Report on the Deliberation Results

December 11, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Hympavzi S.C. Injection 150 mg Pen
Non-proprietary Name	Marstacimab (Genetical Recombination) (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	February 28, 2024

Results of Deliberation

In its meeting held on December 6, 2024, 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 Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of patients have been accrued.

**Japanese Accepted Name (modified INN)*

Review Report

November 25, 2024
Pharmaceuticals and Medical Devices Agency

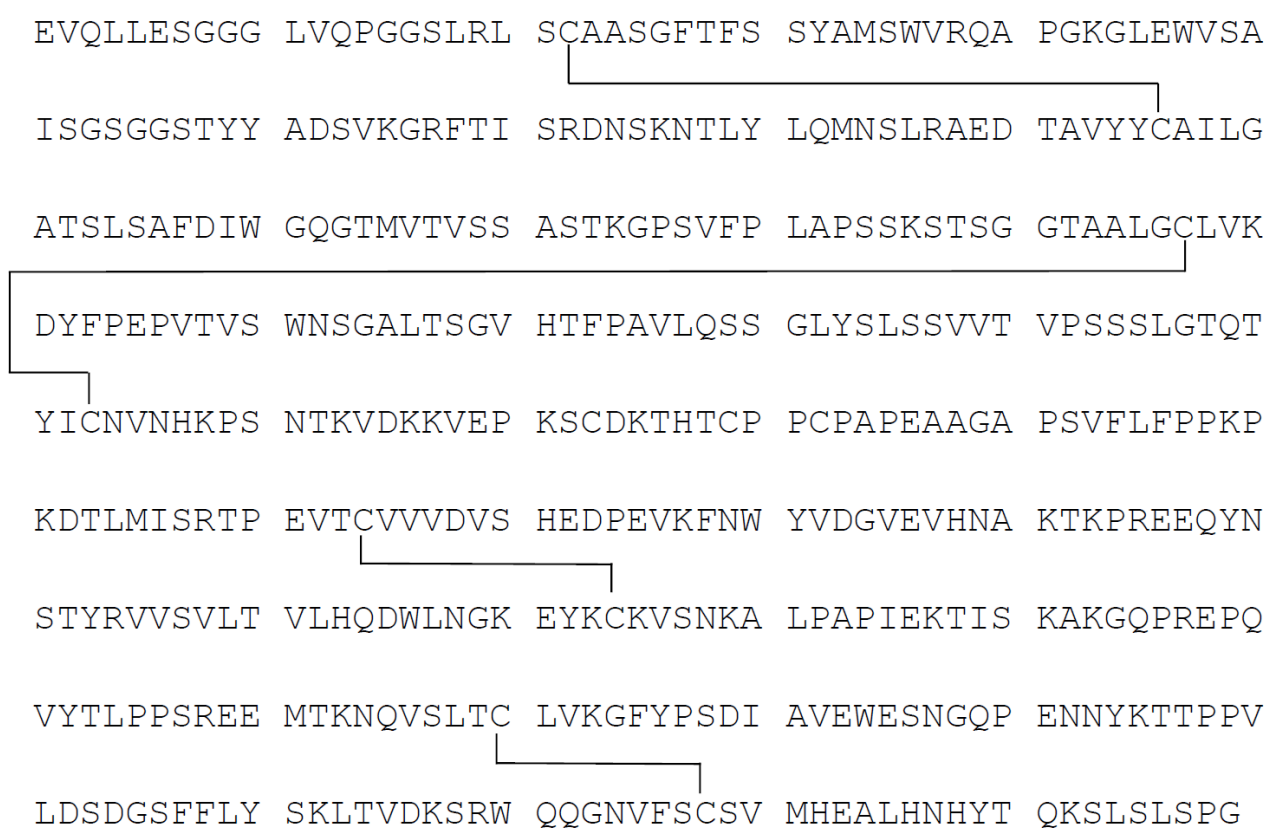
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Hympavzi S.C. Injection 150 mg Pen
Non-proprietary Name	Marstacimab (Genetical Recombination)
Applicant	Pfizer Japan Inc.
Date of Application	February 28, 2024
Dosage Form/Strength	A solution for injection in a prefilled syringe, each containing 150 mg of marstacimab (genetical recombination) in 1 mL of solution
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Marstacimab is a recombinant anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody derived from human IgG1. In the H-chain, the amino acid residues are substituted at 3 positions (L237A, L238A, G240A) and K450 at the C-terminus is deleted. Marstacimab is produced in CHO cells. Marstacimab is a glycoprotein (molecular weight: ca. 146,000) composed of 2 H-chains (γ1-chains) consisting of 449 amino acid residues each and 2 L-chains (λ-chains) consisting of 218 amino acid residues each.

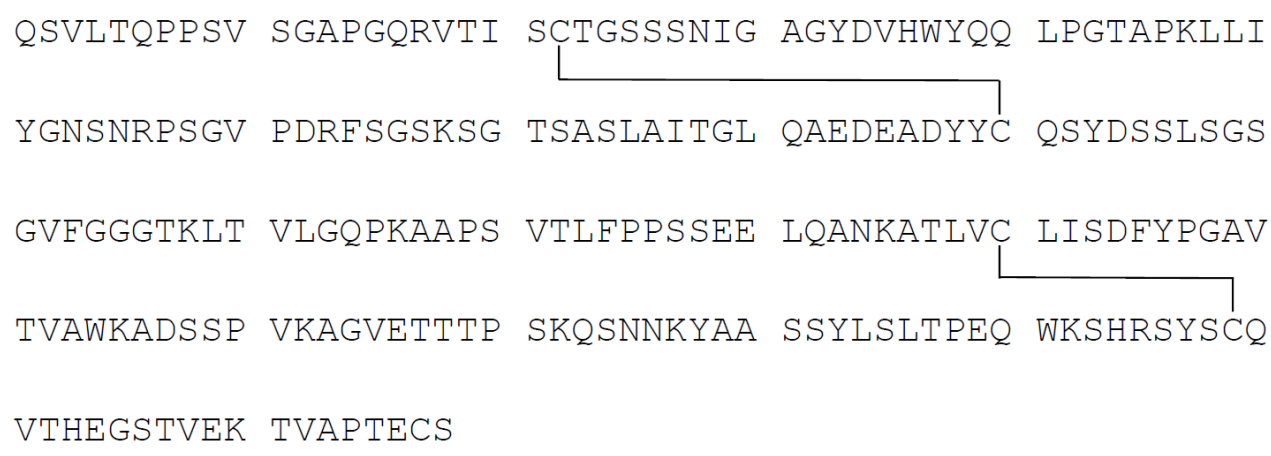
Structure

Amino acid sequence and disulfide bonds:

Heavy (H) chain



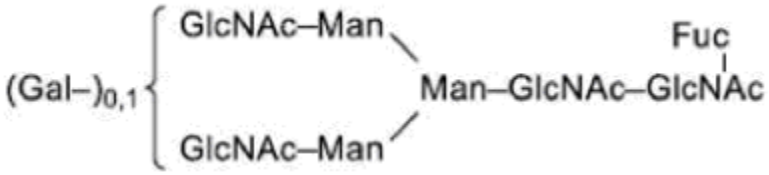
Light (L) chain



H-chain N300, glycosylation; L-chain Q1, pyroglutamic acid (partial)

H-chain C223—L-chain C217, H-chain C229—H-chain C229, H-chain C232—H-chain C232, disulfide bonds

Deduced structure of major glycan:



Molecular formula: $C_{6304}H_{9772}N_{1680}O_{2006}S_{44}$ (protein moiety, four stranded)

H-chain, $C_{2158}H_{3346}N_{572}O_{670}S_{17}$

L-chain, $C_{994}H_{1544}N_{268}O_{333}S_{5}$

Molecular weight: 142,601.95

Items Warranting Special Mention None

Reviewing Office Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the control of bleeding tendency in patients with congenital hemophilia without coagulation factor VIII or factor IX inhibitors, 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 conditions.

Indication

Control of bleeding tendency in patients with congenital hemophilia without coagulation factor VIII or factor IX inhibitors

Dosage and Administration

The usual dosage for patients aged ≥12 years weighing ≥35 kg is an initial dose of 300 mg of marstacimab (genetical recombination) by subcutaneous injection, followed by 150 mg once weekly by subcutaneous injection. The dose may be increased to 300 mg once weekly in patients weighing ≥50 kg when the control of bleeding tendency is inadequate.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of patients have been accrued.

Attachment

Review Report (1)

September 24, 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	Hympavzi S.C. Injection 150 mg
Non-proprietary Name	Marstacimab (Genetical Recombination)
Applicant	Pfizer Japan Inc.
Date of Application	February 28, 2024
Dosage Form/Strength	A solution for injection in a prefilled syringe, each containing 150 mg of Marstacimab (Genetical Recombination) in 1 mL of solution

Proposed Indication

Control of bleeding tendency in patients with hemophilia without coagulation factor VIII or factor IX inhibitors

Proposed Dosage and Administration

The usual dosage for patients aged ≥12 years is an initial loading dose of 300 mg of marstacimab (genetical recombination) by subcutaneous injection, followed by 150 mg once weekly by subcutaneous injection.

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List of Abbreviations

See Appendix.

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

Hemophilia (coagulation factor VIII deficiency [hemophilia A] and coagulation factor IX deficiency [hemophilia B]) is a hemorrhagic disease caused by quantitative reduction or qualitative abnormality of coagulation factor VIII (FVIII) or coagulation factor IX (FIX), and may lead to serious bleeding episodes. Factor replacement therapy using FVIII or FIX products is the primary treatment to maintain hemostasis in patients with hemophilia. For patients with severe hemophilia, prophylactic replacement therapy, i.e., regular administration of agents such as a deficient coagulation factor for a long period of time, has been implemented to reduce the frequency of bleeding episodes (bleeding tendency). Currently approved pharmaceutical products that are used for routine prophylaxis in patients with hemophilia without FVIII or FIX inhibitors are concizumab, a humanized monoclonal antibody that binds to tissue factor pathway inhibitor (TFPI), and emicizumab (for the treatment of hemophilia A only), an anti-FIXa/FX humanized bispecific monoclonal antibody, as well as recombinant FVIII and recombinant FIX products.

Marstacimab (genetical recombination) (hereinafter referred to as marstacimab) is a recombinant humanized monoclonal antibody that binds to TFPI, an inhibitor of the extrinsic coagulation pathway, decreasing the inhibitory activity of TFPI against FXa. This leads to production of FXa, promoting thrombin generation, thereby achieving hemostasis. This mechanism of action is expected to have an effect, regardless of the type of deficient coagulation factor (i.e., FVIII or FIX) in a patient with hemophilia, or the presence/absence of FVIII or FIX inhibitors, and therefore, marstacimab has been developed as a drug for routine prophylaxis in patients with hemophilia with or without inhibitors.

The applicant has filed an application for marketing approval based on the results from studies including the global phase III study (Study B7841005) conducted in patients with hemophilia without FVIII or FIX inhibitors. As of September 2024, marstacimab has not been approved in any country or region, and applications are under review in the US and Europe.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Marstacimab is a human monoclonal immunoglobulin G1 (IgG1) antibody directed against the Kunitz domain 2 (K2) of human TFPI.

Human single chain Fv (scFv) libraries were screened using the phage display technique, and multiple scFvs that had affinity for the combined K1K2 domains of human and murine TFPI and inhibited binding of TFPI to FXa were selected. Antibodies against the selected scFvs were constructed and lead candidates were selected from the antibodies using TFPI affinity, etc. as an indicator. After introducing mutations that impair effector functions into the gene sequence for the heavy chain of the lead candidate antibody, the coding sequence for the heavy chain and light chain was inserted into an expression vector to generate the gene expression construct for marstacimab. Using the gene expression construct, the coding sequence for the heavy and light chains of marstacimab were inserted into the genome of Chinese hamster ovary cells (CHO) by the flippase/flippase

recognition target (FLP/FRT) recombinase-mediated cassette exchange system. The master cell bank (MCB) and working cell bank (WCB) were prepared from the clones optimal for the production of marstacimab.

Characterization and purity testing were conducted for the MCB, WCB, and end of production cells (EOPC) in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines Q5A (R1), Q5B, and Q5D. The results demonstrated genetic stability during production. Within the range tested, no viral or non-viral adventitious agents were detected, other than endogenous retrovirus-like particles commonly found in rodent-derived cells.

Both the MCB and WCB are stored in [redacted] of [redacted]. While [redacted] is not [redacted], the [redacted] is [redacted] as necessary.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of thawing of the WCB, [redacted] expansion culture, [redacted] expansion culture, [redacted] expansion culture, production culture, harvest, [redacted] chromatography, [redacted] virus inactivation, [redacted] chromatography, virus removal filtration, ultrafiltration/dialysis filtration, drug solution preparation/filtration, and filling/freezing/testing.

[redacted], [redacted] chromatography, [redacted] virus inactivation, [redacted] chromatography, virus removal filtration, and [redacted] have been defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug substance.

2.1.3 Safety evaluation of adventitious agents

With the exception of CHO cells, the host cells, no biological materials are used in the manufacturing process of the drug substance.

Purity was tested on the MCB, WCB, and EOPC [see Section 2.1.1]. Post-harvest unprocessed bulk obtained on a commercial scale was subjected to microbial limit testing, *in vitro* virus testing, microscopic analysis, mouse minute virus testing, and mycoplasma testing. Within the range studied, no viral or non-viral adventitious agents were detected. These tests on pre-harvest unprocessed bulk are selected as in-process control tests.

Viral clearance studies were performed with model viruses for the purification process. The results showed that the purification process is capable of virus clearance to a certain extent (Table 1). The virus reduction factor for each step presented in the table is the lowest value among those obtained from independent runs.

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})		
	Xenotropic murine leukemia virus	Minute virus of mice	Reovirus type 3
[redacted] virus inactivation	[redacted]		
[redacted] chromatography			
Virus removal filtration			
Overall virus reduction factor	>18.54	>12.10	≥13.16

2.1.4 Manufacturing process development

The major changes to the manufacturing process during the development of the drug substance are [redacted], [redacted], [redacted], and [redacted] (the manufacturing processes before and after the change are referred to as the pre-change process and the proposed commercial process, respectively). The following are the manufacturing processes for the drug substance used to produce the formulations in the respective studies: the pre-change process and the proposed commercial process (non-clinical studies and phase I studies); the pre-change process (phase Ib/II study); and the proposed commercial process (phase II and phase III studies). Following the above process changes, comparability studies on the quality attributes have demonstrated the comparability of quality attributes of the drug substance before and after the change.

2.1.5 Characterization

2.1.5.1 Structure and properties

Table 2 summarizes the characterization performed.

Table 2. Evaluation items for characterization

Primary/higher-order structure	Amino acid sequence, post-translational modifications ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], disulfide bonds), secondary structure, tertiary structure
Physicochemical properties	Molecular weight, charge heterogeneity, thermal stability, HMMS, LMMS
Glycan structure	N-glycan profile
Biological properties	Activity to inhibit formation of [redacted], activity to inhibit formation of [redacted], FcγR [redacted] ([redacted] [redacted], [redacted] [redacted], and [redacted]), [redacted] binding affinity, post-deglycosylation biological activity ([redacted])

In the evaluation of biological properties, FXa activity was measured using a chromogenic substrate. The results demonstrated that marstacimab inhibits the formation of [redacted] and [redacted].

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization in Section 2.1.5.1, Related Substance A ([redacted], [redacted]), Related Substance B, Related Substance C, and Related Substance D ([redacted]) were identified as product-related substances. Impurity A and Impurity B were identified as product-related impurities. These impurities are controlled by the specifications for the drug substance and those for the drug product.

2.1.5.3 Process-related impurities

Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, and Impurity I were identified as process-related impurities. Impurity D is controlled by the specifications for the drug substance. It was demonstrated that other process-related impurities were adequately removed by the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of content, description (turbidity and color), identification (peptide mapping), pH, charge heterogeneity (imaged capillary isoelectric focusing [icIEF]), purity (size exclusion high performance liquid chromatography [SE-HPLC], capillary gel electrophoresis [CGE; reducing and non-reducing], and host cell protein [HCP]), bacterial endotoxins, microbial limit, biological activity ([redacted]), and assay (ultraviolet visible spectrophotometry).

2.1.7 Stability of drug substance

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

Table 3. Summary of main stability studies for the drug substance

Study type	Manufacturing process	Number of batches	Storage condition	Test period	Storage form
Long-term	Proposed commercial process	3	−20°C ± 5°C	48 months	[redacted] container
Accelerated	Proposed commercial process	3	5°C ± 3°C	6 months	
Stress	Proposed commercial process	1	25°C ± 2°C, 60% ± 5% RH	1 month	
Photostability	Proposed commercial process	1	Overall illumination of 1.2 million lx·h and near ultraviolet energy of 200 W·h/m^2, at 25°C ± 2°C, 60% ± 5% RH		

The long-term study and accelerated study showed no clear changes in quality attributes throughout the test period.

The stress test showed that [redacted] tended to increase.

The photostability study results showed that the drug substance was photolabile.

Based on the above, a shelf life of [redacted] months was proposed when stored at −20°C ± 5°C in a multilayer container with [redacted] inner layer protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection solution supplied in a syringe (1 mL) containing 150 mg of marstacimab (genetical recombination). The drug product contains the following excipients: sucrose, L-histidine, L-histidine hydrochloride hydrate, disodium edetate hydrate, polysorbate 80, and water for injection. The drug product is a combination product comprising a prefilled syringe (PFS) sealed in a dedicated pen-injector (the entire product is called a prefilled pen, or PFP).

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of thawing of the drug substance, [redacted], bioburden reduction filtration, sterile filtration/filling/testing, inspection/storage, assembling, packaging, labeling, testing, and storage.

[redacted] are defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

2.2.3 Manufacturing process development

The major changes to the manufacturing process during the development of the drug product are as follows (manufacturing processes at each stage are referred to as Process A, Process B, and the proposed commercial process).

- From Process A to Process B: changes in [redacted] ([redacted])
- From Process B to the proposed commercial process: changes in [redacted] and [redacted]

The formulation produced by Process A and that by the proposed commercial process were used in phase I studies; the formulation produced by Process A was used in the phase Ib/II study; the formulation produced by Process B was used in the phase II study; and the formulation produced by the proposed commercial process was used in the phase III studies. When these changes were made to the manufacturing process, comparability was evaluated with respect to the quality attributes. The results demonstrated the comparability of the formulations before and after the changes.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description (turbidity and color), identification (peptide mapping), osmolality, pH, charge heterogeneity (icIEF), purity (SE-HPLC and CGE [reducing and non-reducing]), polysorbate 80, bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, glide force profiles, injection time, injection volume, exposed needle length, biological activity ([redacted]), and assay (ultraviolet visible spectrophotometry).

2.2.5 Stability of drug product

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

Table 4. Summary of main stability studies for drug product

Drug product type	Study type	Number of batches[a)]	Storage condition	Test period	Storage form
Syringe	Long-term	3	5°C ± 3°C	36 months[b)]	[redacted] syringe with [redacted] needle and [redacted] plunger stopper (The pen product also has a dedicated pen-injector in addition to the above)
	Accelerated	3	30°C ± 2°C, 75% ± 5% RH	6 months	
	Stress	1	40°C ± 2°C, 75% ± 5% RH	1 month	
	Photostability	1	Overall illumination of 1.2 million lx·h and near ultraviolet energy of 200 W·h/m^2, at 25°C ± 2°C, 60% ± 5% RH		
Pen[c)]	Long-term	1	5°C ± 3°C	24 months[b)]	
	Accelerated	2	30°C ± 2°C, 75% ± 5% RH	6 months	
	Stress	1	40°C ± 2°C, 75% ± 5% RH	1 month	

a) Both for the drug substance and the drug product, the proposed commercial processes were used.
b) The test is ongoing and will continue for up to [redacted] months.
c) Only the tests for the function of the pen were conducted.

The long-term testing showed no clear changes in quality attributes throughout the test period.

The accelerated tests revealed the following findings: [redacted] and [redacted] in [redacted]; [redacted] and [redacted] in [redacted]; [redacted] and [redacted] in [redacted]; [redacted] in [redacted]; [redacted]; [redacted] in [redacted]; [redacted]; and [redacted].

The stress tests revealed the following findings: [redacted] and [redacted] in [redacted]; [redacted] in [redacted]; [redacted] and [redacted] in [redacted]; [redacted] in [redacted]; and [redacted].

The photostability test showed that the drug product is photolabile.

Based on the above, a shelf life of 24 months was proposed for the drug product when stored at 2°C to 8°C in a [redacted] syringe with [redacted] needle and [redacted] plunger stopper as primary packaging protected from light.

2.3 Quality control strategy

The quality control strategy was established as follows. Based on the following process-related findings including process characterization, risk assessment of quality attributes, and other data, the control method for the quality attributes of marstacimab consisting of the control of process parameters, in-process controls, specifications, and stability testing was formulated [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):

  Regarding the quality attributes of product-related impurities, process-related impurities, and general quality attributes, the following CQAs were identified based on information obtained during the development of marstacimab, relevant findings, and other relevant data.

  CQAs of the drug substance: [redacted] ([redacted]), [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted],

CQAs of the drug product: [redacted]

- Process characterization

  Based on the [redacted] analysis and [redacted], risks of process parameters and material characteristics were rated. [redacted] and [redacted] for [redacted] and [redacted] were evaluated according to the impact on quality.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

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

The applicant submitted the results from primary pharmacodynamic studies (*in vitro* studies that evaluated the pharmacodynamic properties, *in vivo* studies in mice, rats, and cynomolgus monkeys), safety pharmacology studies in cynomolgus monkeys, and pharmacodynamic drug interaction studies (*in vitro* studies and an *in vivo* [rat] study that evaluated the interaction with blood coagulation factors).

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity for TFPI (CTD 4.2.1.1.1 and 4.2.1.1.2)

The binding of marstacimab to human, mouse, rat, rabbit, or monkey TFPI K1K2 (recombinant protein of TFPI containing K1 and K2 domains) was evaluated by surface plasmon resonance (SPR). The binding affinity (dissociation constant [K_D]) was 3.7 nmol/L (human), 0.575 nmol/L (mouse), 1.57 nmol/L (rat), 4.25 nmol/L (rabbit), and 1.22 nmol/L (monkey).

A separate study used SPR to evaluate the binding of marstacimab to human TFPI K1, TFPI K2, or TFPI K1K2. The respective K_D values were no binding detected, 2.63 nmol/L, and 7.91 nmol/L.

3.1.1.2 Evaluation of TFPI neutralization

3.1.1.2.1 Effect on the TFPI's inhibition of FXa activation (CTD 4.2.1.1.3)

The effects on FXa activity when marstacimab was added to FXa and human TFPI K1K2, or FVIIa/TF/FX and human TFPI K1K2 were evaluated using chromogenic substrates. In both chromogenic assays, concentration-dependent inhibitory effects of marstacimab against FXa activation inhibition by TFPI were observed.

3.1.1.2.2 Effects on clot formation in human whole blood (CTD 4.2.1.1.4)

The effects of marstacimab on the formation of clots in human whole blood were evaluated by thromboelastography (TEG). The results showed concentration-dependent decreases in clotting time and clot formation time.

3.1.1.2.3 Effects on dilute prothrombin time, thrombin generation, activated partial thrombin time in plasma (CTD 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7)

The effects of marstacimab on the blood coagulation system were evaluated using human plasma (non-hemophilic, hemophilia A [HA], and hemophilia B [HB]). In all plasma samples, marstacimab shortened dilute prothrombin time (dPT) and increased thrombin generation in a concentration-dependent manner, but did not change or only slightly shortened activated partial thrombin time (aPTT). Marstacimab also shortened dPT in a concentration-dependent manner in the studies using rabbit and cynomolgus monkey plasma.

3.1.2 *In vivo* studies

3.1.2.1 Effects on bleeding in FVIII-KO mice and FIX-KO mice, and effects on clot formation in FVIII-KO mice (CTD 4.2.1.1.11, 4.2.1.1.12)

- Marstacimab or vehicle was intravenously administered to FVIII-knockout (KO) mice and FIX-KO mice, and blood loss was quantified after tail transection. The results showed decreased blood loss in the marstacimab group compared to the vehicle control group. In the study using FVIII-KO mice, blood loss was assessed at a series of marstacimab dose levels, and marstacimab dose-dependently reduced blood loss.
- Immediately after tail transection in FVIII-KO mice, marstacimab, vehicle, or recombinant coagulation factor VIII (rFVIII) was intravenously administered, and blood loss was quantified. The results showed decreased blood loss in the marstacimab group and the rFVIII group compared to the vehicle control group.
- After marstacimab or vehicle was administered to FVIII-KO mice, or before and after administration of marstacimab in another study, effects on fibrin and platelets were assessed by micro-vessel laser injury. Fibrin deposition and platelet accumulation in the injury site increased in the marstacimab group compared to the vehicle control group, and those increased post-treatment with marstacimab compared to pre-treatment.

3.1.2.2 Effects on dPT in cynomolgus monkey plasma (CTD 4.2.1.1.10)

Diluted prothrombin time in plasma samples obtained from cynomolgus monkeys before and after (intravenous or subcutaneous) administration of marstacimab was evaluated. In both routes of administration, dPT was shortened after administration of marstacimab compared to pre-treatment.

3.2 Safety pharmacology

Effects of marstacimab on the central nervous system, cardiovascular system, and respiratory system were evaluated in repeated-dose toxicity studies [see Section 5.2] (Table 5). No effects of marstacimab on safety pharmacology endpoints were found in any of the studies.

Table 5. Summary of safety pharmacology study results

Category	Test system	Endpoint/method	Maximum dose	Findings	CTD
Central nervous system	Cynomolgus monkeys (males/females 3 or 5/group)	Clinical signs, activity, motor function, cerebrospinal nervous system function, proprioception, postural reaction	IV 500 mg/kg SC 90 mg/kg	No effects associated with marstacimab	4.2.3.2.5
Cardiovascular system		Electrocardiogram, blood pressure, heart rate, pulse			
Respiratory system		Respiration rate			

3.3 Pharmacodynamic drug interactions

For assessment on interactions between marstacimab and rFVIIa, aPCC, or FVIIa/FX, the applicant submitted results from *in vitro* studies using human plasma and *in vivo* studies in rats. Given that the level of interactions associated with thrombin generation reaction observed in the *in vitro* study is within the range reported in the study using normal human plasma, and that the results from the *in vivo* studies are data in rats with a normal coagulation system, the applicant considered that combined use of marstacimab with rFVIIa, aPCC, or FVIIa/FX in patients with hemophilia can be supported by the results.

3.3.1 *In vitro* studies

3.3.1.1 Interactions with rFVIIa in human plasma (CTD 4.2.1.1.6, 4.2.1.1.7)

The effect of rFVIIa on the increase in thrombin generation by marstacimab and the effect of marstacimab on the increase in thrombin generation by rFVIIa were investigated using human plasma (HA and HB). Thrombin generation was accelerated (increase in generation and shortening of initiation time) in both cases compared to thrombin generation when marstacimab or rFVIIa was added alone.

3.3.1.2 Interactions with aPCC or FVIIa/FX in human plasma (CTD 4.2.1.1.8, 4.2.1.1.9)

The effects of the combined use of marstacimab with aPCC or FVIIa/FX on the increase in thrombin generation were investigated using human plasma (HA [with inhibitor], HB [FIX neutralizing antibodies added]). Following administration of marstacimab in combination with aPCC or FVIIa/FX, the amount of thrombin generated increased compared to that after administration of marstacimab, or aPCC or FVIIa/FX alone. Conversely, no additional shortening in the initiation time for thrombin generation was observed.

3.3.2 *In vivo* studies

3.3.2.1 Interactions with rFVIIa, aPCC, or FVIIa/FX in rats (CTD 4.2.1.1.13, 4.2.1.1.14, 4.2.1.1.15)

The following results were obtained in studies with rats.

- Following administration of marstacimab in combination with rFVIIa, the frequency of thrombi/emboli increased and severity worsened compared to the results after administration of vehicle, marstacimab, or rFVIIa alone.
- Following administration of marstacimab in combination with aPCC, the thrombin-antithrombin complexes (TAT) concentrations and the mean platelet volume increased compared to the results after administration of aPCC alone.
- When marstacimab and FVIIa/FX were administered in combination, coagulation parameters did not

differ markedly from those when FVIIa/FX was administered alone.

3.R Outline of the review conducted by PMDA

On the basis of the data presented on primary pharmacodynamics, PMDA considers that marstacimab has a binding affinity for TFPI, and can be expected to have a hemostatic effect *in vivo*. The evaluation results of safety pharmacology studies presented indicated no particular safety-related concerns for marstacimab.

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

The applicant submitted pharmacokinetic data from studies in rats and cynomolgus monkeys. Plasma marstacimab concentrations were determined by enzyme-linked immunosorbent assay (ELISA) in rats and electrochemiluminescence in monkeys, with the lower limits of quantitation for plasma marstacimab concentrations being 40 to 58.2 ng/mL (rat) and 1,040 ng/mL (monkey). Anti-drug antibodies (ADAs) against marstacimab were detected by electrochemiluminescence.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.3.2.1, 4.2.3.2.2)

Table 6 shows the pharmacokinetic (PK) parameters after single-dose intravenous (IV) or subcutaneous (SC) administration of marstacimab to male rats or male/female cynomolgus monkeys.

Table 6. Pharmacokinetic parameters following single-dose administration of marstacimab to rats and cynomolgus monkeys

Animal species	Route of adminis-tration	Dose (mg/kg)	Number of animals, sex	C_{max} (μg/mL)	AUC[a)] (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} or V_{ss}/F (mL/kg)
Rat	IV	3	3 males	88.5	2,810	0.083	37.8	0.977	43.9
		30	3 males	882	29,700	0.083	45.1	0.893	43.8
		90	3 males	3,480[b)]	111,000	0.083	42.9	0.667	42.2
	SC	3	3 males	27	1,960	72.0	—	—	—
Monkey	IV	3	1 male	183	4,500	96.0	—	0.152	23.3
			1 female	71.9	2,510	0.083	—	1.062	44.9
		30	1 male	608	36,400	0.083	—	0.314	64.3
			1 female	555	33,000	0.083	—	0.313	65.8
		90	1 male	2,650	140,000	0.083	—	0.197	55.0
			1 female	2,710	135,000	0.083	—	0.298	48.6
	SC	3	1 male	6.54	393	72.0	—	—	461
			1 female	7.74	471	2.0	—	—	382

Mean values (rats); individual values (monkeys)
t_{max}, median; —, not calculated
a) $AUC_{0\text{-}120h}$ (rats); $AUC_{0\text{-}96h}$ (monkeys); b) N = 2

4.1.2 Repeated-dose studies (CTD 4.2.3.2.3, 4.2.3.2.5)

Table 7 shows the PK parameters after once-weekly, repeated-dose, intravenous or subcutaneous administration of marstacimab to male and female rats and male and female cynomolgus monkeys. Since there was no consistent difference in exposure between the sexes, the male and female data are combined.

Table 7. Pharmacokinetic parameters following repeated-dose administration of marstacimab to rats and cynomolgus monkeys

Animal species	Route of adminis-tration	Dose (mg/kg)	Timepoint	N	C_{max} (µg/mL)	$AUC_{0\text{-}168h}$ (µg·h/mL)	t_{max} (h)
Rat	IV	60	Day 1	8	1,430 ± 109	62,200 ± 14,000	0.25 [0.25, 0.25]
			Day 29	8	1,670 ± 339	57,700 ± 14,800	0.25 [0.25, 0.25]
			Day 85	8	1,530 ± 327	54,500 ± 19,200	0.25 [0.25, 0.25]
		180	Day 1	8	3,690 ± 965	205,000 ± 45,800	0.25 [0.25, 0.25]
			Day 29	8	6,190 ± 1,930	263,000 ± 27,300	0.25 [0.25, 24]
			Day 85	8	5,410 ± 456	283,000 ± 19,300	0.25 [0.25, 0.25]
		1.000	Day 1	8	21,000 ± 6,630	1,090,000 ± 204,000	0.25 [0.25, 24]
			Day 29	8	28,900 ± 2,480	1,660,000 ± 97,200	0.25 [0.25, 0.25]
			Day 85	8	27,800 ± 3,220	1,940,000 ± 247,000	0.25 [0.25, 0.25]
	SC	180	Day 1	8	693 ± 199	74,800 ± 23,000	60 [48, 96]
			Day 29	8	524 ± 236	57,100 ± 35,000	48 [48, 48]
			Day 85	8	416 ± 170	45,300 ± 22,200	48 [48, 72]
Monkey	IV	30	Day 1	6	817 ± 107	55,700 ± 4,500	0.25 [0.25, 0.25]
			Day 29	6	1,240 ± 81.7	139,000 ± 18,200	0.25 [0.25, 6.0]
			Day 85	6	1,290 ± 233	160,000 ± 38,800	0.25 [0.25, 24]
		90	Day 1	6	1,570 ± 136	173,000 ± 10,300	0.25 [0.25, 24]
			Day 29	6	3,600 ± 225	387,000 ± 31,400	3.13 [0.25, 24]
			Day 85	6	4,510 ± 471	474,000 ± 71,800	0.25 [0.25, 6.0]
		500	Day 1	10	10,500 ± 1,130	937,000 ± 84,200	0.25 [0.25, 6.0]
			Day 29	10	17,300 ± 1,440	1,820,000 ± 177,000	0.25 [0.25, 6.0]
			Day 85	10	18,400 ± 1,100	2,000,000 ± 168,000	0.25 [0.25, 6.0]
	SC	90	Day 1	6	969 ± 83.5	123,000 ± 11,100	60 [48, 96]
			Day 29	6	2,160 ± 141	315,000 ± 22,600	48 [6.0, 48]
			Day 85	6	2,480 ± 361	364,000 ± 66,600	48 [48, 48]

Mean ± standard deviation; t_{max}, median [range]

The applicant's explanation about the results obtained from the study:

Following intravenous administration of marstacimab to rats and cynomolgus monkeys, marstacimab exposure increased with an increase in dose. While no clear impact of repeated-dose administration on marstacimab exposure in rats was noted, marstacimab exposure increased in monkeys following repeated-dose administration. Anti-marstacimab antibodies were detected only in rat studies. Three of 8 animals in the 60 mg/kg IV group (from Day 112 onward in 1 animal; on Day 134 in 2 animals) and 6 of 8 animals in the 180 mg/kg SC group (from Day 29 onward in 1 animal; on Day 134 in 5 animals) tested positive for ADAs. Animals in all of the remaining groups were ADA-negative. The marstacimab exposure in ADA-positive rats was similar to that in ADA-negative rats.

4.2 Distribution

No studies were conducted on the distribution of marstacimab. According to the applicant, marstacimab, a monoclonal antibody, is, in general, unlikely to bind to albumin or α1-acid glycoprotein; in addition, based on the distribution volume of marstacimab calculated for monkeys, marstacimab is predicted to have limited distribution. Furthermore, because it is known that human IgG can generally cross the placenta, the applicant explained that statements to this effect will be included in the package insert and other materials to provide information for healthcare professionals.

4.3 Metabolism and excretion

Marstacimab, a monoclonal antibody consisting of natural amino acids, is assumed to be metabolized to peptides and amino acids, which are reused in the body or excreted. Therefore, in accordance with the ICH S6 (R1) guidelines, no studies on metabolism and excretion were conducted.

4.4 Pharmacokinetic drug interactions (CTD 4.2.1.1.13, 4.2.1.1.14, 4.2.1.1.15)

Marstacimab was administered in combination with coagulation factors (rFVIIa, aPCC, or FVIIa/FX) to male rats, and drug interactions were investigated. The exposure after administration of marstacimab alone was similar to that after administration marstacimab in combination with rFVIIa, aPCC, or FVIIa/FX.

4.R Outline of the review conducted by PMDA

On the basis of the submitted pharmacokinetic study data, PMDA considers that there is no particular problem with the non-clinical pharmacokinetic evaluation.

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data on marstacimab from repeated-dose toxicity studies, reproductive and developmental toxicity studies, a local tolerance study, and other toxicity studies (e.g., tissue cross-reactivity study).

5.1 Single-dose toxicity

No single-dose toxicity studies of marstacimab were conducted. Acute toxicity was evaluated based on clinical signs, etc. following the first dose in repeated-dose toxicity studies in rats and cynomolgus monkeys [see Section 5.2]. No deaths or abnormal clinical signs were reported in any study, and the approximate lethal dose was determined to be >1,000 mg/kg in rats (IV), >300 mg/kg in rats (SC), >500 mg/kg in cynomolgus monkeys (IV), and >90 mg/kg in cynomolgus monkeys (SC).

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of marstacimab were conducted in rats and cynomolgus monkeys (Table 8). Pharmacology-related findings (e.g., a decrease in fibrinogen levels, an increase in D-dimer levels) were noted both in rats and cynomolgus monkeys. While thrombi/emboli in the lung were noted in the 6-month intravenous study in rats, the events were minor in severity and secondary toxicity-related changes were absent; therefore, the applicant explained that these findings were of low toxicological significance.

Table 8. Summary of repeated-dose toxicity study results

Test system	Route of administration	Dosing period	Dose (mg/kg/week)	Major findings	No-observed-adverse-effect level (NOAEL) (mg/kg/week)	CTD
Male/female rats (Wistar Han)	IV or SC	3 months (once weekly) + 6-week recovery period	IV: 0,[a] 60, 180, 1,000 SC: 0,[a] 180	IV At ≥60, decreased fibrinogen, prolonged aPTT[b] At 1,000, shortened PT, decreased serum albumin, decreased A/G, increased serum globulin, increased total protein[c] SC At 180, decreased fibrinogen, shortened PT, prolonged aPTT[b] Reversibility, reversible	IV: 1,000 SC: 180	4.2.3.2.3
	IV	6 months (once weekly) + 6-week recovery period[d]	0,[a] 60, 180, 1,000	At ≥60, decreased fibrinogen, prolonged aPTT,[b] increased D-dimer, increased serum globulin, cellular infiltration with foreign matter/refractile materials in the lung,[e] thrombi/emboli in the lung and injection site[e] At ≥180, increased serum total protein, decreased A/G[c] At 1,000, prolonged PT, decreased serum albumin[c]	1,000	4.2.3.2.4
Male/female cynomolgus monkeys	IV or SC	3 months (once weekly) + 6-week recovery period	IV: 0,[a] 30, 90, 500 SC: 0,[a] 90	IV At ≥30, decreased fibrinogen, prolonged PT,[b] increased D-dimer, increased serum globulin, increased total protein, decreased A/G[c] At 500, prolonged aPTT[b] SC At 90, decreased fibrinogen, prolonged PT,[b] increased D-dimer, increased serum globulin, increased total protein, decreased A/G[c] Reversibility, reversible[f]	IV: 500 SC: 90	4.2.3.2.5

a) Vehicle, an aqueous solution containing 20 mmol/L histidine, 85 mg/mL sucrose, 0.05 mg/mL disodium EDTA, and 0.2 mg/mL polysorbate 80, pH 5.8
b) A change caused by excessive activation of the coagulation cascade and depletion of coagulation factors associated with administration to normal animals. The applicant explained that these findings may not be relevant to patients with hemophilia.
c) The findings were reversible after the recovery period, with no associated histopathological findings; therefore, the applicant explained that the findings are of low toxicological significance.
d) Only a toxicokinetic evaluation of the 60 mg/kg group after the recovery period was performed. Plasma marstacimab concentrations were less than the lower limit of quantitation (58 ng/mL) in 6 of 8 animals.
e) These changes were minor and no secondary toxicological changes were observed; therefore, the applicant explained that these findings are of low toxicological significance. Thrombi/emboli in the lung were found in 5 of 30 animals (60 mg/kg), 9 of 30 animals (180 mg/kg), and 6 of 30 animals (1,000 mg/kg).
f) Effects on coagulation parameters remained at the end of the recovery period.

5.3 Genotoxicity

Because marstacimab is a protein produced by genetic engineering, no genotoxicity studies were conducted.

5.4 Reproductive and developmental toxicity

A fertility and early embryonic development to implantation study of marstacimab was conducted in male rats (Table 9). Female fertility was evaluated in the repeated-dose toxicity studies in rats and cynomolgus monkeys [see Section 5.2], and no effects on reproductive organs were noted.

No reproductive and developmental toxicity studies were conducted using female animals. The applicant explained that since the prevalence of hemophilia, for which marstacimab is indicated, is low in females (*World Federation of Hemophilia Report on the Annual Global Survey 2021*, October 2022), marstacimab is very unlikely to be used in females of reproductive potential. For this and other reasons, the applicant explained that conducting such studies in female animals would not yield results of clinical significance.

Table 9. Summary of reproductive and developmental toxicity study results

Study type	Test system	Route of adminis-tration	Dosing period	Dose (mg/kg/ week)	Major findings	NOAEL (mg/kg/week)	CTD
Fertility and early embryonic development to implantation	Male rats (Wistar Han)	IV	4 weeks prior to mating to the mating period, up to necropsy (once weekly, total 11 doses)	0,[a)] 60, 180, 1,000	Parent animals, none Reproductivity, none Early embryonic development, none[b)]	Parent animals (clinical signs): 1,000 Parent animals (reproductivity): 1,000 Early embryonic development[b)]: 1,000	4.2.3.5.1.1

a) Vehicle, an aqueous solution containing 20 mmol/L histidine, 85 mg/mL sucrose, 0.05 mg/mL disodium EDTA, and 0.2 mg/mL polysorbate 80, pH 5.8
b) Data for treatment-naïve female rats mated with marstacimab-treated male rats

5.5 Carcinogenicity

No carcinogenicity studies were conducted because marstacimab is a protein produced by genetic engineering or because of other reasons.

5.6 Local tolerance

A local tolerance study of marstacimab was conducted in rats (Table 10). Although inflammatory reactions (edema, hemorrhagic/mixed cell infiltration) were noted at the marstacimab injection site, these changes were considered to be reversible changes because they were not observed at 1 week post-dose. Because the concentration of marstacimab (150 mg/mL) and vehicle composition used in the local tolerance study were identical to those in the proposed commercial formulation, the proposed commercial formulation was considered to be well tolerated locally.

Table 10. Summary of local tolerance study results

Test system	Application site	Test method	Major findings	CTD
Male/female rats (Wistar Han)	SC	A single dose of vehicle[a)] or marstacimab 300 mg/kg was administered. Histopathological examination of the injection site was performed at 1 day post-dose or 1 week post-dose.	1 day post-dose Edema, hemorrhagic/mixed cell infiltration at the injection site 1 week post-dose None	4.2.3.6.1

a) an aqueous solution containing 20 mmol/L histidine, 85 mg/mL sucrose, 0.05 mg/mL disodium EDTA, and 0.2 mg/mL polysorbate 80, pH 5.8

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study

A tissue cross-reactivity study of marstacimab was conducted using human, cynomolgus monkey, and rat tissue panels (Table 11). In all the animal species, staining was primarily observed in the cytoplasm of the vascular endothelial cells. Staining was also noted in the decidual granules of human placenta decidual cells.

Table 11. Summary of tissue cross-reactivity study results

Study type	Test system	Test method	Major findings	CTD
Tissue cross-reactivity	Human, cynomolgus monkey, rat tissue panels	Cross reactivity was evaluated by immunostaining using tissue panels for each animal species and marstacimab 5 or 25 µg/mL	Marstacimab binding was observed in the following cells: Humans: the decidual granules of placenta decidual cells; the cytoplasm of placental trophoblasts, decidual cells, epithelial cells, vascular endothelial cells, and oenocytes Cynomolgus monkeys: the cytoplasm of placental trophoblasts, decidual cells, epithelial cells, vascular endothelial cells, mesothelial cells, and pancreatic islet cells; extracellular materials in the ovary Rats: the cytoplasm of vascular endothelial cells and spongiotrophoblasts	4.2.3.7.7.2

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and discussions in the following sections, PMDA concluded that there are no particular toxicological concerns associated with marstacimab.

5.R.1 Cell filtration and other findings observed in rat lungs

In the 6-month repeated-dose toxicity study in rats [hereinafter referred to as "Study 20089324," CTD 4.2.3.2.4, see Section 5.2], cellular infiltration with foreign matter or refractile materials in the lung were noted. PMDA asked the applicant to explain its development mechanism and toxicological significance.

The applicant's explanation:

In Study 20089324, cellular infiltration (granulomatous, mononuclear cells, or mixed cells) with foreign matter or refractile material in the lung was noted in 3 of 30 animals (0 mg/kg), 9 of 30 animals (60 mg/kg), 13 of 30 animals (180 mg/kg), and 23 of 30 animals (1,000 mg/kg) in a dose-dependent manner. Given that there is a report that inflammatory cellular infiltration, etc. in lungs was elicited by hair particles associated with intravenous injection into rats (*Lab Anim.* 1983;17:203-7), and that in Study 20089324, hair fragments were observed in the area of granulomatous inflammation in some animals, findings such as cellular infiltration in lungs observed in Study 20089324 may have been caused by fragments of hair, keratin, etc. which were included as foreign objects at the time of intravenous injection. Furthermore, while cellular infiltration with refractile or foreign matter was noted in 45 animals in the marstacimab group, such cellular infiltration was found within or near thrombi/emboli in 6 of these animals, suggesting that the cellular infiltrates may have contributed to the formation of thrombi/emboli in the lung. The severity of these cellular infiltration and thrombi/emboli in the lung was minor, with no secondary impact on the respiratory organs, suggesting findings of a low toxicological significance. However, given the mechanism of action of marstacimab, thrombi/emboli development during the clinical use of marstacimab may become a safety concern; therefore, thromboembolism will be selected as an important potential risk, and a cautionary statement regarding thromboembolism and thrombi/emboli and other findings reported in the toxicity studies will be included in the package insert to provide information for healthcare professionals.

PMDA's view:

While the underlying mechanism of these findings remains unclear, based on the obtained study results, the applicant's explanation that the findings are of low toxicological significance is acceptable. In addition, although thrombi/emboli reported in the toxicity studies occurred in normal animals, given that thrombi/emboli occurred even at lower dose levels [see Section 5.2], thus safety margin is not provided, it is reasonable to provide the information using the package insert. The details of thromboembolism-related safety will be assessed based on clinical study results [see Section 7.R.3].

5.R.2 Effects on offspring

No reproductive and developmental toxicity studies of marstacimab were conducted except for the male reproductivity study. PMDA asked the applicant to explain the risks in pregnant women, fetuses, and newborns when marstacimab is administered to pregnant women.

The applicant's explanation:

Given that blood coagulation factor concentrations increase during pregnancy in non-hemophilic pregnant women, as reported in a study (*Semin Thromb Hemost.* 2003;29:125-30), there is a risk of spontaneous abortion due to clot formation in pregnant women with hemophilia whose coagulation ability is expected to be normalized by marstacimab treatment; however, the risk is considered to be similar to that in non-hemophilic pregnant women. Conversely, marstacimab is a human monoclonal antibody directed against TFPI. Studies have shown that placental transfer of immunoglobulins to the fetus increases in late pregnancy, and fetal immunoglobulin concentrations increase to 3 times that of maternal concentrations at the time of birth (e.g., *Crit Rev Toxicol.* 2012;42:185-210, *Hum Reprod.* 1995;10:3297-300), and that TFPI is expressed in human fetal tissues from 8 to 24 weeks gestation and in human placental tissues from 10 weeks gestation through term (*Early Hum Dev.* 2000;59:77-84). Given that in the tissue cross-reactivity study of marstacimab, staining was noted in the decidual granules of human placenta decidual cells [see Section 5.7.1], and that embryonic lethality occurs in homozygous ($TFPI^{-/-}$) TFPI knockout mice (*Blood.* 1997;90:944-51, *J Thromb Haemost.* 2021;19:1483-92), the possibility that marstacimab could have effects on fetuses and newborns following administration of marstacimab to pregnant women cannot be ruled out. Therefore, cautionary statements to the following effect will be included in the package insert to provide information for healthcare professionals: (1) for pregnant women or women of reproductive potential, marstacimab may be used only when the therapeutic benefits are deemed to outweigh the risks; (2) the use of contraception is required during treatment and up to 1 month[1)] after the last dose for women of reproductive potential; and (3) no reproductive and developmental toxicity studies have been conducted in female animals.

PMDA's view:

The applicant's explanation is acceptable. However, given that there is no safety margin for thrombi/emboli in the lung observed in the 6-month repeated-dose toxicity study of marstacimab in rats [see Sections 5.2 and 5.R.1], the cautionary statement regarding the risk of clot formation in fetuses and newborns following administration of marstacimab to pregnant women should be included in the package insert and other materials

[1)] Based on the PPK analysis (CTD 5.3.3.5.2), it is estimated that 90% of marstacimab is excreted approximately within 1 month of the last dose.

in an appropriate manner.

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

Three drug delivery presentations for marstacimab (vial, PFS, and PFP) were used in clinical studies: Studies B7841001, B7841002, and B7841003 (vial); Studies B7841007 and B7841009 (PFS and PFP); and Studies B7841005 and B7841010 (PFS). The proposed commercial formulation is a PFP presentation.

Plasma marstacimab concentrations were determined by electrochemiluminescence assay and the lower limit of quantitation was 100 ng/mL. Plasma total TFPI concentrations were determined by liquid chromatography tandem mass spectrometry (LC-MS/MS)[2)] and the lower limit of quantitation was 10 ng/mL. Anti-drug antibodies and neutralizing antibodies against marstacimab were detected by electrochemiluminescence assay.

6.1.1 Bioequivalence study (CTD 5.3.1.2.1, Study B7841009 [March 2021 to November 2021])

A randomized, open-label, 4-period crossover study was conducted to assess the bioequivalence between the PFP and PFS presentations in 22 healthy non-Japanese adult men aged ≥18 years and ≤55 years (target sample size, 38[3)] subjects).

A single dose of marstacimab 300 mg[4)] was administered subcutaneously via PFP or PFS. The washout period in each period was to be ≥21 days. Plasma marstacimab concentrations were measured pre-dose, 1 hour post-dose, and at specified timepoints up to 21 days post-dose. The geometric mean ratios (PFP/PFS) of C_{max} and AUC of plasma marstacimab concentration and the 90% confidence interval (CI) were 1.041 [0.937, 1.156] for C_{max} and 1.075 [0.952, 1.214] for AUC. The results demonstrated the bioequivalence between the PFP and PFS.

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology evaluation data in the form of the results from a foreign phase I study (CTD 5.3.3.1.1, Study B7841001), foreign phase Ib/II study (CTD 5.3.5.2.1, Study B7841002), global phase III studies (CTD 5.3.5.2.3, Study B7841005, CTD 5.3.5.2.4, Study B7841007), the results from population PK (PPK) analysis, and other data.

6.2.1 Foreign phase I study (CTD 5.3.3.1.1, Study B7841001 [August 2015 to July 2016])

This study consisted of 8 cohorts. Thirty-six healthy non-Japanese adult men aged ≥18 years and ≤55 years received a single subcutaneous dose of marstacimab 30, 100, 300 mg, or placebo (4 subjects in Cohort 1; 8

[2)] Total TFPI (including marstacimab bound and unbound forms) was captured from human plasma using a biotinylated noncompeting anti-TFPI antibody and streptavidin magnetic beads. Following standard protein reduction, alkylation, and denaturation, protein digestion was performed with trypsin. Characteristic peptide fragments generated by the procedure were analyzed by LC-MS/MS and total TFPI concentration was quantitatively determined.

[3)] Due to pulmonary embolism in 1 subject (serious adverse event; causal relationship to the study drug, related), the study terminated early.

[4)] For a single dose of marstacimab 300 mg, two injections of 150 mg were given subcutaneously.

subjects each in Cohorts 2 and 3), or a single intravenous dose of marstacimab 150, 440 mg, or placebo (8 subjects each in Cohorts 4 and 5). Four healthy Japanese adult men (residents in foreign countries) received a single subcutaneous dose of marstacimab 300 mg in Cohort 8.[5)] Plasma marstacimab concentrations were measured pre-dose, 1 hour post-dose, and at specified timepoints up to 84 days post-dose. Table 12 shows PK parameters. The applicant explained that marstacimab PK parameters in healthy Japanese adult men do not differ markedly from those in healthy non-Japanese adult men.

Table 12. Pharmacokinetic parameters following single dose administration of marstacimab to healthy adult men

Route of adminis-tration	Non-Japanese/ Japanese	Dose (mg)	N	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	t_{max} (h)	CL or CL/F (L/h)	V or V/F (L)
SC	Non-Japanese	30	4	Because all of these samples were below the lower limit of quantitation, no parameters were calculated.					
		100	6	1.183 (287)	257.7[a)] (34)	33.3 ± 5.4[a)]	48 [48, 72]	0.388[a)] (34)	18.43[a)] (31)
		300	6	16.49 (63)	2,799[b)] (83)	65.8 ± 18.0[b)]	72 [48, 144]	0.107[b)] (83)	9.90[b)] (107)
	Japanese	300	4	18.50 (25)	4,240, 5,670[c)]	74.7, 122[c)]	108 [72, 144]	0.053, 0.071[c)]	7.62, 9.31[c)]
IV	Non-Japanese	150	6	45.64 (5)	2,608 (16)	43.6 ± 5.0	1.07 [1.05, 2.00]	0.058 (16)	3.53 (8)
		440	6	152.8 (12)	14,380[d)] (19)	79.5 ± 17.7[d)]	1.54 [1.08, 2.00]	0.031[d)] (19)	3.88[d)] (17)

Geometric mean (geometric CV%); $t_{1/2}$, mean ± standard deviation; t_{max}, median [range]; individual values for N ≤2
a) N = 4; b) N = 3; c) N = 2; d) N = 5

Marstacimab-related changes in PD parameters include increased total TFPI[6)]; a decrease in time until thrombin first generated (lag time) and increased peak thrombin generation in the thrombin generation assay; increases in downstream biomarkers (D-dimer, prothrombin fragment 1 + 2), and shortened dPT. Table 13 shows the maximum change from baseline in the main PD parameters. The applicant explained that the results in healthy Japanese adult men do not differ markedly from those in healthy non-Japanese adult men.

Table 13. Maximum change from baseline in PD parameters following single-dose administration of marstacimab to healthy adult men

Route of administration	Combined	SC				IV	
Dose	Placebo	30 mg	100 mg	300 mg	300 mg	150 mg	440 mg
Non-Japanese/ Japanese	Non-Japanese	Non-Japanese	Non-Japanese	Non-Japanese	Japanese	Non-Japanese	Non-Japanese
N	9	4	6	6	4	6	6
Total TFPI concentration (ng/mL)	30.6 ± 17.8	19.0 ± 26.9	8.22 ± 12.1	83.8 ± 46.3	100.0 ± 46.8	74.8 ± 21.3	176.7 ± 44.1
Peak thrombin generation (nmol)	39.9 ± 26.2	93.2 ± 24.6	114.5 ± 20.3	139.0 ± 31.5	128.4 ± 21.3	151.0 ± 23.9	109.1 ± 23.3
dPT (sec)	−15.0 ± 22.1	−26.8 ± 17.0	−28.4 ± 17.1	−30.7 ± 12.5	−26.5 ± 9.77	−36.7 ± 21.0	−32.2 ± 11.7

Mean ± standard deviation

[5)] The initial plan was for Cohorts 6 and 7 to receive a single intravenous dose of marstacimab 1,000, 2,000 mg, or placebo. However, prior to entering Cohorts 6 and 7, the sponsor decided that there were sufficient safety, PK, and pharmacodynamic (PD) data to initiate the multiple dose study in patients with hemophilia (Study B7841002) [see Sections 6.2.2 and 7.2.1]. As a result, no subjects were assigned to Cohorts 6 and 7.

[6)] It is assumed that binding of marstacimab with free TFPI delays elimination of marstacimab-bound TFPI, increasing total TFPI concentrations.

6.2.2 Foreign phase Ib/II study (CTD 5.3.5.2.1, Study B7841002 [March 2017 to December 2018])

This study consisted of 4 cohorts. Multiple doses of marstacimab were subcutaneously administered to 26 male patients with HA or HB (FVIII or FIX activity ≤1%) aged ≥18 years and <65 years (N = 7 in Cohort 1, N = 6 in Cohort 2, N = 6 in Cohort 3, and N = 7 in Cohort 4) (Table 14). Plasma marstacimab concentrations were measured pre-dose, 1 day post-dose, and at specified timepoints up to 113 days post-dose. Table 14 shows PK parameters and Table 15 shows main PD parameters.

Table 14. Pharmacokinetic parameters in patients with hemophilia following subcutaneous administration of multiple doses of marstacimab

Cohort No. Patient population Dosage regimen	Time point	N	C_{max} (μg/mL)	C_{min} (μg/mL)	AUC[a)] (μg·h/mL)	t_{max} (h)	CL/F (L/h)
Cohort 1 Without inhibitor 300 mg QW	Day 1	7	14.88 (70)	7.98 (112)	1,818 (79)	70.0 [69.1, 72.8]	—
	Day 29	5	61.85 (47)	42.12 (52)	9,045 (49)	23.7 [23.1, 94.2]	0.033 (49)
	Day 85	6	—	57.05 (58)	—	—	—
Cohort 2 Without inhibitor 300 mg[b)] + 150 mg QW	Day 1	6	19.48 (42)	13.04 (43)	2,675 (41)	69.7 [68.2, 71.1]	—
	Day 29	6	24.15 (44)	15.00 (59)	3,309 (50)	23.7 [22.0, 71.7]	0.045 (50)
	Day 85	5	—	20.63 (43)	—	—	—
Cohort 3 Without inhibitor 450 mg QW	Day 1	6	23.07 (37)	15.66 (44)	2,806 (37)	71.6 [67.6, 72.3]	—
	Day 29	4	73.49 (38)	53.63 (61)	11,090 (43)	58.5 [23.3, 97.0]	0.041 (43)
	Day 85	6	—	37.31 (656)	—	—	—
Cohort 4 With inhibitor 300 mg QW	Day 1	7	19.68 (51)	11.14 (41)	2,495 (40)	70.7 [22.8, 167]	—
	Day 29	5	66.07 (44)	39.49 (37)	9,248 (38)	22.8 [22.1, 94.7]	0.032 (38)
	Day 85	5	—	61.14 (51)	—	—	—

Geometric mean (geometric CV%); t_{max}, median [range]; —, not calculated
The study drug was administered on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.
a) Day 1, AUC_{last}; Day 29, AUC_{tau}; b) 300 mg only as the initial dose

Table 15. Pharmacodynamic parameters in patients with hemophilia following subcutaneous administration of multiple doses of marstacimab

Time point	Total TFPI concentration (ng/mL)				Peak thrombin generation (nmol)			
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 1	Cohort 2	Cohort 3	Cohort 4
BL	145.1 (15)	150.7 (30)	140.4 (16)	154.4 (33)	26.59 (46)	27.60 (51)	13.91 (53)	11.30 (51)
Day 2	148.0 (19)	137.8 (20)	148.2 (18)	159.9 (18)	97.36 (35)	98.88 (26)	82.60 (17)	74.83 (19)
Day 4	182.8 (20)	188.9 (22)	214.5 (13)	239.9 (27)	85.18 (35)	87.30 (27)	64.52 (26)	62.73 (25)
Day 8	177.8 (39)	201.0 (33)	259.0 (18)	214.7 (17)	74.10 (40)	83.50 (30)	65.11 (14)	65.14 (25)
Day 15	275.8 (35)	220.9 (20)	324.6 (17)	311.3 (22)	73.36 (44)	80.66 (27)	59.56 (31)	52.72 (19)
Day 22	385.0 (33)	220.7 (34)	435.7 (20)	374.1 (26)	70.10 (37)	79.26 (32)	52.44 (23)	53.38 (40)
Day 29	450.1 (28)	239.3 (26)	460.3 (31)	364.2 (40)	72.22 (20)	76.77 (35)	51.07 (35)	52.15 (39)
Day 85	509.6 (40)	319.1 (43)	529.6 (89)	516.4 (70)	63.26 (39)	95.37 (39)	43.81 (32)	34.44 (94)
Day 113	166.2 (36)	130, 182[a)]	174.7 (14)	156.3 (15)	33.36 (217)	13.7, 81.3[a)]	26.65 (307)	12.30 (113)

Time point	dPT (sec)			
	Cohort 1	Cohort 2	Cohort 3	Cohort 4
BL	123.84 (17)	111.20 (21)	138.35 (20)	106.09 (28)
Day 2	97.26 (9)	99.47 (11)	107.93 (18)	91.41 (17)
Day 4	95.06 (9)	94.24 (17)	105.13 (14)	94.96 (5)
Day 8	101.16 (12)	97.43 (14)	108.46 (14)	88.52 (8)
Day 15	104.19 (11)	93.59 (10)	105.93 (16)	103.68 (37)
Day 22	103.51 (11)	101.46 (17)	109.95 (27)	87.60 (12)
Day 29	102.32 (11)	105.85 (9)	99.70 (10)	91.00 (14)
Day 85	103.77 (12)	92.92 (11)	114.42 (24)	97.32 (16)
Day 113	107.48 (18)	84.0, 150.9[a)]	109.42 (21)	99.50 (13)

Geometric mean (geometric CV%); BL, baseline
The study drug was administered on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.
Number of subjects at each measurement timepoint:
Cohort 1, N = 6 to 7; Cohort 2, N = 4 to 6
Cohort 3, N = 4 to 6; Cohort 4, N = 6 to 7
a) Individual values (N = 2)

6.2.3 Global phase III study (CTD 5.3.5.2.3, Study B7841005 [ongoing since March 2020, data cut-off on April [redacted], 2023])

Multiple doses of marstacimab were administered to 116 male patients aged ≥12 years and <75 years with

severe HA (FVIII activity <1%) or moderate to severe HB (FIX activity ≤2%) without inhibitors. Subjects received marstacimab 300 mg subcutaneously as the initial dose, followed by 150 mg once weekly (subjects who met the protocol specified criteria[7)] for dose increase could have the dose increased to 300 mg). Table 16 shows the plasma marstacimab concentrations and main PD parameters following subcutaneous administration of marstacimab once weekly.

Table 16. Plasma marstacimab concentrations and PD parameters in patients with hemophilia following subcutaneous administration of multiple doses (marstacimab treatment period)

Dose	BL	Day 7	Day 28	Day 60	Day 120	Day 180	Day 240	Day 300	Day 360
Plasma marstacimab concentrations (µg/mL)									
150 mg	0.12 (6) [114]	8.28 (115) [115]	8.96 (139) [115]	10.61 (138) [114]	10.07 (140) [110]	10.24 (132) [90]	9.86 (169) [103]	9.48 (165) [103]	10.12 (153) [89]
300 mg							48.04 (36) [6]	52.45 (68) [8]	56.19 (75) [13]
Total TFPI concentrations (ng/mL)									
150 mg	125.6 (20) [114]	199.8 (35) [116]	—	283.9 (50) [115]	284.8 (53) [110]	267.8 (55) [69]	277.7 (58) [104]	274.3 (58) [102]	274.2 (54) [91]
300 mg							514.1 (21) [6]	571.8 (31) [8]	495.1 (72) [13]
Peak thrombin generation (nmol)									
150 mg	14.9 (82) [105]	68.8 (43) [103]	—	60.0 (48) [103]	63.5 (46) [97]	58.2 (48) [56]	57.0 (44) [95]	59.5 (44) [96]	57.0 (50) [84]
300 mg							39.3 (55) [5]	33.9 (52) [8]	27.6 (57) [13]

Geometric mean (geometric CV%); number of subjects is shown in brackets [N]; BL, baseline; —, not measured

6.3 Population pharmacokinetic analyses (CTD 5.3.3.5.2)

Population pharmacokinetic analyses were performed using NONMEM version 7.5.0, based on plasma marstacimab concentration data (2,235 timepoints) and total TFPI concentration data (1,597 timepoints) from a total of 213 participants[8)] in foreign phase I studies (Studies B7841001, B7841009, and B7841010), a foreign phase Ib/II study (Study B7841002), a foreign phase II study (Study B7841003), and a global phase III study (Study B7841005).

The median body weight [range] of the subjects in the PPK analyses was 71.1 kg [35, 120]. To develop base models, marstacimab PK was described by a 2-compartment model with first-order absorption process taking into account the lag time, linear elimination process and non-linear elimination process (target-mediated drug deposition [TMDD]), and a model was developed by incorporating the elimination process of marstacimab-TFPI (free in plasma) complex. Body weight was included as a covariate for linear elimination clearance from the central compartment (CL), clearance between the central and peripheral compartments (Q), volume of distribution in the central compartment (V_c), and volume of distribution in the peripheral compartment (V_p). In addition to including body weight in the model, hemophilia type (healthy subjects, HA, or HB), race, ADA status, and renal function level were evaluated as covariates for CL using the full

[7)] After 6 months of marstacimab treatment and after completion of the visit on Day 180 in the marstacimab treatment period, (1) body weight of ≥50 kg; (2) ≥2 spontaneous bleeds treated with FVIII or FIX over the 6-month period in the absence of confirmed FVIII or FIX inhibitor, respectively.

[8)] Subject characteristics (hemophilia type: healthy subjects, 63 subjects, HA, 121 subjects, HB, 29 subjects; race: white, 71 subjects, black or African American, 16 subjects; Asian, 69 subjects; Native Hawaiian, 56 subjects, other, 1 subject; ADA status: positive, 49 subjects, negative, 159 subjects; renal function: normal, 167 subjects, mild impairment, 46 subjects; hepatic function: normal, 198 subjects, mild impairment, 15 subjects)

covariate model approach, and all of these covariates were included in the final model.

The analysis results based on the final model showed that there were no clinically significant differences in marstacimab PK in terms of renal function (normal or mild impairment), hepatic function (normal or mild impairment), ADA status, hemophilia type, and injection site (arm, thigh, or abdomen). The applicant explained that while the median marstacimab CL (L/h) in adolescent patients is estimated to be lower than that in adult patients by approximately 29%, given that the body weight-adjusted CL (L/h/kg) in adolescent patients is estimated to be lower than that in adult patients by approximately 3%, the difference is primarily due to body weight difference.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in PK and PD

The applicant's explanation about the ethnic differences in marstacimab PK and PD:

In Study B7841001, following a single subcutaneous dose of marstacimab in healthy Japanese and non-Japanese adult subjects aged ≥18 years and ≤55 years, no marked differences were noted in exposure (C_{max} and AUC) or PD parameters (Table 12 and Table 13).

The marstacimab PK in Japanese and non-Japanese patients with hemophilia was investigated in Study B7841005. Steady-state marstacimab exposures (C_{max} and AUC) in Japanese, other East Asian, and non-East Asian adult patients after administration of a loading dose of marstacimab 300 mg followed by marstacimab 150 mg once weekly were estimated using PPK analysis [see Section 6.3]. As shown in Table 17, the exposure tended to be higher in Japanese patients than in other ethnic groups. However, given that the difference was mainly due to body weight difference, and that exposures in Japanese patients fell within the range observed in the other ethnic groups, the difference is not considered to be clinically significant.

Table 17. Estimated steady-state marstacimab exposures in adult participants of Study B7841005

Ethnicity (body weight)	N	C_{max} (μg/mL)	AUC (μg·h/mL)
Japanese (60.3 kg [44.2, 81])	4	24.3 [9.12, 45.5]	3,830 [1,460, 7,240]
Other East Asian (69.2 kg [43.2, 85.8])	27	13.8 [2.96, 48.1]	2,220 [443, 7,740]
Non-East Asian (72.5 kg [44.9, 120])	66	12.0 [1.04, 46.6]	1,780 [136, 7,410]

Median [range]

Similarly, analyses were performed for PD parameters (Table 18). While the total TFPI concentrations tended to be higher in Japanese patients than in other ethnic groups, the values are generally within the range observed in other ethnic groups; therefore, the difference is not considered to be clinically significant. There are no marked differences in peak thrombin generation between the groups.

Based on the above, the applicant considers that there are no clinically relevant differences in the PK and PD of marstacimab in Japanese and non-Japanese patients with hemophilia treated with marstacimab.

Table 18. Pharmacodynamic parameters in adult participants of Study B7841005

Ethnicity	BL	Day 7	Day 60	Day 120	Day 240	Day 360
Total TFPI concentrations (ng/mL)						
Japanese	122.5 [104, 194] (4)	250 [114, 307] (4)	439 [231, 562] (4)	430 [230, 604] (4)	475.5 [201, 681] (4)	437 [176, 632] (4)
Other East Asian	127.5 [94.6, 150] (24)	190.5 [87.4, 289] (24)	275 [105, 538] (23)	291 [101, 586] (23)	318 [121, 612] (21)	269 [129, 537] (19)
Non-East Asian	126 [81, 210] (56)	218 [64.1, 300] (57)	272 [80.5, 590] (57)	275 [65.1, 723] (54)	264 [89.7, 578] (55)	267.5 [77.2, 692] (54)
Peak thrombin generation (nmol)						
Japanese	6.6, 16.1 (2)	64.3 [44, 89.6] (4)	54.8 [35.2, 70.5] (4)	56.2 [37.1, 72] (4)	53.8 [37.2, 79.2] (4)	59.3 [29.2, 78.6] (4)
Other East Asian	10.9 [4.4, 33.7] (24)	73 [28.2, 158.7] (24)	79.9 [31.4, 122] (23)	62.1 [18.4, 242.3] (23)	72 [38.7, 109.3] (19)	65.9 [28.3, 92.9] (21)
Non-East Asian	16 [3.6, 141.6] (51)	73.7 [24.3, 193.6] (50)	60.2 [24, 167.4] (48)	64.5 [23.6, 154.3] (45)	57.9 [18.6, 119.7] (49)	62.4 [9.2, 234.2] (43)

Median [range] (N); individual values for N = 2; BL, baseline

PMDA's view:

Although the limited number of subjects evaluated preclude conclusive determination of similarity in PK and PD between Japanese and non-Japanese populations, no significant differences in PK and PD have been observed between Japanese and non-Japanese subjects in clinical studies. Accordingly, from a PK or PD standpoint, there are no particular problems regarding the use of data from foreign clinical studies and global clinical studies involving Japanese participants as evidence to support the efficacy and safety of marstacimab.

6.R.2 Pharmacokinetics and pharmacodynamics in adolescents

The applicant's explanation about the PK and PD of marstacimab in adolescents:

Adult data obtained from phase I and phase II studies, and body weight distribution in the growth curves (29-94 kg, the third to 97th percentile of the growth curves for males aged 12 to 17 years) released from the US Centers for Disease Control and Prevention (CDC) were used to simulate the PK and PD in adolescents. Based on the estimated PK and PD, while plasma marstacimab concentrations and total TFPI concentrations are higher in adolescents than in adults, peak thrombin generation in adolescents was predicted to be similar to that in adults. Accordingly, in Study B7841005, the dosage regimen selected for adolescent patients aged ≥12 years and <18 years was the same as that for patients aged ≥18 years. Although no inclusion criterion on body weight was established at the initiation of Study B7841005, a lower body weight limit of 35 kg for enrolled patients was established during the study in light of the guidance[9)] of a foreign regulatory authority. This change to the inclusion criteria was intended to minimize the risk of blood sampled over a 24-hour period exceeding 1% of estimated total blood in pediatric patients.

In Study B7841005, the median plasma marstacimab concentration at steady state after administration of a loading dose of marstacimab 300 mg followed by marstacimab 150 mg once weekly was 10 to 11 μg/mL for patients aged ≥18 years and 25 to 30 μg/mL for patients aged ≥12 years and <18 years. Furthermore, using the PPK analyses [see Section 6.3], exposures (C_{max} and AUC) at steady state in patients aged ≥12 years and <18

9) European Medicines Agency. Ethical Considerations for Clinical Trials on Medicinal Products Conducted With Minors. Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use. 18 September 2017. (https://health.ec.europa.eu/system/files/2018-02/2017_09_18_ethical_consid_ct_with_minors_0.pdf)

years and patients aged ≥18 years in Studies B7841002, B7841003, and B7841005 were estimated (Table 19). Plasma marstacimab concentrations in patients aged ≥12 years and <18 years were estimated to be approximately 2-fold higher than those in patients aged ≥18 years; however, this difference may have possibly resulted from the difference in body weight between the age groups [see Section 6.3]. In addition, the plasma marstacimab concentration was lower than the C_{max} (152.8 μg/mL) which was observed after intravenous administration of marstacimab 440 mg, a dose level for which safety was demonstrated in the phase I study (Study B7841001) [see Section 6.2.1].

Table 19. Estimated exposure by age group at steady state following subcutaneous administration of multiple doses of marstacimab to patients with hemophilia

Dosage regimen	Age group	N	C_{max} (μg/mL)	AUC (μg·h/mL)
150 mg QW	≥18 years	99	13.6 [0.85, 63.9]	2,110 [110, 10,300]
	12-17 years	17	32.4 [10.2, 62.4]	5,260 [1,460, 10,100]
300 mg QW	≥18 years	32	57.3 [12.6, 131]	9,200 [1970, 21,400]
	12-17 years	2	25.4, 118	3,830, 19,100

Median [range]; individual values for N = 2

Table 20 shows total TFPI concentrations and peak thrombin generation by age group in Study B7841005. The total TFPI concentrations and peak thrombin generation in patients aged ≥12 years and <18 years are generally within the range of those in patients aged ≥18 years, and the differences were not clinically significant.

Based on the above, the same dosage regimen of marstacimab can be established for both age groups, patients aged ≥12 years and <18 years and patients aged ≥18 years.

Table 20. Pharmacodynamic parameters by age group in patients with hemophilia following subcutaneous administration of multiple doses of marstacimab (Study B7841005, marstacimab treatment period)

Age group Dose	BL	Day 7	Day 60	Day 120	Day 240	Day 360
Total TFPI concentrations (ng/mL)						
≥18 years 150 mg	126.5 [81, 210] (84)	211 [64.1, 307] (85)	275 [80.5, 590] (84)	283 [65.1, 723] (81)	272 [89.7, 681] (80)	270 [77.2, 692] (77)
12-17 years 150 mg	122.5 [97.3, 148] (16)	259 [156, 330] (17)	486 [209, 612] (17)	448 [276, 639] (17)	495 [107, 747] (17)	388.5 [143, 692] (14)
≥18 years 300 mg					410 [105, 634] (11)	575 [298, 874] (11)
12-17 years 300 mg					98.6, 549 (2)	70.4, 854 (2)
Peak thrombin generation (nmol)						
≥18 years 150 mg	14.7 [3.6, 141.6] (77)	73.3 [24.3, 193.6] (78)	63.2 [24.0, 167.4] (75)	63.0 [18.4, 242.3] (72)	63.4 [18.6, 119.7] (72)	63.5 [9.2, 234.2] (68)
12-17 years 150 mg	12.7 [6.9, 33.0] (14)	43.7 [20.1, 131.4] (12)	47.9 [27.5, 103.0] (15)	44.7 [34.8, 118.3] (13)	40.8 [27.2, 72.4] (17)	53.8 [24.3, 111.1] (16)
≥18 years 300 mg					55.0 [21.2, 94.5] (9)	32.1 [9.5, 66.5] (11)
12-17 years 300 mg					18.3, 110.7 (2)	14.4, 19.9 (2)

Median [range] (N); individual values for N = 2; BL, baseline

PMDA accepted the applicant's explanation. The appropriateness of the dosage regimen will be finalized taking into account the efficacy and safety evaluation results from clinical studies [see Section 7.R.5].

6.R.3 Anti-drug antibodies (ADA)

The applicant's explanation about the incidence of ADAs:

In Study B7841002, the incidence of ADAs induced by marstacimab was 11.5% (3 of 26 subjects), while no subjects tested positive for neutralizing antibodies. In Study B7841005, among subjects whose ADA data were evaluable, the incidence of ADAs was 19.8% (23 of 116 subjects). Neutralizing antibodies were detected in 6 of 23 ADA-positive subjects. The appearance of neutralizing antibodies was transient and neutralizing antibodies were not detected in any subjects at the end of the study.

Table 21 shows the estimated exposures (C_{max} and AUC) at steady state based on a PPK analysis by ADA and neutralizing antibody status in Study B7841005. Marstacimab exposure tended to decrease due to the development of ADAs, and slightly higher body weight in ADA-positive subjects than in ADA-negative subjects was considered to have partly contributed to the trend. In ADA-positive subjects, neutralizing antibody status did not have a clear effect on marstacimab exposure.

Table 21. Estimated marstacimab exposure at steady state by ADA/neutralizing antibody status in subjects who participated in Study B7841005

ADAs/neutralizing antibody status		ADA-negative	ADA-positive		
				Neutralizing antibody-negative	Neutralizing antibody-positive
Overall population	N	93	23	17	6
	C_{max} (μg/mL)	16.8 (109)	11.5 (122)	11.8 (103)	10.8 (209)
	AUC_{tau} (μg·h/mL)	2,560 (117)	1,710 (133)	1,750 (110)	1,600 (241)
	Body weight (kg)	69.4 [35.0, 102]	73.0 [42.3, 120]	73.0 [42.3, 120]	71.4 [53.7, 99.0]
300 mg escalation group	N	11	3	1	2
	C_{max} (μg/mL)	55.6 (40.6)	23.2 (67.9)	18.2	14.7, 46.7
	AUC_{tau} (μg·h/mL)	8,900 (41.3)	3,580 (75.4)	2,880	2,100, 7,590
	Body weight (kg)	66.5 [44.8, 84.0]	74.0 [60.2, 112]	112	60.2, 74.0

Geometric mean (geometric CV%); body weight, median [range]; individual values for N ≤2

Table 22 shows the PD parameters by ADA and neutralizing antibody status in Study B7841005. Pharmacodynamic parameters tended to decrease after ADAs developed, a trend consistent with decreased marstacimab exposure in ADA-positive patients compared to ADA-negative patients (Table 21).

Table 22. Pharmacodynamic parameters by ADA/neutralizing antibody status in subjects who participated in Study B7841005

Patient population	Timepoint	ADA-negative	ADA-positive		
				Neutralizing antibody-negative	Neutralizing antibody-positive
Total TFPI concentrations (ng/mL)					
Overall population	BL	126.0 [81.0, 210.0] (91)	126.0 [87.4, 162.0] (23)	129.0 [87.4, 162.0] (17)	111.5 [90.0, 150.0] (6)
	Day 7	218.0 [68.8, 330.0] (93)	197.0 [64.1, 315.0] (23)	208.0 [64.1, 315.0] (17)	154.5 [91.8, 223.0] (6)
	Day 360	331.5 [97.5, 874.0] (82)	254.5 [70.4, 616.0] (22)	254.5 [77.2, 616.0] (16)	213.5 [70.4, 575.0] (6)
300 mg escalation group	BL	127.0 [89.8, 168.0] (11)	90.0 [87.4, 132.0] (3)	87.4(1)	90.0, 132.0(2)
	Day 7	206.0 [68.8, 301.0] (11)	118.0 [99.3, 167.0] (3)	99.3(1)	118.0, 167.0(2)
	Day 360	629.0 [488.0, 874.0] (10)	298.0 [70.4, 575.0] (3)	298.0(1)	70.4, 575.0(2)
Peak thrombin generation (nmol)					
Overall population	BL	15.2 [3.6, 141.6] (86)	12.4 [3.6, 103.0] (19)	14.2 [4.5, 103.0] (14)	10.1 [3.6, 40.0] (5)
	Day 7	68.0 [20.1, 193.6] (81)	75.2 [41.7, 116.0] (22)	72.3 [41.7, 116.0] (16)	87.9 [66.0, 106.2] (6)
	Day 360	54.4 [9.2, 234.2] (80)	62.5 [17.4, 84.2] (17)	62.5 [28.3, 84.2] (11)	51.2 [17.4, 79.3] (6)
300 mg escalation group	BL	18.2 [6.0, 87.4] (11)	12.4 [3.6, 22.1] (3)	12.4(1)	3.6, 22.1(2)
	Day 7	62.3 [33.8, 116.5] (10)	81.7 [67.2, 106.2] (3)	106.2(1)	67.2, 81.7(2)
	Day 360	31.0 [9.5, 52.6] (10)	19.9 [17.4, 66.5] (3)	66.5(1)	17.4, 19.9(2)

Median [range] (N); individual values for N ≤2; BL, baseline

Table 23 shows the annualized bleeding rate (ABR) of treated bleeds by ADA/neutralizing antibody status in Study B7841005. Based on the results, ADAs or neutralizing antibodies did not have clear effects on the efficacy of marstacimab.

Table 23. Annualized bleeding rate of treated bleeds by ADA/neutralizing antibody status (Study B7841005)

ADA/neutralizing antibody status	ADA-negative	ADA-positive		
			Neutralizing antibody-negative	Neutralizing antibody-positive
Overall population	4.93 ± 7.69 (93) 2.02 [0.00, 35.51]	3.37 ± 4.34 (23) 2.02 [0.00, 19.48]	2.10 ± 2.33 (17) 1.19 [0.00, 7.06]	6.97 ± 6.66 (6) 5. 28 [2.01, 19.48]
300 mg escalation group	12.42 ± 9.44 (11) 11.18 [1.50, 30.95]	9.47 ± 9.27 (3) 7.73 [1.19, 19.48]	1.19 (1)	7.73, 19.48 (2)

Top row, mean ± standard deviation (N); bottom row, median [range]; individual values for N ≤2

Table 24 shows the incidence of adverse events by ADA/neutralizing antibody status in Study B7841005. There were no particular safety-related concerns associated with the development of ADAs or neutralizing antibodies.

Table 24. Incidence of adverse events by ADA/neutralizing antibody status (Study B7841005)

ADA/neutralizing antibody status	ADA-negative (N = 93)	ADA-positive (N = 23)		
			Neutralizing antibody-negative (N = 17)	Neutralizing antibody-positive (N = 6)
All adverse events	61 (65.6)	13 (56.5)	10 (58.8)	3 (50.0)
Adverse drug reactions	19 (20.4)	4 (17.4)	2 (11.8)	2 (33.3)
Grade ≥3 adverse events	5 (5.4)	1 (4.3)	1 (5.9)	0
Deaths	0	0	0	0
Serious adverse events	6 (6.5)	1 (4.3)	1 (5.9)	0
Adverse events leading to permanent discontinuation	1 (1.1)	0	0	0
Anaphylactic reaction (SMQ narrow)	9 (9.7)	2 (8.7)	1 (5.9)	1 (16.7)
Injection site bruising	0	1 (4.3)	0	1 (16.7)
Injection site erythema	2 (2.2)	1 (4.3)	0	1 (16.7)
Injection site haematoma	1 (1.1)	0	0	0
Injection site induration	0	1 (4.3)	0	1 (16.7)
Injection site oedema	1 (1.1)	0	0	0
Injection site pain	2 (2.2)	0	0	0
Injection site pruritus	3 (3.2)	1 (4.3)	0	1 (16.7)
Injection site swelling	1 (1.1)	1 (4.3)	1 (5.9)	0
Hypersensitivity (SMQ)	7 (7.5)	1 (4.3)	1 (5.9)	0
Haemorrhages (SMQ narrow)	10 (10.8)	3 (13.0)	2 (11.8)	1 (16.7)

n (%) MedDRA ver. 25.1 (MedDRA/J ver. 26.0)

PMDA accepted the applicant's explanation. Because the number of subjects who tested positive for ADAs and/or neutralizing antibodies is limited, it is difficult to draw a definite conclusion regarding the effect of ADAs and neutralizing antibodies. Therefore, while continuing to gather immunogenicity data including data from the ongoing clinical study, the applicant should provide information such as the incidence of ADAs through the package insert and other materials in an appropriate manner.

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 clinical studies summarized in Table 25.

Table 25. List of clinical studies submitted as evaluation data

Region	Study ID	Phase	Study population[a)]	Number of subjects treated (marstacimab, placebo)	Dosage regimen (SC, subcutaneous administration; IV, intravenous administration)	Main evaluation
Foreign	B7841001	I	Healthy adult men (18-55 years)	41 subjects (n = 32, n = 9) Cohort 1, 5 subjects (n = 4, n = 1) Cohort 2, 8 subjects (n = 6, n = 2) Cohort 3, 8 subjects (n = 6, n = 2) Cohort 4, 8 subjects (n = 6, n = 2) Cohort 5, 8 subjects (n = 6, n = 2) Cohorts 6 and 7, 0 subjects[10)] Cohort 8, 4 subjects (Japanese)	Cohort 1: marstacimab 30 mg or placebo, single SC Cohort 2: marstacimab 100 mg or placebo, single SC Cohort 3: marstacimab 300 mg or placebo, single SC Cohort 4: marstacimab 150 mg or placebo, single IV Cohort 5: marstacimab 440 mg or placebo, single IV Cohort 6: marstacimab 1,000 mg or placebo, single IV Cohort 7: marstacimab 2,000 mg or placebo, single IV Cohort 8: marstacimab 300 mg, single SC dose	Safety PK
	B7841009	I	Healthy adult men (18-55 years)	22 subjects	Marstacimab 300 mg, single SC 4-period crossover using PFP/PFS	Bioequivalence
	B7841010	I	Patients with severe HA or HB (18-74 years)	6 subjects	Marstacimab 300 mg, single SC	Safety PK
	B7841002	Ib/ II	Patients with HA or HB with FVIII or FIX activity of ≤1% (18-64 years)	26 subjects Cohort 1, 7 subjects Cohort 2, 6 subjects Cohort 3, 6 subjects Cohort 4, 7 subjects	● denotes "without inhibitor," ■ denotes "with inhibitor" Cohort 1 (●): marstacimab 300 mg SC QW Cohort 2 (●): marstacimab 300 mg + 150 mg SC QW Cohort 3 (●): marstacimab 450 mg SC QW Cohort 4 (■): marstacimab 300 mg SC QW	Efficacy Safety PK/PD
	B7841003	II	Subjects who completed Study B7841002	18 subjects Cohort 1, 5 subjects Cohort 2, 4 subjects Cohort 3, 4 subjects Cohort 4, 5 subjects	Cohort 1: marstacimab 300 mg SC QW Cohort 2: marstacimab 300 mg + 150 mg SC QW Cohort 3: marstacimab 300 mg + 150 mg SC QW Cohort 4: marstacimab 300 mg SC QW	Efficacy Safety
			Patients with HA or HB with FVIII or FIX activity of ≤1% (12-74 years)	2 subjects Cohort 5, 0 subjects Cohort 6, 2 subjects	● denotes "without inhibitor," ■ denotes "with inhibitor" Cohort 5 (●■, 12-17 years) Cohort 6 (■, 18-74 years) For both cohorts, marstacimab 300 mg + 150 mg SC QW	
Global	B7841005[b)]	III	Patients with severe HA, and patients with moderate to severe HB (12-74 years)	128 subjects (4 Japanese) On-demand factor therapy group: 37 subjects Routine factor prophylaxis group: 91 subjects (4 Japanese)	**Observational phase** On-demand FVIII/FIX replacement therapy or routine FVIII/FIX prophylaxis **Marstacimab treatment phase** Marstacimab 300 mg + 150 mg SC QW (if the criteria for dose escalation are met, the dose may be increased to 300 mg SC QW)	Efficacy Safety
	B7841007[b)]	III	Subjects who completed Study B7841005	87 subjects (4 Japanese)	Marstacimab 150 mg SC QW (if the criteria for dose escalation are met, the dose may be increased to 300 mg SC QW)	Safety

a) The severity of HA and HB is in accordance with the FVIII and FIX activities in plasma from the WFH guidelines (*Haemophilia*. 2020;26:1-158).
b) Details of cohorts without inhibitors are presented.

The details of the clinical studies are outlined in the following sections. The main evaluation results for PK, PD, and bioequivalence were described in Sections 6.1 and 6.2. In the safety evaluation, adverse events were evaluated by counting only the event with the highest severity in a single subject experiencing the same event multiple times. While this is the primary evaluation method employed by the applicant, given that information on the number of events reported is also useful, PMDA requested the applicant to aggregate such data. These data were presented as reference data.

[10)] It was determined that the safety, PK, and PD data for the cohorts up to Cohort 5 were sufficient to start Study B7841002, and therefore, no subjects were assigned to Cohorts 6 and 7.

7.1 Phase I studies

7.1.1 Foreign phase I study (CTD 5.3.3.1.1, Study B7841001 [August 2015 to July 2016])

A randomized, double-blind, placebo-controlled, dose-escalation study was conducted at 1 study center in Belgium to evaluate the safety, PK, and PD of marstacimab in healthy adult men aged ≥18 years and ≤55 years (target sample size, 56 subjects; marstacimab vs. placebo, 3:1 ratio [a placebo group was established in each cohort except for Cohort 8]).

Subjects received a single subcutaneous dose of placebo or marstacimab 30 mg (Cohort 1), 100 mg (Cohort 2), and 300 mg (Cohort 3), a single intravenous dose of placebo or marstacimab 150 mg (Cohort 4), 440 mg (Cohort 5), 1,000 mg (Cohort 6), 2,000 mg (Cohort 7), or a single subcutaneous dose of marstacimab 300 mg in Cohort 8 (Japanese cohort).

All 41 subjects[10)] enrolled in this study (in Cohort 1, 4 subjects [marstacimab] and 1 subject [placebo]; in Cohorts 2 to 5, 6 subjects [marstacimab] and 2 subjects [placebo] in each cohort; in Cohort 8, 4 subjects [marstacimab]) received the study drug, and were included in the Safety Analysis Set.

The safety analysis revealed that 39 adverse events[11)] occurred in 20 of 32 subjects (62.5%) in the marstacimab group, and 21 events occurred in 4 of 9 subjects (44.4%) in the placebo group. Adverse events occurring in ≥2 subjects treated with marstacimab were headache (6 subjects), nasopharyngitis (4 subjects), fatigue (3 subjects), and pain in extremity (3 subjects). By severity,[12)] 47 mild events (31 events [marstacimab] and 16 events [placebo]), 13 moderate events (8 events [marstacimab] and 5 events [placebo]), and 0 severe events occurred. Adverse drug reactions occurred in 14 of 32 subjects (43.8%) in the marstacimab group (18 events in total; 1 of 4 subjects [headache, 1 event] in the 30 mg SC group, 1 of 6 subjects [headache, 1 event] in the 100 mg SC group, 4 of 6 subjects [headache, 2 subjects, 2 events; head discomfort, 1 subject, 2 events; visual impairment, 1 subject, 1 event] in the 300 mg SC group, 2 of 6 subjects [fatigue, epistaxis 1 subject, 1 event each] in the 150 mg IV group, 3 of 6 subjects [limb discomfort, musculoskeletal pain, headache, hot flush, 1 subject, 1 event each] in the 440 mg IV group, 3 of 4 subjects [fatigue, 2 subjects, 2 events; headache, 1 subject, 2 events; musculoskeletal discomfort, 1 subject, 1 event] in the 300 mg SC Japanese group). In the placebo group, adverse drug reactions occurred in 4 of 9 subjects (44.4%) (13 events in total; headache [3 subjects, 4 events]; eye pain, gingival bleeding, nausea, axillary pain, fatigue, feeling hot, decreased appetite, pain in extremity, dizziness [1 subject, 1 event each]). Among the adverse drug reactions, those classified as moderate events were headache in 5 subjects (6 events in total; 30 mg SC group [1 subject, 1 event], 100 mg SC group [1 subject, 1 event], 440 mg IV group [1 subject, 1 event], and placebo group [2 subjects, 3 events]). An adverse event led to permanent discontinuation in 1 subject in the 30 mg SC group (toothache), and a causal relationship to the study drug was ruled out. There were no deaths or serious adverse events.

11) Medical Dictionary for Regulatory Activities (MedDRA) ver. 19.0 (MedDRA/Japanese [J] ver. 26.0)

12) Events was assessed according to the 3 severity levels: mild (no effect on daily activities), moderate (some effects on daily activities), and severe (significant effects on daily activities).

In Japanese subjects, 9 adverse events occurred in 3 of 4 subjects (75.0%), with all events being mild in severity. Adverse drug reactions occurred in 3 of 4 subjects (75.0%) (5 events in total; fatigue [2 subjects, 2 events]; headache [1 subject, 2 events]; musculoskeletal discomfort [1 subject, 1 event]). There were no deaths, serious adverse events, or adverse events leading to permanent discontinuation.

7.1.2 Foreign phase I study (CTD 5.3.3.2.1, Study B7841010 [April 2021 to August 2021])

An open-label, uncontrolled study was conducted at 1 study center in China to evaluate the safety, PK, and PD of marstacimab in male patients with severe HA or HB (FVIII or FIX activity <1%) aged ≥18 years and <75 years (target sample size, 6 subjects).

Subjects received a single dose of marstacimab 300 mg subcutaneously.

All 6 subjects enrolled in this study received the study drug, and were included in the Safety Analysis Set.

An adverse event[13)] occurred in 1 of 6 subjects (16.7%) (1 event; upper respiratory tract infection). There were no adverse drug reactions, Grade ≥3 adverse events, deaths, serious adverse events, or adverse events leading to permanent discontinuation.

7.2 Phase Ib/II study, phase II study

7.2.1 Foreign phase Ib/II study (CTD 5.3.5.2.1, Study B7841002 [March 2017 to December 2018])

An open-label, uncontrolled, dose-escalation study was conducted at 8 study centers in 6 countries or regions outside Japan to evaluate the efficacy, safety, PK, and PD of marstacimab in male patients[14)] with HA or HB aged ≥18 years and <65 years (target sample size, 24 subjects, 6 subjects/cohort [patients without inhibitors in Cohorts 1 to 3; patients with inhibitors in Cohort 4]).

In Cohort 1, subjects received marstacimab 300 mg subcutaneously once weekly. In Cohort 2, subjects received marstacimab 300 mg subcutaneously as the initial dose, thereafter, 150 mg subcutaneously once weekly, In Cohort 3, subjects received marstacimab 450 mg subcutaneously once weekly. In Cohort 4, subjects received marstacimab 300 mg subcutaneously once weekly. If safety and tolerability during treatment from Day 1 (initial dose) to Day 29 (fifth dose) were acceptable, the subjects were allowed to continue treatment for 2 months (last dose, on Day 78; completion of study, Day 113).

Of the 27 subjects enrolled in this study (Cohort 1, 8 subjects; Cohort 2, 6 subjects; Cohort 3, 6 subjects; Cohort 4, 7 subjects), 1 subject in Cohort 1 who withdrew consent before receiving the study drug was excluded. The remaining 26 subjects received at least 1 dose of the study drug, and were included in the Safety Analysis Set. Of the Safety Analysis Set, 2 subjects were excluded due to major protocol deviations,[15)] and 24 subjects were

13) MedDRA ver. 24.0 (MedDRA/J ver. 26.0)
14) Patients with FVIII or FIX activity ≤1% who experienced at least 6 acute bleeding episodes (spontaneous/traumatic) during the 6-month period prior to screening
15) One subject (Cohort 1), treatment interruption for >30 days due to appendicitis; 1 subject (Cohort 4), the treatment period was <30 days.

included in the Per Protocol Analysis Set (PPAS), which was the Efficacy Analysis Set.

Efficacy was evaluated based on bleeding events occurring before treatment (for the 6-month period prior to enrollment) and during marstacimab treatment (from Day 1 to Day 85). Table 26 shows the ABR in each period.

Table 26. Annualized bleeding rate before and during marstacimab treatment (PPAS)

Evaluation period	Patients without inhibitors			Patients with inhibitors
	Cohort 1 300 mg QW	Cohort 2 300 mg + 150 mg QW	Cohort 3 450 mg QW	Cohort 4 300 mg QW
Baseline	23.00 ± 7.46 (6) 24.00 [12.0, 30.0]	14.67 ± 1.63 (6) 15.00 [12.0, 16.0]	20.33 ± 10.84 (6) 17.00 [12.0, 42.0]	17.33 ± 3.01 (6) 18.00 [12.0, 20.0]
Marstacimab treatment period	4.22 ± 3.80 (6) 4.15 [0.0, 8.5]	1.62 ± 2.53 (6) 0.00 [0.0, 5.5]	4.17 ± 6.47 (6) 0.00 [0.0, 12.6]	0.65 ± 1.60 (6) 0.00 [0.0, 3.9]

Top row, mean ± standard deviation (n); bottom row, median [range]

A total of 65 adverse events occurred in 21 of 26 subjects (80.8%) (Cohort 1: 18 events in 7 of 7 subjects [100%], Cohort 2: 12 events in 4 of 6 subjects [66.7%], Cohort 3: 22 events in 6 of 6 subjects [100%], Cohort 4: 13 events in 4 of 7 subjects [57.1%]), with the most common events presented in Table 27.

Table 27. Adverse events occurring in ≥2 subjects in overall study (Safety Analysis Set)

Event	Patients without inhibitors			Patients with inhibitors
	Cohort 1 (N = 7) 300 mg QW	Cohort 2 (N = 6) 300 mg + 150 mg QW	Cohort 3 (N = 6) 450 mg QW	Cohort 4 (N = 7) 300 mg QW
Injection site swelling	0	0	2 (33.3)	1 (14.3)
Headache	0	0	2 (33.3)	0
Injection site pain	1 (14.3)	1 (16.7)	1 (16.7)	0
Fatigue	1 (14.3)	0	1 (16.7)	0
Injection site induration	1 (14.3)	0	1 (16.7)	0
Contusion	1 (14.3)	0	1 (16.7)	0
Prothrombin time prolonged	0	0	1 (16.7)	1 (14.3)
Hypertension	0	2 (33.3)	1 (16.7)	0
Troponin I increased	1 (14.3)	1 (16.7)	0	1 (14.3)
Arthralgia	1 (14.3)	0	0	1 (14.3)
Injection site bruising	2 (28.6)	0	0	0
Influenza	0	1 (16.7)	0	1 (14.3)
Periodontitis	0	1 (16.7)	0	1 (14.3)

n (%) MedDRA ver. 21.1 (MedDRA/J ver. 26.0)

In Cohort 1, 8 adverse drug reactions occurred in 4 of 7 subjects (57.1%) (injection site bruising [2 subjects, 2 events]; injection site pain [1 subject, 2 events]; dyspepsia, injection site induration, occupational exposure to product, fibrin D dimer increased [1 subject, 1 event each]), in Cohort 2, adverse drug reactions occurred in 4 of 6 subjects (66.7%) (4 events in total; hypertension [2 subjects, 2 events]; injection site pain, troponin increased [1 subject, 1 event each]), in Cohort 3, adverse drug reactions occurred in 3 of 6 subjects (50.0%) (13 events in total; injection site swelling [2 subjects, 3 events]; injection site pain [1 subject, 6 events]; fatigue, injection site induration, injection site warmth, prothrombin time prolonged [1 subject, 1 event each]), and in Cohort 4, adverse drug reactions occurred in 3 of 7 subjects (42.9%) (8 events in total; injection site erythema, injection site haemorrhage, injection site pruritus, injection site swelling, blood fibrinogen decreased, troponin I increased, pruritus generalised, rash erythematous [1 subject, 1 event each]). Grade ≥3 adverse events occurred in 0 subjects in Cohorts 1 and 2, 2 of 6 subjects (33.3%) in Cohort 3 (4 events in total; injection site

pain [1 subject, 3 events]; injection site swelling [1 subject, 1 event]), and 2 of 7 subjects (28.6%) in Cohort 4 (3 events in total; blood fibrinogen decreased, pruritus generalised, rash erythematous [1 subject, 1 event each]), and all these events were assessed as being causally related to the study drug. The marstacimab dose was reduced in the subject (Cohort 3) who experienced Grade 3 injection site pain multiple times. Serious adverse events occurred in 1 of 7 subjects (14.3%) in Cohort 1 (1 event; appendicitis), 1 of 6 subjects (16.7%) in Cohort 2 (1 event; physical assault), 1 of 6 subjects (16.7%) in Cohort 3 (1 event; cholelithiasis), and 1 of 7 subjects (14.3%) in Cohort 4 (1 event; tooth socket haemorrhage). A causal relationship to the study drug was ruled out for all the serious adverse events. Adverse events leading to permanent discontinuation occurred in 1 of 6 subjects (16.7%, hypertension) in Cohort 2, and 1 of 7 subjects (14.3%, blood fibrinogen decreased) in Cohort 4, and all these events were assessed as being causally related to the study drug. There were no deaths.

7.2.2 Foreign phase II study (CTD 5.3.5.2.2, Study B7841003 [May 2018 to August 2020])

An open-label, uncontrolled study was conducted at 11 study centers in 9 countries or regions outside Japan to evaluate the efficacy, safety, PK, and PD of marstacimab in subjects who completed Study B7841002 (assigned to Cohorts 1 through 4[16)]) and male patients[14)] with HA or HB (assigned to Cohort 5, patients with or without inhibitors aged ≥12 years and <18 years; or Cohort 6, patients with inhibitors aged ≥18 years and <75 years; target sample size, 12 subjects).

In Cohorts 1 and 4, subjects received marstacimab 300 mg subcutaneously once weekly. In Cohorts 2, 3, 5, and 6, subjects received marstacimab 300 mg subcutaneously as the initial dose, thereafter, 150 mg subcutaneously once weekly. The treatment duration was up to 1 year.

All 20 subjects enrolled in this study (Cohort 1, 5 subjects; Cohort 2, 4 subjects; Cohort 3, 4 subjects; Cohort 4, 5 subjects; Cohort 5, 0 subjects; Cohort 6, 2 subjects) received at least 1 dose of study drug, and were included in the Safety Analysis Set. Since there were no protocol deviations leading to exclusion of subjects from the Safety Analysis Set, all subjects in the Safety Analysis Set were included in the PPAS, which was used as the Efficacy Analysis Set.

Efficacy was evaluated based on bleeding events occurring before treatment (for the 6-month period prior to enrollment) and during marstacimab treatment (from Day 1 to Day 393). Table 28 shows the ABR in each period.

16) Cohort numbers 1 to 4 in Study B7841003 are designated so that the cohort numbers are identical to the numbers of corresponding cohorts in the earlier studies (e.g., a subject who had participated in Cohort 1 of Study B7841002 was shown as a subject of Cohort 1 in Study B7841003).

Table 28. Annualized bleeding rate before and during the study period (PPAS)

Cohort/ inhibitor status	Patients without inhibitors			Patients with inhibitors	
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 6
B7841002[a)]	300 mg QW	300 mg + 150 mg QW	450 mg QW	300 mg QW	—
B7841003[a)]	300 mg QW	300 mg + 150 mg QW	300 mg + 150 mg QW	300 mg QW	300 mg + 150 mg QW
Baseline[b)]	22.00 ± 7.87 (5) 20.00 [12.0, 30.0]	14.00 ± 1.63 (4) 14.00 [12.0, 16.0]	22.00 ± 13.56 (4) 17.00 [12.0, 42.0]	18.40 ± 1.67 (5) 18.00 [16.0, 20.0]	12.0, 18.0 (2)
Study period	2.97 ± 2.79 (5) 2.03 [0.0, 6.0]	3.59 ± 7.17 (4) 0.00 [0.0, 14.3[c)]]	1.92 ± 1.45 (4) 2.08 [0.0, 3.5]	0.00 ± 0.00 (5) 0.00 [0.0, 0.0]	0.0, 5.0 (2)

Top row, mean ± standard deviation (n); bottom row, median [range]; individual values for N ≤2

a) The dosage regimens of marstacimab in Study B7841002 or B7841003

b) Cohorts 1 to 4, for the 6-month period prior to enrollment in Study B7841002; Cohort 6, for the 6-month period prior to enrollment in Study B7841003

c) Regarding the subject (with HA) who had the highest ABR, the effect of increased activity was pointed out by the investigator.

The safety analysis revealed that 18 adverse events[17)] occurred in 7 of 10 subjects (70.0%) in the 300 mg QW (combined Cohorts 1/4) group, and 29 adverse events in 7 of 10 subjects (70.0%) in the 300 mg loading + 150 mg QW (combined Cohorts 2/3/6) group. Adverse events occurring in ≥2 subjects in either combined group were haemarthrosis (2 of 10 subjects [20.0%] in the combined Cohorts 1/4 group; 1 of 10 subjects [10.0%] in the combined Cohorts 2/3/6 group) and haematoma (0 of 10 subjects in the combined Cohorts 1/4 group; 2 of 10 subjects [20.0%] in the combined Cohorts 2/3/6 group). Adverse drug reactions occurred in 2 of 10 subjects (20.0%) in the combined Cohorts 1/4 group (3 events in total; injection site reaction [1 subject, 2 events]; injection site haematoma [1 subject, 1 event]) and 1 of 10 subjects (10.0%) in the combined Cohorts 2/3/6 group (1 event; injection site reaction). Grade ≥3 adverse events occurred in 1 of 10 subjects (10.0%) in the combined Cohorts 1/4 group (2 events in total; skull fracture [1 subject, 1 event], cerebral haemorrhage [1 subject, 1 event]) and 1 of 10 subjects (10.0%) in the combined Cohorts 2/3/6 group (1 event; arthralgia). A causal relationship to the study drug was ruled out for these events. Serious adverse events occurred in 1 of 10 subjects (10.0%) in the combined Cohorts 1/4 group (2 events in total; cerebral haemorrhage [1 subject, 1 event], generalised tonic-clonic seizure [1 subject, 1 event]) and 0 of 10 subjects in the combined Cohorts 2/3/6 group. A causal relationship to the study drug was ruled out for these events. There were no deaths or adverse events leading to permanent discontinuation.

[17)] MedDRA ver. 23.0 (MedDRA/J ver. 26.0)

7.3 Phase III studies

7.3.1 Global phase III study (CTD 5.3.5.2.3, Study B7841005 [ongoing since March 2020, data cut-off on April [redacted], 2023])

An open-label, uncontrolled study was conducted at 52 study centers in 19 countries or regions, including Japan, to evaluate the efficacy and safety of marstacimab in male patients[18] aged ≥12 years and <75 years with severe HA or moderate to severe HB (target sample size, 145 subjects; 100 subjects[19] in the non-inhibitor cohort [HA, 80 subjects; HB, 20 subjects] and 45 subjects in the inhibitor cohort [HA, 35 subjects; HB, 10 subjects]).[20] Unless otherwise specified, the data from Study B7841005 and its extension study, Study B7841007, are data for the non-inhibitor cohort.

This study consisted of 2 phases. Subjects were to enter the marstacimab treatment phase (12 months) after completing the observational phase (6 months). During the observational phase, subjects were to receive on-demand FVIII/FIX replacement therapy (on-demand factor therapy group) or routine FVIII/FIX prophylaxis (routine factor prophylaxis group). During the marstacimab treatment phase, subjects were to receive marstacimab 300 mg subcutaneously as the initial dose, thereafter, 150 mg subcutaneously once weekly. Subjects who met the dose escalation criteria[21] could have their dose increased to 300 mg once weekly.

All 128 subjects enrolled in this study (37 subjects in the on-demand factor therapy group and 91 subjects in the routine factor prophylaxis group) completed at least part of the visit process on Day 1 of the observational phase (on-demand factor therapy group), or received at least 1 routine FVIII/FIX prophylactic treatment or on-demand FVIII/FIX replacement therapy during the observational phase (routine factor prophylaxis group), and were included in the Observational Phase Safety Analysis Set. Among these subjects, 116 subjects entered the marstacimab treatment phase (33 subjects in the on-demand factor therapy group and 83 subjects in the routine factor prophylaxis group), and all of these subjects received at least 1 dose of marstacimab. All these

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[18] FVIII activity <1% or FIX activity ≤2%, and body weight ≥35 kg

[19] In the non-inhibitor cohort, at least 100 subjects (≥67 subjects [routine factor prophylaxis] and ≥28 subjects [on-demand factor therapy] in the observational phase) were to receive marstacimab prophylaxis. The sample size was selected based on the following assumptions:

- Regarding the ABR for the on-demand factor therapy group (the primary endpoint for regions except for EU), mean bleeds of 12.5 to 15 over the 6-month period for on-demand factor therapy, mean bleeds of 4 over the 12-month period for marstacimab prophylaxis, with the variance of bleeds being 6 times the mean for each case. Assuming a correlation of 0.2 between marstacimab prophylaxis and on-demand factor therapy in the same subject, a sample size of 25 subjects is required to demonstrate, with ≥90% power and a two-sided significance level of 5%, that the upper bound of the 95% confidence interval for the ABR ratio is below 0.5.
- Regarding the ABR for the routine factor prophylaxis group (the primary endpoint for EU), mean bleeds of 4 over the 12-month period for marstacimab prophylaxis, mean bleeds of 2.5 over the 6-month period for the conventional routine factor prophylaxis, with the variance of bleeds being 6 times the mean for each case. Assuming a correlation of 0.2 between marstacimab prophylaxis and routine factor prophylaxis in the same subject, a sample size of 60 subjects is required to demonstrate, with ≥90% power and a one-sided significance level of 2.5%, that the upper bound of the 95% confidence interval for the difference in ABR is below 2.5.

[20] For the present application, data for the non-inhibitor cohort were submitted as evaluation data. Since data for the inhibitor cohort had not reached the primary reporting step, only safety data were submitted as reference data (data cut-off on April [redacted], 2023 [Study B7841005] and on March [redacted], 2023 [Study B7841007]).

[21] After 6 months of marstacimab treatment and at anytime after completion of the Day 180 visit in the marstacimab treatment phase, if the following are met: (1) body weight of ≥50 kg; (2) ≥2 spontaneous bleeds (atraumatic, joint bleeds, severe soft tissue/intramuscular bleeds, or other site bleeds) treated with FVIII or FIX over the 6-month period in the absence of confirmed FVIII or FIX inhibitor, respectively.

subjects were included in the Marstacimab Safety Analysis Set and the Modified Intent-to-Treat (mITT) set,[22] and the latter was used as the Efficacy Analysis Set.

The primary endpoint was the ABR of treated bleeds.[23] Table 29 shows the ABR of treated bleeds in the on-demand factor therapy group. The upper bound of the 95% confidence interval for the ABR ratio (marstacimab phase/observational phase) was less than the prespecified criterion (0.5). Table 30 shows the ABR of treated bleeds in the routine factor prophylaxis group.

Table 29. Annualized bleeding rate of treated bleeds (on-demand factor therapy group, mITT)

Treatment group/phase		On-demand factor therapy group (N = 33)	
		Observational phase	Marstacimab treatment phase
Duration (days), mean ± standard deviation		173.9 ± 31.9	351.8 ± 38.8
Number of subjects who experienced bleeds, n (%)		32 (97.0)	23 (69.7)
ABR (bleeds/year)	Mean ± standard deviation	39.65 ± 22.20	3.21 ± 3.94
	Least squares mean[a] [95% CI]	39.86 [33.05, 48.07]	3.20 [2.10, 4.88]
ABR (least squares mean[a]) ratio [95% CI]		0.080 [0.057, 0.113]	
P-value[b]		<0.0001	

a) A generalized estimating equation with treatment group as a factor, duration (log years) as an offset term, using log link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)
b) A two-sided test with a null hypothesis that the ABR ratio = 0.5, significance level of 5%

Table 30. Annualized bleeding rate of treated bleeds (routine prophylaxis group, mITT)

Treatment group/phase		Routine factor prophylaxis group (N = 83)	
		Observational phase	Marstacimab treatment phase
Duration (days), mean ± standard deviation		180.2 ± 9.6	331.5 ± 72.5
Number of subjects who experienced bleeds, n (%)		50 (60.2)	52 (62.7)[b]
ABR (bleeds/year)	Mean ± standard deviation	7.93 ± 12.92	5.18 ± 8.04
	Least squares mean[a] [95% CI]	7.90 [5.14, 10.66]	5.09 [3.40, 6.78]
ABR (least squares mean[a]) difference [95% CI]		−2.81 [−5.42, −0.20]	

a) A generalized estimating equation with duration (years) and interaction by duration (years) and treatment group as factors, with no intercept using the identity link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)
b) Including 5 subjects who discontinued treatment during the marstacimab treatment phase

In the on-demand factor therapy group, 13 adverse events occurred in 9 of 37 subjects (24.3%) during the observational phase and 22 adverse events occurred in 12 of 33 subjects (36.4%) during the marstacimab treatment phase. In the routine factor prophylaxis group, 31 adverse events occurred in 20 of 91 subjects (22.0%) during the observational phase and 249 adverse events occurred in 62 of 83 subjects (74.7%) during the marstacimab treatment phase. Table 31 shows the most common adverse events.

[22] In the routine factor prophylaxis group, subjects in whom inhibitors were detected and subjects who changed from the non-inhibitor cohort to the inhibitor cohort by the Day −7 visit of the marstacimab treatment phase were to be excluded from the mITT set.
[23] Bleeds that were treated with coagulation factors within 48 hours after the start of bleeding (regardless of treatment type, i.e., preliminary factor prophylaxis, routine factor prophylaxis, and on-demand factor therapy)

Table 31. Adverse events occurring in ≥5% of subjects in either group (observational phase, Marstacimab Safety Analysis Set)

Event	On-demand factor therapy group		Routine factor prophylaxis group	
	Observational phase (N = 37)	Marstacimab treatment phase (N = 33)	Observational phase (N = 91)	Marstacimab treatment phase (N = 83)
COVID-19	0	2 (6.1)	3 (3.3)	18 (21.7)
Headache	0	1 (3.0)	0	6 (7.2)
Contusion	0	0	0	5 (6.0)
Dental caries	2 (5.4)	0	0	4 (4.8)
Pruritus	0	2 (6.1)	0	2 (2.4)
Upper respiratory tract infection	0	2 (6.1)	1 (1.1)	1 (1.2)
Joint range of motion decreased	1 (2.7)	2 (6.1)	0	0

n (%) MedDRA ver. 25.1 (MedDRA/J ver. 26.0)

Adverse drug reactions[24)] occurred in 4 of 33 subjects (12.1%) during the marstacimab treatment phase in the on-demand factor therapy group (8 events in total; pruritus [2 subjects, 3 events]; haemorrhoids thrombosed [1 subjects, 2 events]; haemorrhoids, injection site haematoma, injection site pain [1 subject, 1 event each]) and 19 of 83 subjects (22.9%) during the marstacimab treatment phase in the routine factor prophylaxis group (93 events in total; injection site pruritus [4 subjects, 29 events]; injection site erythema [3 subjects, 26 events]; prothrombin fragment 1.2 (PF1.2) increased [3 subjects, 3 events]; injection site swelling [2 subjects, 2 events]; fibrin D dimer increased [2 subjects, 2 events]; pruritus [2 subjects, 2 events]; injection site induration [1 subject, 20 events]; headache [1 subject, 2 events]; fatigue, injection site bruising, injection site oedema, injection site pain, peripheral swelling, contusion, arthralgia [1 subject, 1 event each]). In the on-demand factor therapy group, Grade ≥3 adverse events occurred in 1 of 37 subjects (2.7%) during the observational phase (1 event; gastric haemorrhage) and 0 of 33 subjects during the marstacimab treatment phase. In the routine factor prophylaxis group, Grade ≥3 adverse events occurred in 1 of 91 subjects (1.1%) during the observational phase (1 event; enterocolitis infectious) and 6 of 83 subjects (7.2%) in the marstacimab treatment phase (8 events in total; tympanic membrane perforation, ocular implant exposure, tonsillitis, gout, pain in extremity, meningioma, headache, calculus urinary [1 subject, 1 event each]). A causal relationship to marstacimab was ruled out for any of the events that occurred in the marstacimab treatment phase. Serious adverse events occurred in 1 of 37 subjects (2.7%) during the observational phase (1 event; gastric haemorrhage) and 0 of 33 subjects during the marstacimab treatment phase in the on-demand factor therapy group; 2 of 91 subjects (2.2%) during the observational phase (2 events in total; oesophagitis, device occlusion [1 subject, 1 event each]) and 7 of 83 subjects (8.4%) during the marstacimab treatment phase (8 events in total; tympanic membrane perforation, chest pain, peripheral swelling, tonsillitis, traumatic haemorrhage, haemarthrosis, meningioma, haemorrhage [1 subject, 1 event each]) in the routine factor prophylaxis group. Of the events occurring during the marstacimab treatment phase, 1 event (peripheral swelling) in the routine factor prophylaxis group was considered to be related to marstacimab, while the outcome was reported as resolved. An adverse event leading to permanent discontinuation occurred in 1 of 83 subjects (1.2%, meningioma) during the marstacimab treatment phase in the routine factor prophylaxis group. A causal relationship to marstacimab was ruled out for the event. There were no deaths.

[24)] In this study, an adverse reaction was defined as an event that has a causal relationship with marstacimab; therefore, no events occurring during the observational phase were classified as adverse drug reactions.

The safety analysis in Japanese subjects (4 subjects)[25] revealed that 2 adverse events occurred in 1 of 4 subjects (25.0%) during the observational phase and 13 adverse events occurred in 4 of 4 subjects (100%) during the marstacimab treatment phase. Adverse drug reactions occurred in 2 of 4 subjects (50.0%) during the marstacimab treatment phase (4 events in total; PF1.2 increased, fibrin D dimer increased [2 subjects, 2 events each]). Grade ≥3 adverse events occurred in 0 of 4 subjects during the observational phase and 1 of 4 subjects (25.0%) during the marstacimab treatment phase (1 event; calculus urinary). A causal relationship to marstacimab was ruled out for this event. There were no deaths, serious adverse events, or adverse events leading to permanent discontinuation.

7.3.2 Global phase III study (CTD 5.3.5.2.4, Study B7841007 [ongoing since November 2021, data cut-off on March [redacted], 2023])

An open-label, uncontrolled study was conducted in subjects who had completed Study B7841005 at 36 study centers in 14 countries or regions including Japan.[20]

Subjects received marstacimab 150 mg subcutaneously once weekly. Subjects who met the dose escalation criteria[21] in Study B7841005 or this study could be escalated to marstacimab 300 mg once weekly.

Of the 88 subjects enrolled in this study (29 subjects in the on-demand factor therapy group and 59 subjects in the routine factor prophylaxis group in Study B7841005), 1 subject with no data at the time of data cut-off was excluded, and the remaining 87 subjects, who received at least 1 dose of the study drug, were included in the Safety Analysis Set.

A total of 35 adverse events occurred in 25 of 87 subjects (28.7%). Table 32 shows the most common adverse events.

Table 32. Adverse events occurring in ≥2 subjects (Safety Analysis Set)

Event	Subjects treated with marstacimab (N = 87)
Nasopharyngitis	4 (4.6)
COVID-19	3 (3.4)
Influenza	2 (2.3)
Contusion	2 (2.3)

n (%) MedDRA ver. 25.1 (MedDRA/J ver. 26.0)

Adverse drug reactions occurred in 3 of 87 subjects (3.4%) (4 events in total; injection site bruising [1 subject, 2 events]; injection site induration, injection site swelling [1 subject, 1 event each]). A Grade ≥3 adverse event occurred in 1 of 87 subjects (1.1%) (1 event; haemarthrosis), and a causal relationship to the study drug was ruled out. Two serious adverse events occurred in 2 of 87 subjects (2.3%) (contusion [1 subject, 1 event], haemarthrosis [1 subject, 1 event]), and a causal relationship to the study drug was ruled out for these events. There were no deaths, or adverse events leading to permanent discontinuation.

[25] All subjects were enrolled in the routine factor prophylaxis group.

The safety analysis in Japanese subjects revealed that an adverse event occurred in 1 of 4 subjects (25.0%) (1 event; injection site induration), and this event was assessed as being causally related to the study drug. There were no Grade ≥3 adverse events, deaths, serious adverse events, or adverse events leading to permanent discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package

The applicant's explanation about the clinical data package for the present application:

Marstacimab acts on the extrinsic coagulation pathway by inhibiting TFPI, probably regardless of hemophilia type or with or without inhibitors. The applicant, therefore, decided to evaluate all the groups of hemophilia, a rare disorder (HA, HB, with/without inhibitors) using a single master protocol. The patient population for the present application was patients with HA or HB without inhibitors. The efficacy of marstacimab was evaluated in subjects enrolled in the non-inhibitor cohort in Study B7841005, the global phase III study, by comparing bleeding events associated with treatment during the observational phase (on-demand FVIII/FIX therapy or routine FVIII/FIX prophylaxis) and bleeding events associated with marstacimab prophylaxis. The safety of marstacimab was evaluated based on data from Study B7841005 and its extension study, B7841007; as well as data from the foreign phase Ib/II dose-finding study in patients with HA and HB, and a phase II study (Studies B7841002 and B7841003), and foreign phase I studies (Studies B7841001, B7841009, and B7841010) conducted in healthy adult men or patients with HA or HB to assess a single dose of marstacimab. Furthermore, safety data that were obtained from the inhibitor cohort of currently ongoing Studies B7841005 and B7841007, and currently available safety data from Study B7841008 conducted in patients with HA or HB aged ≥1 year and <18 years were also evaluated.

PMDA's view:

The epidemiological profiles, bleeding tendency status, and treatment approach for patients with HA or HB without inhibitors are similar in and outside of Japan. In addition, there are no significant differences in PK/PD between Japanese and non-Japanese [see Section 6.R.1]. Given this situation, intrinsic and extrinsic ethnic factors are not likely to have a significant effect on the safety and efficacy of marstacimab.

Therefore, the efficacy of marstacimab prophylaxis in controlling bleeding tendency was evaluated based on data from Study B7841005, the global phase III study, as the pivotal study. For safety assessment, the incidence of adverse events, etc. was evaluated using all data from clinical studies submitted as evaluation data and reference data.

7.R.2 Efficacy

7.R.2.1 Efficacy of marstacimab

The applicant's explanation about the efficacy of marstacimab:

Study B7841005 was conducted in patients with severe HA or moderate to severe HB without inhibitors, aged ≥12 years and <75 years to evaluate bleeding events associated with the treatment during the observational

phase (on-demand FVIII/FIX therapy or routine FVIII/FIX prophylaxis) and bleeding events associated with marstacimab prophylaxis. Study B7841005, which was conducted as an open-label study, implemented measures[26)] to reduce bias involved in the evaluation.

The results for the primary efficacy endpoint, the ABR of treated bleeds, in the on-demand factor therapy group (Table 29) shows that the upper bound of the 95% confidence interval for ABR ratio (marstacimab treatment phase/observational phase) was less than the prespecified criterion of 0.5 [see Section 7.3.1]. The ABR of treated bleeds in the routine factor prophylaxis group was lower in the marstacimab treatment phase than in the observational phase (Table 30).

The results for key secondary endpoints, the ABR by bleed type, bleeding site, and treatment, are presented in Table 33 (on-demand factor therapy) and Table 34 (routine factor prophylaxis). In the on-demand factor therapy group, the results showed a clinically meaningful decrease in the ABR in the marstacimab treatment phase compared to the observational phase. In both treatment groups and all bleed endpoints, the ABR showed trends similar to the ABR for overall treated bleeds.

Table 33. Annualized bleeding rate by bleeding event (Study B7841005, on-demand factor therapy group, mITT)

Bleeding events	Treated bleeds					
	Spontaneous bleeds		Joint bleeds		Target joint bleeds	
Treatment phase	Observational	Marstacimab	Observational	Marstacimab	Observational	Marstacimab
Number of subjects experiencing bleeds	31 (93.9)	23 (69.7)	32 (97.0)	23 (69.7)	31 (93.9)	20 (60.6)
ABR[a)]	32.63 [25.79, 41.28]	2.45 [1.62, 3.72]	34.52 [27.84, 42.79]	2.85 [1.82, 4.46]	24.38 [18.27, 32.53]	1.84 [1.07, 3.18]
ABR ratio[b)] [95% CI]	0.075 [0.053, 0.107]		0.083 [0.057, 0.119]		0.076 [0.048, 0.119]	

Bleeding events	Treated and untreated bleeds	
	Total bleeds	
Treatment phase	Observational	Marstacimab
Number of subjects experiencing bleeds	33 (100)	29 (87.9)
ABR[a)]	49.97 [42.09, 59.32]	7.41 [5.10, 10.75]
ABR ratio[b)] [95% CI]	0.148 [0.111, 0.198]	

Spontaneous bleeds: bleeding with no clear/known reason particularly into the joints, muscles, and soft tissues
Joint bleeds: bleeding episodes characterized by rapid loss of range of motion compared to baseline that is associated with any combination of pain or an unusual sensation in the joint, palpable swelling, and warmth of the skin over the joint
Target joint bleeds: major joints into which repeated bleeds occur (e.g., hip, elbow, wrist, shoulder, knee, and ankle) (≥3 spontaneous bleeds into a single joint within a consecutive 6-month period)

Number of subjects experiencing bleeds, n (%); ABR, least squares mean [95% CI] (unit, bleeds/year); on-demand factor therapy group, N = 33
a) A generalized estimating equation with treatment group as a factor, duration (log years) as an offset term, using log link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)
b) Least squares mean ratio (marstacimab treatment phase/observational phase)

[26)] (1) Subjects and caregivers received training on how to record bleeds; (2) the investigator was involved in planning for bleeding treatment on a daily basis; and (3) in most sites, changes were assessed by independent physical therapists using the Hemophilia Joint Health Score (HJHS) system.

Table 34. Annualized bleeding rate by bleeding event (Study B7841005, routine factor prophylaxis group, mITT)

Bleeding events	Treated bleeds					
	Spontaneous bleeds		Joint bleeds		Target joint bleeds	
Treatment phase	Observational	Marstacimab	Observational	Marstacimab	Observational	Marstacimab
Number of subjects experiencing bleeds[a)]	43 (51.8)	46 (55.4)	43 (51.8)	48 (57.8)	21 (25.3)	27 (32.5)
ABR[b)]	5.89 [3.57, 8.22]	3.78 [2.25, 5.31]	5.69 [3.36, 8.02]	4.13 [2.59, 5.67]	3.37 [1.60, 5.15]	2.51 [1.26, 3.76]
ABR difference[c)] [95% CI]	−2.11 [−4.26, 0.03]		−1.55 [−3.73, 0.62]		−0.87 [−2.42, 0.69]	

Bleeding events	Treated and untreated bleeds	
	Total bleeds	
Treatment phase	Observational	Marstacimab
Number of subjects experiencing bleeds[a)]	55 (66.3)	59 (71.1)
ABR[b)]	8.90 [6.02, 11.77]	5.98 [4.14, 7.82]
ABR difference[c)] [95% CI]	−2.91 [−5.66, −0.17]	

Number of subjects experiencing bleeds, n (%); ABR, least squares mean [95% CI] (unit, bleeds/year)
Routine factor therapy group, N = 83; see Table 33 for the details of bleeding events
a) Including 5 subjects who discontinued during the marstacimab treatment phase
b) A generalized estimating equation with duration (years) and interaction by duration (years) and treatment as factors, with no intercept using identity link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)
c) Difference in least squares means (marstacimab treatment phase − observational phase)

Table 35 shows the ABR of treated bleeds by treatment period in Study B7841005 and its extension, Study B7841007. The results of analysis by treatment period show maintained efficacy. The median treatment duration [range] in Study B7841007 was 193.0 days [34.0-483.0].

Table 35. Annualized bleeding rate of treated bleeds by treatment period (Study B7841005 [mITT] and Study B7841007 [Safety Analysis Set])

Treatment period	Overall population	Treatment group in Study B7841005	
		On-demand factor therapy	Routine factor prophylaxis
Study B7841005, first half of the marstacimab treatment phase (Months 1 to 6)	4.96 [3.67, 6.70] (116)	3.96 [2.36, 6.63] (33)	5.36 [3.72, 7.73] (83)
Study B7841005, second half of the marstacimab treatment phase (Months 7 to 12)	3.26 [2.39, 4.44] (112)	2.40 [1.54, 3.74] (33)	3.63 [2.45, 5.37] (79)
Study B7841007	2.79 [1.90, 4.10] (87)	3.86 [2.03, 7.37] (29)	2.28 [1.41, 3.68] (58)

Least squares mean[a)] [95% CI] (N) (unit, bleeds/year)
a) A generalized estimating equation with no factors (intercept only), duration (log years) as an offset term, using log link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)

The ABR of treated bleeds by patient characteristics is shown in Table 36 (on-demand factor therapy group) and in Table 37 (routine factor prophylaxis group). The trends of each subgroup were almost consistent with those of the overall population.

Table 36. Annualized bleeding rate of treated bleeds by patient characteristics (Study B7841005, on-demand factor therapy group, mITT)

Patient characteristics		N	Observational phase		Marstacimab treatment phase		ABR ratio[b)] [95% CI]
			Number of subjects experiencing bleeds	ABR[a)]	Number of subjects experiencing bleeds	ABR[a)]	
Overall population		33	32 (97.0)	39.86 [33.05, 48.07]	23 (69.7)	3.20 [2.10, 4.88]	0.080 [0.057, 0.113]
Disease type	HA	26	25 (96.2)	42.89 [34.94, 52.66]	20 (76.9)	3.66 [2.38, 5.64]	0.085 [0.060, 0.122]
	HB	7	7 (100)	23.97 [19.56, 29.39]	3 (42.9)	0.88 [0.28, 2.82]	0.037 [0.012, 0.109]
Age	12-17 years	2	2 (100)	33.93, 36.31	1 (50.0)	0, 3.04	Not estimated (N <5)
	≥18 years	31	30 (96.8)	40.16 [32.96, 48.94]	22 (71.0)	3.32 [2.16, 5.09]	0.083 [0.058, 0.117]
Race	White	11	11 (100)	33.53 [23.54, 47.78]	8 (72.7)	3.68 [1.65, 8.20]	0.110 [0.060, 0.202]
	Asian	22	21 (95.5)	42.83 [34.58, 53.06]	15 (68.2)	2.96 [1.87, 4.69]	0.069 [0.048, 0.100]

Number of subjects experiencing bleeds, n (%); ABR, least squares mean [95% CI] (individual values for subjects aged 12-17 years) (unit, bleeds /year)

a) A generalized estimating equation with treatment group as a factor, duration (log years) as an offset term, using log link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)

b) Least squares mean ratio (marstacimab treatment phase/observational phase)

Table 37. Annualized bleeding rate of treated bleeds by patient characteristics (Study B7841005, routine factor prophylaxis group, mITT)

Patient characteristics		N	Observational		Marstacimab treatment		ABR difference[c)] [95% CI]
			Number of subjects experiencing bleeds[a)]	ABR[b)]	Number of subjects experiencing bleeds[a)]	ABR[b)]	
Overall population		83	50 (60.2)	7.90 [5.14, 10.66]	52 (62.7)	5.09 [3.40, 6.78]	−2.81 [−5.42, −0.20]
Disease type	HA	65	40 (61.5)	9.18 [5.74, 12.62]	42 (64.6)	5.22 [3.20, 7.24]	−3.96 [−7.14, −0.77]
	HB	18	10 (55.6)	3.28 [1.78, 4.78]	10 (55.6)	4.61 [1.91, 7.31]	1.33 [−1.47, 4.12]
Age	12-17 years	17	7 (41.2)	3.35 [0.72, 5.98]	6 (35.3)	2.96 [0.39, 5.53]	−0.39 [−3.32, 2.54]
	≥18 years	66	43 (65.2)	9.07 [5.72, 12.42]	46 (69.7)	5.64 [3.64, 7.65]	−3.43 [−6.60, −0.25]
Race	White	45	26 (57.8)	6.22 [3.07, 9.37]	25 (55.6)	4.02 [2.10, 5.94]	−2.20 [−4.84, 0.44]
	Asian	36	23 (63.9)	10.31 [5.42, 15.20]	25 (69.4)	6.52 [3.51, 9.53]	−3.79 [−8.80, 1.21]
	Other/unknown	2	1 (50.0)	0, 4.35	2 (100)	2.32, 4.73	Not estimated (N <5)

Number of subjects experiencing bleeds, n (%); ABR, least squares mean [95% CI] (individual values for other and unknown) (unit, bleeds/year)

a) Including 5 subjects who discontinued

b) A generalized estimating equation with duration (years) and interaction by duration (years) and treatment as factors, with no intercept using identity link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)

c) Difference in least squares means (marstacimab treatment phase − observational phase)

The above findings suggest the efficacy of marstacimab.

7.R.2.2 Efficacy of marstacimab in Japanese patients

The applicant's explanation about the efficacy of marstacimab in Japanese patients:

In Study B7841005, 4 Japanese subjects were enrolled in the routine factor prophylaxis group and all of these subjects entered Study B7841007. Table 38 shows the ABR of treated bleeds in Japanese subjects in both studies.

Table 38. Annualized bleeding rate of treated bleeds in Japanese subjects (Study B7841005 [mITT], Study B7841007 [Safety Analysis Set], Japanese subgroup)

Subject	Age[a)]	Disease type	B7841005						B7841007		
			Observational			Marstacimab treatment					
			Duration	Bleeding events	ABR	Duration	Bleeding events	ABR	Duration	Bleeding events	ABR
1	4[redacted] years	HB	182	4	8.03	359	5	5.09	162	1	2.25
2	4[redacted] years	HB	171	2	4.27	359	0	0	50	0	0
3	5[redacted] years	HA	183	0	0	362	11	11.10	179	7	14.28
4	6[redacted] years	HB	170	0	0	363	0	0	164	0	0

Duration, days; bleeding events, number of bleeds; ABR, bleeds/year
a) Age at enrollment in Study B7841005

Compared to the ABR of treated bleeds during the observational phase in Study B7841005, the ABR of treated bleeds during marstacimab treatment (the marstacimab treatment phase in Study B7841005, and in Study B7841007) decreased in 2 subjects, remained at 0 in 1 subject, and increased in 1 subject. The subject whose ABR increased was evaluated in terms of PK, PD, ADA, and adherence to regimen during Study B7841005; however, the reason for the increase in the ABR in the marstacimab phase compared to that in the observational phase remains unclear. There were also 7 subjects whose ABR increased in the marstacimab treatment phase compared to that in the observational phase with no clear reasons for increased ABR; therefore, this event is unlikely to be unique to Japanese patients. Given that the efficacy of marstacimab was demonstrated by the data from the overall non-inhibitor cohort of Study B7841005, and that there are no clear differences in the efficacy of marstacimab between races [see Section 7.R.2.1], marstacimab should be effective in Japanese patients.

PMDA's view:

The pivotal study B7841005 was an open-label uncontrolled study conducted using a one-way design in the same patients by dividing the study period into the observational and marstacimab treatment phases. In addition, evaluation of the ABR of treated bleeds, the primary endpoint, involves the investigator making a decision as to whether a bleeding event required treatment. These factors preclude stringent evaluation of the efficacy of marstacimab using this study design. However, given that hemophilia is a rare disease with a variable bleeding risk depending on activity levels and lifestyle, or the treatment status of individual patients, it is understandable that conducting a randomized parallel-group study with a control as a pivotal study is challenging.

The results for the primary endpoint of Study B7841005, the ABR of treated bleeds, showed that the ratio (marstacimab treatment phase/observational phase) met the prespecified criteria in the on-demand factor therapy group, and in the routine factor prophylaxis group, the ABR in the marstacimab treatment phase was similar to that in the observational phase. The results for the secondary endpoints, spontaneous bleeds, joint

bleeds, target joint bleeds, and total bleeds (presumably not depending on the investigator's decision) were similar to the overall results for treated bleeds. The subgroup analysis by patient characteristics showed that the trends for each subgroup were generally consistent with those for the overall population.

Although the number of Japanese patients evaluated was very small, given that the efficacy of marstacimab in the entire non-inhibitor cohort in Study B7841005 was demonstrated, together with the applicant's explanation, PMDA concluded that marstacimab can be expected to be effective in Japanese patients.

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

7.R.3 Safety

The applicant's explanation about the safety of marstacimab:

Table 39 shows the summary of safety data from Studies B7841005 and B7841007, and a pooled population of these studies (B7841005/B7841007 pooled population).

Table 39. Summary of safety data for marstacimab (Safety Analysis Set)

Study/population Treatment phase/group	B7841005			B7841007 Marstacimab-treated (N = 87)	B7841005/ B7841007 pooled population Marstacimab-treated (N = 116)
	Observational		Marstacimab		
	On-demand factor therapy (N = 37)	Routine factor prophylaxis (N = 91)	Marstacimab-treated (N = 116)		
All adverse events	9 (24.3)	20 (22.0)	74 (63.8)	25 (28.7)	80 (69.0)
Adverse drug reactions	—	—	23 (19.8)	3 (3.4)	24 (20.7)
Grade ≥3 adverse events	1 (2.7)	1 (1.1)	6 (5.2)	1 (1.1)	7 (6.0)
Adverse drug reactions	—	—	0	0	0
Deaths	0	0	0	0	0
Serious adverse events	1 (2.7)	2 (2.2)	7 (6.0)	2 (2.3)	9 (7.8)
Adverse drug reactions	—	—	1 (0.9)	0	1 (0.9)
Adverse events leading to permanent discontinuation	0	0	1 (0.9)	0	1 (0.9)
Adverse drug reactions	—	—	0	0	0

n (%); In Study B7841005, an adverse reaction was defined as an event that has a causal relationship with marstacimab; therefore, no events occurring during the observational phase were classified as adverse drug reactions.

Table 40 shows the summary of safety in the B7841005/B7841007 pooled population by age group and Table 41 shows the incidence of the most common adverse events. There were no differences in trends of developing specific adverse events between adolescent and adult patients. The results in each age group were consistent with those in the overall population.

Table 40. Summary of safety data of marstacimab by age group (B7841005/B7841007 pooled population, Safety Analysis Set)

Age group	12-17 years (N = 19)	≥18 years (N = 97)
All adverse events	14 (73.7)	66 (68.0)
Adverse drug reactions	4 (21.1)	20 (20.6)
Grade ≥3 adverse events	1 (5.3)	6 (6.2)
Adverse drug reactions	0	0
Deaths	0	0
Serious adverse events	2 (10.5)	7 (7.2)
Adverse drug reactions	0	1 (1.0)
Adverse events leading to permanent discontinuation	0	1 (1.0)
Adverse drug reactions	0	0

n (%)

Table 41. Adverse events occurring in ≥2 subjects in either age group (B7841005/B7841007 pooled population, Safety Analysis Set)

Event	12-17 years (N = 19)	≥18 years (N = 97)	Event	12-17 years (N = 19)	≥18 years (N = 97)
COVID-19	4 (21.1)	18 (18.6)	Rhinitis allergic	1 (5.3)	2 (2.1)
Headache	1 (5.3)	7 (7.2)	Acne	0	2 (2.1)
Contusion	2 (10.5)	5 (5.2)	Migraine	0	2 (2.1)
Hypertension	0	6 (6.2)	Muscle spasms	0	2 (2.1)
Nasopharyngitis	1 (5.3)	4 (4.1)	Joint range of motion decreased	0	2 (2.1)
Dental caries	0	5 (5.2)	Haemarthrosis	0	2 (2.1)
Injection site pruritus	2 (10.5)	2 (2.1)	Back pain	0	2 (2.1)
Pruritus	0	4 (4.1)	Tooth fracture	0	2 (2.1)
Arthralgia	0	4 (4.1)	Skin laceration	0	2 (2.1)
Tonsillitis	0	4 (4.1)	Joint injury	0	2 (2.1)
PF1.2 increased	0	3 (3.1)	Head injury	0	2 (2.1)
Fibrin D dimer increased	0	3 (3.1)	Rhinitis	0	2 (2.1)
Fall	0	3 (3.1)	Herpes zoster	0	2 (2.1)
Upper respiratory tract infection	0	3 (3.1)	Injection site pain	0	2 (2.1)
Haemorrhoids	0	3 (3.1)	Injection site induration	0	2 (2.1)
Pharyngitis	2 (10.5)	1 (1.0)	Injection site bruising	0	2 (2.1)
Injection site erythema	1 (5.3)	2 (2.1)	Fatigue	0	2 (2.1)
Injection site swelling	1 (5.3)	2 (2.1)	Haematoma	2 (10.5)	0

n (%) MedDRA ver. 25.1 (MedDRA/J ver. 26.0)

In the marstacimab treatment phase of Study B7841005, injection site reactions occurred in 11 subjects (9.5%). The most frequently reported injection site reactions were injection site pruritus (4 subjects, 3.4%) and injection site erythema (3 subjects, 2.6%). While the majority of events were mild (10 subjects), a moderate event occurred in 1 subject (injection site pain), with no severe events. In Study B7841007, injection site reactions occurred in 3 subjects (3.4%, injection site bruising [1 subject, mild], injection site induration [1 subject, mild], and injection site swelling [1 subject, moderate]).

In the following subsections, PMDA conducted a detailed review of the adverse events based on the pharmacology of marstacimab, reported safety profiles of approved anti-TFPI antibodies, and other information. For details on ADAs, see Section 6.R.3.

7.R.3.1 Thromboembolic events

The applicant's explanation about thromboembolic events:

To analyze thromboembolic events, preferred terms (PTs) classified as MedDRA SMQ "embolic and thrombotic events (broad)" were captured. Pulmonary embolism occurred in 1 healthy subject in Study

B7841009. This subject, a white male aged 5[redacted] years, developed pulmonary embolism accompanied by what was presumed to be deep vein thrombosis 9 days after administration of a single dose of marstacimab 300 mg. The event was assessed as being related to the study drug. The subject permanently discontinued the study.

In studies evaluating patients with hemophilia, no thromboembolic events have been reported in the marstacimab treatment period, including the latest data (data cut-off on [redacted], 20[redacted]) from ongoing Study B7841005 (inhibitor cohort), Study B7841007, and Study B7841008. In Studies B7841002 and B7841005, laboratory test parameters that may change as a result of coagulopathy (PT/INR, aPTT, fibrinogen, antithrombin activity, platelet count, and potential thrombotic event-related parameters [e.g., cardiac troponin]) were evaluated. The results indicated no clinically significant symptoms or safety-related concerns.

7.R.3.2 Hypersensitivity (including shock and anaphylaxis)

The applicant's explanation about hypersensitivity (including shock and anaphylaxis):
To analyze shock/anaphylaxis-related events, PTs classified as MedDRA SMQ "anaphylactic reaction (narrow)," "angioedema (broad)," and "hypersensitivity (broad)" were captured.

In Study B7841002, rhinitis allergic (Grade 1) occurred in 1 subject in Cohort 2 (non-inhibitor 300 + 150 mg QW group) and pruritus (Grade 3)/rash erythematous (Grade 3) occurred in 1 subject in Cohort 4 (inhibitor 300 mg QW group). Among these events, pruritus/rash erythematous was assessed as being related to the study drug, with the outcome reported as resolving for both events. In Study B7841003, rhinitis allergic (Grade 1) occurred in 1 subject in Cohort 2 (non-inhibitor 300 + 150 mg QW group) and oedema peripheral (Grade 2) in 1 subject in Cohort 6 (inhibitor 300 + 150 mg QW group). A causal relationship to the study drug was ruled out for all these events. In the marstacimab treatment phase of Study B7841005, pruritus occurred in 3 subjects (Grade 1 [2 subjects], Grade 2 [1 subject]), rhinitis allergic (Grade 1)/pruritus (Grade 1), eczema (Grade 1), conjunctivitis (Grade 1), rhinitis allergic (Grade 2), and rash (Grade 1) in 1 subject each. Among these events, all pruritus events in 4 subjects were considered to be related to marstacimab. In Study B7841007, rhinitis allergic (Grade 1) and hand dermatitis (Grade 1) occurred in 1 subject each. A causal relationship to the study drug was ruled out for both events.

In the ongoing Study B7841005 (inhibitor cohort), rash (Grade 3, serious) occurred in 1 subject, and this event was assessed as being related to marstacimab. The outcome was reported as not resolved at the time of data cut-off.

The applicant's explanation about the safety of marstacimab:
There were no deaths in the clinical studies of marstacimab. Adverse events leading to permanent discontinuation of marstacimab were rare. In Study B7841005, in both the observational phase and marstacimab treatment phase, the majority of adverse events were mild or moderate in severity and the incidence of serious adverse events was low. No clear differences were identified by age, disease type, race, or other characteristics. The results suggest that no unexpected risks have been associated with marstacimab treatment in comparison with the known safety profiles of on-demand factor therapy or routine factor

prophylaxis with FVIII or FIX, factors used in standard treatment.

Although no thromboembolic events were in clinical studies in patients with hemophilia, considering the mechanism of action of marstacimab, thromboembolism is an important risk. Therefore, the applicant plans to include a cautionary statement on the risk of thromboembolic events in the package insert and other materials, and continue to gather data in the post-marketing setting. In addition, there have been reports of injection site reactions considered to be related to marstacimab, and skin symptoms (i.e., rash and pruritus) that could be hypersensitivity reactions to marstacimab. The applicant also plans to include cautionary statements on such events in the package insert and other materials.

PMDA's view:
According to the submitted clinical data, the majority of adverse events occurring following administration of marstacimab were mild or moderate in severity. A causal relationship to the study drug was ruled out for most of the serious adverse events, and marstacimab treatment continued. Furthermore, the subgroup analysis by age group indicated no clear differences in the safety of marstacimab between adolescents and adults. In view of these findings, the safety profile of marstacimab is tolerable in both age groups.

The proposed commercial formulation is a PFP presentation, while in Study B7841005, the pivotal study, PFS was used. In studies in which PFP was mainly used, such as Study B7841007, no clear differences in safety profile were identified between PFS and PFP; therefore, PFP is also well tolerated.

In clinical studies in patients with hemophilia, there have been no reports of thromboembolic events; however, serious pulmonary embolism occurred in 1 subject in Study B7841009, and the event was assessed as being related to the study drug. Hypersensitivity (including shock and anaphylaxis) classified as a serious event (Grade 3 in severity) occurred in a patient with inhibitor, and the event was assessed as being related to the study drug. Since the above events are already recognized as important risks for drugs with similar mechanisms of action and cautionary statements about the risk of the events are provided in the package insert and other materials, similar cautionary statements are necessary for marstacimab. Furthermore, the applicant should continue gathering data on the incidence, etc. of these adverse events after the market launch of marstacimab, and provide the information to healthcare professionals in an appropriate manner.

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

7.R.4 Indication and clinical positioning

Study B7841005, the pivotal study, was conducted in patients with congenital hemophilia without inhibitors. Given this and other factors, the applicant modified the indication proposed at the time of submission of the present application to describe "control of bleeding tendency in patients with congenital hemophilia without coagulation factor VIII or factor IX inhibitors."

The applicant's explanation about the clinical positioning of marstacimab:

Primary treatment for patients with hemophilia is replacement of deficient FVIII or FIX. The coagulation factors used are mostly recombinant factor products (standard or extended half-life products). Factor replacement therapies include on-demand factor therapy in which the factor is administered in response to a bleed as necessary to achieve hemostasis, or routine factor prophylaxis, scheduled routine prophylactic FVIII or FIX administration to maintain coagulation factor activity at >1% to prevent bleeds from occurring. Since FVIII and FIX have relatively short half-lives, routine factor prophylaxis with standard half-life factor products in patients without inhibitors will require multiple intravenous infusions per week. For routine factor prophylaxis as the standard treatment, patients with HA without inhibitors need to receive intravenous infusions of coagulation factor products twice to 4 times a week for, and patients with HB without inhibitors need to receive such therapy twice weekly to once every 2 weeks. These situations make treatment adherence difficult, resulting in worsening of quality of life (QOL) (*Thromb Res.* 2008;122:S2-8). In some cases, routine prophylaxis using coagulation factor products requires placement of an indwelling intravenous catheter, which poses risks of infection and thrombosis (*Br J Haem.* 2007;138:580-6). Emicizumab, a bispecific monoclonal antibody that binds to activated coagulation factor IX (FIXa) and factor X (FX), substituting for FVIII function, is used in the treatment of HA, but it cannot be used for the treatment of HB. Concizumab, which has been approved for the treatment of congenital hemophilia with or without inhibitors, is a monoclonal antibody, like marstacimab, targeting the K2 domain of TFPI; however, its dosage requires calculation based on body weight.

Marstacimab is a monoclonal antibody that binds to TFPI, which is the primary inhibitor of the extrinsic coagulation cascade. It is a subcutaneous drug that reduces inactivation of FVIIa and FXa by TFPI, strengthening the extrinsic coagulation pathway. The previously approved agents require the dose to be adjusted based on the patient's body weight, factor activity, etc. before administration. Marstacimab, however, is administered as a subcutaneous injection at a fixed dose once weekly via PFP, which increases convenience and offers a new treatment option.

PMDA's view:
Based on the submitted data and discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety," the proposed indication of marstacimab, "control of bleeding tendency in patients with congenital hemophilia without coagulation factor VIII or factor IX inhibitors" is acceptable. The applicant's explanation about the clinical positioning is also acceptable. PMDA concluded that marstacimab can be positioned as a new treatment option for congenital hemophilia without inhibitors.

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

7.R.5 Dosage and administration

After reviewing the details of the statements in the "Precautions Concerning Indication" section and the "Precautions Concerning Dosage and Administration" section, the applicant decided it was more appropriate to include a description regarding the patient's body weight and dose increase in the "Dosage and Administration" section. Accordingly, the applicant intends to make the following changes to the proposed

dosage and administration.

Dosage and Administration

(The proposed statement has been modified: underline denotes additions and strikethrough denotes deletions)

The usual dosage for patients aged ≥12 years weighing ≥35 kg is an initial ~~loading~~ dose of 300 mg of marstacimab (genetical recombination) by subcutaneous injection, followed by 150 mg by subcutaneous injection once weekly. The dose may be increased to 300 mg once weekly in patients weighing ≥50 kg when the control of bleeding tendency is inadequate.

7.R.5.1 Selection of dosage regimen

The applicant's explanation about the selection of the dosage regimen:

The dosage regimen of marstacimab was evaluated in Study B7841002, a phase Ib/II study. In all the dosage regimens, the ABR in the marstacimab treatment phase decreased with no marked difference between marstacimab 150 mg and 300 mg administered once weekly subcutaneously [see Section 7.2.1]. The analysis using data from Study B7841002 predicted that subcutaneous administration of the initial dose of marstacimab 300 mg followed by 150 mg once weekly would maintain a trough concentration of marstacimab that is expected to be effective based on the PD parameters. Accordingly, this dosage regimen was adopted for the phase III studies. In Study B7841005, a phase III study, favorable efficacy and safety results were obtained; therefore, taking into consideration the patient population of Study B7841005, the following was selected as the usual dosage regimen of marstacimab: "for patients aged ≥12 years weighing ≥35 kg, administer an initial dose of 300 mg of marstacimab (genetical recombination) by subcutaneous injection, followed by 150 mg by subcutaneous injection once weekly."

7.R.5.2 Dose escalation

The applicant's explanation about marstacimab dose escalation:

In Studies B7841005 and B7841007, marstacimab dose escalation to 300 mg once weekly was allowed after 6 months of treatment with marstacimab and completion of the visit on Day 180 in the marstacimab treatment phase of Study B7841005, provided the subject met the criteria of (1) body weight of ≥50 kg[27)]; and (2) ≥2 spontaneous bleeds (atraumatic, joint bleeds, severe soft tissue/intramuscular bleeds, or other site bleeds) treated with FVIII or FIX over the 6-month period in the absence of confirmed FVIII or FIX inhibitor, respectively.

The dose of marstacimab was escalated to 300 mg once weekly in 3 subjects in the on-demand factor therapy group and 11 subjects in the routine factor prophylaxis group in Study B7841005, and 4 subjects in Study B7841007. In Study B7841005, the median duration of marstacimab treatment before and after the dose escalation was 244.0 days (before) and 125.0 days (after) in the on-demand factor therapy group and 251.0

[27)] Based on 450 mg, the highest dose level at which safety has been confirmed in Study B7841002, and the lowest body weight (74.8 kg) of subjects enrolled in the treatment group, a dose level of 6 mg/kg was calculated. A minimum body weight 50 kg was determined so that the dose level would not exceed 6 mg/kg after the dose was increased to 300 mg.

days (before) and 108.0 days (after) in the routine factor prophylaxis group.

Table 42 and Table 43 show the ABR before and after dose escalation to marstacimab 300 mg once weekly in Study B7841005 or B7841007. The ABR decreased after dose escalation in most subjects.

Table 42. Annualized bleeding rate before and after dose escalation to marstacimab 300 mg once weekly (Study B7841005/B7841007)

B7841005 treatment	Subject No.	ABR (bleeds/year)		
		Observational	Marstacimab treatment[a)]	
			Before escalation	After escalation[b)]
On-demand factor therapy	5	30.3	1.5	0 (0)
	6	55.2	8.0	2.9 (2.1)
	7	9.6	1.2	4.6 (6.9)
Routine factor prophylaxis	8	7.9	7.7	0 (0)
	9	8.9	11.2	3.4 (4.2)
	10	4.3	2.3	0 (0)
	11	0	4.7	0 (0)
	12	7.9	7.7	0.7 (2.0)
	13	5.8	19.5	8.5 (10.1)
	14	4.2	26.2	7.4 (3.4)
	15	0	16.1	4.7 (4.7)
	16	41.6	31.0	0 (0)
	17	19.2	11.2	11.2 (11.2)
	18	55.9	16.7	2.0 (2.0)
	19	0	3.2	0 (—)
	20	2.1	4.5	0 (—)
	21	3.9	6.7	5.7 (—)
	22	0	11.3	15.2 (—)

a) Including the period of Studies B7841005 and B7841007
b) The results for Study B7841005 period alone are presented in parentheses
Subjects No. 5-14, dose increased in Study B7841005, entered Study B7841007
Subjects No. 15-18, dose increased in Study B7841005, did not enter Study B7841007
Subjects No. 19-22, dose increased after entering Study B7841007

Table 43. Annualized bleeding rate before and after dose escalation to marstacimab 300 mg once weekly (Study B7841005/B7841007)

Dose	Before escalation	After escalation
On-demand factor therapy		
Number of subjects	3	3
ABR[a)] [95% CI] (bleeds/year)	3.01 [−0.07, 6.08]	2.54 [1.00, 4.08]
Routine factor prophylaxis		
Number of subjects	15	15
ABR[a)] [95% CI] (bleeds/year)	11.72 [7.40, 16.04]	3.80 [1.64, 5.97]

Least squares mean; Including the period of Studies B7841005 and B7841007
a) A generalized estimating equation with duration (years) and interaction by duration (years) and treatment as factors, with no intercept using identity link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)

Table 44 shows the summary of safety data from subjects who received dose escalation to marstacimab 300 mg once weekly in Studies B7841005 and B7841007. After dose escalation, adverse events occurred in 7 of 18 subjects (COVID-19 infection [2 subjects], rhinitis, laryngitis, nasopharyngitis, arthralgia, injection site induration [1 subject each]). Among these events, injection site induration (1 subject) was assessed as being related to the study drug. Based on the above results, no clear safety concerns were identified before or after dose escalation.

Table 44. Summary of safety data in subjects who received dose escalation to marstacimab 300 mg once weekly (Study B7841005/B7841007)

Dose	Before escalation	After escalation
All adverse events	10 (55.6)	7 (38.9)
Adverse drug reactions	4 (22.2)	1 (5.6)
Grade ≥3 adverse events	0	0
Adverse drug reactions	0	0
Deaths	0	0
Serious adverse events	1 (5.6)	0
Adverse drug reactions	0	0
Adverse events leading to permanent discontinuation	0	0
Adverse drug reactions	0	0

n (%); number of subjects who received dose escalation, 18 subjects

7.R.5.3 Home self-administration

The applicant's explanation about home self-administration:

In Study B7841005, the initial dose was to be injected by trial staff at the study center, and thereafter, the dose was to be administered by the subject or the caregiver. At the visits on Day 7, Day 28, and Day 60, marstacimab was to be administered at the study center if necessary. However, as marstacimab administration at the study center was not specified by the protocol beyond Day 60, it is assumed that almost all subjects used PFS to self-administer marstacimab at home.[28)] Similarly, in Study B7841007, the protocol specified that marstacimab was to be administered by the subject or the caregiver; therefore, it is assumed that marstacimab was self-administered at home by subjects in most cases.[28)] In Study B7841007, PFP was provided to all subjects; 2 subjects who had difficulties in using the PFP device to self-administer received marstacimab via PFS.

Table 45 shows the number of exposure days per subject, the number of missed dose days, and the percentage of missed dose days in Studies B7841005 and B7841007. The percentage of missed dose days was low, indicating good compliance with the study drug.

Table 45. The number of exposure days, the number of missed dose days, and the percentage of missed dose days (Study B7841005/B7841007)

Study	B7841005 (PFS)			B7841007 (PFP[a)]) (N = 87)
Treatment group	On-demand factor therapy (N = 33)	Routine factor prophylaxis (N = 83)	Overall population (N = 116)	
Number of exposure days per subject (days)	51.2 ± 2.4	49.2 ± 8.9	49.8 ± 7.7	29.9 ± 16.9
Number of missed dose days (days)	1.0 ± 2.2	1.0 ± 1.9	1.0 ± 2.0	0.3 ± 0.6
Percentage of missed dose days (%)	1.9 ± 4.2	1.9 ± 3.6	1.9 ± 3.8	1.3 ± 2.9

a) Including data from 2 subjects who received marstacimab using PFS

Medication errors occurred in 7 subjects in the marstacimab treatment phase of Study B7841005 (11 events in total; extra dose administered [6 events]; wrong dose [2 events]; product administration error, inappropriate schedule of product administration, incorrect dose administered [1 event each]), 6 subjects in Study B7841007 (8 events in total; underdose [3 events]; incorrect dose administered [2 events]; intentional product misuse,

[28)] In Studies B7841005 and B7841007, data on the location of administration and person who administered the study drug were not collected.

product dispensing error, inappropriate schedule of product administration [1 event each]). No medication errors related to adverse events occurred.

A substudy was conducted in subjects enrolled in Study B7841007 from whom consent was obtained to evaluate whether marstacimab can be administered effectively by the subject/caregiver using PFP. In this substudy, subjects or caregivers were to administer marstacimab using PFP on Day 1, Day 14, Day 35 at the study center, and on Day 7, Day 21, and Day 28 at home. Of the 23 subjects who participated in the substudy, 20 subjects received 150 mg once weekly and 3 subjects received 300 mg once weekly. The median number of marstacimab exposure days was 6 days (range, 5-6). The delivery system success rate at each visit (defined as successful injection based on observations by the PFP user or by the investigator/designated observer) ranged from 95.0% to 100%. When analyzed by age group, the success rate was 99.1% in subjects aged ≥18 years and 100% in those aged 12 to 17 years.

Four Japanese subjects enrolled in Studies B7841005 and B7841007 used PFS in Study B7841005 and PFP in Study B7841007. As with the case of the overall population, these subjects demonstrated good adherence to home self-administration of the study drug.

The above results suggest that marstacimab can be self-administered properly at home with PFP.

PMDA's view:
The applicant's explanation above is acceptable. The dosage and administration of marstacimab should be "The usual dosage for patients aged ≥12 years weighing ≥35 kg is an initial dose of 300 mg of marstacimab (genetical recombination) by subcutaneous injection, followed by 150 mg by subcutaneous injection once weekly. The dose may be increased to 300 mg once weekly in patients weighing ≥50 kg when the control of bleeding tendency is inadequate." There are no particular concerns regarding home self-administration of marstacimab.

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

7.R.6 Development of marstacimab for pediatric patients with hemophilia aged <12 years

The development of marstacimab for pediatric patients with hemophilia aged <12 years is underway. Currently, a clinical study in patients aged ≥1 year and <18 years is ongoing.

PMDA's view:
Given the prevalence of hemophilia in children aged <12 years, development of marstacimab for pediatric patients aged <12 years is necessary and extremely important. Since the development plan for children with hemophilia aged <12 years has already been confirmed at the consultation with PMDA (Consultation No. [redacted]), PMDA concluded that the plan has been verified in accordance with the "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3, dated January 12, 2024).

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing surveillance of marstacimab:

The applicant plans to conduct a general use-results survey in patients with congenital hemophilia without inhibitors who will be receiving marstacimab to keep track of the occurrence of thromboembolic events following administration of marstacimab in clinical practice (enrollment period, 4 years; follow-up period, approximately 2 years). Based on the projected use in post-marketing settings, approximately 80 patients are expected to be enrolled over 4 years. Although the survey method and other details are currently under consideration, in this survey, the applicant plans to gather safety information not only on thromboembolic events, which are to be included in the safety specification, but also on other adverse events.

PMDA's view:

Because only a small number of subjects were evaluated in the clinical studies of marstacimab, it is appropriate to conduct post-marketing surveillance to clarify the safety profile of marstacimab including the occurrence of thromboembolic events. Furthermore, post-marketing safety data obtained should be promptly and appropriately communicated to healthcare professionals.

In view of the discussions in Section "7.R.3 Safety," in addition to thromboembolism, shock and anaphylaxis should also be included in the safety specification of the survey, and the post-marketing incidence of these events, risk factors, peak time of onset, etc. should be investigated. The applicant should continue to examine the specific methods and details of the survey, and implement the survey in accordance with an appropriate and well-structured plan.

The PMDA's conclusion above 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 is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

The inspection is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that marstacimab has efficacy in the control of bleeding tendency in patients with congenital hemophilia without coagulation factor VIII or factor IX inhibitors, and that marstacimab has acceptable safety in view of its benefits. Marstacimab is clinically meaningful

because it offers a new option for routine prophylaxis in patients with congenital hemophilia without inhibitors.

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

Review Report (2)

November 21, 2024

Product Submitted for Approval

Brand Name	Hympavzi S.C. Injection 150 mg Pen
Non-proprietary Name	Marstacimab (Genetical Recombination)
Applicant	Pfizer Japan Inc.
Date of Application	February 28, 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). The brand name has been changed to "Hympavzi S.C. Injection 150 mg Pen" to facilitate a clearer understanding of the product's features.

1.1 Efficacy, indication, clinical positioning, and dosage and administration

At the Expert Discussion, the PMDA's conclusion presented in Sections "7.R.2 Efficacy," "7.R.4 Indication and clinical positioning," and "7.R.5 Dosage and administration" in Review Report (1) was supported by the expert advisors, and the following comments were made:

- Because marstacimab is administered in a fixed dose irrespective of the patient's body weight, its efficacy may be affected by body weight. Therefore, it is desirable to conduct a subgroup analysis by body weight to assess the effect.
- For dose escalation of marstacimab, more specific information including the timing for determining whether the response is inadequate should be provided to healthcare professionals.

PMDA reviewed the ABR of treated bleeds by baseline body weight in Study B7841005 (Table 46 and Table 47), and determined that body weight had no clear impact on the efficacy of marstacimab. PMDA instructed the applicant to provide information useful for determining inadequate response to marstacimab through information materials intended for healthcare professionals. The applicant responded that they would address this appropriately.

Table 46. Annualized bleeding rate of treated bleeds by body weight (Study B7841005, on-demand factor therapy, mITT)

Patient characteristics	N	Observational		Marstacimab treatment		ABR ratio[b)] [95% CI]
		Number of subjects experiencing bleeds	ABR[a)]	Number of subjects experiencing bleeds	ABR[a)]	
Overall population	33	32 (97.0)	39.86 [33.05, 48.07]	23 (69.7)	3.20 [2.10, 4.88]	0.080 [0.057, 0.113]
<70.0 kg (median)	16	16 (100)	42.28 [33.09, 54.03]	9 (56.3)	2.84 [1.53, 5.29]	0.067 [0.041, 0.109]
≥70.0 kg (median)	17	16 (94.1)	37.53 [28.28, 49.80]	14 (82.4)	3.56 [2.02, 6.27]	0.095 [0.060, 0.151]

Number of subjects experiencing bleeds, n (%); ABR, least squares mean [95% CI] (unit, bleeds/year)
a) A generalized estimating equation with treatment group as a factor, duration (log years) as an offset term, using log link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)
b) Least squares mean ratio (marstacimab treatment phase/observational phase)

Table 47. Annualized bleeding rate of treated bleeds by body weight (Study B7841005, routine factor prophylaxis group, mITT)

Patient characteristics	N	Observational		Marstacimab treatment		ABR difference[c)] [95% CI]
		Number of subjects experiencing bleeds[a)]	ABR[b)]	Number of subjects experiencing bleeds[a)]	ABR[b)]	
Overall population	83	50 (60.2)	7.90 [5.14, 10.66]	52 (62.7)	5.09 [3.40, 6.78]	−2.81 [−5.42, −0.20]
<69.0 kg (median)	41	25 (61.0)	8.28 [3.98, 12.58]	22 (53.7)	5.49 [2.78, 8.21]	−2.79 [−6.61, 1.03]
≥69.0 kg (median)	42	25 (59.5)	7.55 [4.07, 11.04]	30 (71.4)	4.68 [2.67, 6.69]	−2.87 [−6.41, 0.66]

Number of subjects experiencing bleeds, n (%); ABR, least squares mean [95% CI] (unit, bleeds/year)
a) Including 5 subjects who discontinued
b) A generalized estimating equation with duration (years) and interaction by duration (years) and treatment as factors, with no intercept using identity link function, assuming a negative binomial distribution for the number of bleeds (covariance structure was defined as unstructured)
c) Difference in least squares means (marstacimab treatment phase − observational phase)

1.2 Safety, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the PMDA's conclusion presented in Sections "7.R.3 Safety" and "7.R.7 Post-marketing investigations" in Review Report (1) was supported by the expert advisors, and the following comment was made:

- Based on the mechanism of action of marstacimab, serious adverse drug reactions, such as thromboembolism, may develop. In addition, given that only a limited number of patients were evaluated in clinical studies, the applicant should conduct post-marketing surveillance, which may be implemented as an all-case survey, and the obtained information should be provided to healthcare professionals.

After finalization of the Review Report (1), thromboembolism[29)] occurred in 1 non-Japanese subject (hemophilia A, without inhibitor) in Study B7841007, and was classified as a serious adverse event. The event was assessed as being related to the study drug. The applicant is currently gathering additional information, but explained that there would be no change in the plan of Study B7841007 in response to the occurrence of

[29)] In this subject, right subclavian vein thrombosis was reported at more than 3 years after the initiation of marstacimab treatment. Marstacimab treatment in this subject was interrupted. At the time of preparing this report, anticoagulant treatment is ongoing, and the outcome of right subclavian vein thrombosis has been reported as not resolved.

this adverse event.

PMDA's conclusion:

Although the safety profile of marstacimab remains tolerable, the applicant should provide detailed information on thromboembolic events reported in clinical studies of marstacimab to healthcare professionals, while ensuring that the safety measures presented in Review Report (1) are implemented. In addition, in view of the discussions presented in Sections 7.R.3 and 7.R.7 in Review Report (1), and comments from the expert advisers at the Expert Discussion, the risk management plan (draft) for marstacimab should include the safety specification presented in Table 48, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 49 and Table 50.

Table 48. Safety specification in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thromboembolism	• Shock, anaphylaxis • Immunogenicity	• None

Table 49. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Disseminate data gathered through early post-marketing phase vigilance • Organize and disseminate information materials for healthcare professionals (Precautions during treatment with Hympavzi S.C. Injection 150 mg Pen) • Organize and disseminate information materials for patients (For patients with hemophilia and their families using Hympavzi; Hympavzi patient's card)

Table 50. Outline of specified use-results survey (draft)

Objective	To confirm the safety of marstacimab in clinical practice
Survey method	All-case surveillance
Population	Patients with congenital hemophilia without inhibitors treated with marstacimab
Observation period	3 years
Planned sample size	50 patients
Main survey items	Patient characteristics, status of marstacimab use, concomitant medication, adverse events (including thromboembolic events, shock, anaphylaxis), laboratory data (coagulation-related parameters, hepatic function test values, etc.), status of bleeds

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 5.3.5.2.3) 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 modified indication and dosage and administration shown below, with the following conditions. 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

Control of bleeding tendency in patients with congenital hemophilia without coagulation factor VIII or factor IX inhibitors

(The underlined words are added to and the strikethrough word is deleted from the proposed text)

Dosage and Administration

The usual dosage for patients aged ≥12 years weighing ≥35 kg is an initial ~~loading~~ dose of 300 mg of marstacimab (genetical recombination) by subcutaneous injection, followed by 150 mg administered via subcutaneous injection once weekly. The dose may be increased to 300 mg once weekly in patients weighing ≥50 kg when the control of bleeding tendency is inadequate.

(The underlined words are added to and the strikethrough word is deleted from the proposed text)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of patients have been accrued.

Appendix

List of Abbreviations

ABR	Annualized bleeding rate
ADA	Anti-drug antibody
A/G	Albumin/globulin ratio
aPCC	Activated prothrombin complex concentrate
aPCC (product)	Anti-inhibitor coagulant complex Feiba NF for Injection 1000
aPTT	Activated partial thrombin time
AUC	Area under the plasma concentration-time curve
AUC_{inf}	AUC from time 0 to infinite time
AUC_{last}	AUC from time 0 to the time of last measurement
AUC_{tau}	AUC over the dosing interval tau
CDC	Center for Disease Control and Prevention
CGE	Capillary gel electrophoresis
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum observed plasma concentration
Concizumab	Concizumab (genetical recombination) Alhemo Subcutaneous Injection 15 mg, Alhemo Subcutaneous Injection 60 mg, Alhemo Subcutaneous Injection 150 mg, Alhemo Subcutaneous Injection 300 mg
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
dPT	Dilute prothrombin time
EDTA	Ethylenediaminetetraacetic acid
Emicizumab	Emicizumab (genetical recombination) Hemlibra s.c. 30 mg, Hemlibra s.c. 60 mg, Hemlibra s.c. 90 mg, Hemlibra s.c. 105 mg, Hemlibra s.c. 150 mg
EOPC	End of production cells
FcγR	Fcγ receptor
FIX(a)	(Activated) coagulation factor IX
FLP	Flippase
FRT	FLP recognition target
FVIIa/FX (product)	Freeze-dried activated human blood coagulation factor VII concentrate containing factor X Byclot Combination Intravenous Injection
FX(a)	(Activated) coagulation factor X
[redacted]	[redacted]
HA	Haemophilia A
HB	Haemophilia B
[redacted]	[redacted]
HCP	Host cell protein
HMMS	High molecular mass species
Hympavzi	Hympavzi S.C. Injection 150 mg or Hympavzi S.C. Injection 150 mg Pen

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
icIEF	Imaged capillary isoelectric focusing
IgG	Immunoglobulin G
Impurity F	[redacted]
Impurity G	[redacted]
IV	Intravenous injection
K1	Kunitz domain 1
K2	Kunitz domain 2
K_D	Dissociation constant
KO	Knockout
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LMMS	Low molecular mass species
Marstacimab	Marstacimab (genetical recombination)
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities/Japanese version
mITT	Modified Intent-to-Treat
PD	Pharmacodynamic(s)
PF1.2	Prothrombin fragment 1.2
PFP	Prefilled pen (prefilled-pen injector; a drug-filled PFS is sealed in a dedicated pen-injector; the entire product is referred to as a prefilled pen)
PFS	Prefilled syringe
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPAS	Per Protocol Analysis Set
PPK	Population PK
PT	Prothrombin time
PT/INR	Prothrombin time/International normalized ratio
QOL	Quality of Life
QW	Once a week
(r)FIX	(Recombinant) coagulation factor IX
(r)FVII(a)	(Recombinant) (activated) coagulation factor VII
rFVIIa (product)	Eptacog alfa (activated) (genetical recombination) NovoSeven HI Syringe for I.V. Injection 1 mg, NovoSeven HI Syringe for I.V. Injection 2 mg, NovoSeven HI Syringe for I.V. Injection 5 mg
(r)FVIII	(Recombinant) coagulation factor VIII
RH	Relative humidity
SC	Subcutaneous injection
scFv	Single chain Fv
SE-HPLC	Size exclusion high performance liquid chromatography
SMQ	Standardized MedDRA Query
SPR	Surface Plasmon Resonance
$t_{1/2}$	Apparent terminal half-life
TAT	Thrombin-antithrombin complexes
TEG	Thromboelastography
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
t_{max}	Time of occurrence of C_{max}
V/F	Apparent volume of distribution
V_{ss}	Volume of distribution at steady state
V_{ss}/F	Apparent steady-state volume of distribution
WCB	Working cell bank

WFH	World Federation of Hemophilia