relative risk of HAE attacks[17] was predicted to be 14.5 μg/mL for $C_{max,ss}$, 6.00 μg/mL for $C_{min,ss}$, and 7,640 μg·h/mL for $AUC_{tau,ss}$. With once-monthly administration of garadacimab 200 mg, the probability of exceeding the threshold value was estimated to be 0.754 for $C_{max,ss}$, 0.731 for $C_{min,ss}$, and 0.737 for $AUC_{tau,ss}$. The mean monthly frequency of HAE attacks [95% confidence interval (CI)] at Month 3 for 54, 63, 79, 94, and 118 kg body weight, which were on the 5th, 25th, 50th, 75th, and 95th percentiles of body weight,

[16] The relationship between the plasma garadacimab concentration and FXIIa-mediated kallikrein activity was described by a sigmoid maximal effect (E_{max}) model, and FXIIa-mediated kallikrein activity at baseline was selected as a covariate. However, the covariate did not have a strong impact on the half-maximal effective concentration (EC_{50}), showing that it was unlikely to have a clinically significant effect.

[17] Relative risk compared with the monthly frequency of HAE attacks at baseline.

respectively, was estimated to be 0.18 [0.09, 0.29], 0.20 [0.11, 0.33], 0.24 [0.12, 0.37], 0.26 [0.15, 0.43], and 0.30 [0.17, 0.46] times, respectively. Thus, body weight difference had no clear effects on the frequency of HAE attacks.

6.R Outline of the review conducted by PMDA

6.R.1 Effect of patient characteristics on pharmacokinetics

On the basis of the data submitted, PMDA has concluded that there were no clear effects of patient characteristics such as age (12-17 years/≥18 years), body weight, and race (Japanese/non-Japanese) on the pharmacokinetics of garadacimab, and from the viewpoint of clinical pharmacology, no patient populations requiring dose adjustment were identified.

6.R.2 ADA

The applicant's explanation about the status of ADA development in clinical studies and the effect of ADA development on the pharmacokinetics, efficacy, and safety of garadacimab:

In clinical studies in HAE patients (Studies 2001, 3001, and 3002), ADA developed after garadacimab administration in 2.9% (5 of 172 subjects [1 in Study 3001 and 5 in Study 3002 (including the 1 ADA-positive subject in Study 3001)]).

There were no clear differences in plasma garadacimab concentration between patients with and without ADA development in Studies 3001 and 3002.[18)] Table 20 shows the monthly frequency of HAE attacks by ADA development status in Studies 3001 and 3002. Table 21 shows the incidences of adverse events, hypersensitivity, and injection site reaction-related events by ADA development status in Studies 2001, 3001, and 3002. All events of hypersensitivity and injection site reaction observed in ADA-positive subjects were mild or moderate and non-serious.

Table 20. Monthly frequency of HAE attacks (times/month) by ADA development status

	ADA negative		ADA positive[a)]	
	Run-in period	Treatment period	Run-in period	Treatment period
Study 3001[b)]	3.12 ± 2.05 (38)	0.28 ± 0.69 (38)	1.22 (1)	0.0 (1)
Study 3002[b)]	3.61 ± 2.42 (156)	0.16 ± 0.37 (156)	2.28 ± 1.68 (5)	0.04 ± 0.08 (5)

Mean ± standard deviation (N) or individual data

a) ADA was positive at any of the measurement time points.

b) For study design, see Section 7.2.1 or 7.2.2.

[18)] In Study 3001, the trough plasma garadacimab concentrations on Day 182 in ADA-positive and ADA-negative subjects were 10.8 μg/mL (1 subject) and 8.02 ± 4.31 μg/mL (38 subjects), respectively. In Study 3002, the trough plasma garadacimab concentrations at Month 6 in ADA-positive and ADA-negative subjects were 9.69 μg/mL (1 subject) and 7.70 ± 4.46 μg/mL (138 subjects), respectively, and those at Month 12 in ADA-positive and ADA-negative subjects were 6.06 to 8.03 μg/mL (3 subjects) and 7.44 ± 4.81 μg/mL (99 subjects), respectively. For reference, the plasma garadacimab concentration in 1 ADA-positive subject who discontinued the study due to injection site reaction in Study 3002 was 2.39 μg/mL approximately 40 days after the last dose of garadacimab.

Table 21. Incidences of adverse events by ADA development status (pooled analysis [Studies 2001, 3001, and 3002])

	ADA negative (N = 167)	ADA positive[a)] (N = 5)
All adverse events	145 (86.8)	3 (60.0)
Hypersensitivity (SMQ)	33 (19.8)	1 (20.0)
Serious events	1 (0.6)	0
Injection site reaction-related events	31 (18.6)	2 (40.0)

n (%)

a) ADA was positive at any of the measurement time points.

In view of the above, no clear effects of ADA on the pharmacokinetics, efficacy, or safety of garadacimab have been identified at present.

PMDA's view:

The information obtained to date does not suggest any clinical problems associated with ADA development. However, since the number of subjects with ADA development in clinical studies is limited, it is difficult to draw a definite conclusion regarding the effect of ADA on the pharmacokinetics, efficacy, and safety of garadacimab. The applicant is required to provide appropriate information in the package insert regarding the status of ADA development in the clinical studies of garadacimab, and to continue collecting information on the effect of ADA development even after the market launch and immediately provide new information to healthcare professionals when it becomes available.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 3 studies shown in Table 22.

Table 22. Efficacy and safety evaluation data

Phase	Study identifier	Region	Population	N	Outline of dosage regimen	Main endpoints [Primary endpoint]
II	CSL312_2001	Foreign	Patients with C1-INH HAE (HAE Type 1 or Type 2) and patients with nC1-INH HAE (FXII HAE or PLG HAE)	Patients with C1-INH HAE (HAE Type 1 or Type 2) [Double-blind part] (1) 9 (2) 8 (3) 7 (4) 8 [Open-label part] (5) 6 Patients with nC1-INH HAE (FXII HAE or PLG HAE) [Open-label part] (6) 6	**Treatment period 1** (1) Garadacimab 75 mg Q4W SC (garadacimab 40 mg IV as the initial dose)[a)] (2) Garadacimab 200 mg Q4W SC (garadacimab 100 mg IV as the initial dose)[a)] (3) Garadacimab 600 mg Q4W SC (garadacimab 300 mg IV as the initial dose)[a)] (4) Placebo Q4W SC (placebo IV as the initial dose)[a)] (5) Garadacimab 400 mg Q2W SC (6) Garadacimab 600 mg Q4W SC (garadacimab 300 mg IV as the initial dose)[a)] **Treatment period 2** Open-label garadacimab 200 mg or 600 mg, depending on the treatment in treatment period 1 and the HAE type, Q4W SC	Efficacy [Monthly frequency of HAE attacks confirmed by the investigator during the double-blind part in patients with C1-INH HAE (HAE Type 1 or Type 2) in treatment period 1] Safety
III	CSL312_3001	Global	Patients with C1-INH HAE (HAE Type 1 or Type 2)	(1) 39 (2) 25	The following treatment was provided under blinded conditions: (1) Garadacimab 200 mg (garadacimab 400 mg as the initial dose only) once a month SC (2) Placebo once a month SC	Efficacy [Monthly frequency of HAE attacks confirmed by the investigator during the treatment period] Safety Pharmacokinetics
III	CSL312_3002 (Extension study)	Global	Patients with C1-INH HAE (HAE Type 1 or Type 2)[b)] and patients with nC1-INH HAE (FXII HAE)[b)]	161	Open-label garadacimab 200 mg (garadacimab 400 mg as the initial dose only, for new participants) once a month SC	Safety Efficacy

SC, subcutaneous administration; IV, intravenous administration

a) Garadacimab was administered IV as the initial dose, followed by garadacimab SC starting 1 week later.

b) Subjects who completed the preceding study (Study 2001 or 3001) and new participants with C1-INH HAE (HAE Type 1 or Type 2) aged ≥12 years who had not previously received garadacimab.

7.1 Phase II study

7.1.1 Foreign study (CTD 5.3.5.1: Study CSL312_2001 [October 2018 to October 2021])

A placebo-controlled, randomized, parallel-group study was conducted in 5 countries or regions, including Germany, the United States (US), and Israel, to investigate the efficacy, safety, and pharmacokinetics of garadacimab in patients with C1-INH HAE (HAE Type 1 or Type 2) (target sample size: up to 40 subjects [double-blind part, 32 subjects (8 in each group)[19)]; open-label part, 8 subjects (8 in the 400 mg every 2 weeks [Q2W] group)[20)]]) and patients with nC1-INH HAE (FXII HAE or PLG HAE) (open-label part; target sample size: up to 10 subjects).

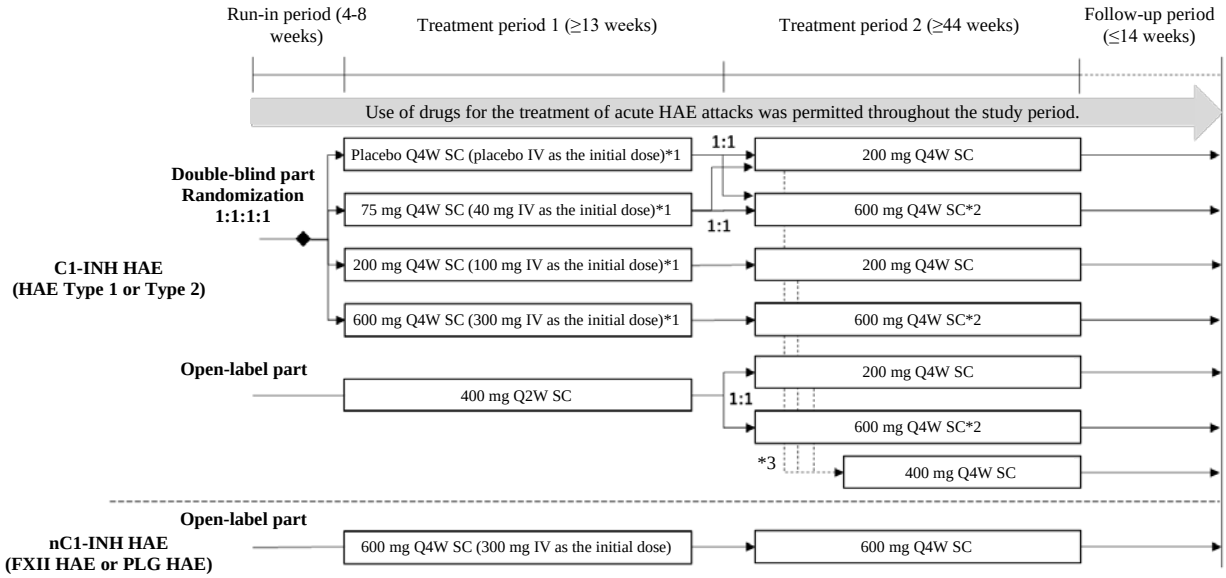
[19)] Assuming an expected monthly frequency of HAE attacks, which was assessed as the primary endpoint, of 0.6 times in the 200 mg Q4W and 600 mg Q4W groups and 2.9 times in the placebo group, the number of subjects necessary to ensure ≥82% power at a 2-sided significance level of 2.5% using the Mann-Whitney test for pairwise comparisons between the 200 mg Q4W and placebo groups and between the 600 mg Q4W and placebo groups was calculated to be 7 in each group. The 75 mg Q4W group was established for pharmacokinetic measurement and consisted of 7 subjects as in other groups to ensure blindness. Taking dropouts into account, the target sample size was set as 8 subjects in each group.

[20)] The first 32 patients with C1-INH HAE (HAE Type 1 or Type 2) were randomized under blinded conditions, and up to 8 subjects were then enrolled in the 400 mg Q2W group.

Table 23 shows the main inclusion/exclusion criteria in this study.

Table 23. Main inclusion/exclusion criteria

Inclusion criteria	**Run-in period** (1) Patients aged 18-65 years (inclusive) at the time of informed consent (2) Patients who met the following criteria and were given a definite diagnosis of C1-INH HAE (HAE Type 1 or Type 2) or nC1-INH HAE (FXII HAE or PLG HAE) [C1-INH HAE (HAE Type 1 or Type 2)] • Having a documented medical history corresponding to HAE (subcutaneous or mucosal non-pruritic edema attacks without urticaria) • Having medical records of C1-INH protein level or activity <50% of the reference range and C4 protein level below the lower limit of the reference range [nC1-INH HAE (FXII HAE or PLG HAE)] • Having a documented medical history corresponding to HAE (subcutaneous or mucosal non-pruritic edema attacks without urticaria) • Having medical records of documented HAE-related *FXII* or *PLG* gene mutations and C1-INH protein level or activity within the range of 70% to 120% of the normal values (3) [Patients with C1-INH HAE (HAE Type 1 or Type 2)] Patients with a medical record of ≥4 HAE attacks during 2 consecutive months within 3 months before screening (for subjects who had been treated with drugs for the prophylaxis of HAE attacks within 3 months before screening, ≥4 HAE attacks during 2 consecutive months within 3 months before receiving the treatment for the prophylaxis of HAE attacks) (4) [Patients with nC1-INH HAE (FXII HAE or PLG HAE)] Patients with a medical record of ≥1 HAE attack within 3 months before screening (for subjects who had been treated with drugs for the prophylaxis of HAE attacks within 3 months before screening, ≥1 HAE attack within 3 months before receiving the treatment for the prophylaxis of HAE attacks) **Treatment period 1** (1) Patients who participated in the run-in period for ≥4 weeks (28 days) (2) [Patients with C1-INH HAE (HAE Type 1 or Type 2)] Patients with a definite diagnosis of C1-INH HAE (HAE Type 1 or Type 2) (C1-INH protein level or activity <50% of the reference range and C4 protein level below the lower limit of the reference range), and having had ≥2 HAE attacks within 4 consecutive weeks during the run-in period (3) [Patients with nC1-INH HAE (FXII HAE or PLG HAE)] Patients who developed ≥1 HAE attack during the run-in period
Exclusion criteria	**Run-in period** (1) Patients with a past history of uncontrollable abnormal bleeding due to abnormal blood coagulation or with a current clinically significant blood coagulation abnormality or a current bleeding risk (2) Patients with C1-INH HAE (HAE Type 1 or Type 2) who had resistance to C1-INH treatment for HAE



*1: Garadacimab or placebo was intravenously administered as the initial dose, followed by subcutaneous administration of garadacimab or placebo Q4W starting 1 week later.
*2: After the revision of Protocol Version 2 (March 20, 2020), all patients with C1-INH HAE (HAE Type 1 or Type 2) received 200 mg SC Q4W.
*3: For subjects who developed ≥3 HAE attacks within 8 weeks after receiving 200 mg Q4W, the dose could be increased to 400 mg Q4W at the investigator's discretion in consultation with the applicant.

Figure 1. Design of Study 2001 (SC, subcutaneous administration; IV, intravenous administration)

This study consisted of a run-in period (up to 8 weeks), treatment period 1 (13 weeks), treatment period 2 (≥44 weeks[21)]), and a follow-up period (≤14 weeks) (Figure 1), and subjects who completed the study were allowed to enter a long-term study (Study 3002). The frequency of HAE attacks in each subject was evaluated during the run-in period before the study treatment. If the onset of HAE attacks at the predetermined frequency (Table 23) was confirmed by the investigator, the subject was allowed to enter treatment period 1.

The dosage regimen in treatment period 1 was as follows: In the double-blind part in patients with C1-INH HAE (HAE Type 1 or Type 2), garadacimab[22)] 40, 100, or 300 mg or placebo was intravenously administered as the initial dose under blinded conditions, followed by subcutaneous administration of garadacimab 75, 200, or 600 mg or placebo Q4W, starting 1 week later, through Week 13. In the open-label part in patients with C1-INH HAE (HAE Type 1 or Type 2), garadacimab 400 mg was subcutaneously administered Q2W through Week 13 under open-label conditions. In the open-label part in patients with nC1-INH HAE (FXII HAE or PLG HAE), garadacimab 300 mg was intravenously administered as the initial dose under open-label conditions, followed by subcutaneous administration of garadacimab 600 mg Q4W, starting 1 week later, through Week 13. Subcutaneous administration in treatment period 1 was performed by subjects themselves under the supervision of the investigator, etc.

The dosage regimen in treatment period 2 was as follows: Subjects who received subcutaneous administration of garadacimab 75 mg or placebo Q4W in the double-blind part in patients with C1-INH HAE (HAE Type 1 or Type 2) and subjects who received subcutaneous administration of garadacimab 400 mg Q2W in the open-

21) Treatment period 2 was set as at least 44 weeks and was extended until either the start of the long-term study (Study 3002), to which subjects could transition, or discontinuation of the current study.
22) A vial product of Formulation 1 (100 mg/mL) was used.

label part in patients with C1-INH HAE (HAE Type 1 or Type 2) in treatment period 1 were randomized again[23] to receive subcutaneous administration of garadacimab 200 or 600 mg Q4W for ≥44 weeks (Figure 1). Other subjects continued the same dosage regimen as that for subcutaneous administration in treatment period 1 for ≥44 weeks. In subjects who developed ≥3 HAE attacks within 8 weeks after receiving 200 mg Q4W, the dose could be increased to 400 mg Q4W at the investigator's discretion in consultation with the applicant. Since the dose in the confirmatory study was determined based on the results of treatment period 1, all patients with C1-INH HAE (HAE Type 1 or Type 2) received 200 mg Q4W SC after the revision of Protocol Version 2 (March 20, 2020). In treatment period 2, the first 3 doses were self-administered by subjects under the supervision of the investigator, etc. at the study site, and the subsequent doses could be self-administered by the subjects at home or the study site.

Throughout the study period, it was permitted to use drugs for the treatment of acute HAE attacks (plasma-derived or genetically-modified C1-INH products [for intravenous injection], icatibant acetate, and ecallantide) and to use C1-INH products (for intravenous injection) for the prophylaxis of HAE attacks before invasive procedures (once per procedure). The use of drugs for the prophylaxis of HAE attacks (C1-INH products or antifibrinolytic drugs) and androgen products was prohibited throughout the run-in period and treatment periods (1 and 2).

The disposition of the intent-to-treat (ITT) population of each part was as follows: (a) double-blind part in randomized patients with C1-INH HAE (HAE Type 1 or Type 2), 32 subjects (9 in the 75 mg Q4W group, 8 in the 200 mg Q4W group, 7 in the 600 mg Q4W group, and 8 in the placebo group); (b) open-label part in patients with C1-INH HAE (HAE Type 1 or Type 2), 6 subjects (400 mg Q2W group); and (c) open-label part in patients with nC1-INH HAE (FXII HAE or PLG HAE), 6 subjects (600 mg Q4W group). The subjects in the ITT populations were included in the efficacy analysis. All subjects who received at least 1 dose of the study drug were included in the safety analysis in each part.

In treatment period 1, the study was discontinued in 1 subject in the nC1-INH HAE (FXII HAE or PLG HAE) group, and the reason for discontinuation was lack of efficacy.

Table 24 shows the monthly frequency of HAE attacks during treatment period 1 [see Section 10 for definitions], which was assessed as the primary efficacy endpoint. Statistically significant differences were observed in pairwise comparisons between the 200 mg Q4W and placebo groups and between the 600 mg Q4W and placebo groups, which demonstrated the superiority of garadacimab 200 mg Q4W and 600 mg Q4W over placebo.

Table 25 shows the results of the primary endpoint in the open-label part in patients with C1-INH HAE (HAE Type 1 or Type 2) and the open-label part in patients with nC1-INH HAE (FXII HAE or PLG HAE).

[23] The treatment (placebo Q4W, garadacimab 75 mg Q4W, or garadacimab 400 mg Q2W) in treatment period 1 was used as a stratification factor.

Table 24. Monthly frequency of HAE attacks during treatment period 1 (double-blind part in patients with C1-INH HAE [HAE Type 1 or Type 2], ITT population)

	75 mg Q4W	200 mg Q4W	600 mg Q4W	Placebo
Monthly frequency of HAE attacks (times/month) during the run-in period	6.13 ± 1.76 (9) 6.30 [3.15, 8.40]	5.68 ± 3.71 (8) 5.67 [1.96, 13.6]	3.48 ± 1.52 (7) 2.95 [1.69, 6.27]	5.07 ± 2.42 (8) 4.57 [2.17, 8.45]
Monthly frequency of HAE attacks (times/month) during the treatment period	0.48 ± 1.06 (9) 0.00 [0.00, 3.26]	0.05 ± 0.13 (8) 0.00 [0.00, 0.36]	0.35 ± 0.41 (7) 0.34 [0.00, 1.05]	4.24 ± 1.80 (8) 4.61 [1.40, 7.16]
P value[a)]	-	<0.001	<0.001	

Upper row, mean ± standard deviation (N); lower row, median [minimum, maximum]; -, not calculated.

a) Two-sided significance level of 2.5%, Mann-Whitney test, adjustment for multiplicity in hypothesis testing using Bonferroni correction.

Table 25. Monthly frequency of HAE attacks during treatment period 1 (open-label part in patients with C1-INH HAE [HAE Type 1 or Type 2] or patients with nC1-INH HAE [FXII HAE or PLG HAE], ITT population)

	C1-INH HAE (HAE Type 1 or Type 2)	nC1-INH HAE (FXII HAE or PLG HAE)
	400 mg Q2W	600 mg Q4W
Monthly frequency of HAE attacks (times/month) during the run-in period	3.27 ± 1.43 (6) 3.32 [1.45, 5.07]	2.95 ± 0.99 (6) 3.20 [1.45, 4.35]
Monthly frequency of HAE attacks (times/month) during the treatment period	0.14 ± 0.22 (6) 0.00 [0.00, 0.43]	2.60 ± 2.50 (6) 2.46 [0.00, 6.80]

Upper row, mean ± standard deviation (N); lower row, median [minimum, maximum].

In treatment period 1, adverse events were observed as follows: (a) double-blind part in patients with C1-INH HAE (HAE Type 1 or Type 2), 77.8% of subjects in the 75 mg Q4W group (7 of 9 subjects), 87.5% of subjects in the 200 mg Q4W group (7 of 8 subjects), 100% of subjects in the 600 mg Q4W group (7 of 7 subjects), and 87.5% of subjects in the placebo group (7 of 8 subjects); (b) open-label part in patients with C1-INH HAE (HAE Type 1 or Type 2), 66.7% of subjects in the 400 mg Q2W group (4 of 6 subjects); and (c) open-label part in patients with nC1-INH HAE (FXII HAE or PLG HAE), 66.7% of subjects in the 600 mg Q4W group (4 of 6 subjects). Table 26 shows the main events.

There were no deaths or adverse events leading to discontinuation.

Serious adverse events were observed in 16.7% (1 of 6 subjects [hereditary angioedema]) of patients with nC1-INH HAE (FXII HAE or PLG HAE). However, a causal relationship to the study drug was ruled out.

Adverse drug reactions were observed as follows: (a) double-blind part in patients with C1-INH HAE (HAE Type 1 or Type 2), 22.2% of subjects in the 75 mg Q4W group (2 of 9 subjects), 12.5% of subjects in the 200 mg Q4W group (1 of 8 subjects), 71.4% of subjects in the 600 mg Q4W group (5 of 7 subjects), and 37.5% of subjects in the placebo group (3 of 8 subjects); (b) open-label part in patients with C1-INH HAE (HAE Type 1 or Type 2), 50.0% of subjects in the 400 mg Q2W group (3 of 6 subjects); and (c) open-label part in patients with nC1-INH HAE (FXII HAE or PLG HAE), 16.7% of subjects in the 600 mg Q4W group (1 of 6 subjects).

Table 26. Adverse events observed in ≥2 subjects in any group (treatment period 1, safety analysis set)

Population	C1-INH HAE (HAE Type 1 or Type 2)					nC1-INH HAE (FXII HAE or PLG HAE)
Part	Double-blind part				Open-label part	Open-label part
Event	75 mg Q4W (N = 9)	200 mg Q4W (N = 8)	600 mg Q4W (N = 7)	Placebo (N = 8)	400 mg Q2W (N = 6)	600 mg Q4W (N = 6)
Upper respiratory tract infection	2 (22.2)	3 (37.5)	0	2 (25.0)	0	0
Nasopharyngitis	0	2 (25.0)	1 (14.3)	0	0	1 (16.7)
Injection site erythema	0	1 (12.5)	1 (14.3)	2 (25.0)	0	0
Headache	0	1 (12.5)	2 (28.6)	1 (12.5)	2 (33.3)	0
Rash	0	1 (12.5)	2 (28.6)	0	0	0
Injection site pain	0	0	3 (42.9)	0	1 (16.7)	0
Chest discomfort	0	0	2 (28.6)	0	0	0
Nausea	0	0	1 (14.3)	2 (25.0)	0	1 (16.7)

n (%) MedDRA ver. 24.1

In treatment period 2, adverse events were observed as follows: (a) patients with C1-INH HAE (HAE Type 1 or Type 2), 83.3% of subjects treated at 200 mg Q4W (30 of 36 subjects), 66.7% of subjects treated at 400 mg Q4W (2 of 3 subjects), 94.4% of subjects treated at 600 mg Q4W (17 of 18 subjects), and 94.7% of garadacimab-treated subjects (36 of 38 subjects); and (b) patients with nC1-INH HAE (FXII HAE or PLG HAE), 100% of subjects treated at 600 mg Q4W (2 of 2 subjects). Table 27 shows the main events.

There were no deaths or adverse events leading to discontinuation.

Serious adverse events were observed in patients with C1-INH HAE (HAE Type 1 or Type 2) as follows: 2.8% of subjects treated at 200 mg Q4W (1 of 36 subjects [diverticular perforation]), 5.6% of subjects treated at 600 mg Q4W (1 of 18 subjects [asthma]), and 5.3% of garadacimab-treated subjects (2 of 38 subjects [diverticular perforation, asthma]). However, a causal relationship to the study drug was ruled out for all of these events.

Adverse drug reactions were observed in patients with C1-INH HAE (HAE Type 1 or Type 2) as follows: 13.9% of subjects treated at 200 mg Q4W (5 of 36 subjects), 22.2% of subjects treated at 600 mg Q4W (4 of 18 subjects), and 21.1% of garadacimab-treated subjects (8 of 38 subjects).

Table 27. Adverse events observed in ≥2 subjects in any group (treatment period 2, safety analysis set)

Population	C1-INH HAE (HAE Type 1 or Type 2)				nC1-INH HAE (FXII HAE or PLG HAE)
Event	200 mg Q4W (N = 36)	400 mg Q4W (N = 3)	600 mg Q4W (N = 18)	Garadacimab-treated subjects (N = 38)	600 mg Q4W (N = 2)
Headache	6 (16.7)	0	4 (22.2)	9 (23.7)	1 (50.0)
Abdominal pain	5 (13.9)	1 (33.3)	1 (5.6)	7 (18.4)	0
Upper respiratory tract infection	4 (11.1)	0	1 (5.6)	5 (13.2)	0
Nasopharyngitis	3 (8.3)	0	3 (16.7)	5 (13.2)	0
Arthralgia	3 (8.3)	0	1 (5.6)	4 (10.5)	0
Rotator cuff syndrome	3 (8.3)	0	0	3 (7.9)	0
Cough	2 (5.6)	0	3 (16.7)	5 (13.2)	0
Sinusitis	2 (5.6)	0	2 (11.1)	4 (10.5)	0
Toothache	2 (5.6)	0	2 (11.1)	4 (10.5)	0
Back pain	2 (5.6)	0	2 (11.1)	4 (10.5)	0
Urinary tract infection	2 (5.6)	0	1 (5.6)	3 (7.9)	1 (50.0)
Contusion	2 (5.6)	0	1 (5.6)	3 (7.9)	0
Hordeolum	2 (5.6)	0	0	2 (5.3)	0
Abdominal pain upper	2 (5.6)	0	0	2 (5.3)	0
Dyspepsia	2 (5.6)	0	0	2 (5.3)	1 (50.0)
Inguinal hernia	2 (5.6)	0	0	2 (5.3)	0
Torticollis	2 (5.6)	0	0	2 (5.3)	0
Pregnancy of partner	2 (5.6)	0	0	2 (5.3)	0
Pneumonia	1 (2.8)	1 (33.3)	0	2 (5.3)	0
Vulvovaginal mycotic infection	1 (2.8)	1 (33.3)	0	2 (5.3)	0
Pain in extremity	1 (2.8)	0	4 (22.2)	5 (13.2)	0
Injection site erythema	1 (2.8)	0	3 (16.7)	4 (10.5)	0
Nausea	1 (2.8)	0	2 (11.1)	3 (7.9)	0
Fatigue	1 (2.8)	0	2 (11.1)	3 (7.9)	0
Paraesthesia	1 (2.8)	0	1 (5.6)	2 (5.3)	0
Asthma	1 (2.8)	0	1 (5.6)	2 (5.3)	0
Ligament sprain	1 (2.8)	0	1 (5.6)	2 (5.3)	0
Erythema	1 (2.8)	0	1 (5.6)	2 (5.3)	0
SARS-CoV-2 test positive	1 (2.8)	0	1 (5.6)	2 (5.3)	0
Pregnancy	1 (2.8)	0	1 (5.6)	2 (5.3)	0
Gastritis	0	0	2 (11.1)	2 (5.3)	0
Anxiety	0	0	2 (11.1)	2 (5.3)	0

n (%) MedDRA ver. 24.1

Tabulated based on the dose of garadacimab at the onset of the adverse event.

7.2 Phase III studies

7.2.1 Global study (CTD 5.3.5.1: Study CSL312_3001 [January 2021 to June 2022])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 7 countries or regions, including Japan, the US, and Germany, to investigate the superiority over placebo and safety of garadacimab in patients with C1-INH HAE (HAE Type 1 or Type 2) aged ≥12 years (target sample size: 60 subjects[24)] [36 in the garadacimab group and 24 in the placebo group]).

Table 28 shows the main inclusion/exclusion criteria in this study.

[24)] Assuming an expected monthly frequency of HAE attacks, which was assessed as the primary endpoint, of 0.3125 times in the garadacimab group and 1.3 times in the placebo group, the number of subjects necessary to ensure ≥90% power at a 2-sided significance level of 5%, with a garadacimab-placebo allocation ratio of 3:2, was calculated to be 24 in the garadacimab group and 16 in the placebo group. To increase the potential enrollment of adolescent patients (aged 12-17 years) in the study in an attempt to randomize approximately 5 adolescent patients to the garadacimab and placebo groups at a ratio of 3:2 in the treatment period, thus ensuring that 40 subjects complete the treatment period in the study, and to obtain sufficient safety information, 20 subjects were added to the sample size. Thus, the target sample size was eventually set as 60 subjects (36 in the garadacimab group and 24 in the placebo group).

Table 28. Main inclusion/exclusion criteria

Inclusion criteria	**Run-in period** (1) Patients aged ≥12 years at the time of informed consent (2) Patients who met the following criteria and were given a definite diagnosis of C1-INH HAE (HAE Type 1 or Type 2) • Having a documented medical history corresponding to HAE (subcutaneous or mucosal non-pruritic edema attacks without urticaria) • Having a medical record of C1-INH protein level or activity ≤50% of the reference range • Having a medical record of C4 protein level below the lower limit of the reference range (3) Patients with a medical record of ≥3 HAE attacks within 3 months before screening (for subjects who had been treated with drugs for the prophylaxis of HAE attacks within 3 months before screening, ≥3 HAE attacks within 3 consecutive months before receiving the treatment for the prophylaxis of HAE attacks) **Treatment period** (1) Patients who participated in the run-in period for ≥1 month (2) Patients whose mean monthly frequency of HAE attack during the run-in period was ≥1 times (3) Patients with C1-INH activity, C1-INH protein level, and C4 protein level documented before randomization
Exclusion criteria	**Run-in period** (1) Patients with other concurrent angioedemas such as idiopathic or acquired angioedema, recurrent angioedema with urticaria, and nC1-INH HAE (HAE Type 3) (2) (Only for adult patients) Patients who had received treatment with drugs for the prophylaxis of HAE attacks (C1-INH products, androgen products, antifibrinolytic drugs, or other small-molecule drugs) within 2 weeks before the run-in period (Only for patients aged ≤17 years) Patients who had received long-term treatment with drugs for the prophylaxis of HAE attacks before screening (3) Patients who had received monoclonal antibodies such as lanadelumab (genetical recombination) within 3 months before the run-in period

This study consisted of a run-in period (up to 2 months) and a treatment period (6 months), and subjects who completed the study then entered the follow-up period (2 months) or a long-term study (Study 3002). The frequency of HAE attacks in each subject was evaluated during the run-in period. If the development of ≥2 HAE attacks was confirmed by the investigator during the run-in period, the subject was allowed to enter the treatment period.

The dosage regimen in the treatment period was as follows: Garadacimab[25] 200 mg (400 mg as the initial dose only) or placebo was subcutaneously administered once a month for 6 months. After receiving training on the administration method, the first 3 doses were self-administered by subjects or their caregivers under the supervision of the investigator, etc. at study visits, and the subsequent doses could be self-administered by the subjects or their caregivers.

Throughout the study period, while the use of drugs for the prophylaxis of HAE attacks (C1-INH products, androgen products, antifibrinolytic drugs, danazol, lanadelumab [genetical recombination], etc.) was prohibited, it was permitted to use drugs for the treatment of acute HAE attacks (plasma-derived or genetically-modified C1-INH products, icatibant acetate, and ecallantide) and to use C1-INH products (for intravenous injection) for the prophylaxis of HAE attacks before invasive procedures.

A total of 65 randomized[26] subjects (39 in the garadacimab group and 26 in the placebo group) were included in the ITT population. Of them, 1 subject who did not receive the study drug due to an allocation error was excluded, and the remaining 64 subjects (39 in the garadacimab group and 25 in the placebo group) were included in the efficacy and safety analyses.

[25] An NSD product of Formulation 2 (170 mg/mL) was used.
[26] The monthly frequency of HAE attacks during the run-in period (baseline) (1-<3 times/month, ≥3 times/month; only for adult patients) and age (≤17 years, ≥18 years) were used as stratification factors.

The study was discontinued in 12.0% of subjects in the placebo group (3 of 25 subjects), and the reason for discontinuation was withdrawal of consent for all of these subjects.

Of the subjects included in the efficacy and safety analyses, 6 subjects (4 in the garadacimab group and 2 in the placebo group) were included in the Japanese subpopulation. None of the Japanese subjects discontinued the study.

Table 29 shows the monthly frequency of HAE attacks during the treatment period, which was assessed as the primary efficacy endpoint. A statistically significant difference was observed in pairwise comparisons between the garadacimab and placebo groups, which demonstrated the superiority of garadacimab over placebo.

Table 29. Monthly frequency of HAE attacks (efficacy analysis set)

		Garadacimab	Placebo
Overall population	Monthly frequency of HAE attacks (times/month) during the run-in period	3.07 ± 2.05 (39) 2.61 [0.9, 10.1]	2.52 ± 0.94 (25) 2.23 [1.0, 4.3]
	Monthly frequency of HAE attacks (times/month) during the treatment period	0.27 ± 0.68 (39) 0.00 [0.0, 3.8]	2.01 ± 1.34 (24) 1.35 [0.2, 4.4]
	P value[a)]	<0.001	
Japanese subpopulation	Monthly frequency of HAE attacks (times/month) during the run-in period	3.48 ± 0.77 (4) 3.41 [2.6, 4.5]	2.7, 3.3 (2)
	Monthly frequency of HAE attacks (times/month) during the treatment period	1.04 ± 1.86 (4) 0.17 [0.0, 3.8]	3.1, 3.4 (2)

Upper row, mean ± standard deviation (N); lower row, median [minimum, maximum]; individual data in case of ≤2 subjects.
One subject in the placebo group whose treatment period was <30 days was excluded from the analysis.
a) Wilcoxon rank sum test, with a 2-sided significance level of 5%.

In the treatment period, adverse events were observed in 64.1% of subjects in the garadacimab group (25 of 39 subjects) and 60.0% of subjects in the placebo group (15 of 25 subjects). Table 30 shows the main events.

There were no deaths or adverse events leading to discontinuation.

Serious adverse events were observed in 2.6% of subjects in the garadacimab group (1 of 39 subjects [hereditary angioedema]). However, a causal relationship to the study drug was ruled out.

Adverse drug reactions were observed in 10.3% of subjects in the garadacimab group (4 of 39 subjects) and 12.0% of subjects in the placebo group (3 of 25 subjects).

Table 30. Adverse events that occurred in ≥2 subjects (treatment period, safety analysis set)

Event	Garadacimab (N = 39)	Placebo (N = 25)
Upper respiratory tract infection	4 (10.3)	2 (8.0)
Headache	3 (7.7)	4 (16.0)
Nasopharyngitis	3 (7.7)	1 (4.0)
Diarrhoea	2 (5.1)	1 (4.0)
Back pain	2 (5.1)	1 (4.0)
Gastrointestinal infection	2 (5.1)	1 (4.0)
Oropharyngeal pain	2 (5.1)	1 (4.0)
Conjunctivitis	2 (5.1)	0
Sinusitis	2 (5.1)	0
Urinary tract infection	2 (5.1)	0
Abdominal pain	2 (5.1)	0
Visual impairment	2 (5.1)	0
Injection site erythema	1 (2.6)	2 (8.0)
Pyrexia	1 (2.6)	2 (8.0)
COVID-19	0	3 (12.0)
Fatigue	0	3 (12.0)
Nausea	0	2 (8.0)
Pain in extremity	0	2 (8.0)

n (%) MedDRA ver. 25.0

In the Japanese subpopulation, adverse events were observed in 100% of subjects in the garadacimab group (4 of 4 subjects [back pain/conjunctivitis, upper respiratory tract infection, noninfective gingivitis/pyrexia, and prothrombin fragment 1.2 increased in 1 subject each]) and 100% of subjects in the placebo group (2 of 2 [prothrombin fragment 1.2 increased/hypertension and pyrexia/COVID-19 in 1 subject each]).

There were no deaths, serious adverse events, or adverse events leading to discontinuation.

An adverse drug reaction was observed in 25.0% of subjects in the garadacimab group (1 of 4 subjects [prothrombin fragment 1.2 increased]).

7.2.2 Long-term study (CTD 5.3.5.2: Study CSL312_3002 [March 2021 to ongoing (data cut-off, February 2023 [all subjects][27]; data cut-off, [redacted] 20[redacted] [only for adolescent subjects (aged 12-17 years)])

An open-label, uncontrolled study was conducted in 14 countries or regions, including Japan, the US, and Germany, to investigate the long-term safety and efficacy of garadacimab in subjects who had completed the preceding study (Study 2001 or 3001) and new participants with C1-INH HAE (HAE Type 1 or Type 2) aged ≥12 years who had not previously received garadacimab (target sample size: 150 subjects).

Table 31 shows the main inclusion/exclusion criteria for new participants in this study.

[27] The time point when ≥100 subjects including 4 Japanese subjects in the garadacimab group from Study 3001 and 6 new Japanese participants in Study 3002 had received garadacimab for ≥1 year.

Table 31. Main inclusion/exclusion criteria (new participants)

Inclusion criteria	**Run-in period** (1) Patients aged ≥12 years at the time of informed consent (2) Patients who met the following criteria and were given a definite diagnosis of C1-INH HAE (HAE Type 1 or Type 2) • Having a documented medical history corresponding to HAE (subcutaneous or mucosal non-pruritic edema attacks without urticaria) • Having a medical record of C1-INH protein level or activity ≤50% of the reference range • Having a medical record of C4 protein level below the lower limit of the reference range (3) Patients with a medical record of ≥3 HAE attacks within 3 months before screening (for subjects who had been treated with drugs for the prophylaxis of HAE attacks within 3 months before screening, ≥3 HAE attacks within 3 consecutive months before receiving the treatment for the prophylaxis of HAE attacks) **Treatment period** (1) Patients who participated in the run-in period for ≥1 month (2) Patients whose mean monthly frequency of HAE attack during the run-in period was ≥1 times (3) Patients with C1-INH activity, C1-INH protein level, and C4 protein level documented at screening
Exclusion criteria	**Run-in period** (1) Patients with other concurrent angioedemas such as idiopathic or acquired angioedema and recurrent angioedema with urticaria (2) Patients who had received treatment with drugs for the prophylaxis of HAE attacks (C1-INH products, androgen products, antifibrinolytic drugs, or other small-molecule drugs) within 2 weeks before the run-in period (3) Patients who had received monoclonal antibodies such as lanadelumab (genetical recombination) within 3 months before the run-in period

This study consisted of a run-in period (up to 2 months, only for new participants), an open-label treatment period (≥12 months), and a follow-up period (2 months). When subjects completed the preceding study, they directly entered the open-label treatment period of this study to continue the treatment with garadacimab. In case of new participants, the frequency of HAE attacks in each subject was evaluated during the run-in period. If the investigator confirmed that ≥2 HAE attacks developed during the run-in period, the subject was allowed to enter the open-label treatment period.

The dosage regimen was as follows: To subjects from the preceding studies, garadacimab[28)] 200 mg was subcutaneously administered once a month under open-label conditions; to new participants, garadacimab 200 mg (400 mg as the initial dose only) was subcutaneously administered once a month under open-label conditions. The dose could be increased up to 400 mg in patients with C1-INH HAE (HAE Type 1 or Type 2) and up to 600 mg in 200 mg increments in patients with FXII HAE, if the applicant agreed in consultation between the investigator and the applicant. All subjects underwent training on the method of self-administration at baseline (Day 1 of the open-label treatment period). Subjects from Study 3001 and new participants were allowed to self-administer garadacimab at the study site through Month 3 and at home from Month 4 and thereafter. Subjects from Study 2001 received the initial dose of garadacimab at the study site and were allowed to self-administer the subsequent doses at home.

Throughout the study period, while the use of drugs for the prophylaxis of HAE attacks (C1-INH products, androgen products, antifibrinolytic drugs, danazol, lanadelumab [genetical recombination], etc.) was prohibited, it was permitted to use drugs for the treatment of acute HAE attacks (plasma-derived or genetically-modified C1-INH products, icatibant acetate, and ecallantide) and to use C1-INH products (for intravenous injection) for the prophylaxis of HAE attacks before invasive procedures.

28) An NSD product of Formulation 2 (170 mg/mL) was used.

All 161 subjects[29)] who received ≥1 dose of the study drug (159 patients with C1-INH HAE [HAE Type 1 or Type 2] and 2 patients with FXII HAE) were included in the all treated subjects (ATS) population, and the subjects in the ATS population were included in the safety analysis.

The study was discontinued in 6.8% of subjects (11 of 161 subjects), and the main reasons for discontinuation were withdrawal of consent in 1.9% of subjects (3 of 161 subjects) and closing of the study site in 1.9% of subjects (3 of 161subjects). Of the 161 subjects who entered the open-label treatment period, 3 subjects completed the study after receiving the treatment for ≥12 months.

Of the subjects included in the safety analysis, 12 patients with C1-INH HAE (HAE Type 1 or Type 2) were included in the Japanese subpopulation, and none of them discontinued the study.

Adverse events were observed in 83.6% of patients with C1-INH HAE (HAE Type 1 or Type 2) (133 of 159 subjects) and 100% of patients with FXII HAE (2 of 2 subjects). Table 32 shows the main events.

No deaths were reported.

Serious adverse events were observed in 1.9% of patients with C1-INH HAE (HAE Type 1 or Type 2) (3 of 159 subjects [COVID-19 in 2 subjects and hereditary angioedema in 1 subject]). However, a causal relationship to the study drug was ruled out for all of these events.

An adverse event leading to discontinuation was observed in 0.6% of patients with C1-INH HAE (HAE Type 1 or Type 2) (1 of 159 subjects).

Adverse drug reactions were observed in 13.2% of patients with C1-INH HAE (HAE Type 1 or Type 2) (21 of 159 subjects).

Table 32. Adverse events that occurred in ≥3% of subjects in either group (ATS population)

Population	C1-INH HAE (HAE Type 1 or Type 2)	FXII HAE
Event	200 mg Q4W (N = 159)	200 mg Q4W (N = 2)
COVID-19	57 (35.8)	1 (50.0)
Nasopharyngitis	27 (17.0)	0
Influenza	11 (6.9)	0
Injection site erythema	11 (6.9)	0
Headache	10 (6.3)	0
Upper respiratory tract infection	9 (5.7)	0
Toothache	6 (3.8)	0
Back pain	6 (3.8)	0
Sinusitis	5 (3.1)	0
Diarrhoea	5 (3.1)	0
Cough	5 (3.1)	0
Syncope	0	1 (50.0)

n (%) MedDRA ver. 25.1

[29)] Consisted of 35 subjects from Study 2001 (all subjects received garadacimab in the preceding study), 57 subjects from Study 3001 (36 subjects received garadacimab and 21 subjects received placebo in the preceding study), and 69 new participants.

In the Japanese subpopulation, adverse events were observed in 91.7% of patients with C1-INH HAE (HAE Type 1 or Type 2) (11 of 12 subjects), and the events observed in ≥2 subjects were COVID-19 and nasopharyngitis in 5 subjects each, and pyrexia, abdominal distension, back pain, and headache in 2 subjects each.

There were no deaths, adverse events leading to discontinuation, or adverse drug reactions.

Serious adverse events were observed in 8.3% of patients with C1-INH HAE (HAE Type 1 or Type 2) (1 of 12 subjects [COVID-19]). However, a causal relationship to the study drug was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of garadacimab:

There were no substantial differences in the definition, classification, diagnostic criteria, or treatment policy of HAE between Japan and foreign countries (*Allergy*. 2022;77:1961-1990, Japanese guideline). It has been reported that the pathophysiology and clinical presentation of HAE are similar in adults and adolescents (*Allergy*. 2017;72:300-313). In the phase I study in Japanese and non-Japanese healthy adult subjects (Study 1003), there were no clear ethnic differences in the pharmacokinetics of garadacimab, and the safety also showed no particular differences between Japanese and non-Japanese subjects [see Section 6.2.1.2].

In view of the above, Study 3001, a confirmatory study to demonstrate the efficacy and to confirm the safety of garadacimab in adult patients and patients aged ≥12 years with a major form of HAE (C1-INH HAE [HAE Type 1 and Type 2]) was conducted as a global study, and the clinical data package was constructed based mainly on the results of this study to evaluate the efficacy and safety of garadacimab in Japanese HAE patients. For nC1-INH HAE (HAE Type 3), a rare form of HAE, patients with FXII HAE and those with PLG HAE were enrolled in Study 2001 to confirm the efficacy and safety of garadacimab in these patients.

The efficacy endpoints and dosage regimen in Study 3001 were specified as described below.

- **Efficacy endpoints**

HAE is a serious disease that significantly affects the activities of daily living of patients by causing HAE attacks and has the potential to progress to a life-threatening condition. Drugs for the prophylaxis of HAE attacks are used to minimize the frequency and severity of HAE attacks, reduce the disease burden, and normalize the daily lives of patients. To evaluate the prophylaxis of HAE attacks by garadacimab, the monthly frequency of HAE attacks in the treatment period [see Section 10 for definitions] was set as the primary endpoint in Study 3001.

- **Dosage regimen**

In the phase II study in non-Japanese HAE patients (Study 2001), the monthly frequency of HAE attacks during treatment period 1, which was assessed as the primary endpoint, showed statistically significant differences in pairwise comparisons between the 200 mg Q4W and placebo groups and between the 600 mg Q4W and placebo groups. An exposure-response analysis using the results of Study 2001 predicted that subcutaneous administration of garadacimab 200 mg (400 mg as the initial dose only) once a month for 6 months would result in a ≥90% reduction in the monthly frequency of HAE attacks from baseline in 70% of subjects, and increasing the dose to >200 mg would not further improve the efficacy.[30)] Therefore, the dosage regimen in Study 3001 was specified as subcutaneous administration of garadacimab 200 mg (400 mg as the initial dose only) once a month for 6 months. The dosage regimen in children aged ≥12 years was specified to be the same as that in adults, because the pathophysiology and clinical presentation of HAE are similar in adults and adolescents (*Pediatr Allergy Immunol*. 2014;25:420-427) and the pharmacokinetics of garadacimab was estimated to be similar in adolescents and adults.

PMDA accepted the applicant's explanation. PMDA has concluded that the efficacy and safety of garadacimab in Japanese HAE patients can be evaluated based mainly on the results of Study 3001, using the submitted clinical data package.

7.R.2 Efficacy

The applicant's explanation about the efficacy of garadacimab for HAE:

In Study 3001 in patients with C1-INH HAE (HAE Type 1 or Type 2) aged ≥12 years, the monthly frequency of HAE attacks during the treatment period, which was assessed as the primary endpoint, showed statistically significant differences in pairwise comparisons between the garadacimab and placebo groups, which demonstrated the superiority of garadacimab over placebo (Table 29).

Table 33 shows the results of the main efficacy endpoints, including secondary endpoints [see Section 10 for definitions]. All of the endpoints showed a tendency for greater improvement in the garadacimab group than in the placebo group. The monthly frequency of HAE attacks in the larynx during the treatment period of Study 3001 was low (2 times in the garadacimab and 7 times in the placebo group), and caution is therefore required when interpreting the results. However, since the frequency tended to be lower in the garadacimab group than in the placebo group, garadacimab can also be expected to prevent HAE attacks in the larynx.

Table 29 shows the results of the primary endpoint and Table 33 shows the results of the main efficacy endpoints in the Japanese subpopulation of Study 3001. The results of all endpoints in the Japanese subpopulation showed a tendency for greater improvement in the garadacimab group than in the placebo group, as observed in the overall population. Table 34 shows the results in each Japanese subject.

[30)] When administering garadacimab 75, 100, 200, 300, or 600 mg (2-fold each as the initial dose) or placebo subcutaneously once a month for 6 months, the monthly frequency of HAE attacks (mean [95% CI]) at Month 6 was predicted to be 0.88 [0.64, 1.3], 0.67 [0.50, 0.90], 0.49 [0.34, 0.67], 0.47 [0.31, 0.66], 0.46 [0.29, 0.65], and 5.4 [4.7, 6.1], respectively.

Table 33. Main efficacy endpoints (Study 3001, efficacy analysis set)

	Overall population		Japanese subpopulation	
	Garadacimab (N = 39)	Placebo (N = 25)	Garadacimab (N = 4)	Placebo (N = 2)
Percent reduction in the monthly frequency of HAE attacks during the treatment period relative to the run-in period[a)]	90.7 ± 22.4 (39)	20.2 ± 42.7 (24)	76.1 ± 41.3 (4)	−15.9, −3.1 (2)
Percentage of subjects with a reduction of at least a certain level in the monthly frequency of HAE attacks during the treatment period relative to the run-in period				
≥50% reduction	94.9 (37/39)	33.3 (8/24)	75.0 (3/4)	0 (0/2)
≥70% reduction	92.3 (36/39)	16.7 (4/24)	75.0 (3/4)	0 (0/2)
≥90% reduction	74.4 (29/39)	8.3 (2/24)	50.0 (2/4)	0 (0/2)
Percentage of subjects who achieved attack-free status	61.5 (24/39)	0 (0/24)	50.0 (2/4)	0 (0/2)
Monthly frequency of HAE attacks that required treatment at onset (times/month)	0.23 ± 0.66 (39) 0.00 [0.0, 3.8]	1.86 ± 1.41 (24) 1.35 [0.0, 4.4]	1.04 ± 1.86 (4) 0.17 [0.0, 3.8]	3.1, 3.4 (2)
Monthly frequency of moderate or severe HAE attacks (times/month)	0.13 ± 0.30 (39) 0.00 [0.0, 1.2]	1.35 ± 1.17 (24) 0.83 [0.0, 4.4]	0.13 ± 0.16 (4) 0.08 [0.0, 0.3]	0.0, 3.1 (2)
Monthly frequency of HAE attacks in the larynx (times/month)	0.01 ± 0.04 (39) 0.00 [0.0, 0.2]	0.07 ± 0.20 (24) 0.00 [0.0, 0.9]	0.00 ± 0.00 (4) 0.00 [0.0, 0.0]	0.2, 0.2 (2)
Percentage of subjects with SGART "moderate improvement" or "marked improvement" at the end of the treatment period	81.6 (31/39)	33.3 (8/24)	75.0 (3/4)	0 (0/2)
Change in AE-QoL total score from baseline at the end of the treatment period[b)]	−26.5 ± 17.9 (33)	−2.21 ± 19.1 (20)	−31.3 ± 15.4 (4)	−19.1, −16.2 (2)

Percent reduction in the monthly frequency of HAE attacks and change in AE-QoL from baseline, mean ± standard deviation (n); percentage of subjects, % (n/N).
Monthly frequency of HAE attacks: upper row, mean ± standard deviation (n); lower row, median [range]; individual data (n) in case of ≤2 subjects.
One subject in the placebo group whose treatment period was <30 days was excluded from the analysis.

a) (1 − monthly frequency of HAE attacks during the treatment period [times/month] / monthly frequency of HAE attacks during the run-in period [times/month]) × 100.
b) Assessed only in subjects aged ≥18 years.

Table 34. Monthly frequency of HAE attacks in Japanese patients with C1-INH HAE (HAE Type 1 or Type 2) (Study 3001, efficacy analysis set)

Age/sex	Treatment group	Run-in period			Treatment period		
		No. of attacks	Duration (months)	Monthly frequency of HAE attacks (times)	No. of attacks	Duration (months)	Monthly frequency of HAE attacks (times)
2[redacted] years/male	Garadacimab	4	1.2	3.3	2	5.9	0.3
4[redacted] years/male[a)]	Garadacimab	3	1.1	2.6	0	6.0	0
4[redacted] years/female[a)]	Garadacimab	5	1.1	4.5	23	6.0	3.8
6[redacted] years/female	Garadacimab	5	1.4	3.5	0	6.0	0
5[redacted] years/male[a)]	Placebo	3	1.1	2.7	18	5.8	3.1
4[redacted] years/female	Placebo	6	1.8	3.3	20	5.9	3.4

a) The study drug was self-administered.

Table 35 shows the long-term efficacy of garadacimab in terms of the monthly frequency of HAE attacks and the percentage of subjects who achieved attack-free status by treatment period in the ATS population of Study 3002 in subjects from the preceding studies (Studies 2001 and 3001) and newly enrolled patients with C1-INH HAE (HAE Type 1 or Type 2) (data cut-off, February 2023). The efficacy of garadacimab was maintained throughput the treatment period in all patient populations.

Table 35. Monthly frequency of HAE attacks (times/month) and the percentage of subjects who achieved attack-free status by treatment period (Study 3002, ATS population)

Patient population/treatment period	Months 0-1	Months 1-3	Months 4-6	Months 7-9	Months 10-12
Overall population					
New participants[a)]	0.38 ± 0.93 (69) 78.3 (54/69)	0.32 ± 0.71 (69) 68.1 (47/69)	0.21 ± 0.52 (69) 72.5 (50/69)	0.20 ± 0.51 (63) 77.8 (49/63)	0.17 ± 0.44 (59) 81.4 (48/59)
Subjects from the preceding studies[b)]	0.07 ± 0.33 (92) 94.6 (87/92)	0.13 ± 0.41 (92) 81.5 (75/92)	0.09 ± 0.32 (92) 84.8 (78/92)	0.12 ± 0.33 (90) 81.1 (73/90)	0.12 ± 0.41 (89) 86.5 (77/89)
Subjects switched from the placebo group[b)]	0.09 ± 0.43 (21) 95.2 (20/21)	0.19 ± 0.67 (21) 85.7 (18/21)	0.13 ± 0.22 (21) 71.4 (15/21)	0.21 ± 0.46 (21) 66.7 (14/21)	0.26 ± 0.65 (20) 80.0 (16/20)
Subjects who continued garadacimab treatment[b)]	0.07 ± 0.30 (71) 94.4 (67/71)	0.11 ± 0.30 (71) 80.3 (57/71)	0.08 ± 0.35 (71) 88.7 (63/71)	0.09 ± 0.29 (69) 85.5 (59/69)	0.08 ± 0.31 (69) 88.4 (61/69)
Subjects who continued treatment (garadacimab 200 mg) from the garadacimab group in Study 3001[b)]	0.05 ± 0.33 (36) 97.2 (35/36)	0.12 ± 0.38 (36) 83.3 (30/36)	0.12 ± 0.46 (36) 86.1 (31/36)	0.11 ± 0.28 (34) 82.4 (28/34)	0.05 ± 0.16 (34) 88.2 (30/34)
Japanese subpopulation					
New participants[a)]	0.82 ± 0.74 (6) 33.3 (2/6)	0.78 ± 0.75 (6) 33.3 (2/6)	0.50 ± 0.55 (6) 50.0 (3/6)	0.61 ± 0.49 (6) 33.3 (2/6)	0.33 ± 0.52 (6) 66.7 (4/6)
Subjects from the preceding studies[b)]	0.65 ± 1.01 (6) 66.7 (4/6)	0.84 ± 1.33 (6) 66.7 (4/6)	0.56 ± 1.05 (6) 50.0 (3/6)	0.78 ± 0.78 (6) 33.3 (2/6)	0.74 ± 1.03 (6) 50.0 (3/6)
Subjects switched from the placebo group[b)]	0.0, 2.0 (2) 50.0 (1/2)	0.0, 3.0 (2) 50.0 (1/2)	0.3, 0.3 (2) 0 (0/2)	0.7, 2.0 (2) 0 (0/2)	1.1, 2.6 (2) 0 (0/2)
Subjects who continued garadacimab treatment[b)]	0.49 ± 0.98 (4) 75.0 (3/4)	0.50 ± 1.00 (4) 75.0 (3/4)	0.67 ± 1.34 (4) 75.0 (3/4)	0.50 ± 0.64 (4) 50.0 (2/4)	0.19 ± 0.38 (4) 75.0 (3/4)
Subjects who continued treatment (garadacimab 200 mg) from the garadacimab group in Study 3001[b)]	0.49 ± 0.98 (4) 75.0 (3/4)	0.50 ± 1.00 (4) 75.0 (3/4)	0.67 ± 1.34 (4) 75.0 (3/4)	0.50 ± 0.64 (4) 50.0 (2/4)	0.19 ± 0.38 (4) 75.0 (3/4)

Upper row, monthly frequency of HAE attacks (mean ± standard deviation [N]); lower row, percentage of subjects who achieved attack-free status (% [n/N]); individual data (N) in case of ≤2 subjects.

a) Garadacimab 200 mg (400 mg as the initial dose only) once a month SC; b) Garadacimab 200 mg once a month SC.

Table 36 shows the results of the monthly frequency of HAE attacks during the treatment period by patient characteristics in Study 3001. Caution is required when interpreting the results because the number of subjects is limited in some patient subgroups. However, there were no clear differences in the monthly frequency of HAE attacks in each subgroup, including those involving age (adolescent subpopulation [12-17 years]/adult subpopulation [≥18 years]), and no background factors that clearly affect the efficacy of garadacimab were identified.

In 10 subjects in the adolescent subpopulation (aged 12-17 years) of the ATS population in Study 3002, the monthly frequency of HAE attacks during the treatment period and the percent reduction in the monthly frequency of HAE attacks during the treatment period relative to the run-in period[31)] at the data cut-off time point were 0.09 ± 0.13 times/month and 91.5% ± 11.9%, respectively, which were not clearly different from those (0.16 ± 0.38 times/month and 94.9% ± 12.0%) in 151 subjects in the adult subpopulation (aged ≥18 years).

[31)] Calculated using the run-in period of the preceding study for subjects from those studies, and the run-in period of Study 3002 for new participants.

Table 36. Monthly frequency of HAE attacks during the treatment period (times/month) by patient characteristics in Study 3001 (efficacy analysis set)

Patient characteristics		Garadacimab (N = 39)	Placebo (N = 25)
Sex	Male	0.09 ± 0.12 (15)	2.15 ± 1.55 (10)
	Female	0.38 ± 0.85 (24)	1.90 ± 1.22 (14)
Age	Adolescent subpopulation (12-17 years)	0.35 ± 0.60 (4)	1.2, 0.2 (2)
	18-64 years	0.31 ± 0.76 (29)	2.13 ± 1.33 (22)
	≥65 years	0.03 ± 0.07 (6)	- (0)
	Adult subpopulation (≥18 years)	0.26 ± 0.70 (35)	2.13 ± 1.33 (22)
Race	Japanese	1.04 ± 1.86 (4)	3.1, 3.4 (2)
	Others	0.18 ± 0.37 (35)	1.89 ± 1.35 (22)
Body weight	<65 kg	0.16 ± 0.41 (9)	1.64 ± 1.28 (10)
	65-<75 kg	0.69 ± 1.54 (6)	- (0)
	≥75 kg	0.21 ± 0.38 (24)	2.27 ± 1.37 (14)
Frequency of attacks during the run-in period	1-<3 times/month	0.12 ± 0.32 (16)	1.21 ± 0.91 (10)
	≥3 times/month	0.38 ± 0.84 (23)	2.57 ± 1.33 (14)
HAE type	HAE Type 1	0.27 ± 0.70 (34)	1.96 ± 1.40 (21)
	HAE Type 2	0.30 ± 0.67 (5)	2.34 ± 0.91 (3)
Administration of drugs for the prophylaxis of HAE attacks within 3 months before screening	Yes	0.43 ± 1.03 (14)	2.69 ± 1.65 (6)
	No	0.18 ± 0.38 (25)	1.78 ± 1.19 (18)
Drugs for the prophylaxis of HAE attacks used within 3 months before screening	Berotralstat hydrochloride	0.07 ± 0.15 (5)	0.2, 4.2 (2)
	C1-INH	0.31 ± 0.44 (6)	1.2, 3.3 (2)
	Danazol	0 (1)	4.2 (1)
	Tranexamic acid	0, 3.8 (2)	3.1 (1)
History of prior HAE attacks in the larynx	Yes	0.36 ± 0.89 (21)	1.95 ± 1.40 (16)
	No	0.16 ± 0.30 (18)	2.13 ± 1.30 (8)
Family history of HAE	Yes	0.19 ± 0.38 (34)	2.03 ± 1.39 (22)
	No	0.80 ± 1.69 (5)	1.2, 2.3 (2)

Mean ± standard deviation (n); individual data (n) in case of ≤2 subjects.

In Study 2001, 6 patients with mutations in the *FXII* or *PLG* gene, which are known gene mutations in nC1-INH HAE (HAE Type 3) (3 patients with FXII HAE and 3 patients with PLG HAE) were enrolled in the open-label part and received subcutaneous administration of garadacimab 600 mg Q4W (300 mg IV as the initial dose). Table 25 and Table 37 show the efficacy results in patients with nC1-INH HAE (FXII HAE or PLG HAE). Of the 6 patients with nC1-INH HAE (FXII HAE or PLG HAE), 2 patients with FXII HAE had a reduction in the monthly frequency of HAE attacks throughout the study period of Study 2001. Neither of these patients developed any HAE attacks during the 18-month treatment period of Study 3002 in which they continued with treatment that was switched to garadacimab 200 mg SC once a month. Two patients with PLG HAE had an increase in the monthly frequency of HAE attacks during the treatment period 1 of Study 2001, but no clear factors for this tendency were identified. In the other patient with PLG HAE, the monthly frequency of HAE attacks during the treatment period tended to be reduced relative to the run-in period by the treatment with garadacimab. In view of the mechanism of action of garadacimab, the efficacy of garadacimab can also be expected in patients with nC1-INH HAE (HAE Type 3) when FXII is excessively activated or when the kallikrein-kinin pathway is involved in the formation of angioedema.

Table 37. Monthly frequency of HAE attacks in patients with nC1-INH HAE (FXII HAE or PLG HAE) (Studies 2001 and 3002)

Age/sex	Gene mutation	Monthly frequency of HAE attacks during the run-in period	Study 2001				Study 3002	
			Garadacimab 600 mg Q4W (300 mg IV as the initial dose)				Garadacimab 200 mg once a month	
			Treatment period 1		Treatment period 2		Treatment period	
			Monthly frequency of HAE attacks (times)	Percent reduction in the monthly frequency of HAE attacks relative to the run-in period	Monthly frequency of HAE attacks (times)	Percent reduction in the monthly frequency of HAE attacks relative to the run-in period	Monthly frequency of HAE attacks (times)	Percent reduction in the monthly frequency of HAE attacks relative to the run-in period
3[redacted] years/female	FXII HAE	3.24	0.36	89%	0.05[a)]	98%	0[b)]	100%
4[redacted] years/female	FXII HAE	3.2	0	100%	0.17[c)]	95%	0[d)]	100%
3[redacted] years/female	FXII HAE	4.35	3.51	19%	-	-	-	-
3[redacted] years/female	PLG HAE	2.28	6.8	−198%	-	-	-	-
5[redacted] years/female	PLG HAE	1.45	3.17	−119%	-	-	-	-
4[redacted] years/female	PLG HAE	3.2	1.75	45%	-	-	-	-

-: The subject did not enter treatment period 2. a) Treatment duration, 20.3 months; b) treatment duration, 18.1 months; c) treatment duration, 17.5 months; d) treatment duration, 18.2 months.

PMDA's view:

In Study 3001, the superiority of garadacimab over placebo was demonstrated by the monthly frequency of HAE attacks in the treatment period, which was the primary endpoint, and other efficacy endpoints, and the results of analysis by patient characteristics also showed a tendency for greater improvement in the garadacimab group than in the placebo group. Thus, the efficacy of garadacimab was demonstrated in pediatric (aged ≥12 years) and adult patients with C1-INH HAE (HAE Type 1 or Type 2). The efficacy of garadacimab can also be expected in Japanese patients with C1-INH HAE (HAE Type 1 or Type 2) because a similar tendency to that in the overall population was also observed in the Japanese subpopulation. For nC1-INH HAE (HAE Type 3), there are limitations to the evaluation because the number of patients is limited and many points remain unclarified at present due to a lack of information on the genetic background and pathophysiology. However, the efficacy of garadacimab treatment was suggested in some subjects in Study 2001 and Study 3002 in which the treatment was switched to garadacimab 200 mg once a month. In view of this, and considering its mechanism of action, garadacimab may also be effective in patients with nC1-INH HAE (HAE Type 3) at the same dosage regimen as in patients with C1-INH HAE (HAE Type 1 or Type 2) when FXII is excessively activated or when the kallikrein-kinin pathway is involved in the formation of angioedema.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Summary of safety

The applicant's explanation about the safety of garadacimab in HAE patients based on the results of Study 3001 and the results of analyses using pooled data from 3 clinical studies in HAE patients (Studies 2001, 3001, and 3002) (hereinafter referred to as "3-study pooled population"):

Table 38 shows a summary of the safety of garadacimab in Study 3001. No deaths or adverse events leading to discontinuation were observed, and there were no clear differences in the incidences of adverse events or

adverse drug reactions between the garadacimab and placebo groups. A serious adverse event was observed in 2.6% of subjects in the garadacimab group (1 of 39 subjects [hereditary angioedema]); however, a causal relationship to the study drug was ruled out. There were no clear differences in the safety profile between the overall population and the Japanese subpopulation.

Table 39 shows a summary of the safety of garadacimab in the 3-study pooled population and Table 40 shows the incidences of the main adverse events in this population. There were no clear differences in the incidences of adverse events between subjects treated with garadacimab 200 mg and those treated with placebo, except that serious adverse events and adverse events leading to study discontinuation were observed only in subjects treated with garadacimab 200 mg.

Serious adverse events were observed in 3.0% of subjects treated with garadacimab 200 mg (5 of 166 subjects [hereditary angioedema and COVID-19 in 2 subjects each, and diverticular perforation in 1 subject]); however, a causal relationship to the study drug was ruled out for all of these events. An adverse event leading to study discontinuation was observed in 0.6% of subjects treated with garadacimab 200 mg (1 of 166 [injection site irritation]), and a causal relationship to the study drug was not ruled out. The event resolved.

Although the number of Japanese subjects enrolled in clinical studies is limited, there were no clear differences in the incidences of adverse events between the overall population and the Japanese subpopulation.

Table 38. Summary of the safety of garadacimab (Study 3001, safety analysis set)

Population	Overall population		Japanese subpopulation	
Treatment group	Garadacimab	Placebo	Garadacimab	Placebo
N	39	25	4	2
All adverse events	25 (64.1)	15 (60.0)	4 (100)	2 (100)
Serious adverse events	1 (2.6)	0	0	0
Death	0	0	0	0
Adverse events leading to study discontinuation	0	0	0	0
Adverse drug reactions	4 (10.3)	3 (12.0)	1 (25.0)	0

n (%) MedDRA ver. 25.0

Table 39. Summary of the safety of garadacimab (3-study pooled population, safety analysis set)

Population	Overall population		Japanese subpopulation	
Subjects	Garadacimab 200 mg[a)]	Placebo	Garadacimab 200 mg[a)]	Placebo
N	166	33	12	2
Total exposure period (patient-years)	262.7	13.6	13.7	1.0
All adverse events	143 (86.1) 2.88	21 (63.6) 4.84	11 (91.7) 5.53	2 (100) 4.09
Serious adverse events	5 (3.0) 0.019	0	1 (8.3) 0.073	0
Death	0	0	0	0
Adverse events leading to study discontinuation	1 (0.6) 0.004	0	0	0
Adverse drug reactions	29 (17.5) 0.270	5 (15.2) 0.587	1 (8.3) 0.073	0

Upper row, n (%); lower row, number of events per patient-year adjusted for total exposure period. MedDRA ver. 25.1

Excluding adverse events that occurred in the period between the intravenous administration of the initial dose and the first subcutaneous administration in Study 2001.

a) Subjects who received garadacimab 200 mg Q4W or once a month (including those switched from each dose of garadacimab [75, 400, or 600 mg] or placebo).

Table 40. Main adverse events[a] (3-study pooled population, safety analysis set)

Population	Overall population		Japanese subpopulation	
Subjects	Garadacimab 200 mg[b]	Placebo	Garadacimab 200 mg[b]	Placebo
N	166	33	12	2
Total exposure period (patient-years)	262.7	13.6	13.7	1.0
COVID-19	59 (35.5) 0.232	3 (9.1) 0.220	5 (41.7) 0.364	1 (50.0) 1.023
Nasopharyngitis	30 (18.1) 0.167	1 (3.0) 0.073	5 (41.7) 0.437	0
Headache	19 (11.4) 0.141	4 (12.1) 0.293	2 (16.7) 0.146	0
Upper respiratory tract infection	17 (10.2) 0.084	4 (12.1) 0.293	1 (8.3) 0.073	0
Injection site erythema	13 (7.8) 0.065	4 (12.1) 0.293	0	0
Back pain	9 (5.4) 0.042	2 (6.1) 0.147	3 (25.0) 0.218	0
Pyrexia	5 (3.0) 0.023	2 (6.1) 0.147	3 (25.0) 0.291	1 (50.0) 1.023
Abdominal distension	4 (2.4) 0.030	1 (3.0) 0.073	2 (16.7) 0.291	0

Upper row, n (%); lower row, number of events per patient-year adjusted for total exposure period. MedDRA ver. 25.1
Excluding adverse events that occurred in the period between the intravenous administration of the initial dose and the first subcutaneous administration in Study 2001.

a) Overall population, ≥10% in any group; Japanese subpopulation, ≥2 subjects in any group.
b) Subjects who received garadacimab 200 mg Q4W or once a month (including those switched from each dose of garadacimab [75, 400, or 600 mg] or placebo).

The safety results in the adolescent subpopulation (aged 12-17 years) are as follows: Adverse events were observed in 7 of 10 subjects in the adolescent subpopulation (aged 12-17 years) of the ATS population in Study 3002 (data cut-off, [redacted]20[redacted] for adolescent subjects) at the data cut-off time point (duration of exposure [median [range]], 14.4 [8.9, 22.9] months). However, a causal relationship to the study drug was ruled out for all of these events. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. Although the number of subjects investigated is limited in the adolescent subpopulation (aged 12-17 years), no clear safety concerns were identified in the adolescent subpopulation (aged 12-17 years).

The safety results in patients with nC1-INH HAE (FXII HAE or PLG HAE) are as follows: Adverse events were observed in 5 of 6 subjects in Studies 2001 and 3002 (data cut-off, February 2023). Although a causal relationship to the study drug was not ruled out for injection site reaction observed in 1 subject, the event was mild and resolved. A serious adverse event was also observed in 1 patient with FXII HAE (hereditary angioedema), but a causal relationship to the study drug was ruled out. There were no deaths or adverse events leading to study discontinuation. In view of the above, no particular safety concerns have been identified in patients with nC1-INH HAE (FXII HAE or PLG HAE).

Taking the pharmacological action of garadacimab and the incidences of adverse events in clinical studies into account, PMDA focused its safety review on the events discussed in the subsequent sections.

7.R.3.2 Hypersensitivity-related events and injection site reaction-related events

The applicant's explanation about the incidences of hypersensitivity-related events and injection site reaction-related events during treatment with garadacimab:

Table 41 shows the incidences of hypersensitivity-related events and injection site reaction-related events in the 3-study pooled population.

The incidences of hypersensitivity-related events tended to be higher in the garadacimab 200 mg group than in the placebo group. Although events for which a causal relationship could not be ruled out were observed only in subjects treated with garadacimab 200 mg (injection site urticaria in 2 subjects, and erythema, rash maculo-papular, and dermatitis in 1 subject each), all of these events were non-serious.

The incidences of injection site reaction-related events showed no clear differences between subjects treated with garadacimab 200 mg and those treated with placebo, and there were no serious injection site reaction-related events.

In addition, there were no particular differences in the incidences of hypersensitivity-related events or injection site reaction-related events between the overall population and the Japanese subpopulation.

Table 41. Incidences of hypersensitivity-related events and injection site reaction-related events (3-study pooled population, safety analysis set)

Population	Overall population		Japanese subpopulation	
Subjects	Garadacimab 200 mg[a)]	Placebo	Garadacimab 200 mg[a)]	Placebo
N	166	33	12	2
Total exposure period (patient-years)	262.7	13.6	13.7	1.0
Hypersensitivity-related events[b)]				
Adverse events	33 (19.9) 0.232	1 (3.0) 0.073	5 (41.7) 0.510	0
Adverse drug reactions	5 (3.0) 0.046	0	0	0
Serious adverse events	0	0	0	0
Injection site reaction-related events[c)]				
Adverse events	23 (13.9) 0.194	5 (15.2) 0.440	2 (16.7) 0.146	0
Adverse drug reactions	18 (10.8) 0.167	4 (12.1) 0.367	0	0
Serious adverse events	0	0	0	0

Upper row, n (%); lower row, number of events per patient-year adjusted for total exposure period. MedDRA ver. 25.1
Excluding adverse events that occurred in the period between the intravenous administration of the initial dose and the first subcutaneous administration in Study 2001.

a) Subjects who received garadacimab 200 mg Q4W or once a month (including subjects switched from each dose of garadacimab [75, 400, or 600 mg] or placebo).
b) Hypersensitivity (SMQ) (broad), anaphylactic reaction (SMQ) (broad), and anaphylactic/anaphylactoid shock conditions (SMQ) (broad).
c) The following preferred terms were defined as injection site reaction-related events: Injection site bruising, injection site erythema, injection site haematoma, injection site irritation, injection site pain, injection site pruritus, injection site reaction, injection site swelling, injection site urticaria, vaccination site pain, vaccination site reaction, and vaccination site swelling.

In view of the above, although serious hypersensitivity including anaphylaxis has not been observed with the use of garadacimab to date, the risk of serious hypersensitivity including anaphylaxis following the administration of a monoclonal antibody cannot be ruled out. Therefore, serious hypersensitivity including

anaphylaxis will be specified as an important potential risk, and a precaution regarding this risk will be provided in the package insert and other materials.

PMDA's view:
Although no serious hypersensitivity reactions including anaphylaxis were observed in clinical studies, products containing protein as an active ingredient, such as antibody therapeutics, generally may induce serious hypersensitivity including anaphylaxis. Taking the tendency for higher incidences of hypersensitivity-related events in the garadacimab group than in the placebo group in clinical studies also into account, a precaution regarding serious hypersensitivity reactions including anaphylaxis should be provided in the Significant Adverse Reactions section of the package insert, and it should be specified as an important identified risk in the risk management plan. In addition, information should be continuously collected in post-marketing surveillance, and new information should be appropriately provided to healthcare professionals if it becomes available.

7.R.3.3 Blood coagulation-related events

The applicant's explanation about the incidences of blood coagulation-related events during treatment with garadacimab:

FXII is known to be involved in fibrin formation via FXI. In addition, APTT prolongation was observed in the repeated-dose toxicity studies of garadacimab in rats and cynomolgus monkeys [see Sections 3.R.2, 5.2, and 5.R]. Therefore, blood coagulation-related events were investigated. Table 42 shows the incidences of bleeding events and thromboembolic events in the 3-study pooled population.

There were no clear differences in the incidences of bleeding events between the garadacimab 200 mg and placebo groups, and all of the observed events were non-serious. Bleeding events for which a causal relationship to the study drug could not be ruled out were observed in 4 subjects (injection site bruising in 2 subjects, and contusion and prothrombin fragment 1.2 increased in 1 subject each), and all of the events were mild. In clinical studies in HAE patients (Studies 2001, 3001, and 3002), APTT prolongation was observed after garadacimab administration in some subjects (16 in Study 2001, 3 in Study 3001, and 13 in Study 3002). Among them, bleeding events were observed in 3 subjects (injection site bruising, epistaxis, and haematuria in 1 subject each).[32)] Although a causal relationship to the study drug was not ruled out for injection site bruising, the event was considered to be an injection site reaction. There were subjects with abnormalities in other

[32)] APTT prolongation and bleeding events were observed in 3 subjects in Study 2001.
[Subject with injection site bruising]
The subject received garadacimab 600 mg Q4W in treatment periods 1 and 2. After the revision of Protocol Version 2 (March 20, 2020), the subject received garadacimab 200 mg Q4W and developed injection site bruising on Day 595 (the same day as receiving a 200 mg dose). This subject showed APTT prolongation (47.5-105.9 seconds) at multiple visits, but did not show APTT prolongation at the onset of the bleeding event.
[Subject with epistaxis]
The subject received placebo SC in treatment period 1 and garadacimab 600 mg Q4W SC in treatment period 2. The subject developed epistaxis on Day 206 (3 days after receiving a 600 mg dose) and showed APTT prolongation of >160 seconds on laboratory tests the next day. Other bleeding-related coagulation parameters such as PT were within the respective reference ranges.
[Subject with haematuria]
The subject received garadacimab 600 mg Q4W SC in treatment period 1 and developed haematuria on Day 38 (the same day as receiving a 600 mg dose) and Day 74 (10 days after receiving a 600 mg dose) and showed APTT prolongation of 45 seconds on Day 35 and 51.2 seconds on Day 63 on laboratory tests. Other bleeding-related coagulation parameters such as PT were within their respective reference ranges.

coagulation parameters such as PT, but these abnormalities were not accompanied by abnormal bleeding or clinical presentations of bleeding.

A thromboembolic event was observed in 1 subject treated with garadacimab 200 mg (vessel puncture site thrombosis). The event was mild and a causal relationship to the study drug was ruled out.

There were no particular differences in the incidences of bleeding events or thromboembolic events between the overall population and the Japanese subpopulation.

Table 42. Incidences of bleeding events and thromboembolic events (3-study pooled population, safety analysis set)

Population	Overall population		Japanese subpopulation	
Subjects	Garadacimab 200 mg[a)]	Placebo	Garadacimab 200 mg[a)]	Placebo
N	166	33	12	2
Total exposure period (patient-years)	262.7	13.6	13.7	1.0
Bleeding events[b)]				
Adverse events	17 (10.2) 0.080	3 (9.1) 0.220	2 (16.7) 0.146	1 (50.0) 1.023
Adverse drug reactions	4 (2.4) 0.019	0	1 (8.3) 0.073	0
Serious adverse events	0	0	0	0
Thromboembolic events[c)]				
Adverse events	1 (0.6) 0.004	0	0	0
Adverse drug reactions	0	0	0	0
Serious adverse events	0	0	0	0

Upper row, n (%); lower row, number of events per patient-year adjusted for total exposure period. MedDRA ver. 25.1
Excluding adverse events that occurred in the period between the intravenous administration of the initial dose and the first subcutaneous administration in Study 2001.

a) Subjects who received garadacimab 200 mg Q4W or once a month (including subjects switched from each dose of garadacimab [75, 400, or 600 mg] or placebo).
b) Haemorrhages (SMQ) (narrow).
c) Embolic and thrombotic events (SMQ) (narrow).

In view of the above results as well as the results obtained in non-clinical studies suggesting that the inhibition of FXIIa suppresses thrombus formation, which may involve FXII, without compromising the hemostatic action [see Section 3.2], the risk of blood coagulation-related events associated with garadacimab is considered to be low. However, taking the mechanism of action and non-clinical and clinical study results of garadacimab into account, information will be provided in the package insert regarding the possibility that treatment with garadacimab may prolong APTT.

PMDA's view:

On the basis of the clinical study results obtained to date, the applicant's explanation that there is little concern about thromboembolic events is understandable. As for bleeding events, although there were no subjects with significant bleeding during the treatment with garadacimab, APTT prolongation accompanied by bleeding and changes in other coagulation parameters such as PT have been observed with the use of garadacimab. In view of this, information on APTT prolongation during treatment with garadacimab should be provided in the package insert, and bleeding should be specified as an important potential risk in the risk management plan. In addition, information on bleeding-related events should be continuously collected after the market launch, and new information should immediately be provided to healthcare professionals if it becomes available.

PMDA's view on the safety of garadacimab based on the reviews in Sections 7.R.3.1 to 7.R.3.3:

On the basis of the clinical study results submitted, no significant safety concerns about garadacimab treatment or events specific to Japanese HAE patients have been suggested in HAE patients. Therefore, the observed adverse events can be managed by taking appropriate safety measures.

The above PMDA's conclusion, which is described in Section 7.R.3, will be discussed at the Expert Discussion.

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning of garadacimab in the treatment of HAE:

In addition to the results of the efficacy and safety of garadacimab in patients with C1-INH HAE (HAE Type 1 or Type 2) obtained from Study 3001, results suggesting the efficacy of garadacimab in nC1-INH HAE (FXII HAE or PLG HAE) have been obtained in Studies 2001 and 3002, although the number of subjects investigated is limited [see Sections 7.R.2 and 7.R.3]. In view of these findings and the current treatment algorithm for HAE in Japan [see Section 1], garadacimab can be an option for the long-term control of HAE attacks in HAE patients and can be used regardless of the HAE type.

PMDA's view:

In view of the efficacy [see Section 7.R.2] and safety [see Section 7.R.3] of garadacimab based on the clinical study results submitted, garadacimab can be a treatment option for the long-term prophylaxis of HAE attacks, in line with approved drugs for the long-term prophylaxis of HAE attacks, regardless of the disease type. The genetic background and pathophysiology of nC1-INH HAE (HAE Type 3) are still being elucidated. There are also many unclarified points concerning the detailed mechanism involved in the development of HAE, although the causative genes such as *FXII* and *PLG* have been identified. For these reasons, the appropriateness of garadacimab use in patients with nC1-INH HAE (HAE Type 3) should be carefully determined taking the clinical study results as well as the mechanism of action of garadacimab and the latest information on nC1-INH HAE (HAE Type 3) into account, and the course of patients should be carefully observed. Therefore, it is important to appropriately provide the currently available information such as clinical results to healthcare professionals and to continuously collect useful information to determine the appropriateness of garadacimab use and provide new information to healthcare professionals as needed if it becomes available.

In view of the above, PMDA has concluded that the indication of garadacimab should be modified to "prophylaxis of acute attacks of hereditary angioedema," in line with approved drugs for the prophylaxis of HAE attacks that have the same clinical positioning.

Garadacimab is a drug that is administered for the long-term prophylaxis of HAE attacks. The efficacy and safety of garadacimab in the prophylaxis of acute attacks due to invasive procedures have not been investigated

in clinical studies. In view of these, a precaution should be provided regarding the proper use of garadacimab, in line with approved drugs for the long-term prophylaxis of HAE attacks, as described below.

Since acute attacks can also occur during the treatment with garadacimab, a system should be established that allows for the appropriate management of the acute attacks with drugs for the treatment of HAE attacks.

Indication
Prophylaxis of acute attacks of hereditary angioedema

Precautions Concerning Indication
The efficacy and safety of garadacimab in the prophylaxis of acute attacks due to invasive procedures have not been investigated in clinical studies.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

On the basis of the data submitted and the reviews in Sections 7.R.2 and 7.R.3, PMDA has concluded that the indication of garadacimab in adult and pediatric (aged ≥12 years) HAE patients can be specified as follows: The usual dosage for adults and children aged 12 years or older is 400 mg of garadacimab (genetical recombination) administered subcutaneously as the initial dose, followed by doses of 200 mg administered subcutaneously once a month.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.6 Self-administration

The applicant's explanation about the efficacy and safety of garadacimab when self-administered in Japanese HAE patients based on the results in Japanese HAE patients in Study 3001:

In Study 3001, garadacimab could be self-administered by subjects or their caregivers who had undergone training [see Section 7.2.1], and 2 of 4 Japanese subjects in the garadacimab group performed self-administration. Table 34 shows the efficacy results in Japanese subjects. There were no clear differences in efficacy by self-administration status. The safety results in Japanese subjects (4 subjects) in the garadacimab group in Study 3001 are presented in Section 7.2.1. There were no adverse events associated with self-administration.

In view of the above, there are no particular safety concerns about the efficacy and safety of garadacimab when self-administered in Japanese HAE patients.

PMDA's view:
Although experience with the self-administration of garadacimab in Japanese HAE patients is limited, no

particular problems regarding the efficacy or safety of garadacimab when self-administered in HAE patients have been suggested by clinical studies. Self-administration should be performed only after the physician has carefully assessed its appropriateness, provided sufficient training to the patient, and confirmed that the patient understands the risks associated with garadacimab administration and how to manage them, and can self-administer the drug without fail. In addition, precautions should be provided to ensure that self-administration is immediately discontinued when adverse drug reactions of garadacimab such as hypersensitivity are suspected or when continuation of self-administration becomes difficult, and appropriate measures should then be taken under the supervision of the physician.

7.R.7 Post-marketing investigations

PMDA's view:

As described in the review in Section 7.R.3, the clinical study results suggest that the safety of garadacimab treatment is acceptable. However, the safety, etc. of garadacimab in clinical practice, including the incidences of serious hypersensitivity reactions including anaphylaxis and bleeding-related events, should be continuously investigated in post-marketing surveillance, and new information should immediately be provided to healthcare professionals if it becomes available.

In addition, the currently available results and the latest pathophysiological information in patients with nC1-INH HAE (HAE Type 3) should be provided to healthcare professionals so that they can appropriately determine the appropriateness of garadacimab use in patients with nC1-INH HAE (HAE Type 3), and useful information for the proper use of garadacimab must be continuously collected, even after the market launch, and new information should be provided to healthcare professionals as needed if it becomes available to promote the proper use of garadacimab.

The above PMDA's conclusion and additional safety measures will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection and assessment are currently ongoing. The results and PMDA's conclusion are reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. The results and PMDA's conclusion are reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that garadacimab has efficacy in the prophylaxis of acute HAE attacks, and that garadacimab has acceptable safety in view of its benefits. Garadacimab is clinically

meaningful because it offers a new treatment option for the prophylaxis of acute HAE attacks. The safety, etc. of garadacimab in clinical practice should be further investigated in post-marketing surveillance.

PMDA has concluded that garadacimab may be approved if garadacimab is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

Efficacy endpoints in clinical studies are defined as shown below.

Endpoint	Definition
Monthly frequency of HAE attacks during the treatment/run-in period	Monthly frequency of HAE attacks confirmed by the investigator during the treatment/run-in period: Frequency of HAE attacks confirmed by the investigator / assessment period of the subject (days) × 30.4375
Percent reduction in the monthly frequency of HAE attacks during the treatment period relative to the run-in period	(1 – monthly frequency of HAE attacks during the treatment period [times/month] / monthly frequency of HAE attacks during the run-in period [times/month]) × 100
Percentage of subjects who achieved attack-free status	Percentage of subjects without HAE attacks confirmed by the investigator during the treatment period
Frequency of moderate or severe HAE attacks (times/month)	Monthly frequency of moderate or severe HAE attacks confirmed by the investigator during the treatment period Moderate: Activities of daily living are difficult due to HAE attacks/some assistance is necessary for activities of daily living/on-demand therapy for HAE may be required to manage the attack. Severe: Activities of daily living are significantly restricted due to the HAE attack/medical assistance or intervention including transfer by ambulance and hospitalization is required/on-demand therapy for HAE was used to treat the attack.
SGART	Subject's Global Assessment of Response to Therapy. Treatment response is assessed based on the following 5-grade scale: No improvement; minimal improvement; mild improvement; moderate improvement; and marked improvement. Higher scores indicate a better treatment response.
AE-QoL total score	A specialized angioedema QOL questionnaire based on the subject's assessment. Using the 17-item questionnaire, the total score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition) are calculated based on the following 5-point scale: 0 (never); 1 (rarely), 2 (occasionally); 3 (often); 4 (very often). Lower scores indicate better control (score range, 0-100).

The definition of each category of events described in Section 7.R.3 is shown below.

Category	Definition
Bleeding events	Haemorrhages (SMQ) (narrow)
Thromboembolic events	Embolic and thrombotic events (SMQ) (narrow)
Hypersensitivity-related events	Hypersensitivity (SMQ) (broad), anaphylactic reaction (SMQ) (broad), and anaphylactic/anaphylactoid shock conditions (SMQ) (broad)
Injection site reaction-related events	Injection site reaction-related events were defined as follows: Injection site bruising, injection site erythema, injection site haematoma, injection site irritation, injection site pain, injection site pruritus, injection site reaction, injection site swelling, injection site urticaria, vaccination site pain, vaccination site reaction, and vaccination site swelling.

Review Report (2)

January 8, 2025

Product Submitted for Approval

Brand Name	Andembry S.C. Injection 200 mg Pens
Non-proprietary Name	Garadacimab (Genetical Recombination)
Applicant	CSL Behring K.K.
Date of Application	February 26, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, safety, clinical positioning and indication, dosage and administration, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusions concerning the efficacy, safety, clinical positioning and indication, dosage and administration, and post-marketing investigations of garadacimab described in the Review Report (1), and raised the following comments:

- On the basis of the clinical study results submitted, the indication of garadacimab can be specified as "prophylaxis of acute attacks of hereditary angioedema," in line with approved drugs for the prophylaxis of HAE attacks. However, for nC1-INH HAE (HAE Type 3), there are limitations to the evaluation because the number of patients in clinical studies is limited.
- Information on the efficacy and safety of garadacimab in nC1-INH HAE (HAE Type 3) should be continuously collected after the market launch, and the necessity of additional safety measures should be examined based on the obtained information.
- Taking the latest information on the pathophysiology of nC1-INH HAE (HAE Type 3) also into account, it is important to provide useful information on garadacimab treatment for nC1-INH HAE (HAE Type 3) to healthcare professionals.

In view of the review in Section "7.R.7 Post-marketing investigations" of the Review Report (1) and the discussions at the Expert Discussion, PMDA instructed the applicant to address the following points, and the applicant responded that appropriate actions would be taken:

- The currently available clinical study results and the latest pathophysiological information in patients with nC1-INH HAE (HAE Type 3) should be appropriately provided to healthcare professionals using materials for information provision so that they can appropriately determine the appropriateness of garadacimab use in patients with nC1-INH HAE (HAE Type 3).
- After the market launch, information for the proper use of garadacimab including information during treatment with garadacimab in patients with nC1-INH HAE (HAE Type 3) and the latest information on the pathophysiology of HAE Type 3 should be continuously collected. If new information is obtained, the necessity of additional safety measures should be examined, and the information should then be appropriately provided to healthcare professionals.

In view of the reviews in Section "7.R.7 Post-marketing investigations" of the Review Report (1) and the discussions at the Expert Discussion, PMDA concluded that the safety specification presented in Table 43 should be included in the current risk management plan (draft) for garadacimab and the additional pharmacovigilance activities and risk minimization activities presented in Table 44 should be conducted, and instructed the applicant to conduct post-marketing surveillance in which these specified items can be investigated.

Table 43. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity including anaphylaxis	• Bleeding • Immunogenicity	None
Efficacy specification		
• None		

Table 44. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	None	• Provision of information collected through early post-marketing phase vigilance

The applicant's explanation:

As shown in Table 45, the applicant plans to conduct a specified use-results survey in HAE patients to investigate the safety and efficacy of garadacimab in clinical practice.

Table 45. Outline of the specified use-results survey (draft)

Objective	To confirm the safety and efficacy of garadacimab treatment in clinical practice
Survey method	Central registry system
Population	HAE patients
Run-in period	1 year from the initial dose of garadacimab
Planned sample size	50 patients (for safety analysis)
Main survey item(s)	• Safety specification: Serious hypersensitivity including anaphylaxis, bleeding • Patient characteristics (age, body weight, HAE type, medical history, and complications, etc.) • Status of garadacimab treatment • History of prior treatments for HAE • Concomitant drugs • Adverse events • Laboratory data related to adverse events • Status of HAE attacks, etc.

PMDA has accepted the applicant's actions and considers that collected information should be provided to healthcare professionals in an appropriate and prompt manner.

1.2 Changes to the manufacturing process of the drug product

In the manufacturing process of the drug product, [redacted] is specified to be conducted. To ensure more robust sterility assurance, it was decided to conduct a [redacted] step in the course of regulatory review. PMDA confirmed that the change in the manufacturing process was appropriately implemented, including comparability assessment of the drug product in response to the change, and accepted the change.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration below, after modifying the proposed indication as shown below and with the following condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

~~Long-term p~~Prophylaxis of acute attacks of hereditary angioedema

(The underlined word is added to, and the strikethrough word is deleted from the proposed text.)

Dosage and Administration

The usual dosage for adults and children aged 12 years or older is 400 mg of garadacimab (genetical recombination) administered subcutaneously as the initial dose, followed by doses of 200 mg administered

subcutaneously once a month.

(No changes from the proposed text.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

AAE-C1-INH	Acquired angioedema
ACEi	Angiotensin converting enzyme inhibitor
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
APC	Activated protein C
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	All treated subjects
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time 0 to t hours
AUC_{inf}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last observed concentration
$AUC_{last-inf}$	AUC from the last observed concentration to infinity
$AUC_{tau,ss}$	AUC in 1 dosing interval at steady state
BEAD	Biotin-drug extraction and acid dissociation
C1q	Complement component C1q
C1-INH	C1-esterase inhibitor
C1-INH HAE	Hereditary angioedema with C1-esterase inhibitor deficiency
nC1-INH HAE	Hereditary angioedema with normal C1-esterase inhibitor
C3a	Complement component C3a
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CEX-HPLC	Cation exchange chromatography
CL	Clearance
C_{max}	Maximum plasma drug concentration
$C_{max,ss}$	Maximum plasma drug concentration at steady state
$C_{min,ss}$	Minimum plasma drug concentration at steady state
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
CRP	C-reactive protein
EC_{50}	Half-maximal effective concentration
ECL	Electrochemiluminescence
EFD	Embryo-fetal development
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
E_{max}	maximal effect
FcRn	Neonatal Fc receptor
FcγR	Fcγ receptor
FEED	Fertility and early embryonic developmental
FVIIa	Activated blood coagulation factor VII
FIXa	Activated blood coagulation factor IX
FXa	Activated blood coagulation factor X
FXI	Coagulation factor XI
FXIa	Activated blood coagulation factor XI
FXII	Coagulation factor XII
FXIIa	Activated blood coagulation factor XII
βFXIIa	Active catalytic fragment of FXII
FXII HAE	Hereditary angioedema with normal C1-esterase inhibitor, factor XII mutation
G-CSF	granulocyte colony stimulating factor
HAE	Hereditary angioedema

HCP	Host cell protein
[redacted]	[redacted]
IC_{50}	50% inhibitory concentration
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
ITT	Intent-to-treat
Japanese guideline	Guideline for hereditary angioedema (HAE) by the Japanese Association for Complement Research: The 2023 revision and update (*Journal of the Japanese Association for Complement Research*. 2023;60:103-131)
KC	Keratinocyte-derived chemokines
K_D	Dissociation constant
LIVCA	Limit-of-*in-vitro*-cell-age
[redacted]	[redacted]
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
NMRI	Naval medical research institute
NSD	Needle safety device
NZW	New Zealand white
PLG	Plasminogen
PLG HAE	Hereditary angioedema with normal C1-esterase inhibitor, plasminogen gene mutation
PMDA	Pharmaceuticals and Medical Devices Agency
PPND	Pre- and postnatal developmental
PT	Prothrombin time
qPCR	Quantitative polymerase chain reaction
QxW	At x-week intervals
RH	Relative humidity
SE-HPLC	Size exclusion chromatography
SGART	Subject's global assessment of response to therapy
SMQ	Standardised MedDRA queries
SPR	Surface plasmon resonance
Study xxxx	Study CSL312_xxxx
$T_{1/2}$	Elimination half life
T_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
tPA	Tissue plasminogen activator
uPA	Urokinase type plasminogen activator
Vd	Volume of distribution
WCB	Working cell bank