Report on the Deliberation Results

August 29, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Cablivi Injection 10 mg
Non-proprietary Name	Caplacizumab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	February 10, 2022

Results of Deliberation

In its meeting held on August 25, 2022, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 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. Since data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a certain number of patients have been gathered, to understand the characteristics of patients using the product. The applicant is also required to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 10, 2022
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	Cablivi Injection 10 mg
Non-proprietary Name	Caplacizumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	February 10, 2022
Dosage Form/Strength	Lyophilized powder for injection in a vial for reconstitution before use: Each vial contains 12.5 mg of Caplacizumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Caplacizumab is a recombinant single-chain bivalent monoclonal antibody (VH-VH) composed of variable regions of humanized anti-human von Willebrand factor (vWF) antibody at positions 1 – 128 and 132 – 259, whose complementarity-determining regions are derived from heavy-chain antibody from *Lama glama*. Caplacizumab is a protein consisting of 259 amino acid residues.

Structure

Amino acid sequence:

EVQLVESGGG LVQPGGSLRL SCAASGRTFS YNPMGWFRQA PGKGRELVAA

ISRTGGSTYY PDSVEGRFTI SRDNAKRMVY LQMNSLRAED TAVYYCAAAG

VRAEDGRVRT LPSEYTFWGQ GTQVTVSSAA AEVQLVESGG GLVQPGGSLR

LSCAASGRTF SYNPMGWFRQ APGKGRELVA AISRTGGSTY YPDSVEGRFT

ISRDNAKRMV YLQMNSLRAE DTAVYYCAAA GVRAEDGRVR TLPSEYTFWG

QGTQVTVSS

Intrachain disulfide bonds: Solid line in the figure

Schematic diagram:

Molecular formula: $C_{1213}H_{1891}N_{357}O_{380}S_{10}$

Molecular weight: 27876

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 416 of 2018 [30 yaku]; PSEHB/PED Notification No. 0605-1 dated June 5, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of acquired thrombotic thrombocytopenic purpura, 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 approval conditions. Risks such as haemorrhage and serious hypersensitivity reaction, safety of re-administration, and information on use in children aged ≥12 years weighing ≥40 kg need to be further investigated via post-marketing surveillance.

Indication

Acquired thrombotic thrombocytopenic purpura

Dosage and Administration

In adults and in children aged ≥12 years weighing ≥40 kg, 10 mg of caplacizumab is administered intravenously prior to plasma exchange, followed by a 10 mg subcutaneous injection after completion of plasma exchange on the first day of treatment. During the subsequent plasma exchange period, 10 mg of caplacizumab is administered subcutaneously, once daily, after the daily plasma exchange. After the plasma exchange period, 10 mg is administered subcutaneously once daily for 30 days.

Treatment with caplacizumab may be extended beyond 30 days after the plasma exchange period depending on the condition of the patient.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a certain number of patients have been gathered to understand the characteristics of patients using the product. The applicant is also required to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

July 7, 2022

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	Cablivi Injection 10 mg
Non-proprietary Name	Caplacizumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	February 10, 2022
Dosage Form/Strength	Lyophilized powder for injection in a vial for reconstitution before use: Each vial contains 12.5 mg of Caplacizumab (Genetical Recombination).

Proposed Indication

Acquired thrombotic thrombocytopenic purpura

Proposed Dosage and Administration

In adults and in children aged ≥12 years weighing ≥40 kg, 10 mg of caplacizumab is administered intravenously prior to plasma exchange followed by a 10 mg subcutaneous injection after completion of plasma exchange on the first day of treatment. During the subsequent plasma exchange period, 10 mg of caplacizumab is administered subcutaneously, once daily, after the daily plasma exchange. After the plasma exchange period, 10 mg is administered subcutaneously once daily for 30 days. If signs showing persistence of the underlying immunological disease (e.g., persistent decrease in a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 [ADAMTS13] activity) are observed, caplacizumab should be administered beyond 30 days until disappearance of underlying immunological disease under optimal immune suppression.

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List of Abbreviations

See Appendix.

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

von Willebrand factor (vWF) is a high molecular weight plasma glycoprotein which plays an important role in recruiting platelets to sites of vascular injury. It also plays a role as a carrier of blood coagulation factor VIII. Ultra large vWF (ULvWF) multimers, which are produced mainly in vascular endothelial cells and secreted into circulating blood, are cleaved by a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS13), a specific cleavage enzyme, into vWF multimer of standard molecular weight appropriate for hemostatic function. Usually, the platelet glycoprotein Ib-IX-V (GPIb-IX-V) receptor-binding site on A1 domain is embedded within vWF molecule and, upon exposure of the binding site by surface immobilization or shear stress, vWF becomes activated to bind platelets, resulting in platelet recruitment. In contrast, ULvWF has a structure prone to bind to platelets, resulting in spontaneous binding with platelets under high shear stress in microvessels, etc., leading to platelet adhesion and aggregation.

In thrombotic thrombocytopenic purpura (TTP), a deficiency of ADAMTS13 activity allows unrestrained accumulation of ULvWF multimers and their adhesion with platelets, forming platelet plugs within microvessels, leading to platelet-consuming thrombopenia, hemolytic anemia, and local ischemia, organ damages, etc., due to platelet thrombosis. TTP is classified into congenital TTP caused by abnormal ADAMTS13 gene and acquired TTP caused by anti-ADAMTS13 autoantibody production.

Caplacizumab is a recombinant, single-chain, bivalent monoclonal antibody discovered by Ablynx N.V. It consists of two identical variable regions of a heavy chain of lama-derived humanized anti-human vWF antibody linked by a three-alanine linker. Caplacizumab is considered to suppress vWF-mediated platelet adhesion and aggregation by binding to A1 domain of vWF, thereby inhibiting the interaction between vWF and platelets.

In foreign countries, clinical development of caplacizumab was initiated in 2007 by Ablynx N.V. Caplacizumab was approved with the indication for acquired TTP, in Europe in August 2018 for adults and in June 2020 for children aged ≥12 years weighing ≥40 kg and in the US in February 2019 for adults. Caplacizumab is approved in ≥40 countries as of June 2022.

In Japan, a clinical study was initiated in October 2019, and a marketing application has recently been submitted by the applicant, with the proposed indication of "acquired thrombotic thrombocytopenic purpura," based on the results of Japanese and foreign clinical studies, etc.

Caplacizumab was designated as an orphan drug for the intended indication of "thrombotic thrombocytopenic purpura" on June 5, 2020 (Orphan Drug Designation No. 416 of 2018 [*30 yaku*]; PSEHB/PED Notification 0605-1 dated June 5, 2020).

2. Quality and Outline of the Review Conducted by PMDA

2.1.1 Generation and control of cell substrate

From a phage display library generated from ribonucleic acid (RNA) of tissues (including B cells) derived from a lama immunized with A1 domain of recombinant human vWF, a single-chain monoclonal antibody was selected with the specific binding to A1 domain of vWF as the index. The sequence of

single-chain monoclonal antibody underwent coupling to form a bivalent structure, optimization, and humanization to generate the gene expression construct of caplacizumab. *Escherichia coli* (*E. coli*) cells were transformed with the gene expression construct thus obtained, and the optimal clone for production of caplacizumab was selected from the transformed cells and used for the generation of master cell bank (MCB) and working cell bank (WCB).

MCB, WCB, end of production cells (EPC), and cells at the limit of in vitro cell age (CAL) were subjected to characterization and purity test according to Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Q5B Guidelines) and Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D Guidelines). Results confirmed the genetic stability during the production of caplacizumab. No contamination with microorganisms other than E. coli was detected within the range of tests conducted.

MCB and WCB are stored in liquid nitrogen (gas phase). There is no plan for regeneration of MCB or WCB.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of seed culture, pre-cultivation, cultivation, harvesting, clarification, [redacted] chromatography, [redacted] chromatography, filtration/pooling/splitting, [redacted] chromatography (final purification), [redacted], [redacted], dilution/preparation/pooling, filtration/filling, and pretreatment for cryopreservation/storage/test.

The critical steps are pre-cultivation, cultivation, harvesting, clarification, [redacted] chromatography, [redacted] chromatography, [redacted] chromatography (final purification), [redacted], dilution/preparation/pooling, and filtration/filling.

The commercial-scale manufacturing process of the drug substance was subjected to process validation.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin are used in the manufacturing process of the drug substance.

2.1.4 Manufacturing process development

During the development of the drug substance, the following major changes were made to the manufacturing process (each manufacturing process is referred to as Process A, Process B, and the proposed commercial process). The formulations manufactured from [redacted] drug substance was used in the foreign phase I study (Study ALX0681-C103), Japanese phase II/III study (Study ALX0681-C202), foreign phase III study (Study ALX0681-C301), and foreign phase IIIb study (Study ALX0681-C302/LTS16371).

- Process A to Process B: [redacted], [redacted], and [redacted]
- Process B to proposed commercial process: [redacted], [redacted], [redacted], and [redacted]

In association with the above changes of the manufacturing processes, comparability of the quality attributes was evaluated, and the results confirmed the comparability of pre- and post-change drug substances.

2.1.5 Characterization

2.1.5.1 Structure and characteristics

Caplacizumab was subjected to characterization tests described in Table 1.

Table 1. Parameters for characterization

Primary/higher-order structure	Amino acid sequence, disulfide bonds, posttranslational modification, secondary structure, tertiary structure
Physicochemical properties	[redacted], [redacted], molecular weight, absorption coefficient
Biological properties	[redacted] activity [redacted] inhibitory activity

As for biological properties, [redacted] and [redacted] activities were confirmed. Also, the activity to inhibit [redacted] was confirmed by [redacted] and [redacted].

2.1.5.2 Product-related substances/Product-related impurities

Impurity A, Impurity B, Impurity C, and Impurity D were identified as product-related substances based on the results of characterization tests in Section "2.1.5.1. Structure and characteristics." Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, and Impurity L were identified as product-related impurities. Among the product-related substances, Impurity A, Impurity B, and Impurity C are controlled by the specifications for the drug substance and the drug product. Among the product-related impurities, Impurity E, Impurity F, Impurity G, and Impurity H are controlled by the specifications for the drug substance and the drug product.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell deoxyribonucleic acid (DNA), bacterial endotoxins, Impurity M, Impurity N, Impurity O, and Impurity P, and elemental impurities were identified as process-related impurities. Process-related impurities were confirmed to be adequately removed during the manufacturing process. Bacterial endotoxins are controlled by the specifications for the drug substance and the drug product, and HCP and host cell DNA by the specifications for the drug substance.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (sodium dodecyl sulfate [SDS] capillary electrophoresis [redacted], peptide mapping, cation exchange high-performance liquid chromatography [CEX-HPLC], surface plasmon resonance [SPR]), osmotic pressure, pH, purity (SDS capillary electrophoresis [redacted], size exclusion high-performance liquid chromatography [SE-HPLC], reverse phase high-performance liquid chromatography [RP-HPLC], peptide mapping, HCP [enzyme-linked immunosorbent assay (ELISA)], host cell DNA [redacted]), [redacted], bacterial endotoxins, microbial limits, potency (SPR), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 2 shows a summary of the main stability studies on the drug substance.

Table 2. Summary of the main stability studies on drug substance

	Manufacturing process for drug substance	Number of batches	Storage condition	Study period	Storage form
Long-term testing	[redacted]	3	≤[redacted]°C	[redacted] months	[redacted] bag
Accelerated testing	[redacted]	3	[redacted]±[redacted]°C	[redacted] months	
Stress testing	[redacted]	3	[redacted]±[redacted]°C/[redacted]±[redacted]% RH	[redacted] months	

The long-term testing did not show any clear changes in quality attributes throughout the study period. The accelerated testing showed an increase in [redacted] and a tendency of an increase in [redacted], [redacted], [redacted], and Impurity B. The stress testing showed an increase in [redacted], [redacted], [redacted], [redacted], [redacted], and Impurity B and a decrease in [redacted] and [redacted].

On the basis of the above, the shelf life of [redacted] months has been proposed for the drug substance when stored at ≤[redacted]°C in a [redacted] bag.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a combination product consisting of the frozen lyophilized drug product and the diluent for reconstitution (water for injection) filled in a syringe.

The drug product is lyophilized injection containing 12.5 mg of the drug substance in a glass vial (2 mL). The drug product contains anhydrous citric acid, sodium citrate hydrate, sucrose, and polysorbate 80 as excipients. The vial contains the drug product in excess of the labeled amount to allow administration of 10 mg of caplacizumab reconstituted with 1 mL of water for injection, with a loss in preparation and administration of the injection solution in mind.

The attached solution for reconstitution is 1 mL of water for injection (Japanese Pharmacopoeia [JP] grade) filled in a glass syringe (1.5 mL).

2.2.2 Manufacturing process

The manufacturing process of the lyophilized drug product consists of thawing/taking out of the bulk drug substance, pooling/mixing of the drug substance solution, preliminary filtration, sterile filtration, filling/partial stoppering, lyophilization/stoppering, clamping, visual inspection/storage/testing, packaging/labeling/storage/testing.

The critical steps are [redacted], [redacted], [redacted], [redacted], and [redacted].

The commercial-scale manufacturing process of the drug product was subjected to process validation.

2.2.3 Manufacturing process development

[redacted], [redacted], and [redacted] are major changes made to the lyophilized drug product manufacturing process during development. The formulation [redacted] was used in main clinical studies. In association with the above changes of the manufacturing processes, the comparability of quality attributes and pharmacokinetics [see Section "6.1.1 Bioequivalence study"] were evaluated, and the results confirmed the comparability of pre- and post-change drug product.

2.2.4 Control of drug product

The proposed specifications for the lyophilized drug product include strength, description, identification ([redacted]), osmotic pressure, water content, pH, purity (SDS capillary electrophoresis [redacted], SE-HPLC, RP-HPLC, CEX-HPLC, [redacted]), bacterial endotoxin, uniformity of dosage units (content uniformity), foreign insoluble matter, insoluble particulate matters, sterility, dissolution time, potency (SPR), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 3 shows the main stability studies on the lyophilized drug product. All of the drug substance and the drug product used in stability studies were manufactured by [redacted].

Table 3. Summary of the main stability studies on lyophilized drug product

	Number of batches	Storage condition	Study period	Storage form
Long-term testing	3	5 ± 3°C	60 months	Glass vial with butyl rubber stopper
Accelerated testing	3	25 ± 2°C/60 ± 5% RH	60 months	
Stress testing	3	40 ± 2°C/75 ± 5% RH	24 months	
Photostability	2	Overall illumination of ≥1.2 million lux·h, and an integrated near ultraviolet energy of ≥200 W·h/m^2		

The long-term testing did not show any clear changes in quality attributes throughout the study period. The accelerated testing showed a tendency of an increase in Impurity B and [redacted]. The stress testing showed an increase in Impurity B and [redacted], and a decrease in [redacted], within [redacted] months.

The photostability testing showed that the drug product was photostable.

On the basis of the above, the shelf life of 60 months has been proposed for the drug product when stored at 2°C to 8°C in a primary container consisting of a glass vial sealed with a butyl rubber stopper.

2.3 Quality control strategy

A quality control strategy on the drug substance and on the lyophilized drug product was developed, based on the following investigations and on the know-how on the product and the manufacturing process thus far obtained.

- Identification of critical quality attributes (CQAs):

Regarding the product-related impurities, process-related impurities, and general quality attributes, the following CQAs were identified based on the information obtained during the process of the development of caplacizumab and related findings:

CQA of drug substance: Purity, bacterial endotoxin, bioburden, pH, osmotic pressure, [redacted], Impurity F, Impurity G, [redacted], [redacted], appearance (transparency), appearance (color), [redacted], [redacted] and [redacted], potency, Impurity E, [redacted], [redacted], [redacted] Impurity N, [redacted] Impurity M, and identification

CQA of drug product: Purity, bacterial endotoxin, bioburden, sterility, pH, container integrity, osmotic pressure, [redacted], Impurity F, Impurity G, water content, [redacted], [redacted], appearance (transparency), appearance (visible particular matters), appearance (color), protein content and [redacted], potency, Impurity E, [redacted], dissolution time, [redacted], [redacted], [redacted], and identification

- Process characterization

  The risk of each process control factor was evaluated in the risk assessment of process characterization, input variables (critical process parameters or monitoring process parameters) and output variables (in-process control or in-process monitoring) significantly affecting CQA were identified.

2.R Outline of the review conducted by PMDA

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

2.R.1 Control of biological activity

Regarding the potency in the specifications for the drug substance and the drug product, PMDA considers that the competitive ELISA (test to evaluate the activity of caplacizumab to inhibit the binding of vWF and platelets in the presence of ristocetin), an assay conducted for characterization of caplacizumab, more closely reflects the pharmacological effect of caplacizumab than SPR (test to evaluate the binding of caplacizumab with A1 domain of vWF) which was the assay method proposed by the applicant. PMDA asked the applicant to explain the necessity of controlling the biological activity by the competitive ELISA.

The applicant's explanation:

Since the competitive ELISA uses a component of human origin, it is inappropriate to use it in daily quality control. It was conducted as a characterization test during the process of development. It has been confirmed that SPR is a test system more sensitive than the competitive ELISA, based on the results of both assays conducted using the drug substance and the drug product treated under stress conditions. Both assay methods were found to be capable of detecting the decrease in the potency under the stress

condition. Under the normal storage conditions, the potency of the drug substance and the drug product did not decrease, either by SPR or competitive ELISA. These results, along with the observation that caplacizumab exhibits its pharmacological effect by binding to A1 domain of vWF, suggest that it is appropriate to control the biological activity of caplacizumab by SPR and that it is unnecessary to include the competitive ELISA in the specification. In cases where a significant change is made to the manufacturing process, a risk-based evaluation and an appropriate characterization will be conducted, including the evaluation by the competitive ELISA.

PMDA considers that the applicant's explanation is appropriate, given the following: (a) Caplacizumab is a single-chain, bivalent monoclonal antibody without glycosylation or higher-order structure, and (b) the long-term testing of the drug substance and the drug product did not show clear change in the quality attributes throughout the study period.

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

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to human vWF (CTD 4.2.1.1-2)

Caplacizumab (5 pmol/L) was incubated with purified human vWF (3-fold serial dilution from 2.63 mg/mL,[1)]) followed by capture of free-form caplacizumab on vWF-adsorbed beads, and binding affinity of caplacizumab to vWF was determined. The mean dissociation constant (K_D) [95% confidence interval (CI)] was 3.76 [2.91, 4.61] pmol/L.

3.1.1.2 Analysis of the binding region of caplacizumab to A1 domain of vWF (CTD 4.2.1.1-1)

X-ray crystallography of the complex of vWF A1 domain and PMP12A2hum1, the monovalent protein constituting caplacizumab, showed that caplacizumab bound to the epitope not overlapping with the binding domain of GPIb-IX-V, the glycoprotein on the membrane of platelets, on vWF A1 domain.

3.1.1.3 Effect on platelet adhesion and aggregation (CTD 4.2.1.1-3)

A cover slip coated with purified human vWF, human type I collagen, or human type III collagen was placed in a flow chamber. Caplacizumab (0-0.6 μg/mL) was added to whole blood (5 mL) collected from healthy subjects and platelets were perfused under a high shear stress (1600 s^{-1}). Platelet thrombi on the cover slip were stained with May-Grünwald-Giemsa technique, and the effect on platelet adhesion was assessed under the light microscope with the fraction of surface coverage as the index. Caplacizumab inhibited the platelet adhesion to type I and type III collagen and to vWF, all in a concentration-dependent manner. A cover slip coated with type III collagen was placed in a flow chamber. Caplacizumab (0 or 0.8 μg/mL) was added to whole blood (5 mL) collected from healthy subjects, and platelets were perfused under varying degree of shear stress (100-2500 s^{-1}) and the effect on platelet adhesion was assessed in a similar manner. Caplacizumab inhibited platelet adhesion to type III collagen in a shear stress-dependent manner, with the complete inhibition attained at ≥1500 s^{-1}.

1) When vWF is expressed in units of molarity, it is shown as the concentration using its molecular mass (250 kDa) per monomer.

Caplacizumab (0-0.4 μg/mL) was incubated with platelet-rich plasma derived from healthy subjects, followed by the addition of ristocetin (2 mg/mL) to induce platelet aggregation. Ristocetin-induced platelet aggregation (RIPA) measurement using an aggregometer showed that caplacizumab inhibited RIPA in a concentration-dependent manner, showing a complete inhibition at ≥0.3 μg/mL. In a similar manner, caplacizumab (1 μg/mL) was added to platelet-rich plasma derived from healthy subjects at the start of ristocetin (2 mg/mL)-induced aggregation reaction and at the time points of 15%, 30%, 35%, 40%, and 60% of maximal platelet aggregation, and the effect on the platelet aggregation process was investigated. RIPA was terminated after caplacizumab addition at any time point.

An incubated mixture of purified human vWF (1 μg/mL), ristocetin (1.5 mg/mL), and caplacizumab (0-10 μg/mL) was added to a plate pre-coated with human platelets, and the binding of vWF to platelets was measured by competitive ELISA. Caplacizumab inhibited the binding of vWF to platelets in a concentration-dependent manner with half maximal inhibitory concentration (IC_{50}) of 0.23 nmol/L, showing a complete inhibition at 1.43 nmol/L (approximately 30% of molar concentration of vWF [4 nmol/L]).

Caplacizumab (3-fold serial dilution from 50 μmol/L) or ADAMTS13 activity-neutralizing monoclonal antibody Mab4245 (3-fold serial dilution from 1.5 μmol/L), a positive control, was added to purified human vWF-coated plates, followed by the addition of recombinant human ADAMTS13 (3.65 μg/mL). After incubation, binding of ADAMTS13 to vWF was measured by ELISA. Mab4245 inhibited the binding of ADAMTS13 to vWF in a concentration-dependent manner, whereas caplacizumab showed no inhibitory activity.

3.1.1.4 Effect on platelet adhesion to human ULvWF (CTD 4.2.1.1-4)

Endothelial cells collected from human umbilical vein were attached to a cover glass, which was placed within the flow chamber, and the cells were stimulated by histamine (1 μmol/mL) to secrete fibrous ULvWF strings on the surface of the cover glass. Platelets derived from healthy subjects were added to 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer (pH 7.4) containing caplacizumab (0, 0.2, 2.0, or 10.0 μg/mL) and to plasma derived from patients with acquired TTP, and the suspensions were perfused through a flow chamber under a low shear stress (100-300 s^{-1}) to allow the formation of platelet string bound to ULvWF, which was assessed under a real time video microscope. Platelet string formation was observed in platelet suspension containing either the buffer or the plasma of patients with acquired TTP in the absence of caplacizumab, whereas in the presence of caplacizumab, no platelet string formation was observed at any concentration of caplacizumab added. Platelet strings were allowed to form in a similar manner without caplacizumab, followed by addition of caplacizumab (10.0 μg/mL). Results showed that caplacizumab did not affect the platelet strings that had already been formed. In still another study, platelet strings were allowed to form without caplacizumab, after which healthy subjects-derived plasma, a supply source of ADAMTS13, was added, followed by addition of caplacizumab (10.0 μg/mL). Caplacizumab did not affect the cleavage of platelet strings by ADAMTS13 in this system.

3.1.1.5 Cross-reactivity with vWF of various animal species (CTD 4.2.1.1-8, 4.2.1.1-9, and 4.2.2.1.1-10)

Interspecies cross-reactivity of caplacizumab with vWF was investigated by SPR, ELISA, and competitive ELISA. Cross reactivity of caplacizumab was observed with vWF of baboons, cynomolgus monkeys, rhesus monkeys, pigs, minipigs, and guinea pigs, but not with vWF of mice, rabbits, rats, or dogs. Caplacizumab was added to platelet-rich plasma of humans, cynomolgus monkeys, and guinea pigs (n = 4-6 each), and RIPA was measured by an aggregometer. Caplacizumab concentration required for complete RIPA inhibition was 0.4, 1, and 1 to 10 μg/mL, respectively, in humans, cynomolgus monkeys, and guinea pigs.

The difference in the affinity of caplacizumab to vWF of various animal species was quantified by SPR using A1 domain of recombinant vWF of each animal species. Caplacizumab irreversibly bound to A1 domain of human vWF, precluding the calculation of the affinity constant. The affinity of caplacizumab to A1 domain of recombinant vWF of each animal species was investigated using PMP12A2hum1, the monovalent protein constituting caplacizumab. K_D of PMP12A2hum1 to vWF of each animal species was 1.05, 0.87 to 1.11, 14.5, and 160 nmol/L, respectively, for humans, cynomolgus monkeys, guinea pigs, and mice.

Plasma of humans, cynomolgus monkeys, or guinea pigs (n = 6 each) was added to plates coated with anti-vWF antibody, and the von Willebrand factor antigen (vWF:Ag) level in each sample was measured by ELISA. Plasma of humans, cynomolgus monkeys, or guinea pigs (n = 6 each) incubated with serially diluted caplacizumab was added to anti-vWF antibody-coated plates, and binding of caplacizumab to vWF was measured by competitive ELISA. The target occupancy rate was calculated from the vWF:Ag level observed. A mixture of incubated plasma of each animal (humans, cynomolgus monkeys, or guinea pigs, n = 6 each), ristocetin (1.5 mg/mL), and serially diluted caplacizumab was added to human platelet-coated plates, and binding of vWF to platelets was measured by competitive ELISA. The target neutralization rate was calculated from the results obtained. Human platelet suspensions were incubated with ristocetin (1.0 mg/mL for human plasma, 1.5 mg/mL for guinea pig platelet plasma), followed by addition of human or guinea pig plasma, and ristocetin cofactor activity (RICO) was measured by an aggregometer. Table 4 shows the results of the above studies.

Table 4. Comparison of the effect of caplacizumab in plasma samples of various animal species

Animal species	vWF:Ag (IU/mL)	Target occupancy rate EC_{50} (μg/mL)	Target neutralization rate IC_{50} (μg/mL)	RICO IC_{50} (μg/mL)
Human	1.52	0.38	0.31	0.24
Cynomolgus monkey	2.78	0.52	0.73	—[b]
Guinea pig	0.70	0.83	—[a]	0.43[c]

Mean

a Affinity of guinea pig vWF to human platelets was weak, precluding the calculation of the neutralization rate.

b Not investigated.

c Because of the weak affinity of guinea pig vWF to human platelets, RICO was calculated based on the maximum turbidity during the process of platelet aggregation.

3.1.1.6 Effect on vWF of patients with acquired TTP (CTD 4.2.1.1-7 and 4.2.1.1-11)

Plasma of healthy subjects (5 subjects and 2 pooled plasma samples) and patients with acquired TTP during the remission phase (7 subjects) or acute phase (1 subject) was added to anti-vWF antibody-coated plates to incubate. The vWF:Ag level measured by ELISA was 0.474 to 1.381 U/mL in healthy

subjects, and 0.63 to 1.57 and 4.5 U/mL, respectively, in patients with acquired TTP during the remission phase and acute phase. Human platelet suspension was incubated with ristocetin (10 mg/mL), followed by addition of plasma of healthy subjects (2 subjects) and patients with acquired TTP (11 subjects) containing serially diluted caplacizumab, and RICO was measured by an aggregometer. Caplacizumab concentration required to decrease RICO by 50% (IC_{50}) was 350.9 and 160.8 to 936.2 ng/mL, respectively, in healthy subjects and patients with acquired TTP, showing a tendency that the higher the vWF:Ag level before addition of caplacizumab in each sample, the higher the IC_{50}.

Serially diluted caplacizumab was added to plasma of patients with acquired TTP during acute phase (11 subjects) and, after incubation, the mixture was added to anti-vWF antibody-coated plates, and binding of caplacizumab to vWF was measured by competitive ELISA. The target occupancy rate was calculated using the vWF:Ag level before caplacizumab addition (45-117 nmol/L). The same plasma samples containing serially diluted caplacizumab was incubated, followed by addition of ristocetin (1.5 mg/mL), and the mixture was added to human platelet-coated plates. Binding of vWF to platelet was measured by competitive ELISA, and target neutralization rate was calculated. The mean target occupancy rate [95% CI] required to decrease the target neutralization rate to <20% was 84.91% [78.02, 89.92].

3.1.1.7 Effect on vWF secretion by human endothelial cells (CTD 4.2.1.1-5)

Human umbilical vein endothelial cells (HUVECs) derived from healthy subjects (3 subjects) were cultured in the presence or absence of caplacizumab (10 μg/mL), and the amount of vWF (U/mL) in the culture supernatant was measured at 0, 4, 6, 24, 48, and 72 hours after the start of cultivation. No significant difference was observed between the caplacizumab group and the control group at any time point. In a similar manner, HUVECs were cultured in the presence or absence of caplacizumab (10 μg/mL), and the amount of vWF (U/mL) in the culture supernatant at 0, 0.25, 1, 3, 4, and 24 hours after stimulation with histamine (100 μmol/L) was measured by ELISA. The vWF level was lower in the caplacizumab group than in the control group at 1 hour after the stimulation, whereas no significant difference was observed in the vWF level between the two groups at all other time points.

3.1.2 *In vivo* studies

3.1.2.1 Studies on acquired TTP model of baboons (CTD 4.2.1.1-12)

Monoclonal antibody 3H9 (0.6 mg/kg) which inhibits ADAMTS13 activity was administered intravenously to male baboons (n = 4/group) 5 times 48 hours apart over 9 days, and, from 5 days after the start of 3H9 administration, caplacizumab (2.5 mg/kg) or vehicle ([redacted], [redacted] mol/L [redacted], [redacted]% Tween 80, pH [redacted] ± [redacted]) was administered subcutaneously once daily for 7 days. Onset of acquired TTP was confirmed by a severe decrease in platelet count and the haptoglobin level and an increase in schizocyte count at 5 days after the start of 3H9 administration before the start of caplacizumab administration (*Blood.* 2010;116:2005-10). The caplacizumab group showed a partial recovery of schizocyte count and complete inhibition of RICO (decrease below the lower limit of quantitation) from Day 6, recovery of platelet count to the level below the start of 3H9 administration from Day 8, and recovery of the haptoglobin level from Day 9. No such changes were observed in the vehicle group. No animal in the caplacizumab group or in the vehicle group showed signs of intracranial haemorrhage by brain computed tomography (CT) scan or bleeding of other organs by necropsy or

histopathological examination. The mean Factor VIII procoagulant activity (FVIII:C) and vWF:Ag level remained at lower levels in the caplacizumab group than in the vehicle group from Day 6 up to the end of caplacizumab administration.

3H9 (0.6 mg/kg) was administered to male baboons (n = 4/group) twice 48 hours apart over 3 days, and, at the same time with the start of 3H9 administration, caplacizumab (2.5 mg/kg) or vehicle ([redacted], [redacted] mol/L [redacted], [redacted]% Tween 80, pH [redacted] ± [redacted]) was administered once daily for 5 days. The vehicle group showed a decrease in platelet count and the haptoglobin level and an increase in schizocyte count. The caplacizumab group did not show such changes and, instead, showed a complete inhibition of RICO (decrease below the lower limit of quantitation).

3.1.2.2 Effect on vWF:Ag of cynomolgus monkeys (CTD 4.2.1.1-5)

Caplacizumab (6 mg/kg) or vehicle ([redacted], [redacted] mol/L [redacted], [redacted]% Tween 80, pH [redacted] ± [redacted]) was administered intravenously to cynomolgus monkeys (n = 3-4/group), followed by intravenous administration of caplacizumab (2 mg/kg) or vehicle 6 times daily 4 hours apart for 2 weeks. The concentrations of vWF:Ag and von Willebrand factor propeptide (vWFpp), a newly synthesized vWF propeptide, were measured in plasma samples collected at 1 to 14-day intervals. The vWFpp level did not show any significant difference between the caplacizumab group and the vehicle group until the end of the study. The vWF:Ag level was significantly lower in the caplacizumab group than in the vehicle group from 2 days after the start of caplacizumab administration, but did not differ between the groups from Day 22 on. vWFpp/vWF:Ag ratio, a parameter of synthesis and elimination of vWF, was significantly higher in the caplacizumab group than in the vehicle group from 2 days after the start of caplacizumab administration. The between-group difference reached the maximum level after 11 days, then decreased to an insignificant level from after 22 days. The increase in vWFpp/vWF:Ag ratio was due not to increase in vWFpp but to decrease in mature vWF.

3.2 Secondary pharmacodynamics

3.2.1 Study of specificity using guinea pig and cynomolgus monkey tissues (CTD 4.2.1.2-4 and 4.2.1.2-5)

Cross-reactivity with various tissues was investigated by immunohistochemical staining using tissue panels of guinea pigs and cynomolgus monkeys. Caplacizumab was bound only to vWF-expressing cells, i.e., megakaryocytes and endothelial cells, and not to any other tissues.

3.2.2 Study of specificity using human blood and tissues (CTD 4.2.1.2-1 and 4.2.1.2-6)

Cross-reactivity with various tissues was investigated by immunohistochemical staining using human tissue panels. Caplacizumab was bound only to vWF-expressing cells, i.e., megakaryocytes and endothelial cells, and not to any other tissues.

Using vWF-immobilized beads, ^{125}I-labeled caplacizumab (0.1 μg/mL) was incubated with human whole blood, platelet-rich plasma, or platelet-poor plasma in the presence or absence of excess amount of unlabeled caplacizumab, and residual radioactivity was measured in a gamma counter. Results did not show interaction between caplacizumab and blood cells or platelets.

3.2.3 Effect on binding of collagen to vWF (CTD 4.2.1.1-3 and 4.2.1.2-2)

Mixture of purified human vWF (0.45 μg/mL) and caplacizumab (0-100 μg/mL) or a positive control C37H (single-chain monoclonal antibody targeted at A3 domain of human vWF) was added to plates coated with type I or III collagen. C37H inhibited the binding of vWF with type I and III collagen in a concentration-dependent manner, whereas caplacizumab did not affect the binding up to the maximum concentration tested.

A mixture of purified human vWF (1 μg/mL) and caplacizumab (0-10 μg/mL) or anti-vWF polyclonal antibody, the positive control, was added to plates coated with type VI collagen. Anti-vWF polyclonal antibody inhibited the binding of vWF with type VI collagen in a concentration-dependent manner, whereas caplacizumab did not affect the binding up to the maximum concentration tested.

3.2.4 Effect on FVIII binding to vWF (CTD 4.2.1.2-9)

Caplacizumab (10 nmol/L) or FVIII (5 nmol/L) alone, or caplacizumab (10 nmol/L) and FVIII (5 nmol/L) in combination, were added to a SPR sensor chip bound with human recombinant vWF, and FVIII binding to vWF was investigated by SPR. The amount of FVIII bound to vWF in combined addition of caplacizumab and FVIII was similar to the sum of the bound FVIII observed when each test substance was added alone.

3.2.5 Effect on bleeding risk (CTD 4.2.1.2-7)

Injury was made to the inguinal area of male baboons (n = 2-4/group) and, from after 60 minutes, caplacizumab (10, 30, 90, and 270[2)] μg/kg), clopidogrel (2.5, 2.5, 5, and 10 mg/kg) or abciximab (100, 250, and 500 μg/kg), positive control, or physiological saline was administered intravenously in escalating and cumulative doses 30 minutes apart. In another treatment group, caplacizumab (30 μg/kg) was bolus administered intravenously at 60 minutes after injury was made to the inguinal area, followed by continuous intravenous administration of caplacizumab for 5 hours at the speed of 45 μg/kg/h. In the study of escalating and cumulative administration, an injury was made to an arm before the administration of the test substance and at each time point after administration, the injured site was tapped with filter paper lightly 15 seconds apart up to 15 minutes at the maximum, and the time to hemostasis was assessed as the skin bleeding time. A gauze patch was inserted into the injury at the inguinal area, changed every 30 minutes, and weighed to assess the amount of bleeding. The skin bleeding time increased from the minimal concentration of each test substance group, compared with the bleeding time in the physiological saline group. The maximum bleeding volume was the highest in the abciximab group (9.7-fold increase from before the administration of test substance), similar between the caplacizumab group and the clopidogrel group (4.6-fold increase in the caplacizumab dose escalation group, 3.5-fold increase in the continuous caplacizumab dose group, 4.0-fold increase in the clopidogrel group), and the lowest in the physiological saline group (1.2-fold increase). In all test substance groups, platelet count, vWF:Ag level, FVIII:C, prothrombin time (PT), and activated partial thromboplastin time [aPTT] at 10 minutes (every 30 minutes in the continuous caplacizumab dose group) after administration of each test substance were not significantly different from the levels before administration of the test substance.

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2) Using the plasma samples in this study, it was confirmed that platelet aggregation was inhibited partially by ≥10 μg/kg of caplacizumab and completely by ≥30 μg/kg.

3.3 Safety pharmacology

Table 5 shows the results of safety pharmacology studies.

Table 5. Outline of the results of safety pharmacology studies

Organ system	Test system	Evaluation parameters and methods	Dose	Route of administration	Findings	CTD
Central nervous system/respiratory system/ cardiovascular systems	Cynomolgus monkeys (n = 3/sex/group)	Clinical observations including those of respiratory system, body temperature, blood pressure, heart rate, and ECG	0,[a] 0.009 (0.006/0.0015), 1.2 (0.6/0.2), 12 (6/2) mg/kg/day[b] Administered 6 times daily for 2 weeks	i.v.	No effect	4.2.3.2-2
	Cynomolgus monkeys (s.c.: n = 3/sex/group; i.v.: n = 1-3/sex/group)	Clinical observations including those of respiratory system, body temperature, blood pressure, heart rate, and ECG	s.c.: 0,[a] 0.12, 2.4, 12 mg/kg/day i.v.: 0,[a] 12 mg/kg/day Administered 6 times daily for 2 weeks	s.c., or i.v.	No effect	4.2.3.2-3
	Cynomolgus monkeys (n = 3/sex/group)	Clinical observations including those of respiratory system, body temperature, blood pressure, heart rate, and ECG	0,[a] 0.4, 4, 40 mg/kg/day Administered 4 times daily for 13 weeks	s.c.	No effect	4.2.3.2-4
	Cynomolgus monkeys (n = 4/sex/group)	Clinical observations including those of respiratory system, body temperature, blood pressure, heart rate, and ECG	0,[a] 0.4, 4, 40 mg/kg/day Administered 3 times daily for 26 weeks	s.c.	No effect	4.2.3.2-5

a [redacted] mol/L [redacted], [redacted]% Tween 80, pH [redacted] ± [redacted]
b Figures in the parentheses are loading dose/maintenance dose in each administration.
c The exposure ($AUC_{0\text{-}24h}$: 1388 μg·h/mL [male monkeys] and 832 μg·h/mL [female monkeys]) following a 26-week repeated administration of caplacizumab at the maximum dose studied (40 mg/kg/day) was 111 times (male monkeys) and 66.6 times (female monkeys) the median estimated exposure ($AUC_{ss,\tau}$: 12.473 μg·h/mL) following the once daily subcutaneous administration of caplacizumab 10 mg to humans.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action of caplacizumab

The applicant's explanation about the pharmacological action of caplacizumab:

ULvWF produced in vascular endothelial cells and secreted into circulating blood is usually cleaved by a specific cleavage enzyme ADAMTS13 and, as a result, GP1b-IX-V receptor binding site on A1 domain of vWF embedded within vWF molecule is exposed when immobilized in the body or caused by shear stress. vWF is thus converted to the activated form capable of binding platelets, leading to thrombus formation. In TTP, ULvWF is not cleaved because of reduced ADAMTS13 activity and remains in a constitutively activated state, resulting in adhesion to platelets and aggregation, leading to thrombus formation. Caplacizumab is a recombinant single-chain, bivalent monoclonal antibody consisting of 259 amino acid residues. It has been confirmed by X-ray crystallography that caplacizumab binds to vWF at a site (different from GP1b-IX-V receptor binding site) on A1 domain available even under inactive state of vWF, and thereby contributes to allosteric regulation (*Nat Commun*. 2021;21:12(1):2360, *Biochem Biophys Res Commun*. 2021;567:49-55).

In vitro studies showed that caplacizumab binds to vWF of not only humans but also baboons, cynomolgus monkeys, guinea pigs, etc., and suppressed vWF activity to a similar level and extent among animal species, as assessed by the target occupancy rate, the target neutralization rate, and RICO. In a study with human endothelial cells under a low shear stress condition (100-300 s^{-1}), caplacizumab inhibited platelet adhesion to ULvWF secreted from endothelial cells. In a study with plasma of healthy subjects and patients with acquired TTP, the higher the vWF:Ag level before caplacizumab administration, the higher the caplacizumab concentration necessary to inhibit vWF activity as assessed by RICO, and the relationship was similar to that observed between healthy subjects and patients with acquired TTP. In an *in vivo* study with a baboon model of acquired TTP, when caplacizumab (2.5 mg/day) was repeatedly administered intravenously after the onset of TTP, platelet count recovered to the level before TTP onset, vWF activity (RICO) was neutralized, vWF:Ag level decreased, and schizocyte count and haptoglobin levels recovered partially, demonstrating the treatment effect against thrombopenia, erythrocytoschisis, and hemolytic anemia. A prophylactic administration before the onset of TTP suppressed changes in these parameters related to the onset and progression of the pathology. At the start of this study with baboons, plasma vWF:Ag level was 30 to 40 nmol/L, which was similar to the mean concentration in humans (vWF:Ag level in the standard plasma of healthy subjects is 1 U/mL, which corresponds to 40 nmol/L in molar concentration). Also, the plasma concentration range of caplacizumab (0.152-0.287 μg/mL) in baboons at steady state following the administration at the specified dose was not significantly different from the plasma concentration ($C_{ss,\ min}$, 0.44 μg/mL; $C_{ss,\ max}$, 0.6 μg/mL) in humans at steady state in once daily administration of caplacizumab 10 mg. Caplacizumab did not affect spontaneous or histamine-stimulated vWF secretion from vascular endothelial cells or vWFpp level. These findings suggest that the decrease in the vWF:Ag level by caplacizumab was caused by increased clearance due to structural changes in vWF. Thus, caplacizumab exhibits its pharmacological action through mechanical inhibition of the binding of vWF to platelets and a transient decrease in the vWF:Ag level. In the 13- and 26-week repeated-dose toxicity studies in cynomolgus monkeys, several animals receiving caplacizumab continuously for a certain period showed recovery of the vWF:Ag level to some extent after the decrease at an early stage of administration but did not return to the baseline level during the continued administration period. Also, the extent of the observed recovery of the vWF:Ag level was only slight. The above results suggest the persistence of the efficacy of caplacizumab.

As for effects on the blood coagulation system other than vWF, *in vitro* studies confirmed that caplacizumab does not affect the binding of FVIII to vWF, the binding of ADAMTS13 to vWF, the binding of vWF to type I, III, and VI collagens, nor does it affect their functions.

These results suggest that caplacizumab specifically binds to vWF, thereby inhibiting ULvWF activity in patients with acquired TTP, leading to reduction of platelet consumption and recovery of decreased platelet count.

PMDA's view:
In vitro studies showed that caplacizumab selectively binds to A1 domain of vWF, binds to ULvWF which characterizes the pathology of acquired TTP even under low shear stress, and thereby decreases

the vWF:Ag level and vWF activity. *In vivo* studies with an animal model of acquired TTP showed that caplacizumab improves symptoms including recovery of platelet count, inhibited vWF activity to a biologically significant extent, and decreased the vWF:Ag level. These findings indicate that caplacizumab is expected to suppress platelet thrombosis and improve symptoms by inhibiting vWF activity in patients with acquired TTP.

3.R.2 Risks suspected from the mechanism of action of caplacizumab

PMDA asked the applicant to explain the possibility of caplacizumab causing clinically significant problems on various organs and tissues suspected from its mechanism of action, based on the biodistribution and physiological functions of vWF, findings obtained from *in vitro* and *in vivo* studies of caplacizumab, and findings related to von Willebrand disease.

The applicant's explanation:

vWF is produced in the form of ULvWF in endothelial cells, megakaryocytes, and subendothelial connective tissue, and excreted within blood vessels. Cross-reactivity studies on caplacizumab using guinea pig, cynomolgus monkey, and human tissues showed that, in all animal species studied, caplacizumab binds specifically to vascular endothelial cells and megakaryocytes in the bone marrow, the vWF-expressing cells, suggesting no off-target binding. Also, it is shown that caplacizumab does not interact with biological factors related to human blood cells or blood coagulation. When caplacizumab was repeatedly administered intravenously to a baboon model of acquired TTP, brain CT scan did not detect any sign of intracranial haemorrhage, and necropsy of other organs and histopathological examination did not reveal haemorrhage, even at the dose that caused recovery of platelet count to the baseline level, suggesting that there is little risk of spontaneous haemorrhage caused by caplacizumab. On the other hand, the 13- and 26-week repeated-dose toxicity studies using cynomolgus monkeys showed a decrease in the vWF:Ag level (20%-70% of the normal level) accompanied by a decreased FVIII:C level (10%-60% of the normal level) to an extent similar to vWF:Ag and FVIII:C levels observed in patients with type I and II von Willebrand disease (20%-50% of the normal level in both parameters) (*Blood*. 1992;79:2507-19). These results suggest the possibility that caplacizumab may have a bleeding risk as observed in patients with mild-type von Willebrand disease, hypermenorrhea and other mucocutaneous bleeding risk, increased perioperative bleeding risk, etc. (*Blood*. 2003;101:2089-93).

PMDA's view:

In safety pharmacology studies, no clinical findings were observed up to the maximum dose of caplacizumab of 40 mg/kg/day tested. Given the results of studies on the specificity of caplacizumab using tissue panels of various animal species, caplacizumab is unlikely to cause problems due to off-target effects. On the other hand, caplacizumab inhibits vWF activity, possibly causing an excessive decrease in the vWF:Ag level accompanied by an excessive decrease in the FVIII:C level, thereby affecting the normal hemostatic function. Bleeding risk should be investigated continuously [see Section "7.R.3.2 Bleeding risk"].

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

Plasma caplacizumab concentrations in guinea pigs, baboons, and monkeys were measured by ELISA. The lower limit of quantitation was 30 and 80 ng/mL, respectively, in guinea pigs and monkeys, and

could not be determined in baboons. Radioactivity of ^{125}I-labeled caplacizumab was measured by a gamma counter.

In the 26-week repeated-dose toxicity study in monkeys [see Section "4.1.2 Repeated-dose study"], anti-caplacizumab antibody (ADA) in plasma was measured by immunofluorescence assay. The detection limit was 66.1 ng/mL.

Pharmacokinetics (PK) parameter values are expressed in mean or mean ± standard deviation (SD), unless specified otherwise.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-5 and CTD 4.2.2.2-6)

Table 6 shows PK parameter values of caplacizumab following a single intravenous administration of caplacizumab to female guinea pigs.

Table 6. PK parameter values of caplacizumab following a single intravenous administration of caplacizumab to guinea pigs

Dose (mg/kg)	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V (mL/kg)
1	9.776 ± 1.043	0.083	17.41 ± 2.760	12.30 ± 2.359	58.39 ± 8.085	1032 ± 232.7
7	69.44 ± 5.080	0.083	50.40 ± 6.572	11.98 ± 4.537	140.7 ± 18.32	2357 ± 631.2
20	214.1 ± 32.74	0.083	142.5 ± 20.86	13.69 ± 4.532	142.4 ± 19.05	2823 ± 1036

n = 4 each
a Median value

Table 7 shows PK parameter values of caplacizumab following a single intravenous administration of caplacizumab to male baboons.

Table 7. PK parameter values of caplacizumab following a single intravenous administration of caplacizumab to baboons

Dose (μg/kg)	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
10[b]	0.12, 0.19	0.08	1.867, 2.18	7.96, 10.97	4.59, 5.36	52.7, 84.8
20	0.27 ± 0.02	0.08	4.066 ± 0.838	10.76 ± 2.06	5.07 ± 1.12	76.5 ± 2.7
40	0.68 ± 0.10	0.08	5.297 ± 1.221	8.09 ± 1.45	7.82 ± 1.74	88.8 ± 6.4
80	1.08 ± 0.18	0.08	5.837 ± 1.355	8.67 ± 0.42	14.16 ± 2.92	176.1 ± 31.1

n = 3 each
a, Median value; b, n = 2

4.1.2 Repeated-dose study (CTD 4.2.3.2-5)

Table 8 shows PK parameter values of caplacizumab in 26-week repeated subcutaneous administration of caplacizumab to male and female monkeys. ADA was observed in 1 of 8 animals in the caplacizumab 0.4 mg/kg/day group, in 1 of 8 animals in the 4 mg/kg/day group, and in 2 of 8 animals in the 40 mg/kg/day group. In 1 ADA-positive animal in the 0.4 mg/kg/day group, the plasma caplacizumab concentration was below the lower limit of quantitation, and this animal was excluded from toxicokinetics (TK) and toxicity assessment.

Table 8. PK parameter values of caplacizumab in 26-week subcutaneous administration of caplacizumab in monkeys

Dose[a] (mg/kg/day)	N	Measuring time point (Day)	C_{max} (μg/mL)	t_{max}[b] (h)	AUC_{0-24h} (μg·h/mL)
0.4	8	0	1.17 ± 0.339	8.00	19.4 ± 4.89
		91[c]	6.18 ± 5.27	12.0	125 ± 113
		181[c]	8.05 ± 4.79	6.00	168 ± 99.1
4	8	0	2.52 ± 0.675	14.0	42.5 ± 8.57
		91	21.1 ± 14.4	13.0	404 ± 296
		181	38.5 ± 47.4	10.0	602 ± 578
40	12	0	14.9 ± 3.16	14.0	235 ± 45.2
		91[d]	106 ± 175	14.0	1960 ± 3280
		181[d]	115 ± 216	10.0	1985 ± 3850

a, Two doses were administered 6 hours apart, followed by a single-dose administration after 12 hours
b, Median value; c, n = 7; d, n = 11

4.2 Distribution (CTD 4.2.2.3-1)

^{125}I-labeled caplacizumab (30 μg/kg) was administered intravenously in a single dose to male and female pigmented mice, and radioactivity concentration in each tissue was measured at 0.05, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5.5, 8, and 24 hours after administration (n = 3/time point). The percentage of radioactivity concentration (relative to the radioactivity administered) in blood, kidney, and liver was 80.4%, 13.6%, and 8.7%, respectively, at 0.05 hours after administration, 15.9%, 41.1%, and 2.8% at 0.25 hours after administration, 16.4%, 14.0%, and 2.8% at 0.5 hours after administration, and 15.7%, 4.8%, and 2.9% at 1 hour after administration. Little or no radioactivity was detected at 24 hours after administration (percentage of radioactivity concentration was 0.2%, 0.1%, and 0.1%, respectively).

A complex of ^{125}I-labeled caplacizumab (30 μg/kg) and vWF was administered intravenously in a single dose to male and female pigmented mice, and radioactivity concentration in each tissue was measured at 0.05, 0.5, 1, 3, 8, and 24 hours after administration (n = 3/time point). The percentage of radioactivity concentration in blood, kidney, and liver was 75.1%, 2.7%, and 8.2%, respectively, at 0.05 hours after administration, 63.2%, 3.1%, and 19.9% at 0.5 hours after administration, and 49.6%, 2.5%, and 24.9% at 1 hour after administration. Little or no radioactivity was detected at 24 hours after administration (percentage of radioactivity concentration, 0.4%, 0.2%, and 0.2%, respectively).

Little or no radioactivity was detected in any other organs tested, following the administration of caplacizumab either in free form or in complex with vWF.

The applicant's explanation about the distribution of caplacizumab:
In the single intravenous administration study in baboons [see "Section 4.1.1 Single dose studies"], there was no significant difference between V_z of caplacizumab in the low dose group and the plasma volume in baboons (38.6 mL/kg, *J Med Primatol.* 1985;14:345-56), which suggested that most of caplacizumab in plasma is bound to vWF, with the distribution of caplacizumab limited to plasma. On the other hand, V_z increased with an increase in the dose of caplacizumab and, in the high dose group, plasma caplacizumab concentration changed in a biphasic manner. The results suggest that when all available vWF molecules in plasma are saturated with caplacizumab, superfluous free caplacizumab molecules migrate to other tissues (mainly kidney) and are eliminated [see Section "4.3 Metabolism and excretion"]. Since caplacizumab is a high molecular weight (28 kDa) protein product without Fc region, it is unlikely to cross the placenta by simple diffusion or via Fc receptor. However, exposure to

caplacizumab in fetuses was qualitatively observed in a TK study using pregnant guinea pigs, suggesting the possibility that caplacizumab crosses the placenta. Caution will be included in the package insert that, in pregnant women or in women who may possibly be pregnant, caplacizumab should be used only if the expected therapeutic benefits are considered to outweigh the possible risks associated with treatment.

4.3 Metabolism and excretion

No study on metabolism and excretion of caplacizumab was conducted.

The applicant's explanation about the metabolism and excretion of caplacizumab:
Caplacizumab is considered to be degraded into peptides and then to amino acids by the catabolic reactions as are the cases with other proteins. Results of the tissue distribution study on caplacizumab suggest that free caplacizumab is mainly eliminated by catabolic reactions in the kidney and by excretion through glomerular filtration and that caplacizumab in complex with vWF is eliminated mainly by catabolism in the liver. This is corroborated by the observations that most of free caplacizumab was detected in urine in the repeated-dose toxicity studies and that the *in vivo* behavior of caplacizumab in complex with vWF in the tissue distribution study resembled the behavior of vWF reported (*J. Biol. Chem.* 2004;279:12102-9). Although the possibility is undeniable that caplacizumab, being a protein product, may be distributed in human milk, the extent of distribution in milk would be minimal. Also, bioavailability following oral administration will be low as are the cases with other protein products. Thus, breast-feeding is unlikely to cause any effect of caplacizumab on suckling babies. Nevertheless, risk to infants mediated by breast-feeding cannot be excluded completely. Caution will be included in the package insert to continue or discontinue breast-feeding with the consideration given to the merits of the treatment versus the merits of breast-feeding.

4.R Outline of the review conducted by PMDA

PMDA's view:
Placental transfer, metabolism, and excretion of caplacizumab were not investigated by non-clinical studies but are possible to estimate from the information already available. The non-clinical pharmacokinetics of caplacizumab has been evaluated appropriately in the submitted document and the applicant's explanation. The proposed precautions related to PK of caplacizumab included in the package insert provided by the applicant are generally appropriate. Information on the exposure to caplacizumab in fetuses in TK studies should be also provided.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of the following toxicology studies of caplacizumab: Single-dose toxicity studies, repeated-dose toxicity studies, reproductive and developmental toxicity studies, and local tolerance studies. Cynomolgus monkeys and guinea pigs were used because they are responsive to caplacizumab. The target affinity in cynomolgus monkeys is similar to that in humans, but approximately 10 times lower in guinea pigs [see Section "3.1.1.5 Cross-reactivity with vWF of various animal species"].

5.1 Single-dose toxicity

Acute toxicity of caplacizumab was investigated in guinea pigs and cynomolgus monkeys (Table 9).

Table 9. Summary of results of single-dose toxicity studies

Test system	Route of administration	Dose	Main findings	Approximate lethal dose	Attached document CTD
Male and female guinea pigs (Dunkin Hartley)	i.v.	0,[a] 2, 20 mg/kg	No noteworthy findings	>20 mg/kg	4.2.3.1-1
Male and female cynomolgus monkeys	i.v.	0,[a] 7.5, 74.7, 747 µg/kg	No noteworthy findings	>747 µg/kg	4.2.3.1-2
Male and female cynomolgus monkeys	i.v. or s.c.	0,[a] 0.02, 0.4, 8 mg/kg	i.v.: 8: Decreased FVIII:C level (female), decreased vWF:Ag level (female) s.c.: ≥0.4: Decreased FVIII:C level (male) 8: Decreased VIII: C level	>8 mg/kg	4.2.3.1-3

a [redacted] mol/L [redacted], [redacted]% Tween 80, pH [redacted] ± [redacted]

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in guinea pigs (13-week subcutaneous administration) and in cynomolgus monkeys (2-week intravenous administration, 2-week subcutaneous or intravenous administration, 13-week subcutaneous administration, 26-week subcutaneous administration) (Table 10). Most of the findings were haemorrhagic changes caused by the pharmacological action of caplacizumab and accompanying secondary changes, and were not toxicity findings according to the opinion of the applicant. The no observed adverse effect level (NOAEL) of caplacizumab (4 mg/kg/day) in the 26-week repeated-dose toxicity study in cynomolgus monkeys was 511 µg·hr/mL ($AUC_{0\text{-}24h}$ in male monkeys) and 176 µg·hr/mL ($AUC_{0\text{-}24h}$ in female monkeys), which was 41 times (male monkeys) and 14 times (female monkeys) the estimated median exposure ($AUC_{ss,\tau}$, 12.473 µg·h/mL) in once daily multiple subcutaneous administration of caplacizumab 10 mg in humans.

Table 10. Summary of results of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female guinea pigs (Dunkin Hartley)	s.c.	13 weeks + 8-week withdrawal	0,[a] 0.4, 4, 40[c]	≥0.4: Decreased FVIII:C level, decreased vWF:Ag level, bleeding in subcutaneous tissue at the injection site ≥4: Increased globulin level (female), decreased A/G ratio (female) 40: Increased globulin level, decreased A/G ratio, increased total protein Reversible (decreased FVIII:C level persisted)	40	4.2.3.2-1
Male and female cynomolgus monkeys	i.v.	2 weeks	0,[a] 0.009 (0.006/0.0015), 1.2 (0.6/0.2), 12 (6/2)[b, d]	≥0.009: Decreased FVIII:C level, decreased vWF:Ag level	12	4.2.3.2-2
Male and female cynomolgus monkeys	s.c. or i.v.	2 weeks	s.c.: 0,[a] 0.12, 2.4, 12[d] i.v.: 0,[a] 12[d]	s.c.: ≥0.12: Decreased FVIII:C level, decreased vWF:Ag level i.v.: 12: Decreased FVIII:C level, decreased vWF:Ag level	s.c.: 12 i.v.: 12	4.2.3.2-3
Male and female cynomolgus monkeys	s.c.	13 weeks + 8-week withdrawal	0,[a] 0.4, 4, 40[c]	≥0.4: Injection site hematoma/swelling, decreased FVIII:C level, decreased vWF:Ag level ≥4: Abnormal haemorrhage (female only in 40 mg/kg/day group), increased bilirubin in urine (female) 40: Increased bilirubin in urine Reversible	40	4.2.3.2-4
Male and female cynomolgus monkeys	s.c.	26 weeks + 13-week withdrawal	0,[a] 0.4,[e] 4, 40[f]	Death/moribund sacrifice: 0 (1 of 6 males[g]), 40 (1 of 6 males[h]) ≥0.4: Injection site induration/oedema, haemorrhage abnormal, decreased erythrocyte parameter level, aPTT prolonged, decreased FVIII:C level, decreased vWF:Ag level, haemorrhage accompanied by fibrin deposition/lymphocyte aggregation, development of secondary lymphoid follicles in axillary lymph nodes and spleen Reversible	4	4.2.3.2-5

a [redacted] mol/L [redacted] % Tween 80. pH [redacted] ± [redacted]
b Figures in the parentheses are loading dose/maintenance dose in each dose.
c 4-time daily administration, 6 hours apart
d 6-time daily administration, 4 hours apart
e One female in the caplacizumab 0.4 mg/kg/day group was excluded from TK and toxicity evaluation because ADA was positive and plasma caplacizumab concentration was below the lower limit of quantitation.
f Two doses were administered 6 hours apart, followed by a single-dose administration after 12 hours
g Detailed cause of death unknown
h Moribund sacrificed on Day 85 because of symptom aggravation due to haemorrhage caused by caplacizumab administration.

5.3 Genotoxicity

No genotoxicity studies were conducted on caplacizumab according to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6 [R1] Guidelines).

5.4 Carcinogenicity

No carcinogenicity studies were conducted on caplacizumab according to ICH S6 (R1) Guidelines.

Preneoplastic or neoplastic lesions or effects on immune system were not observed in the repeated-dose toxicity studies in cynomolgus monkeys (26-week subcutaneous administration) and guinea pigs (13-week subcutaneous administration) [see Section "5.2 Repeated-dose toxicity"] or in the embryofetal development study in guinea pigs [see Section "5.5 Reproductive and developmental toxicity"], and there were no findings suggestive of a relationship to carcinogenesis from the pharmacological mechanism of action. Also, caplacizumab is unlikely to be continued without careful consideration. On the basis of the above, the applicant determined that clinical use of caplacizumab does not pose any significant risk of carcinogenicity.

5.5 Reproductive and developmental toxicity

Embryofetal development studies were conducted in guinea pigs (Table 11).

The applicant's explanation about the reproductive and developmental toxicity of caplacizumab based on the results of the above studies and on the information obtained from other non-clinical and clinical studies:

In order to investigate the effect of caplacizumab on reproductive capacity, a 13-week repeated-dose toxicity study in cynomolgus monkeys was conducted. No changes related to caplacizumab administration were observed in the histopathological examination on male and female reproductive organs, testis size and sperm function in males, or estrous cycles in females.

As for effects on pre- and post-natal development, there were no findings suggestive of embryonal toxicity of caplacizumab up to the late pregnancy (Gestation Day 61), and no effect on embryofetal development is suggested in female patients with von Willebrand disease type I, a disease with decreased plasma vWF and FVIII levels (*J Thromb Haemost.* 2005;3:246-53). These findings indicated that caplacizumab poses little risk, if any, on prenatal embryonic development. Since caplacizumab is a high molecular weight (28 kDa) protein without Fc portion, it is unlikely to cross the placenta by simple diffusion or mediated by Fc receptor. Nevertheless, given the exposure, albeit at a low level, to caplacizumab observed in a TK study in pregnant guinea pigs, the possibility cannot be excluded that caplacizumab crosses the placenta [see Section 4.2 Distribution"]. Precautions will be included in the package insert that caplacizumab should be used to pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risk associated with treatment. Although the possibility of caplacizumab distribution in milk cannot be excluded, since caplacizumab is a protein product, it is unlikely to pose any significant risk when it is ingested orally by neonates via breast-feeding [see Section "4.3 Metabolism and excretion"]. Bleeding is identified as a risk of caplacizumab related to reproduction and development. Caution is required because perinatal bleeding might result in fatal outcome. In the embryofetal development study, the exposure ($AUC_{0\text{-last}}$) at the NOAEL (20 mg/kg/day) was 729.4 μg·hr/mL, which was 58.5 times the estimated median exposure ($AUC_{ss,\tau}$: 12.473 μg·h/mL) in once daily multiple subcutaneous administration of caplacizumab 10 mg in humans.

Table 11. Summary of results of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Embryofetal development study	Female guinea pigs (Dunkin Hartley)	i.m.	Gestation Day 6 to 41	0,[a] 0.05, 1, 20	No noteworthy findings either in maternal animals or in fetuses	Maternal animals, fetuses: 20	4.2.3.5.2-1
			Gestation Day 6 to 41, or Gestation Day 6 to 61	0,[a] 20, 40	No noteworthy findings either in maternal animals or in fetuses	Maternal animals, fetuses: 40	4.2.3.5.2-2

a, [redacted], [redacted] mol/L [redacted], [redacted]% Tween 80, pH [redacted] ± [redacted]

5.6 Local tolerance

Local tolerance was evaluated in rabbits following intravenous, intraarterial, perivenous, subcutaneous, and intramuscular administrations. No local irritation caused by caplacizumab was observed (Table 12). Local tolerance in repeated administration of caplacizumab was evaluated in guinea pigs (13-week subcutaneous administration) and in cynomolgus monkeys (13-week subcutaneous administration, 26-week subcutaneous administration) [see Section "5.2 Repeated-dose toxicity"]. Injection site edema, induration, erythema, swelling, hematoma, and haemorrhage were observed. The applicant determined that they are findings related to haemorrhage caused by the pharmacological action of caplacizumab and within the tolerable range in clinical use of caplacizumab.

Table 12. Summary of results of local tolerance study

Test system	Site of application	Study method	Main findings	Attached document CTD
Male rabbits (Himalayan)	Intravenous, intraarterial, perivenous, subcutaneous, intramuscular	Caplacizumab 2.35 mg A single-dose administration of 0.5 mL	No noteworthy findings	4.2.3.6-1

5.7 Other toxicity studies

5.7.1 Immunogenicity

The applicant's explanation:

Immunogenicity of caplacizumab was evaluated from the results of toxicity studies in cynomolgus monkeys and guinea pigs and from TK assessment. Although there were cases of positive ADA affecting the exposure to caplacizumab [see Section "4.1.2 Repeated-dose study,"] they were sporadic, suggesting that caplacizumab is poorly immunogenic.

5.R Outline of the review conducted by PMDA

On the basis of the submitted documents and the following reviews, PMDA concluded that problems related to clinical use of caplacizumab were not observed in non-clinical toxicity studies.

5.R.1 Anti-FVIII antibody production

PMDA asked the applicant to explain the mechanism of the occurrence of anti-FVIII antibody observed in repeated-dose toxicity studies in cynomolgus monkeys, and to discuss the possibility of occurrence of similar changes in clinical use of caplacizumab.

The applicant's explanation:
In the caplacizumab 40 mg/kg/day group of the 26-week repeated-dose toxicity study in cynomolgus monkeys, anti-FVIII antibody was detected in 1 male animal. The animal showed signs of anemia, bleeding tendency, and abnormalities in parameter values of haematology and clinical chemistry on Day 27, and was euthanized on Day 85. These findings were likely to be secondary effects of the pharmacological action of caplacizumab or related to anti-FVIII antibody. A retrospective study detected, in the repeated-dose toxicity study in cynomolgus monkeys, anti-FVIII antibody in 2 of 32 animals (13-week administration) and in 3 of 40 animals (26-week administration), but no related changes in clinical signs were observed except in 1 animal described above. The mechanism of the occurrence of anti-FVIII antibody is unclear, and it is uncertain whether it is directly related to caplacizumab administration. In some of the animals with anti-FVIII antibody, immune regulation by infection or antibiotics administration (*Med Sci Monit.* 2007;13:RA55-61, *Thromb Haemost.* 1993;69:403) and a transient increase in free FVIII due to the decreased vWF:Ag level caused by caplacizumab are suggested to be factors causing the occurrence of anti-FVIII antibody (*Haematologica*. 2015;100:149-56). However, anti-FVIII antibody occurs spontaneously in a certain percentage (approximately 17%) of healthy people (*Proceedings of the National Academy of Sciences of the United States of America.* 1992;89:3795-9). In addition, in the 26-week repeated-dose toxicity study in cynomolgus monkeys, the NOAEL of caplacizumab (4 mg/kg/day) was more than 10 times the exposure following once daily multiple subcutaneous administration of caplacizumab 10 mg in humans. It is therefore unlikely that anti-VIII antibody occurs due to caplacizumab administration in humans.

PMDA's view:
The mechanism of the occurrence of anti-FVIII antibody observed in toxicity studies is largely unknown. The possibility cannot be excluded that occurrence of anti-FVIII antibody observed in the repeated-dose toxicity studies in cynomolgus monkeys may occur in humans by caplacizumab administration. Bleeding risk suspectedly due to anti-FVIII antibody production should be investigated continuously [see Section "7.R.3.2 Bleeding risk"].

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

PK parameter values are expressed in mean or in mean ± SD, unless specified otherwise.

6.1 Summary of biopharmaceutic studies and associated analytical methods

The formulation of caplacizumab proposed for marketing is a lyophilized drug product, which was used in Studies ALX0681-C103, ALX0681-C301, ALX0681-C302/LTS16371, and ALX0681-C202.

Plasma caplacizumab concentration was determined by ELISA. The lower limit of quantitation was 100 ng/mL. Serum ADA was detected by ECL. ADA-positive samples were subjected to classification into pre-existing antibodies (pre-Ab) and treatment-emergent anti-caplacizumab antibody (TE-ADA).[3)]

[3)] After the detection of ADA in samples, TE-ADA unbound to the C-terminal domain of caplacizumab (pre-Ab-binding domain) was detected specifically (revised ADA assay method) in order to differentiate between the caplacizumab-binding antibody that had been present in subjects or was transferred from a donor plasma (pre-Ab) by plasma exchange (PE) and ADA produced in response to administration of the study drug (TE-ADA). TE-ADA that binds to the C-terminal domain of caplacizumab cannot be differentiated.

Presence or absence of neutralizing antibody (NAb) against caplacizumab in all ADA-positive samples was evaluated by measurements based on pharmacological action[4)] and on epitope analysis.

The platelet-aggregating activity of vWF in plasma samples was determined mainly by RICO assay, and the vWF:Ag level by immunonephelometry.

6.1.1 Bioequivalence study (Study ALX0681-C102, CTD 5.3.1.2-1 [Reference data], study period July to September 2014)

A 2-treatment, 2-period cross-over study was conducted to evaluate the biological equivalence between lyophilized caplacizumab formulation and caplacizumab liquid solution. A total of 24 non-Japanese healthy male subjects received a single dose of lyophilized caplacizumab formulation 10 mg or caplacizumab liquid solution 10 mg subcutaneously (a ≥14-day washout period).

Geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ following the administration of lyophilized caplacizumab formulation to those following the administration of caplacizumab liquid solution were 0.9722 [0.9381, 1.0075] and 1.0240 [0.9777, 1.0725], respectively.

6.2 Clinical pharmacology

6.2.1 Studies in healthy subjects

6.2.1.1 Phase I study in Japanese and non-Japanese healthy subjects (Study ALX0681-C103, CTD 5.3.3.3-1, study period June to October 2017)

Caplacizumab was administered to Japanese and non-Japanese healthy subjects intravenously or subcutaneously in a single dose. Table 13 shows the PK parameter values of caplacizumab observed. Tables 14 and 15 show changes over time in RICO and vWF:Ag level, respectively, following a single intravenous or subcutaneous administration of caplacizumab 10 mg. No TE-ADA-positive cases were observed.

Table 13. PK parameter values of caplacizumab following a single intravenous or subcutaneous administration of caplacizumab

Subjects	Dose (mg)	n	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL[b] (mL/h)	V_z[c] (mL)
i.v.								
Japanese	5	6	1240 ± 129.9	0.2500	14740 ± 4419	21.29 ± 4.866	310.3 ± 104.6	8952 ± 1060
	10	8	1986 ± 165.5	0.2500	17020 ± 3837	21.06 ± 5.433	569.8 ± 123.6	16630 ± 1986
Non-Japanese	10	8	1626 ± 587.6	0.2600	14510 ± 7594	19.23 ± 7.467	769 ± 343.1	18300 ± 2610
s.c.								
Japanese	10	8	749.8 ± 205.3	3.020	31850 ± 10380	36.88 ± 9.943	326.1 ± 137.9	16190 ± 5023
Non-Japanese	10	8	574.9 ± 122.7	3.040	26670 ± 10680	38.52 ± 22.23	386.3 ± 160.2	19150 ± 9585

a, Median value; b, CL/F in subcutaneous administration; c, V_z/F in subcutaneous administration

4) Mixture of purified human vWF, ristocetin, and caplacizumab was added to plates precoated with human platelets in the presence or absence of serum samples, and platelet-bound vWF was determined by ELISA. Since this test is affected by caplacizumab in samples that are derived from administration, serum samples were collected after washout of the drugs during the follow-up period, and IgG extraction and pre-treatment with protein G were performed in order to avoid interference.

Table 14. Changes over time in RICO and vWF:Ag level (following a single intravenous administration)

Measuring time point	RICO[a] (%)		vWF:Ag level (%)	
	Japanese (n = 8)	Non-Japanese (n = 8)	Japanese (n = 8)	Non-Japanese (n = 8)
Baseline	84.08 ± 17.67	84.50 ± 24.02	103.8 ± 30.86	88.64 ± 25.91
1 hour post dose	11.90 ± 0	15.14 ± 9.157	99.48 ± 20.01	69.16 ± 14.54
3 hours post dose	11.90 ± 0	11.90 ± 0	96.65 ± 18.44	66.08 ± 17.38
9 hours post dose	11.90 ± 0	11.90 ± 0	85.50 ± 12.07	51.21 ± 17.05
24 hours post dose	13.84 ± 1.712	17.45 ± 7.678	87.46 ± 14.03	58.66 ± 22.54
48 hours post dose	59.94 ± 6.799	52.96 ± 23.67	109.7 ± 17.18	82.63 ± 32.16
72 hours post dose	75.18 ± 8.668	84.70 ± 25.44	114.7 ± 22.23	95.25 ± 33.74
96 hours post dose	100.0 ± 15.38	91.31 ± 35.63	132.5 ± 20.45	93.75 ± 32.35
120 hours post dose	94.43 ± 21.69	85.33 ± 31.18	122.2 ± 25.83	91.58 ± 34.50

a The lower limit of quantitation was 11.90 (%).

Table 15. Changes over time in RICO and vWF:Ag level (following a single subcutaneous administration)

Measuring time point	RICO[a] (%)		vWF:Ag level (%)	
	Japanese (n = 8)	Non-Japanese (n = 8)	Japanese (n = 8)	Non-Japanese (n = 8)
Baseline	84.51 ± 23.54	91.48 ± 23.79	111.4 ± 33.02	102.0 ± 28.56
1 hour post dose	32.16 ± 22.55	38.11 ± 33.55	114.7 ± 35.56[b]	88.39 ± 30.67
3 hours post dose	11.90 ± 0	11.90 ± 0	98.43 ± 39.81	75.61 ± 33.18
9 hours post dose	11.90 ± 0	11.90 ± 0	88.86 ± 34.45	65.66 ± 20.53
24 hours post dose	11.90 ± 0	11.90 ± 0	61.51 ± 24.79	58.90 ± 17.43
48 hours post dose	19.68 ± 12.07	18.45 ± 9.414	84.29 ± 27.92	79.70 ± 15.72
72 hours post dose	63.49 ± 26.92	64.29 ± 11.26	109.8 ± 27.08	110.2 ± 21.76
96 hours post dose	91.98 ± 36.80	92.04 ± 23.42	131.9 ± 38.49	116.2 ± 36.66
120 hours post dose	98.80 ± 29.30	94.73 ± 20.70	119.2 ± 43.78	107.8 ± 35.86

a, The lower limit of quantitation was 11.90 (%); b, n = 7

Caplacizumab 10 mg was administered subcutaneously to Japanese healthy subjects once daily for 7 days. Table 16 shows the PK parameter values of caplacizumab observed. There were no TE-ADA-positive cases.

Table 16. PK parameters in multiple subcutaneous administration of caplacizumab

Dose (mg)	n	Measuring time point (Day)	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
10	9	1	679.2 ± 275.9	3.000	11360 ± 4273
	9	7	468.3 ± 150.8	3.000	8439 ± 1836

a Median value

6.2.2 Studies in patients

6.2.2.1 Japanese phase II/III study (Study ALX0681-C202, CTD 5.3.5.2-1, study period October 2019 to May 2021)

Caplacizumab was administered to Japanese patients with acquired TTP according to the dosage regimen described in Section "7.2.2 Japanese phase II/III study." Table 17 shows changes over time in plasma caplacizumab concentration, RICO, and vWF:Ag level (blood sampling time points not pre-specified).

Table 17. Changes over time in plasma caplacizumab concentration, RICO, and vWF:Ag level

Measuring time point	n	Plasma caplacizumab concentration (ng/mL)	RICO (%)	vWF:Ag level (%)
Baseline [a]	21	-	158 ± 67.8	220 ± 85.1
2 days post dose	21	653 ± 176	15.4 ± 13.1	149 ± 39.3
3 days post dose	21	661 ± 121	11.4 ± 0.33	104 ± 34.7
1 week post dose	19	630 ± 153	13.2 ± 7.86	109 ± 46.3[b]
2 weeks post dose	17	611 ± 126	11.4 ± 0.34	122 ± 43.2
3 weeks post dose	17	641 ± 167	11.3 ± 0.35	121 ± 44.6
4 weeks post dose	15	618 ± 220	29.2 ± 69.3	130 ± 39.4
5 weeks post dose	14	636 ± 168	11.4 ± 0.36	122 ± 41.0
6 weeks post dose	7	656 ± 170	11.2 ± 0.33	129 ± 43.7
7 weeks post dose	7	658 ± 178	11.2 ± 0.33	135 ± 47.8
8 weeks post dose	3	738 ± 274	11.3 ± 0.46	157 ± 83.6
9 weeks post dose	2	411, 762	11.0, 11.8	75.8, 210.4
10 weeks post dose	1	785	10.9	214
Day 7 of follow-up period	19	—	208 ± 75.4	296 ± 79.4
Day 28 of follow-up period	20	—	213 ± 79.3	267 ± 88.7

—, Not calculated
a, Before intravenous administration on Day 1; b, n = 18

Among patients receiving caplacizumab, 38.1% (8 of 21) of patients were positive for pre-Ab and 14.3% (3 of 21) of patients were positive for drug-induced TE-ADA. There were no treatment-emergent neutralizing antibody (TE-NAb)-positive cases by the measurement based on the pharmacological action,[4)] whereas 14.3% (3 of 21) of patients were positive for TE-NAb by the measurement based on epitope analysis.

6.2.2.2 Foreign phase III study (Study ALX0681-C301, CTD 5.3.5.1-2, study period November 2015 to August 2017)

Caplacizumab was administered to non-Japanese patients with acquired TTP according to the dosage regimen described in Section "7.2.1 Foreign phase III study." Table 18 shows changes over time in plasma caplacizumab concentration, RICO, and vWF:Ag level (blood sampling time points not pre-specified).

Table 18. Changes over time in plasma caplacizumab concentration, RICO, and vWF:Ag level (double-blind administration period)

Measuring time point	n	Plasma caplacizumab concentration (ng/mL)	n	RICO (%)	n	vWF:Ag level (%)
Baseline	—	—	66	123 ± 53.4	65	159 ± 52.4
2 days post dose	69	441 ± 147	69	13.5 ± 11.8	68	95.2 ± 40.4
3 days post dose	68	443 ± 139	68	11.6 ± 0.378	68	83.2 ± 34.8
1 week post dose	59	441 ± 136	61	11.6 ± 0.372	59	89.8 ± 30.8
2 weeks post dose	57	443 ± 162	56	11.6 ± 0.37	55	94.7 ± 37.7
3 weeks post dose	54	462 ± 182	53	11.7 ± 0.507	53	102 ± 40.7
4 weeks post dose	56	460 ± 184	55	14.5 ± 21.2	55	105 ± 53
5 weeks post dose	57	476 ± 176	54	11.9 ± 1.47	52	95.5 ± 40.5
6 weeks post dose	19	472 ± 187	19	11.6 ± 0.372	19	103 ± 35.7
7 weeks post dose	17	458 ± 210	18	11.6 ± 0.389	17	92 ± 25.9
8 weeks post dose	12	529 ± 374	14	11.5 ± 0.41	14	121 ± 84.4
9 weeks post dose	9	498 ± 362	9	11.8 ± 0.288	9	114 ± 76.8
Day 7 of follow-up period	—	—	58	136 ± 65.3	58	194 ± 90.7
Day 28 of follow-up period	—	—	56	136 ± 60.6	55	165 ± 70.7

—, Not calculated

Among patients receiving caplacizumab during the double-blind administration and the open-label administration period, 56.7% (55 of 97) of patients were positive for pre-Ab and 3.1% (3 of 97) of patients were positive for drug-induced TE-ADA. Among them, 2.1% (2 of 97) of patients were TE-NAb-positive by the measurement based on the pharmacological action,[4)] and 4.1% (4 of 97) of patients were TE-NAb-positive by the measurement based on epitope analysis.

6.2.3 PK-PD analysis (REP-1-ALX-antiVWF-PMX-1, CTD 5.3.4.2-1)

Using the PK data (plasma caplacizumab concentration at 3629 points) and pharmacodynamics (PD) data (vWF:Ag level at 6295 points) obtained from a total of 541 subjects in the foreign clinical studies in healthy subjects (Studies ALX-0081/0681-01/06, ALX-0081/0681-1.1/08, and ALX0681-C102), the foreign clinical studies in patients with percutaneous coronary intervention (PCI) (Studies ALX-0081/0681-1.2/08 and ALX-0081/0681-2.1/09), and the foreign clinical studies in patients with acquired TTP (Studies ALX-0681-2.1/10 and ALX0681-C301), PK-PD analysis (NONMEM version 7.3.0) was conducted to elucidate the relationship between the plasma caplacizumab concentration and vWF:Ag level in intravenous and subcutaneous administration. Main characteristics of subjects analyzed were as follows: Sex (317 males, 224 females), race (484 Caucasians, 36 blacks, other in 9 subjects, missing in 12 subjects), blood type (O in 89 subjects, A in 88 subjects, B in 31 subjects, AB in 4 subjects, missing in 329 subjects), anticoagulant co-administration (yes in 345 subjects, no in 196 subjects), immunosuppressant co-administration (yes in 225 subjects, no in 316 subjects), antibiotics co-administration (yes in 130 subjects, no in 411 subjects), ADA (positive in 193 subjects, negative in 337 subjects, missing in 11 subjects), pre-Ab (positive in 124 subjects, negative in 106 subjects, missing in 311 subjects), TE-ADA (positive in 6 subjects, negative in 224 subjects, missing in 311 subjects), age 52 [18, 85] (median [minimum, maximum], body weight 80.0 [46.5, 150] kg, CRCL 102 [11.9, 537] mL/min, and baseline vWF:Ag level 57.7 [9.00, 224] nmol/L.

Changes over time in plasma caplacizumab concentration were described by a linear 2-compartment model with two first-order absorption processes following the subcutaneous administration and the first-order elimination process of caplacizumab (free form). An allometric scaling was applied to the base model with the assumption that total CL, Q, V_C, and V_P are proportional to a power of body weight (allometry coefficient was fixed to 0.75 for CL and Q, and to 1 for V_C and V_P). The following parameters were handled as candidates of covariates: Sex, age, race (blacks vs. non-blacks), blood type (O vs. other), CRCL, body weight, use/non-use of concomitant drug (immunosuppressant), ADA, and TE-ADA. In the final model involving patients with acquired TTP, CRCL was identified as a significant covariant for CL. The base model also included the following consideration: Process of complex formation of caplacizumab with vWF (dimer or trimer); process of production, maturation, and release of vWF; and feedback effect enhancing vWF production and release.

The final model constructed included the following factors: Effect of disease progression of patients with acquired TTP on the baseline vWF level (free form); and effect of removal by plasma exchange (PE) of caplacizumab (free form), vWF (free form), and complex of caplacizumab and vWF (Figure 1). The population mean parameters of the final model were 5.47 L/h for CL, 6.33 L for V_C ($Drug_C$), 27.4 L for V_P ($Drug_P$) (fixed), 0.0639 for ka_1 (1/h, fixed), and 0.0125 for ka_2 (1/h, fixed). Relative variable error was 11.8% for CL and 6.81% for V_C ($Drug_C$).

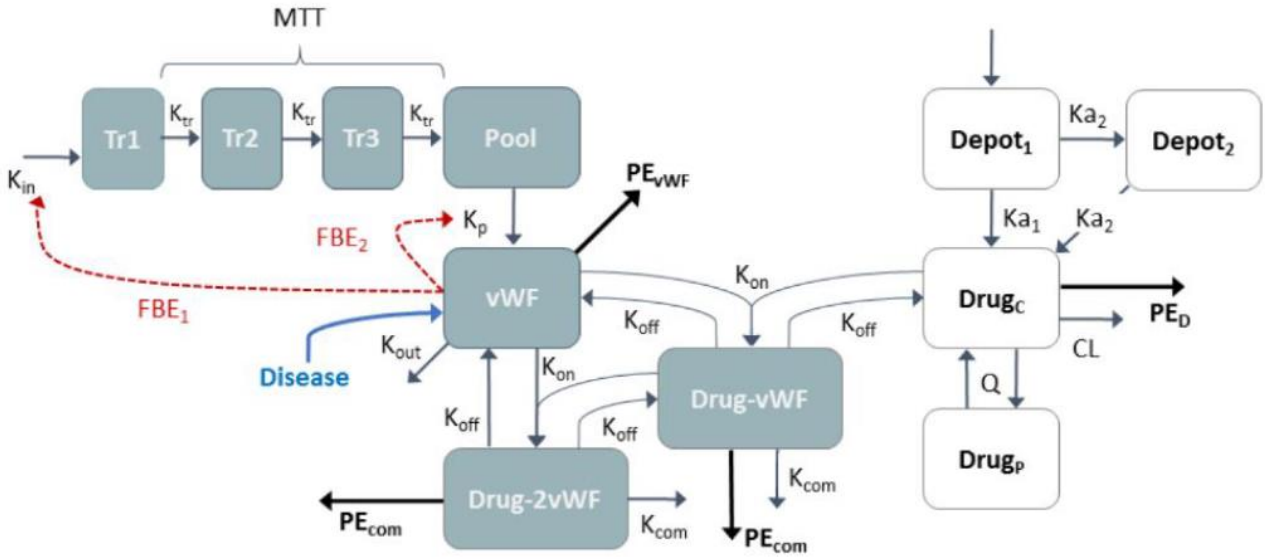

Figure 1. Outline of PK-PD model

$Depot_1$: Storage compartment following subcutaneous administration
$Depot_2$: Delayed absorption compartment
$Drug_C$: Central compartment of caplacizumab (free form)
$Drug_P$: Peripheral compartment of caplacizumab (free form)
Drug-vWF: Compartment of dimer
Drug-2VWF: Compartment of trimer
Tr1, Tr2, Tr3: Transfer compartments of vWF precursors
MTT: Mean transfer time
Pool: Pool compartment of vWF precursors
vWF: Compartment of vWF (free form)
Ka_1: First-order absorption rate following subcutaneous administration
Ka_2: Delayed first-order absorption rate following subcutaneous administration
CL: Total body clearance of caplacizumab (free form)
Q: Transfer clearance of caplacizumab (free form) between systemic compartment and peripheral compartment
PE_D: Elimination rate constant of caplacizumab by PE
K_{on}: Binding rate constant
K_{off}: Dissociation rate constant
K_{com}: Elimination rate constant of complex (dimer or trimer)
PE_{com}: Elimination rate constant of complex (dimer or trimer) by PE
K_{out}: Elimination rate constant of vWF (free form)
PE_{vWF}: Elimination rate constant of vWF (free form) by PE
K_{in}: Generation rate constant of vWF
K_{tr}: Transfer rate constant of vWF
K_p: Transfer rate constant of vWF from pool compartment
FBE_1: Feedback effect parameter (1)
FBE_2: Feedback effect parameter (2)
Disease: Effect of progression of acquired TTP on baseline vWF (free form) concentration

* Total caplacizumab concentration and total vWF concentration were calculated according to the following equations:
Total caplacizumab concentration = caplacizumab (free form) concentration/Vc (distribution volume of caplacizumab in $Drug_c$) + caplacizumab (dimer complex) concentration + caplacizumab (trimer complex) concentration
Total vWF concentration = vWF (free form) concentration + vWF (dimer complex) concentration + 2 × vWF (trimer complex) concentration

Using the final model, PK parameter values (median [5 percentile, 95 percentile]) at steady state (Day 40) were calculated after first intravenous administration of caplacizumab 10 mg to randomly generated patients with acquired TTP,[5)] followed by 40-day once daily multiple subcutaneous administration of

[5)] Random patients (n = 1000) were generated in such a way to show patient characteristics (body weight, height, CRCL, age, and sex) in median values and mean values similar to those in patients of Studies ALX-0681-2.1/10 and ALX0681-C301.

caplacizumab 10 mg without PE. $C_{ss,max}$ was 609.4 [355.1, 1079.0] ng/mL, $C_{ss,min}$ was 435.5 [230.2, 843.4] ng/mL, and $AUC_{ss,\tau}$ was 12473 [7033, 23051] ng·h/mL.

Table 19 shows PK parameter values of caplacizumab at steady state estimated from patient data in the final model and in Japanese and foreign clinical studies, stratified by renal function.

Table 19. Stratified analysis of estimated PK parameter values of caplacizumab at steady state

	CRCL (mL/min)	n	$C_{ss,max}$ (ng/mL)	$AUC_{ss,\tau}$ (ng·h/mL)
Japanese[a]	≥90	4	844.6 [765, 984.6]	15448 [13561, 18320]
	≥60 and <90	4	765.3 [744.5, 802.2]	14089 [13726, 14727]
	≥30 and <60	7	1020.5 [802.4, 1063.1]	17604 [15366, 19663]
	≥15 and <30	1	688.7	13642
	<15	3	697.5 [696.2, 944.4]	13454 [13309, 17966]
Non-Japanese[b]	≥90	66	614.9 [491.9, 711.9]	11406 [8409, 13487]
	≥60 and <90	25	658.7 [550.4, 887.1]	11722 [8971, 15161]
	≥30 and <60	7	648.4 [508.5, 677.1]	11986 [8679, 13224]
	≥15 and <30	2	1264 [942.9, 1584]	13797 [13213, 14381]
	<15	5	682.1 [572.4, 720.8]	12066 [11940, 15357]

Median [first quartile, third quartile]
a Data of Study ALX0681-C202 are used.
b Pooled data of Study ALX-0681-2.1/10 and Study ALX0681-C301 are used.

6.R Outline of the review conducted by PMDA

6.R.1 Difference in PK and PD between Japanese and non-Japanese subjects

The applicant's explanation about the difference in PK and PD of caplacizumab between Japanese and non-Japanese subjects:

In Study ALX0681-C103, the exposure (C_{max}, $AUC_{0-\infty}$) to caplacizumab was higher in Japanese healthy subjects than in non-Japanese healthy subjects (Table 13), due probably to the difference in body weight and the vWF:Ag level between the two populations. Comparison of plasma caplacizumab concentration in Study ALX0681-C202 (Table 17) and in Study ALX0681-C301 (Table 18) showed that, in patients with acquired TTP as in healthy subjects, the exposure was higher in Japanese subjects than in non-Japanese subjects. However, when pooled data of clinical studies in non-Japanese patients with acquired TTP (Studies ALX-0681-2.1/10 and ALX0681-C301) were used to stratify plasma caplacizumab concentration into quartiles, plasma caplacizumab concentration in the fourth quartile group (625.5 ± 87.3 ng/mL) was similar to the plasma caplacizumab concentration in Japanese patients with acquired TTP in Study ALX0681-C202 (Table 17).

As for PD, comparison of data in Study ALX0681-C202 (Table 17) and Study ALX0681-C301 (Table 18) showed that the vWF:Ag level and RICO following caplacizumab administration were similar between Japanese and non-Japanese patients with acquired TTP.

The above results suggest that the exposure to caplacizumab is higher in Japanese subjects than in non-Japanese subjects due to the difference in body weight and the vWF:Ag level. However, the difference in PK between Japanese and non-Japanese subjects will only minimally affect the clinical efficacy of caplacizumab, given the absence of any significant difference in PD of caplacizumab between these populations.

PMDA's view:

The submitted data show a higher exposure to caplacizumab in Japanese subjects than in non-Japanese subjects. No significant difference was observed in PD following the administration of the clinically recommended dose (10 mg), suggesting no clear correlation between PK and PD under exposure following caplacizumab 10 mg administration. In addition, there is no evidence suggesting the relationship between PD and clinical efficacy or safety of caplacizumab. The effect of the difference in the exposure to caplacizumab between Japanese and non-Japanese subjects and its significance should be investigated continuously, by taking into account the efficacy and safety results in clinical studies [see Section "7.R.5.1 Dosage regimen in adults"].

6.R.2 Rationale for the proposed dosage regimen

6.R.2.1 Rationale for the proposed dosage regimen in clinical studies in patients with acquired TTP

The applicant's explanation about the process of investigating the dosage regimen in clinical studies in adult patients with acquired TTP:

During the process of caplacizumab development, RIPA[6)] and RICO,[7)] parameters for vWF activity in blood (platelet-binding capacity of vWF), were used as indices for PD of caplacizumab. RIPA of "<10%" was used as the index for complete inhibition of vWF-mediated platelet aggregation, and RICO of "<20%" as the index corresponding to the above index.

The initial dose of caplacizumab was administered by intravenous route in order to promptly achieve the inhibitory effect against platelet aggregation. In the phase I study in non-Japanese healthy subjects (Study ALX-0681-1.1/06) and in the phase I study in non-Japanese patients with PCI (Study ALX-0081/0681-1.2/08), when a single dose of caplacizumab 2 to 12 mg was administered intravenously (drip infusion over 1 hour), RIPA could be suppressed to <10% from the end of administration at ≥2 mg and the effect tended to persist for a long time at approximately 8 to 12 mg. Accordingly, 10 mg was selected as the intravenous administration.

In the phase I study in non-Japanese healthy subjects (Study ALX-0681-1.1/08) in which caplacizumab 2, 4, 8, 10, or 16 mg was administered subcutaneously as a single dose, results suggested that RICO could be stably suppressed to <20% up to 24 hours after dosing by caplacizumab at ≥10 mg. When caplacizumab 10 mg was administered subcutaneously once daily for 7 or 14 days, the RICO level was maintained at <20% throughout the administration period, and returned close to baseline after treatment discontinuation. The scatter diagram of the plasma caplacizumab concentration and RICO level at each measuring time point in the above clinical study showed that the RICO level could be suppressed to <20% by caplacizumab over a wide range of 100 to 500 ng/mL, suggesting that the target level of RICO suppression (<20%) could be achieved even at a relatively low plasma caplacizumab concentration. Hence it was surmised that a sufficient RICO-suppressive effect could be obtained by daily

6) Ristocetin was added to platelet-rich plasma samples, and the rate of turbidity change was measured by an aggregometer to calculate maximum aggregation rate (%).

7) Lyophilized platelets were added to platelet-poor plasma samples, and change in the turbidity in the presence of ristocetin was measured by an aggregometer to calculate %RICO from the calibration curve. RIPA measurement requires fresh platelet-rich plasma samples, whereas frozen plasma and lyophilized platelets are used in RICO measurement. During the later stage of development, RICO was used from the practical point of view.

subcutaneous administration of caplacizumab 10 mg, even in patients with acquired TTP who are supposed to have a higher vWF level than healthy subjects.

On the basis of the above considerations, the foreign phase II study in patients with acquired TTP (Study ALX-0681-2.1/10) and the subsequent Japanese and foreign phase III studies (Studies ALX0681-C301 and ALX0681-C202) were conducted according to the following dosage regimen: A single dose of caplacizumab 10 mg was administered intravenously to achieve prompt inhibition of binding of platelets with vWF, followed by multiple subcutaneous administration of caplacizumab 10 mg after each PE in order to normalize platelet count while maintaining vWF binding inhibition during the period of daily PE. Also, in order to prevent relapse of TTP by maintaining vWF binding inhibition after the duration of daily PE, multiple doses of caplacizumab 10 mg were administered subcutaneously for a certain period. In both of Studies ALX0681-C301 and ALX0681-C202, the RICO level was maintained at <20% throughout the treatment period in most of the patients receiving caplacizumab (Tables 17 and 18), suggesting that the dosage regimen used in clinical studies was sufficient for complete inhibition of vWF-mediated platelet aggregation.

PMDA's view:
The clinical significance of using the threshold of the RICO level of "20%" as the index for the platelet aggregation-inhibitory effect of caplacizumab is unclear. However, given the rare occurrence of the target disease, it is difficult to explore the effective dose based on the clinical efficacy in patients with acquired TTP. It is reasonable to have determined the dosage regimen in order to promptly inhibit the binding of vWF to platelets and suppress platelet aggregation, and then to maintain the pharmacodynamic effect (RICO level <20%), the target of the maximal inhibition specified by the applicant, based on the results of phase I study in healthy subjects, etc. In the Japanese and foreign clinical studies in patients with acquired TTP, it was actually possible to maintain the RICO level below 20% (Tables 17 and 18). The dosage regimen used in clinical studies in patients with acquired TTP was appropriate for achieving suppression of platelet aggregation. However, because of the uncertainty between RICO- and platelet aggregation-suppressive effects of caplacizumab and clinical efficacy or safety, the appropriateness of the proposed dosage regimen of caplacizumab should be investigated continuously, also taking account of the efficacy and safety in clinical studies [see Section "7.R.5.1 Dosage regimen in adults"].

6.R.2.2 Rationale for the dosage regimen in children aged ≥12 years weighing ≥40 kg

The applicant's explanation about the process of investigating the dosage regimen in children aged ≥12 years weighing ≥40 kg:
The index of the therapeutic effect on acquired TTP is platelet count. However, in healthy subjects without reduction in platelet count due to spontaneous platelet aggregation by ULvWF, it is impossible to investigate the relationship between exposure and response using platelet count as the index. Because of the rarity of acquired TTP, only a limited number of patients were available for enrollment in a clinical study and, consequently, only a single dose level of caplacizumab could be investigated, precluding the investigation of the exposure-response relationship in patients with acquired TTP using platelet count as the index. In patients with acquired TTP, ULvWF spontaneously induces platelet aggregation, resulting in consumption of platelets and ULvWF by thrombus formation, which suggests that there is

theoretically a correlation between the free vWF:Ag level and platelet count. Taking account of this assumption and of the mechanism of action of caplacizumab, the PK-PD relationship was investigated using the vWF:Ag level. The appropriateness of the above method was confirmed by PK-PD model constructed using the clinical study data of healthy adults and adult patients with acquired TTP [see Section "6.2.3 PK-PD analysis"]. Because patients with acquired TTP aged <18 years were not enrolled either in Japanese or foreign clinical studies, neither PK and PD data nor information on efficacy or safety of caplacizumab is available in this patient population. However, given the following points, the exposure-response relationship of caplacizumab will be similar between elder children and adults. Accordingly, it was considered possible to determine the dosage regimen in elder children with acquired TTP based on the results of the simulation using the PK-PD model constructed from the data set obtained from adults [see Section "6.2.3 PK-PD analysis"].

- It was estimated from the exploration of covariates in the PK-PD model that body weight and the baseline vWF:Ag level affect the PK of caplacizumab. The vWF:Ag level does not significantly differ between healthy children (1-5 years, 6-10 years, 11-18 years) and adults (*J Pediatr Hematol Oncol*. 2007;29:19-22).
- The mechanism of the onset of acquired TTP, its pathophysiological characteristics, diagnosis, disease course, and index for disease progression are considered to be similar between children and adults.
- Results of the report of hemostatic parameters in different age populations among healthy subjects (populations of 1-5 years, 6-10 years, 11-18 years, >18 years) (*J Pediatr Hematol Oncol*. 2007;29:19-22) suggested that it is acceptable to assume that children aged ≥6 years have a mature coagulation system.

With the above assumptions, patients were divided into multiple age groups (2-3 years, 4-5 years, 6-7 years, 8-9 years, 10-11 years, 12-13 years, 14-15 years, 16-17 years, and ≥18 years; n = 1,000/group), each of which was further sorted by body weight depending on the corresponding to age. Mean parameter values (CL, Q, V_C, and V_P) in the population aged <18 years were estimated from those of adults obtained from PK-PD model analysis by allometric scaling. The random subpopulations thus generated were subjected to simulation of PK parameters of caplacizumab in once daily multiple subcutaneous administration of caplacizumab 10 mg. It was estimated that the population aged <12 years has a higher exposure than adults (Table 20).

Table 20. PK parameter values of caplacizumab at steady state in once daily multiple subcutaneous administration of caplacizumab 10 mg (estimate)

Age	$C_{ss,\ max}$ (ng/mL)	$C_{ss,\ min}$ (ng/mL)	$AUC_{ss,\ \tau}$ (ng·h/mL)
2-3	936.9 [673.1, 1431.3]	559.6 [371.6, 956.9]	17954 [12652, 28913]
4-5	856.5 [594.1, 1357.7]	530.2 [341.6, 925.3]	16590 [11300, 27232]
6-7	797.6 [530.3, 1324.8]	506.6 [316.4, 929.1]	15585 [10165, 26920]
8-9	739.6 [484.2, 1243.4]	483.6 [294.3, 896.3]	14649 [9359, 25610]
10-11	689.5 [436.2, 1190.4]	463.9 [268.9, 880.5]	13703 [8403, 24663]
12-13	648.2 [408.7, 1159.4]	443.8 [256.8, 871.1]	13099 [7919, 24025]
14-15	629.2 [398.3, 1139.0]	437.2 [250.3, 860.3]	12762 [7753, 24028]
16-17	622.5 [388.3, 1121.4]	434.1 [242.9, 861.1]	12723 [7555, 24113]
≥18	608.8 [371.8, 1123.7]	435.3 [242.1, 873.4]	12381 [7295, 23794]

Median [5 percentile, 95 percentile]

Next, using the similar populations as above, PK parameters of caplacizumab were simulated in once daily multiple subcutaneous administration of caplacizumab 5 mg in subjects aged <18 years weighing <40 kg or in once daily multiple subcutaneous administration of caplacizumab 10 mg in subjects aged <18 years weighing ≥40 kg and subjects aged ≥18 years. Results suggested that the exposure in all pediatric populations was similar to that in the adult population (Table 21).

Table 21. PK parameter values of caplacizumab at steady state in once daily multiple subcutaneous administration of caplacizumab at a body weight-adjusted dose (estimate)

	Dose (mg)	$C_{ss, max}$ (ng/mL)	$C_{ss, min}$ (ng/mL)	$AUC_{ss, \tau}$ (ng·h/mL)
<18 years weighing <40 kg	5	600.0 [379.6, 1005.9]	376.0 [230.6, 661.9]	11820 [7438, 20507]
<18 years weighing ≥40 kg	10	640.0 [398.7, 1050.2]	442.0 [249.3, 872.4]	12970 [7745, 24126]
≥18 years	10	609.0 [371.8, 1123.6]	435.0 [242.1, 873.4]	12381 [7295, 23794]

Median [5 percentile, 95 percentile]

In addition to the above results of the simulation (Tables 20 and 21), the developmental state (organ maturation, functions of organ systems and enzymes) affecting PK of drugs is considered not to differ between children aged ≥12 years and adults. Therefore, the same dosage regimen for adults used in clinical studies may be applicable to children aged ≥12 years weighing ≥40 kg with acquired TTP. In children aged ≥12 years weighing <40 kg with acquired TTP, it is estimated that caplacizumab 5 mg is sufficient to achieve the same exposure as observed in adults. However, in the present application, patients aged ≥12 years weighing <40 kg with acquired TTP were not included in the patients eligible for treatment with this dose, for the following reasons: (a) Currently, formulation allowing administration of exactly 5 mg of caplacizumab has not been developed; (b) appropriateness of administering a half of the proposed dose (5 mg) has not been investigated due to the pharmaceutical characteristics of the caplacizumab drug product, and (c) some pediatric patients may have body weight far below 40 kg. Interaction of age with parameters other than body weight is unlikely to affect the exposure to caplacizumab. Results of the above simulation (Table 21) suggest that it would be more appropriate to administer 5 mg even to adults if body weight is less than 40 kg. However, since it is supposed that there are not many patients weighing far below 40 kg, it is considered acceptable to administer 10 mg in adults regardless of body weight.

PMDA's view:

Given that caplacizumab has never been administered to <18-year-old healthy subjects or patients with acquired TTP in clinical studies, and that even PK or PD data have not been obtained from these populations, there are limitations to assessing the appropriateness of estimating the exposure and response to caplacizumab in patients aged <18 years with acquired TTP based on the PK-PD model constructed from the data set obtained from adults. Nevertheless, it may be possible to estimate the exposure to caplacizumab in patients aged <18 years with acquired TTP using the above PK-PD model, given the following:

- In adults, body weight and the vWF:Ag level are parameters that mainly affect PK of caplacizumab. The vWF:Ag level in children is reported to be similar in adults. The effect of body weight on PK of caplacizumab was taken into consideration in the construction of the above PK-PD model to which allometric scaling was applied.
- Given the applicant's explanation that the disease course and extent of progression of acquired TTP in children are similar to those in adults, the difference in the vWF:Ag level between heathy subjects

and patients with acquired TTP affects the PK of caplacizumab to a similar extent in children and adults.

Also, the relationship between exposure and response to caplacizumab is unlikely to differ significantly between children with a mature coagulation system and adults, taking account of the applicant's explanation that the mechanism of the onset of acquired TTP, pathophysiological characteristics, diagnosis, disease course, and index for disease progression are similar between children and adults [see Section "7.R.5.5 Administration in children aged ≥12 years weighing ≥40 kg"]; and children aged ≥6 years may be regarded as having a mature coagulation system.

Results of the simulation using the PK-PD model under the above assumptions suggested that, in once daily multiple subcutaneous administration of caplacizumab 10 mg, the exposure at steady state in the population of patients with acquired TTP aged <18 years weighing ≥40 kg is similar to that in adult patients with acquired TTP. In addition, the applicant asserts that the developmental state affecting the PK of patients aged ≥12 years is not different from that in adults. Taking account of the above assertions, PMDA concluded that caplacizumab given at the same dosage regimen as that proposed for adult patients provides similar extent of efficacy and safety in patients with acquired TTP aged ≥12 years weighing ≥40 kg as those observed in adult patients. Necessity of developing a formulation for patients with acquired TTP weighing <40 kg, including the development of the formulation for these patients, should be further investigated. Whether patients with acquired TTP aged ≥12 years weighing ≥40 kg should be included in the target population will be discussed further in Section "7.R.5.5 Administration in children aged ≥12 years weighing ≥40 kg."

6.R.3 Effect of decreased hepatic and renal functions on PK and PD of caplacizumab

No clinical pharmacology study of caplacizumab was conducted in patients with hepatic or renal impairment.

The applicant's explanation about the effect of hepatic and renal impairment on PK and PD (vWF:Ag level) of caplacizumab:
Results of non-clinical studies suggest that free caplacizumab undergoes catabolism mainly in the kidney and is excreted by glomerular filtration, and caplacizumab in complex with vWF is catabolized mainly in the liver and eliminated.

The vWF:Ag level increases with the severity of hepatic cirrhosis (*Hepatology*. 2006;44:53-61), which suggested the possibility that increase in vWF:Ag by decreased hepatic function may affect the PK of caplacizumab. However, analysis by the constructed PK-PD model [see Section "6.2.3 PK-PD analysis"] showed that changes over time in estimated PK parameter values at steady state (Table 22), vWF:Ag level, and RICO did not differ significantly between subpopulations when data were stratified by any of baseline hepatic function markers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) in each clinical study (Studies ALX-0681-2.1/10, ALX0681-C301, ALX0681-C202). These results suggest that increase in vWF:Ag by decreased hepatic function does not significantly affect PK and reactivity of caplacizumab, although it is necessary to keep in mind that there

are limitations to using the baseline values of hepatic markers as surrogate indices for the severity of hepatic impairment.

Table 22. Stratified analysis of PK parameter values (estimates) of caplacizumab at steady state

Clinical study	Hepatic function marker	Criterion	n	$C_{ss,\,max}$ (ng/mL)	$AUC_{ss,\,\tau}$ (ng·h/mL)
ALX-0681-2.1/10	ALT/AST	>3 times the ULN	1	899.36	16881.27
		≤3 times the ULN	33	618.54 [531.25, 706.89][a]	11512.47 [9156.40, 13497.97]
	Bilirubin	>1.5 times the ULN	21	570.99 [476.09, 832.77][b]	10743.45 [8515.10, 14277.68]
		≤1.5 times the ULN	13	657.39 [557.56, 687.77][c]	12341.45 [11721.61, 13497.97]
ALX0681-C301	ALT/AST	>3 times the ULN	8	738.12 [630.95, 1503.60]	14535.35 [12307.22, 15115.70]
		≤3 times the ULN	57	633.80 [490.01, 766.45][d]	11662.06 [8954.56, 13660.21]
	Bilirubin	>1.5 times the ULN	23	586.95 [511.01, 688.51][e]	11539.56 [9263.86, 12984.89]
		≤1.5 times the ULN	42	685.42 [504.87, 844.45][f]	12078.91 [9420.55, 14965.48]
ALX0681-C202	ALT/AST	>3 times the ULN	2	697.49, 779.67	13454.20, 13529.88
		≤3 times the ULN	17	824.80 [754.44, 1022.59]	15819.80 [13833.68, 19120.00]
	Bilirubin	>1.5 times the ULN	9	824.80 [697.49, 1103.67]	15819.80 [13642.43, 20206.94]
		≤1.5 times the ULN	10	777.92 [754.44, 1020.48]	14628.59 [13571.10, 17604.10]

Median [first quartile, third quartile]
a, n = 24; b, n = 14; c, n = 11; d, n = 52; e, n = 22; f, n = 3

In the analysis using the above PK-PD model, CRCL was identified as a covariate that significantly affects CL of caplacizumab. However, this analysis showed that the estimated PK parameter values of caplacizumab (Table 19) and changes over time in vWF:Ag level are similar among subpopulations classified by renal function, suggesting that decrease in renal function does not significantly affect PK and PD (vWF:Ag level) of caplacizumab.

Therefore, the applicant considers that it is unnecessary to raise caution in caplacizumab administration to patients with hepatic or renal impairment from the aspect of PK and PD.

PMDA's view:
Results of non-clinical studies show that PK characteristics differ between free caplacizumab and caplacizumab in complex with vWF [see Section "4.3 Metabolism and excretion"], suggesting the possibility that variations in blood vWF concentration may affect PK of caplacizumab. Findings on the relationship between the severity of hepatic cirrhosis and the vWF:Ag level (*Hepatology.* 2006;44:53-61), although not investigated in patients with acquired TTP, suggest that PK of caplacizumab in patients with acquired TTP with hepatic impairment is different from that in patients with acquired TTP without hepatic impairment because of an increase in the blood vWF level due to impaired hepatic function. On the other hand, results of PK-PD model analysis presented by the applicant do not suggest the effect of reduced hepatic and renal functions on the PK and PD of caplacizumab, although there are limitations to assessing the severity of hepatic impairment using hepatic function markers as surrogate indices. Thus, currently the applicant's proposal that "no precautions from the aspect of PK and PD are necessary for

patients with hepatic or renal impairment" is acceptable. PMDA will draw a final conclusion, taking account of comments raised in the Expert Discussion.

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

The applicant submitted efficacy and safety evaluation data, mainly from 5 clinical studies shown in Table 23 [for PK, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

Table 23. Outline of main clinical studies on efficacy and safety

Category	Region	Study identifier	Phase	Study population	No. of subjects	Outline of dosage regimen	Main endpoints
Evaluation	Foreign	ALX0681-C103	I	Healthy subjects	60 [a]	• Part I: ➢ Cohort 1/group 1: Placebo or caplacizumab 5 mg was administered intravenously as a single dose. ➢ Cohort 2/group 2: Placebo or caplacizumab 10 mg was administered intravenously as a single dose. ➢ Cohort 2/group 3: Placebo or caplacizumab 10 mg was administered subcutaneously as a single dose. • Part 2: ➢ Cohort 3/group 4: Placebo or caplacizumab 10 mg was administered subcutaneously once daily for 7 days.	Safety Tolerability PK, PD
	Foreign	ALX0681-C301	III	Patients with acquired TTP	145[a]	• Daily PE period: On Day 1, placebo or caplacizumab 10 mg was administered bolus intravenously before PE, followed by subcutaneous administration of placebo or caplacizumab 10 mg after the end of PE. From Day 2, placebo or caplacizumab 10 mg was administered subcutaneously once daily after the end of PE. • Post-daily PE period (30 days from the end of daily PE period): Placebo or caplacizumab 10 mg was administered subcutaneously once daily. • Extended treatment period (≤4 weeks from the end of post-daily PE period): Placebo or caplacizumab 10 mg was administered subcutaneously once daily.	Efficacy Safety
	Japan	ALX0681-C202	II/III	Patients with acquired TTP	21[b]	• Daily PE period: On Day 1, caplacizumab 10 mg was administered bolus intravenously before PE, followed by subcutaneous administration of caplacizumab 10 mg after the end of PE. From Day 2, caplacizumab 10 mg was administered subcutaneously once daily after the end of PE. • Post-daily PE period (30 days from the end of daily PE period): Caplacizumab 10 mg was administered subcutaneously once daily. • Extended treatment period (≤8 weeks from the end of post-daily PE period): Caplacizumab 10 mg was administered subcutaneously once daily.	Efficacy Safety
Reference	Foreign	ALX-0681-2.1/10	II	Patients with acquired TTP	75[a]	• PE period: On Day 1, placebo or caplacizumab 10 mg was administered bolus intravenously before PE, followed by subcutaneous administration of placebo or caplacizumab 10 mg after the end of PE. From Day 2, placebo or caplacizumab 10 mg was administered subcutaneously once daily. • Post-PE period (30 days from the end of daily PE period): Placebo or caplacizumab 10 mg was administered subcutaneously once daily.	Efficacy Safety
	Foreign	ALX0681-C302/ LTS16371	III	Patients with acquired TTP	104[b]	• Daily PE period: On Day 1, caplacizumab 10 mg was administered bolus intravenously before PE, followed by subcutaneous administration of caplacizumab 10 mg after the end of PE. From Day 2, caplacizumab 10 mg was administered subcutaneously once daily after the end of PE. • Post-daily PE period (30 days from the end of daily PE): Caplacizumab 10 mg was administered subcutaneously once daily. • Extended treatment period (≤4 weeks from the end of post-daily PE period): Caplacizumab 10 mg was administered subcutaneously once daily.	Safety Efficacy

a Number of subjects randomized
b Number of subjects enrolled

7.1 Phase I studies

7.1.1 Phase I study in Japanese and non-Japanese healthy subjects (Study ALX0681-C103, CTD 5.3.3.3-1, study period June to October 2017)

A placebo-controlled, randomized, double-blind study was conducted in Japanese and non-Japanese healthy subjects to investigate the safety, tolerability, PK, and PD of caplacizumab administered in a single dose or in multiple doses (target sample size, 60 subjects [48 in part 1 (including 28 Japanese), 12 in part 2 (Japanese only)]) at a single study site in the US.

In part 1, the study drug was administered by any of the following methods: Placebo or caplacizumab 5 mg was administered intravenously in a single dose (cohort 1/group 1); placebo or caplacizumab 10 mg was administered intravenously in a single dose (cohort 2/group 2); or placebo or caplacizumab 10 mg was administered subcutaneously in a single dose (cohort 2/group 3). In part 2, placebo or caplacizumab 10 mg was administered subcutaneously once daily for 7 days (cohort 3/group 4).

All of 60 subjects assigned to treatment groups (see Table 24 for breakdown) received the study drug and were included in the safety analysis population. One Japanese subject in the caplacizumab 10 mg group of cohort 3/group 4 was lost to follow-up, and the study in this subject was discontinued.

Table 24. Breakdown of assigned subjects

	Part 1						Part 2	
	Single intravenous administration				Single subcutaneous administration		Multiple subcutaneous administration	
	Cohort 1		Cohort 2				Cohort 3	
	Group 1		Group 2		Group 3		Group 4	
	Placebo	Caplacizumab 5 mg	Placebo	Caplacizumab 10 mg	Placebo	Caplacizumab 10 mg	Placebo	Caplacizumab 10 mg
Japanese	2	6	2	8	2	8	3	9
Caucasians	0	0	2	8	2	8	0	0

Number of subjects

Table 25 shows the incidences of all adverse events and adverse events observed in ≥2 subjects in any group.

Table 25. Incidences of all adverse events and adverse events observed in ≥2 subjects in any group (Study ALX0681-C103, safety analysis population)

	Part 1							Part 2	
	Single intravenous administration			Single subcutaneous administration		Placebo (combination of single subcutaneous administration and single intravenous administration		multiple subcutaneous administration	
	Caplacizumab 5 mg	Caplacizumab 10 mg		Caplacizumab 10 mg				Caplacizumab 10 mg	Placebo
	Japanese (n = 6)	Japanese (n = 8)	Caucasians (n = 8)	Japanese (n = 8)	Caucasians (n = 8)	Japanese (n = 6)	Caucasians (n = 4)	Japanese (n = 9)	Japanese (n = 3)
All adverse events	33.3 (2)	12.5 (1)	62.5 (5)	0 (0)	25.0 (2)	16.7 (1)	25.0 (1)	44.4 (4)	0 (0)
Nausea	16.7 (1)	0 (0)	12.5 (1)	0 (0)	0 (0)	0 (0)	25.0 (1)	22.2 (2)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	22.2 (2)	0 (0)
Dizziness	0 (0)	0 (0)	25.0 (2)	0 (0)	0 (0)	16.7 (1)	0 (0)	11.1 (1)	0 (0)
Epistaxis	0 (0)	0 (0)	25.0 (2)	0 (0)	0 (0)	0 (0)	0 (0)	11.1 (1)	0 (0)
Ecchymosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	22.2 (2)	0 (0)

Incidence % (number of subjects with events)

No adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation were observed.

7.2 Phase III studies

7.2.1 Foreign phase III study (Study ALX0681-C301, CTD 5.3.5.1-2, study period November 2015 to August 2017)

A placebo-controlled, randomized, double-blind, parallel group study was conducted in non-Japanese patients with acquired TTP to investigate the efficacy and safety of caplacizumab (target sample size, approximately 132 subjects[8)]) at 55 study sites.

The main inclusion criteria were patients with acquired TTP[9)] aged ≥18 years[10)] who required starting daily PE therapy and had received PE once before randomization.[11)] Patients who fell under any of the following criteria were excluded from the study: Platelet count ≥100 × 10^9/L; platelet count >30 × 10^9/L and serum creatinine >200 μmol/L, suggesting atypical hemolytic uremic syndrome (aHUS); patients with congenital TTP; patients known cause for thrombocytopenia[12)]; patients with clinically serious active haemorrhage or with a high risk of haemorrhage; and patients who could not discontinue (interrupt) chronic treatment with an anticoagulant drug (vitamin K antagonist [VKA], heparin, or low-molecular weight heparin) and non-steroidal anti-inflammatory drugs (NSAIDs) other than acetylsalicylic acid for safety reason.

The study consisted of a daily PE period, a post-daily PE period (30 days from the end of daily PE), an extended treatment period (≤4 weeks after the end of the post-daily PE period), and a follow-up period (4 weeks after the end of the study drug administration).

PE and immunosuppressive therapy were performed as the standard therapies. PE was performed once daily at 1 to 1.5 times the estimated plasma volume, and continued for ≥2 days after platelet count increased to ≥150 × 10^9/L for the first time. Corticosteroid (methylprednisolone, prednisolone, etc., was administered intravenously at ≥1 mg/kg/day or orally according to the approved dosage regimen) was administered throughout the daily PE period and for 1 week after the end of the daily PE period, and could be tapered off during the post-daily PE period at the discretion of the investigator for the discontinuation of administration. At 2 weeks after the start of the post-daily PE period, tapering-off of corticosteroid was to be re-evaluated,[13)] based on the ADAMTS13 activity level and clinical findings of TTP at the past 2 clinical visits. Also, use of immunosuppressants such as rituximab (genetical

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8) Taking account of the median period to normalization of platelet count in subjects who received PE once before the first dose of caplacizumab in the foreign phase II study (Study ALX-0681-2.1/10) (4.31 days in the placebo group, 2.44 days in the caplacizumab group), the published report (*Journal of Clinical Apheresis*. 1998;13:133-41), and opinions of medical experts, etc., the median time to platelet count normalization was estimated to be 7 days in the placebo group and 4.2 days in the caplacizumab group (40% reduction). By assuming the drop-out rate within 10 days after the first dose of the study drug to be 10%, the number of subjects required to detect a significant reduction in the period to platelet count normalization at a two-sided significance level of 5% and statistical power of 80% was determined to be 132 (assumed event number, 121).

9) Includes thrombocytopenia and microscopic findings of erythrocyte fragmentation (e.g., schizocytes).

10) The clinical study protocol was revised (revised version 3.0, [July 20, 2016], pediatric version 1.0 [August 31, 2016]) to allow enrollment of pediatric patients aged ≥2 and <18 years at some study sites. During the daily PE period and the post-daily PE period, open-label caplacizumab was administered (a) at 3 mg to children weighing <25 kg, (b) at 5 mg in children weighing ≥25 and <50 kg, and (c) at 10 mg in children weighing ≥50 kg. The dosage regimen was the same as in adults except for dose adjustment for body weight.

11) Time from PE before randomization to the start of PE after randomization (the first PE during the treatment period) should be 24 hours at the maximum.

12) Patients with other causes for thrombocytopenia including but not limited to (a) to (e) below were excluded:
(a) Clinical findings of enteric infection caused by *E. coli* O-157 or other related microorganisms, (b) aHUS, (c) thrombotic microangiopathy associated with hematopoietic stem cell transplantation or organ transplantation, (d) sepsis, and (e) disseminated intravascular coagulation (DIC).

13) Optimization of immunosuppressive therapy (gradual increase in the tapered dose of corticosteroid, gradual dose increase or resumption of corticosteroid, or the start or continuation of other immunosuppressants such as rituximab) was to be considered.

recombination) (rituximab) was permitted at the discretion of the investigator throughout the study period.

Table 26 shows dosage regimens. The study drug was administered throughout the daily PE period and the post-daily PE period (30 days after the end of daily PE). Whether the study drug should be administered in the extended treatment period was decided by the investigator every week based on the risk factors of TTP relapse (ADAMTS13 activity [measured once weekly], signs and symptoms showing persisting TTP). The study drug could be continued for a maximum of 4 weeks from the end of the post-daily PE period. The study drug administration was to be discontinued when ADAMTS13 activity of >10% lasted or when TTP findings showed signs of improvement. In subjects who showed relapse[14] of TTP during the study drug administration period, caplacizumab could be administered regardless of the initial assignment without disclosure of the assignment. In the following, the period of study drug administration under double-blind conditions was described as the "double-blind administration period,"[15] and the period of study drug administration under open-label conditions as the "open-label administration period."

Table 26. Dosage regimen in Study ALX0681-C301

Period	Dosage regimen	Measures to be taken against TTP relapse[c]
Daily PE period[a]	• Day 1: Placebo or caplacizumab 10 mg was bolus administered intravenously during the period from 6 hours to 15 minutes before the first PE after randomization, followed by subcutaneous administration of placebo or caplacizumab 10 mg within 2 hours after the end of PE. • From Day 2: Placebo or caplacizumab 10 mg was administered subcutaneously once daily within 2 hours after the end of PE.	—
Post-daily PE period (30 days after the end of daily PE)[b]	Placebo or caplacizumab 10 mg was administered subcutaneously once daily.	• Fist relapse: Daily PE and immunosuppressant therapy were resumed, and open-label caplacizumab was administered according to the same schedule as that in the first study drug administration period. • Second and further relapses: Caplacizumab administration was discontinued, and daily PE and immunosuppressant therapy were started.
Extended treatment period (≤4 weeks after the end of post-daily PE period)	Placebo or caplacizumab 10 mg was administered subcutaneously once daily.	
Follow-up period	—	Daily PE and immunosuppressant therapy were started. Caplacizumab administration was not resumed.

a PE period was determined for each subject by the investigator.
b Self-administration after discharge was permitted only in subjects who mastered the method for study drug preparation and subcutaneous injection.
c Defined as thrombocytopenia that relapsed after the first normalization of platelet count (cases in which platelet count increased to ≥150 × 10^9/L and daily PE was discontinued within 5 days after the increase) and required resumption of daily PE.

Subjects enrolled in the study were assigned to the placebo group or the caplacizumab group at a 1:1 ratio, stratified by the severity of neurological symptoms (Glasgow coma scale [GCS] ≤12 or 13-15). All of 145 randomized subjects (73 in the placebo group, 72 in the caplacizumab group) were included in the intent-to-treat (ITT) population, and the ITT population was handled as the main efficacy analysis

[14] Defined as thrombocytopenia that relapsed after the first normalization of platelet count (when platelet count increased to ≥150 × 10^9/L and daily PE was discontinued within 5 days after the increase) and required resumption of daily PE.
[15] The time from the start of the daily PE period to the data cut-off time point defined as either of the following events whichever occurred first: "Discontinuation of daily PE," "discontinuation of the study drug," or "45 days after the start of the study drug administration with daily PE."

population. Of these, 144 subjects (73 in the placebo group, 71 in the caplacizumab group) receiving the study drug were included in the safety analysis population. A total of 37 subjects (23 in the placebo group, 14 in the caplacizumab group) discontinued the study. The causes of discontinuation were adverse events (5 subjects, 6 subjects), consent withdrawal (5 subjects, 4 subjects), physician's discretion (4 subjects, 2 subjects), death (3 subjects, 1 subject), lost to follow up (1 subject, 0 subject), non-compliance (1 subject, 0 subject), consent withdrawal by the patient's authorized representative (1 subject, 0 subject), and other (3 subjects, 1 subject). During the double-blind period, 133 subjects (65 in the placebo group, 68 in the caplacizumab group) completed the daily PE period and the post-daily PE period, and 28 subjects (6 in the placebo group, 22 in the caplacizumab group) proceeded to the extended treatment period. The median extended treatment period (minimum-maximum) was 24.5 (4-28) days in the placebo group and 21.5 (0-30) days in the caplacizumab group. During the double-blind administration period, the study drug was administered for 23.0 (2-66) days in the placebo group and for 35.0 (1-65) days in the caplacizumab group. During the double-blind administration period, TTP relapsed in 31 subjects (28 in the placebo group, 3 in the caplacizumab group). A total of 28 subjects (26 in the placebo group, 2 in the caplacizumab group) of them, excluding 3 subjects who discontinued the study, received caplacizumab under open-label conditions. A total of 20 of 28 subjects completed the daily PE period and the post-daily PE period, and 8 subjects proceeded to the extended treatment period of 27.5 (7-29) days. During the open-label administration period, caplacizumab was administered for 36.5 (3-65) days.

As for efficacy, time to normalization of platelet count[16] (median [95% CI]), the primary endpoint, was 2.88 [2.68, 3.56] days in the placebo group and 2.69 [1.89, 2.83] days in the caplacizumab group, showing a significantly shorter time in the caplacizumab group than in the placebo group (two-sided log-rank test stratified by severity of neurological symptoms [GCS ≤12 or 13-15], $P = 0.0099$). The rate of achieving normalization of platelet count at an arbitrary time point was 90.4% (66 of 73 subjects) in the placebo group and 93.0% (66 of 71 subjects) in the caplacizumab group, and the hazard ratio [95% CI] of the rate of achieving normalization of platelet count [95% CI] in the caplacizumab group to that in the placebo group was 1.55 [1.095, 2.195] (Cox proportional hazard model with explanation variables of group and severity of neurological symptoms). The data obtained during the period from the start of the daily PE period in the double-blind administration period until data cut-off[15] were used for the analysis of the primary endpoint.

Table 27 shows the results of the main secondary endpoints.

16) When platelet count increased to ≥150 × 10^9/L, and daily PE was discontinued within 5 days after the increase.

Table 27. Results of main secondary endpoints (double-blind administration period, ITT population)

Main secondary endpoints	Placebo (n = 73)	Caplacizumab (n = 72)
TTP relapse rate throughout the study period	38.4 (28/73)	12.7 (9/71)
TTP relapse rate during the study drug administration period	38.4 (28/73)	4.2 (3/71)
TTP relapse rate during the follow-up period	0 (0/73)	9.1 (6/66)
Percentage of subjects with TTP-related events during the study drug administration period	49.3 (36/73)	12.7 (9/71)
TTP-related death[a]	4.1 (3/73)	0 (0/71)
TTP relapse	38.4 (28/73)	4.2 (3/71)
Serious thromboembolic events that occurred during study drug administration[b]	8.2 (6/73)	8.5 (6/71)
Percentage of subjects with refractory TTP[c]	4.2 (3/73)	0 (0/71)
Time (days) to normalization of organ injury markers (LDH, cTnI, and serum creatinine)	3.36 [1.88, 7.71] (n = 66)	2.86 [1.93, 3.86] (n = 66)
Days of PE during the study drug administration period	7.0 (3-46) (n =73)	7.0 (3-46) (n = 73)
Total volume of PE (L) during the study drug administration period	26.94 (4.0-254.0) (n = 73)	18.06 (5.3-102.2) (n = 71)

Incidence (%) (number of subjects with events/number of subjects analyzed), Median [95% CI] (number of subjects analyzed), Median (minimum-maximum) (number of subjects analyzed)

a Adverse events with death outcome that were classified in "clinically significant TTP-related events" and regarded as "death caused by TTP" and/or "TTP-related" by the investigator.

b Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

c When platelet count did not double and lactate dehydrogenase (LDH) exceeded the upper limit of normal after the 4-day standard treatment.

The incidence of adverse events[17] was 97.3% (71 of 73 subjects) in the placebo group and 97.2% (69 of 71 subjects) in the caplacizumab group during the double-blind administration period, and 89.3% (25 of 28 subjects) during the open-label period. Table 28 shows adverse events reported by ≥10% of subjects in either group during the double-blind administration period.

Table 28. Adverse events reported by ≥10% of subjects in either group during the double-blind administration period (safety analysis population)

MedDRA PT	Double-blind administration period		Open-label administration period (n = 28)
	Placebo (n = 73)	Caplacizumab (n = 71)	
Epistaxis	2.7 (2)	32.4 (23)	17.9 (5)
Headache	8.2 (6)	22.5 (16)	21.4 (6)
Gingival bleeding	1.4 (1)	18.3 (13)	14.3 (4)
Urticaria	6.8 (5)	16.9 (12)	3.6 (1)
Fatigue	8.2 (6)	14.1 (10)	7.1 (2)
Pyrexia	8.2 (6)	14.1 (10)	3.6 (1)
Nausea	9.6 (7)	14.1 (10)	7.1 (2)
TTP	39.7 (29)	12.7 (9)	14.3 (4)
Paraesthesia	8.2 (6)	11.3 (8)	0 (0)
Dizziness	11.0 (8)	9.9 (7)	7.1 (2)
Hypokalaemia	19.2 (14)	8.5 (6)	7.1 (2)
Insomnia	11.0 (8)	8.5 (6)	0 (0)
Rash	12.3 (9)	7.0 (5)	14.3 (4)
Contusion	13.7 (10)	7.0 (5)	7.1 (2)
Hypertension	11.0 (8)	5.6 (4)	3.6 (1)

Incidence % (number of patients with events)

During the double-blind administration period, adverse events resulting in death occurred in 4.1 % (3 of 73) of subjects in the placebo group (haemorrhagic transformation stroke, TTP, hypoxia in 1 subject

17) The following adverse events that occurred during each of the following periods were subjected to analysis:
- Double-blind administration period: Adverse events occurring during the double-blind administration period + the follow-up period in subjects without the open-label administration period; and adverse events occurring during the double-blind administration in subjects with the open-label administration period.
- Open-label administration period: Adverse events occurring during the open-label period + the follow-up period in subjects who proceeded to the open-label period.

each) and in 1.4% (1 of 71) of subjects in the caplacizumab group (cerebral ischaemia[18]). Adverse events resulting in death for which a causal relationship to the study drug could not be ruled out were observed in 2.7% (2 of 73) of subjects in the placebo group (haemorrhagic transformation stroke and TTP in 1 subject each). No adverse events resulting in death were observed during the open-label administration period.

During the double-blind administration period, serious adverse events were observed in 53.4% (39 of 73) of subjects in the placebo group and in 39.4% (28 of 71) of subjects in the caplacizumab group. Adverse events reported by ≥2% of subjects in either group were headache (0% in the placebo group, 2.8% in the caplacizumab group), epistaxis (0%, 5.6%), septic shock (2.7%, 0%), TTP (39.7%, 12.7%), and anaphylactic transfusion reaction (4.1%, 0%). Serious adverse events for which a causal relationship to the study drug could not be ruled out were observed in 5.5% (4 of 73) of subjects in the placebo group (TTP in 2 subjects, haemorrhagic transformation stroke, and gamma-glutamyl transpeptidase [γ-GTP] increased in 1 subject each) and in 14.1% (10 of 71) of subjects in the caplacizumab group (epistaxis in 3 subjects, epistaxis/haematemesis, gingival bleeding, upper gastrointestinal haemorrhage, pain in extremity, ventricular fibrillation, subarachnoid haemorrhage, and menorrhagia in 1 subject each). During the open-label administration period, serious adverse events were observed in 25.0% (7 of 28) of subjects. The event observed in ≥2 subjects was TTP (14.3%). Serious adverse events for which a causal relationship to the study drug could not be ruled out were observed in 7.1% (2 of 28) of subjects (upper gastrointestinal haemorrhage and rash erythematous in 1 subject each).

During the double-blind administration period, adverse events leading to discontinuation of the study drug were observed in 12.3% (9 of 73) of subjects in the placebo group (TTP in 2 subjects, haemorrhagic transformation stroke, hypoxia, deep vein thrombosis, jugular vein thrombosis, myocardial infarction, anaphylactic transfusion reaction, and γ-GTP increased in 1 subject each) and 7.0% (5 of 71) of subjects in the caplacizumab group (upper gastrointestinal haemorrhage, epistaxis, TTP, myocardial infarction, and atrial fibrillation in 1 subject each). Adverse events leading to discontinuation of the study drug for which a causal relationship to the study drug could not be ruled out were observed in 4.1% (3 of 73) of subjects in the placebo group (TTP, γ-GTP increased, and haemorrhagic transformation stroke in 1 subject each) and 4.2% (3 of 71) of subjects in the caplacizumab group (ventricular fibrillation, upper gastrointestinal haemorrhage, and epistaxis in 1 subject each). During the open-label administration period, an adverse event leading to discontinuation of the study drug occurred in 3.6% (1 of 28) of subjects (TTP), and its causal relationship to the study drug was denied.

7.2.2 Japanese phase II/III study (Study ALX0681-C202, CTD 5.3.5.2-1, study period October 2019 to May 2021)

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of caplacizumab in Japanese patients with acquired TTP (target sample size, 15 subjects[19]) at 15 study sites in Japan.

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[18] 7[redacted]-year-old woman with hypertension and hypercholesterolaemia. Baseline ADAMTS13 activity was 28%. Time to platelet count normalization was 35 days. PE was performed every day for 36 days. Caplacizumab administration was given for 64 days starting from day 2 of PE. ADAMTS13 activity at the discontinuation of caplacizumab was 57%. The patient had cerebral ischaemia 6 days after discontinuation of caplacizumab and 2 days later died of cerebral ischaemia. A causal relationship of death with caplacizumab and corticosteroid was denied.

[19] With the feasibility of enrollment in Japan taken into account, a total of 15 subjects were to be ensured as the PP population (subjects without critical protocol deviations who completed the follow-up period or relapsed TTP).

The main inclusion criteria were patients with acquired TTP[9)] aged ≥18 years who required initiation of daily PE therapy and did not receive PE more than once before enrollment.[20)] Patients who met any of the following criteria were excluded: Platelet count ≥100 × 10^9/L; platelet count >30 × 10^9/L and serum creatinine >2.3 mg/dL suggesting aHUS; patients with congenital TTP; patients with known cause for thrombocytopenia[12)]; patients with clinically serious active haemorrhage or with a high risk of haemorrhage; and patients who could not discontinue (interrupt) chronic treatment with an anticoagulant drug (VKA, direct acting anticoagulant drug [oral], heparin, or low-molecular weight heparin) for safety reason.

The study consisted of a daily PE period, a post-daily PE period (30 days from the end of daily PE), an extended treatment period (≤8 weeks after the end of the post-daily PE period), and a follow-up period (4 weeks after the end of the study drug administration).

PE and immunosuppressive therapy were performed as the standard therapies. PE was performed daily at 1 to 1.5 times the estimated plasma volume, and continued for ≥2 days after platelet count increased to ≥150 × 10^9/L for the first time. Corticosteroid (methylprednisolone 1 g/day for 3 days or prednisolone 1 mg/kg/day) was administered throughout the daily PE period and for the first 1 week of the post-daily PE period, and could be tapered off during the post-daily PE period at the discretion of the investigator. At 2 weeks after the start of the post-daily PE period, tapering-off of corticosteroid could be re-evaluated if the ADAMTS13 activity was decreased (to <10%) at the past 2 clinical visits. Also, use of immunosuppressants such as rituximab was permitted at the discretion of the investigator throughout the study period.

Caplacizumab was administered according to the same dosage regimen as that in Study ALX0681-C301 (Table 26). Caplacizumab was administered during the daily PE period and the post-daily PE period (30 days after the end of daily PE). The criteria for continued caplacizumab administration during the extended treatment period were the same as those in Study ALX0681-C301. Caplacizumab could be administered for 8 weeks at the maximum after the end of the post-daily PE period. Caplacizumab administration was to be discontinued when ADAMTS13 activity was >10% at 2 consecutive measurements of ≥1-week interval.

All of 21 subjects enrolled in the study received caplacizumab and were included in the modified intent-to-treat (mITT) population, which was handled as the safety analysis population. Of these, 15 subjects who completed the study without critical protocol deviations were included in the per protocol (PP) population, which was handled as the primary efficacy analysis population. Six subjects discontinued the study (excluded from PP population). The reasons for the discontinuation were physician's discretion in 4 subjects[21)] and adverse events in 2 subjects.[22)] A total of 15 subjects completed the daily PE and post-daily PE periods, and 7 subjects proceeded to the extended treatment period. The median

[20)] As a result, 7 subjects had received PE once, and 14 subjects had not received PE, before enrollment.
[21)] Baseline ADAMTS13 activity was ≥10% in 2 of 4 subjects. ADAMTS13 activity in each subject at discontinuation was 73% (Day 18), 47% (Day 18), ≥101% (Day 7), and 70% (Day 29), respectively.
[22)] Adverse events were pulmonary alveolar haemorrhage (4[redacted]-year-old man with baseline ADAMTS13 activity of 48%. ADAMTS13 activity at discontinuation was 72% (Day 28), and hepatic function abnormal (7[redacted]-year-old man with baseline ADAMTS13 activity of <1%. ADAMTS13 activity at discontinuation was 44% (Day 26).

(minimum-maximum) extended treatment period was 14.0 (11-36) days. Caplacizumab was administered for 35.0 (5-69) days.

As for efficacy, the percentage of TTP relapse[14)] throughout the study period, the primary endpoint, was 6.7% (1 of 15 subjects), meeting the pre-specified success criterion (≤20%[23)]).

Table 29 shows results of main secondary endpoints.

Table 29. Results of main secondary endpoints (PP population)

Main secondary endpoints	N = 15
Rate of achieving normal platelet count at an arbitrary time point	100 (15/15)
Time (days) to normalization of platelet count	2.79 [1.758, 3.588] (n = 15)
TTP relapse rate during the study drug administration period	6.7 (1/15)
TTP relapse rate during the follow-up period	0 (0/15)
Percentage of subjects with TTP-related events during the study drug administration period	6.7 (1/15)
TTP-related death[a]	0 (0/15)
TTP relapse	6.7 (1/15)
Serious thromboembolic events that occurred during study drug administration[b]	0 (0/15)
Percentage of subjects with refractory TTP [c]	0 (0/15)
Time (days) to normalization of organ injury markers (LDH, cTnI, and serum creatinine)	2.65 [0.977, 4.980] (n = 15)
Days of PE during the study drug administration period	5 (3-11) (n = 15)
Total volume of PE (L) during the study drug administration period	24.60 (13.4-50.0) (n = 15)

Incidence (%) (number of subjects with events/number of subjects analyzed), Median [95% CI] (number of subjects analyzed), Median (minimum-maximum) (number of subjects analyzed)

a Adverse events with death outcome that were classified as "clinically significant TTP-related events" and regarded as "death caused by TTP" and/or "TTP-related" by the investigator.

b Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

c Despite 5 PEs and treatment with corticosteroid, a persistent increase in platelet count was not observed or platelet count was <50 × 10^9/L with a persistent increase in LDH (>1.5 times the upper limit of normal).

The incidence of adverse events occurring during the study period (up to 28 days after the final dose of caplacizumab) was 100% (21 of 21 of subjects). Table 30 shows adverse events observed in ≥2 subjects.

[23)] Taking account of the rate of TTP relapse in the placebo group throughout the study period of Study ALX0681-C301 (38.4%, double-blind administration period) and the opinion of medical experts, the rate of TTP relapse in Japanese patients with acquired TTP during the period not receiving caplacizumab was assumed to be 30%. Taking account of the relative risk reduction rate (approximately 67%) in the caplacizumab group compared to the placebo group in Study ALX0681-C301, the TTP relapse rate during caplacizumab administration in this study was assumed to be 15% (relative risk reduction rate 50%). Since the number of subjects with TTP relapse among the target number (15) of subjects in the study is calculated to be 2.25, the success criterion was "≤20%" which corresponds to "≤3 of 15 subjects."

Table 30. Adverse events observed in ≥2 subjects (safety analysis population)

MedDRA PT	N = 21
Constipation	42.9 (9)
Urticaria	19.0 (4)
Hypokalaemia	19.0 (4)
Insomnia	28.6 (6)
Allergic transfusion reaction	19.0 (4)
Rash	14.3 (3)
ATT increased	14.3 (3)
Anal erythema	9.5 (2)
Gastrointestinal haemorrhage	9.5 (2)
Nausea	9.5 (2)
Device related infection	9.5 (2)
Oral candidiasis	9.5 (2)
Electrocardiogram QT prolonged	9.5 (2)
Hypomagnesaemia	9.5 (2)
Epistaxis	9.5 (2)
Hepatic function abnormal	9.5 (2)

Incidence % (number of subjects with events)

There were no adverse events resulting in death. Serious adverse events were observed in 23.8% (5 of 21) of subjects (cholecystitis acute/pulmonary alveolar haemorrhage, hepatic function abnormal/TTP, hepatitis C/pneumonia aspiration, gastrointestinal perforation, and *Pneumocystis jirovecii* pneumonia in 1 subject each). The serious adverse event for which a causal relationship to the study drug could not be ruled out was pulmonary alveolar haemorrhage in 1 subject.[24)]

Adverse events leading to discontinuation of the study drug occurred in 9.5% (2 of 21) of subjects (hepatic function abnormal and pulmonary alveolar haemorrhage in 1 subject each). A causal relationship to the study drug could not be ruled out for either of them.

7.3 Other clinical studies

7.3.1 Foreign phase II study (Study ALX-0681-2.1/10, CTD 5.3.5.1-1 [Reference data], study period January 2011 to March 2014)

A placebo-controlled, randomized, single-blind, parallel group study was conducted to investigate the PK, PD, efficacy, and safety of caplacizumab in non-Japanese patients with acquired TTP (target sample size, 110 subjects [adults][25)]) at 32 study sites. The study was terminated prematurely due to the lower-than-expected speed of enrollment.

[24)] 4[redacted]-year-old man with dermatomyositis accompanied by interstitial pneumonia, old myocardial infarction, sleep apnoea syndrome, hypertension, hyperlipidaemia, renal impairment, hepatic impairment, thyroid mass, and hyperuricaemia. Baseline ADAMTS13 activity was 48%. PE was performed for 5 days. Cholecystitis acute was noticed on Day 16 of caplacizumab administration and operated surgically. Mild wound haemorrhage was observed on Day 17, but cholecystitis acute and wound haemorrhage resolved on Day 22. Moderate renal dysfunction was observed on Day 23. Pulmonary alveolar haemorrhage was observed on Day 25. Caplacizumab had been discontinued before Day 25. Extracorporeal membrane oxygenation (ECMO) was performed from Day 30 to 44. Blood stool was observed on Day 38, and colorectal ulcer was detected by gastrointestinal endoscopy on Day 45. The patient died of lower gastrointestinal haemorrhage on Day 57 (33 days after the last dose of caplacizumab). A causal relationship to caplacizumab was denied, while a causal relationship to corticosteroid could not be ruled out. The patient had been on oral acetylsalicylic acid as a treatment for old myocardial infarction (discontinued when pulmonary alveolar haemorrhage occurred).

[25)] With the assumption that the median time to normalization of platelet count was 6 days in the placebo group (*Journal of Clinical Apheresis.* 1998;13:133-41) and 3.36 days in the caplacizumab group (44% reduction in the time to normalization of platelet count in the caplacizumab group) and that the dropout rate within 30 days after the first dose of the study drug was 15%, the number of subjects necessary for detecting the significant reduction of the time to normalization of platelet count by the log-rank test at a one-sided significance level of 2.5% and statistical power of 80% was estimated to be 110.

The main inclusion criteria were patients with acquired TTP[26] aged ≥18 years who required initiation of daily PE therapy and had not received PE more than once before enrollment.[11] Patients who met any of the following criteria were excluded: Platelet count ≥100 × 10^9/L; patients with congenital TTP; clinical findings of enteric infection caused by *E.coli* O-157 or other related microorganisms; antiphospholipid syndrome; thrombotic microangiopathy related to hematopoietic stem cells or bone-marrow transplantation; patients with severe active infection or disseminated intravascular coagulation (DIC) due to sepsis; patients with active haemorrhage or high risk of haemorrhage; and patients who could not discontinue (interrupt) chronic treatment with an anticoagulant drug (VKA, heparin, or low-molecular weight heparin) and NSAIDs other than acetylsalicylic acid for safety reason.

The study consisted of a PE period,[27] post-PE period (30 days after the end of PE period), and a follow-up period (12 months from the end of post-PE period).

As the standard therapies, PE and immunosuppressive therapy considered to be appropriate by the investigator were to be performed.

On Day 1 of the PE period (adjustable for each subject), placebo or caplacizumab 10 mg was bolus administered intravenously during the period from 6 hours to 15 minutes before the first PE after randomization, followed by subcutaneous administration of placebo or caplacizumab 10 mg within 30 minutes after the end of PE. From Day 2, placebo or caplacizumab 10 mg was administered subcutaneously once daily within 30 minutes after the end of each PE. During the post-PE period, placebo or caplacizumab 10 mg was administered subcutaneously once daily. When PE was resumed due to TTP relapse during the post-PE period (thrombocytopenia that relapsed after the first normalization of platelet count[28] and required resuming daily PE), the study drug administration was resumed according to the same schedule as that during the initial treatment period, for the maximum of 90 days after the first dose of the study drug.

Subjects enrolled in the study were assigned to the placebo group or the caplacizumab group at a 1:1 ratio, stratified by the presence or absence of a PE before randomization. All of the 75 enrolled subjects (39 in the placebo group, 36 in the caplacizumab group) were included in the ITT population, which was handled as the main efficacy analysis population. Of these, 72 subjects (37 in the placebo group, 35 in the caplacizumab group) receiving the study drug were included in the safety analysis population. Study discontinuation occurred in 34 patients (18 in the placebo group, 16 in the caplacizumab group). The reasons for the discontinuation were premature discontinuation by the applicant (10 subjects, 9 subjects), consent withdrawal (3 subjects, 1 subject), adverse events (0 subjects, 3 subjects), physician's discretion (1 subject, 1 subject), lost to follow up (0 subject, 1 subject), death (1 subject, 0 subject), protocol violation (1 subject, 0 subject), pregnancy (1 subject, 0 subject), and other (1 subject, 1 subject).

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[26] The study protocol was revised (ver. 11.0 [September 25, 2012]) to allow enrollment of pediatric patients aged ≥12 and <18 years at some study sites and to administer caplacizumab to all subjects without randomization. Patients weighing ≤65 kg received the body weight-adjusted dose and patients weighing >65 kg received the same dosage regimen as that in adults.

[27] If PE was performed twice or more a day at the discretion of the investigator, the study drug was administered within 30 minutes after the end of each PE. Decreasing the frequency of PE to less than once daily was defined as tapering of PE, which was allowed according to the standard treatment at each study site. During the time of PE tapering, the study drug was administered once daily.

[28] Defined as platelet count of ≥150 × 10^9/L and LDH of ≤2 times the upper limit of normal in the new measurements 48 hours after the first report of platelet count normalization (150 × 10^9/L).

The duration of the study drug administration (median [minimum-maximum]) was 37.0 (2-90) days in the placebo group and 36.0 (3-77) in the caplacizumab group.

The median time to normalization of platelet count [95% CI], the primary endpoint, was 4.79 [3.51, 5.94] days in the placebo group and 2.97 [2.74, 3.65] days in the caplacizumab group, which was significantly shorter in the caplacizumab group than in the placebo group (one-sided log-rank test stratified by the presence/absence of 1 PE before randomization [one-sided significance level of 0.025], $P = 0.005$). The platelet count normalization rate at an arbitrary time point was 71.8% (28 of 39 subjects) in the placebo group and 86.1% (31 of 36 subjects) in the caplacizumab group, and the hazard ratio [95% CI] of the rate of achieving platelet count normalization in the caplacizumab group to that in the placebo group was 2.197 [1.278, 3.778] (stratified Cox proportional hazard model with the presence/absence of 1 PE before randomization as a covariate).

The rate of TTP relapse during the post-PE period, a main secondary endpoint, was 28.2% (11 of 39 subjects) in the placebo group and 8.3% (3 of 36 subjects) in the caplacizumab group. The rate of TTP relapse during the follow-up period was 7.7% (3 of 39 subjects) in the placebo group and 30.6% (11 of 36 subjects) in the caplacizumab group.

The incidence of adverse events during 1 month after the study drug administration was 100.0% (37 of 37 subjects) in the placebo group and 97.1% (34 of 35 subjects) in the caplacizumab group. Table 31 shows adverse events reported by ≥20% of subjects in either group.

Table 31. Adverse events reported by ≥20% of subjects in either group (safety analysis population)

MedDRA PT	Placebo (n = 37)	Caplacizumab (n = 35)
TTP	37.8 (14)	37.1 (13)
Headache	27.0 (10)	34.3 (12)
Epistaxis	10.8 (4)	31.4 (11)
Nausea	29.7 (11)	28.6 (10)
Hypokalaemia	21.6 (8)	25.7 (9)
Paraesthesia	21.6 (8)	22.9 (8)
Dizziness	8.1 (3)	22.9 (8)
Constipation	27.0 (10)	20.0 (7)
Vomiting	21.6 (8)	20.0 (7)
Myalgia	2.7 (1)	20.0 (7)
Pain in extremity	21.6 (8)	14.3 (5)
Anaemia	21.6 (8)	8.6 (3)
Arthralgia	21.6 (8)	8.6 (3)

Incidence % (number of subjects with events)

Adverse events resulting in death occurred in 5.4% (2 of 37) of subjects in the placebo group (TTP and cerebral haemorrhage in 1 subject each). A causal relationship to the study drug was denied for both events.

Serious adverse events were observed in 51.4% (19 of 37) of subjects in the placebo group and 57.1% (20 of 35) of subjects in the caplacizumab group. Adverse events reported by ≥5% of subjects in either group were TTP (35.1% in the placebo group, 37.1% in the caplacizumab group) and dizziness (0%, 5.7%). Serious adverse events for which a causal relationship to the study drug could not be ruled out were observed in 20.0% (7 of 35) of subjects in the caplacizumab group (TTP in 2 subjects,

TTP/autoantibody test/dermatitis allergic, subarachnoid haemorrhage, anaemia/ hypertransaminasaemia/metrorrhagia, headache, and transaminases increased in 1 subject each).

Adverse events leading to discontinuation of the study drug were observed in 5.4% (2 of 37) of subjects in the placebo group (depression and cerebral haemorrhage in 1 subject each) and in 11.4% (4 of 35) of subjects in the caplacizumab group (sepsis, pulmonary embolism, transaminases increased, and anaemia/hypertransaminasaemia/metrorrhagia/epistaxis/gingival bleeding/ecchymosis/haematoma in 1 subject each). Adverse events leading to discontinuation of the study drug for which a causal relationship with the study drug could not be ruled out were observed in 5.7% (2 of 35) of subjects in the caplacizumab group (anaemia/hypertransaminasaemia/metrorrhagia/epistaxis/gingival bleeding/ecchymosis/haematoma and transaminases increased in 1 subject each).

7.3.2 Foreign phase III study (Study ALX0681-C302/LTS16371, CTD 5.3.5.2-2 [Reference data], study period October 2016 to October 2020)

An open-label, uncontrolled study was conducted at 43 study sites to investigate the safety and efficacy of a long-term administration and a re-administration of caplacizumab in patients with acquired TTP who had completed Study ALX0681-C301.

Caplacizumab was administered under open-label conditions to subjects who had shown TTP relapse, according to the same dosage regimen as in Study ALX0681-C301 (Table 26). The observation period was 36 months.

All of the 104 subjects enrolled in the study (29 subjects who did not receive caplacizumab in Study ALX0681-C301 [hereinafter “untreated subjects”], 75 subjects who received caplacizumab in Study ALX0681-C301 [hereinafter “treated subjects”] including 20 subjects who were assigned to placebo group in Study ALX0681-C301 but received caplacizumab during the open-label period) were included in the intent-to-observe (ITO) population, which was handled as the safety analysis population. Of these, 78 subjects who did not show TTP relapse during Study ALX0681-C301 or before this study (29 in the placebo group and 49 in the caplacizumab group in Study ALX0681-C301) were included in the efficacy ITO population, which was handled as the efficacy analysis population. During the study, total of 13 subjects had TTP relapse and received caplacizumab. The median (minimum-maximum) administration period was 69.0 (17-417) days. The study was discontinued in 11 subjects (6 untreated subjects, 5 treated subjects). The reasons for the discontinuation were lost to follow up (4 subjects, 1 subject), discretion of physician (0 subjects, 3 subjects), consent withdrawal (1 subject, 1 subject) and death (1 subject, 0 subject).

Table 32 shows the incidences of TTP-related events observed in the efficacy ITO population.

Table 32. Incidences of TTP-related events (efficacy ITO population[a])

	Placebo group in Study ALX0681-C301 (n = 29)	Caplacizumab group in Study ALX0681-C301 (n = 49)
TTP-related events	37.9 (11)	8.2 (4)
TTP-related death[b]	3.4 (1)	0 (0)
TTP relapse	27.6 (8)	8.2 (4)
At least 1 serious thromboembolic event[c]	37.9 (11)	8.2 (4)

Incidence % (number of subjects with events)

a Subjects without TTP relapse during Study ALX0681-C301 or before the start of this study

b Adverse events with death outcome that were classified as "clinically significant TTP-related events" and regarded as "death caused by TTP" and/or "TTP-related" by the investigator.

c Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

Table 33 shows adverse events reported by ≥10% of subjects in either group in the ITO population.

Table 33. Adverse events reported by ≥10% of subjects in either group (ITO population)

MedDRA PT	Untreated subjects (n = 29)	Treated subjects (m = 75)
Headache	31.0 (9)	21.3 (16)
TTP	27.6 (8)	14.7 (11)
ADAMTS13 activity decreased	0 (0)	17.3 (13)
Nasopharyngitis	20.7 (6)	8.0 (6)
Dizziness	6.9 (2)	13.3 (10)
Upper respiratory tract infection	13.8 (4)	9.3 (7)
Influenza	10.3 (3)	9.3 (7)
Cough	10.3 (3)	9.3 (7)
Arthralgia	6.9 (2)	10.7 (8)
Diarrhoea	17.2 (5)	6.7 (5)
Paraesthesia	17.2 (5)	5.3 (4)
Urinary tract infection	10.3 (3)	6.7 (5)
Back pain	10.3 (3)	5.3 (4)
Abdominal pain upper	10.3 (3)	5.3 (4)
Pyrexia	10.3 (3)	4.0 (3)
Hypertension	10.3 (3)	1.3 (1)

Incidence % (number of subjects with events)

Adverse events resulting in death occurred in 3.4% (1 of 29) of the untreated subjects (TTP), but its causal relationship to the study drug was denied. Serious adverse events were observed in 55.2% (16 of 29) of the untreated subjects and in 37.3% (28 of 75) of the treated subjects. Serious adverse events observed in ≥2 of subjects in either group were pneumonia (0% in untreated subjects, 2.7% in treated subjects), TTP (27.6%, 14.7%), back pain (6.9%, 0%), abortion spontaneous (0%, 2.7%), and abortion induced (0%, 2.7%).

Adverse events leading to discontinuation of the study drug were not evaluated in the ITO population because subjects who did not receive the study drug were included in the population.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

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

In acquired TTP, ADAMTS13 activity is decreased by autoantibody against ADAMTS13, a cleavage enzyme specific to ULvWF, and the cleavage of ULvWF is suppressed, leading to accumulation of ULvWF multimers, resulting in failure of preventing thrombogenesis due to the binding of ULvWF and platelets and platelet aggregation in microvessels. Platelet thrombosis in microvessels causes severe platelet-depleted thrombocytopenia and hemolytic anemia. Blood clots generated within inflowing

blood vessels of brain, heart, and kidneys induce acute thromboembolic events such as cerebral stroke, myocardial infarction, and renal dysfunction.

As the standard treatment for acquired TTP, corticosteroid and immunosuppressants such as rituximab are used in combination with PE. Although introduction of PE significantly improved the life expectancy of patients with acquired TTP, the mortality during the acute phase of acquired TTP is as high as 20% even in patients receiving the standard therapy with PE and immunosuppressants (*J Thromb Haemost*. 2015;13:293-302, *Am J Hematol*. 2015;90:709-14). Death occurs mostly within 30 days after the diagnosis (*Haematologica*. 2012;97:1181-6, etc.) with the median time to death being 9 days (*Transfusion*. 2016;56:1451-8). Patients with any of the following symptoms are diagnosed with refractory acquired TTP and have an increased risk of death (*J Thromb Haemost*. 2015;13:293-302): Thrombopenia does not improve after the standard therapy for 7 days; platelet count does not double after 4-day standard therapy while the lactate dehydrogenase (LDH) level has increased (*Blood.* 2015;125:3860-7); or despite treatment with PE and corticosteroid for 5 days, platelet count has not increased to a sufficient level, or the LDH level continues to increase while platelet count remains below 50×10^9/L (*J Thromb Haemost.* 2017;15:312-22).

For the treatment of acute phase (first onset or relapse) of acquired TTP, the "Consensus report on the diagnosis and management of thrombotic thrombocytopenic purpura 2020 (in Japanese)" recommend corticosteroid (not covered by health insurance) as the drug therapy to be given in combination with PE (recommendation level IB). PE removes ULvWF and autoantibodies against ADAMTS13 from plasma, thereby supplementing normal ADAMTS13, and the immunosuppressive therapy suppresses the production of autoantibodies against ADAMTS13. In Japan, rituximab is the only drug approved for the treatment of acquired TTP, and is recommended to use in refractory cases and in early relapse cases (recommendation level IB). In addition, rituximab is strongly recommended when the titer of autoantibody against ADAMTS13 increases in response to ADAMTS13 contained in the donor plasma used for PE (ADAMTS13 inhibitor boosting). Other immunosuppressants such as cyclophosphamide, vincristine, and cyclosporine are also described in the above guidelines, but none of them are covered by the health insurance.

Prompt and effective interventions are essential for the improvement of life expectancy and for the short-term and long-term prevention of thrombus-related complications. However, PE and immunosuppressant therapy do not directly inhibit the pathogenic platelet adhesion of ULvWF, and it takes more than several days before the current standard therapy exhibits its effect and, if the response to the treatment is insufficient, the symptoms may become aggravated after the discontinuation of the treatment. Caplacizumab directly inhibits the adhesion of platelets to ULvWF, thereby suppressing platelet thrombosis within microvessels. Caplacizumab is thus expected to promptly exhibit the therapeutic effect against severe thrombocytopenia and organ injuries. During the acute phase (first onset or relapse) of acquired TTP, it is essential to suppress as early as possible the platelet thrombosis within microvessels by caplacizumab while suppressing autoantibodies against ADAMTS13 by immunosuppressive treatment. Caplacizumab thus should be used in combination with immunosuppressants such as corticosteroid. The International Society on Thrombosis and Haemostasis

(ISTH) Guidelines (*J Thromb Haemost.* 2020;18:2496-502) recommends the use of caplacizumab in combination with PE and immunosuppressants such as corticosteroid and rituximab.

PMDA's view:
In Japan, currently, daily PE in combination with immunosuppressant therapy with corticosteroid, etc., is performed as the standard therapy for the acute phase of acquired TTP. In the Japanese and foreign clinical studies, treatment with caplacizumab was started in patients with acute phase (first onset or relapse) of acquired TTP in addition to the standard therapy, and caplacizumab was continued for a certain period after the end of the daily PE. Results of the studies demonstrated efficacy of caplacizumab. Although precaution against haemorrhage is necessary, caplacizumab was demonstrated to have acceptable safety profile given the seriousness of the disease and the observed efficacy of caplacizumab [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. Caplacizumab is a drug with a novel mechanism of action, i.e., it inhibits the binding of platelets and ULvWF, thereby preventing thrombogenesis in microvessels. Caplacizumab thus has clinical significance as a novel treatment option provided to the clinical practice for first-onset and relapsed acquired TTP, where administration of caplacizumab is started during the acute phase of acquired TTP in combination with daily PE and immunosuppressants, and caplacizumab is continued for a certain period after the end of daily PE [see Section "7.R.4 Indication and intended population" for intended population].

7.R.2 Efficacy

PMDA concluded that the efficacy of caplacizumab in Japanese patients with acquired TTP has been demonstrated, given the combined results of Studies ALX0681-C301, ALX0681-C202, etc., as discussed below.

7.R.2.1 Japanese and foreign clinical study designs

The applicant's explanation about the designs of the foreign Study ALX0681-C301 and the Japanese Study ALX0681-C202:
Study ALX0681-C301 was conducted as a placebo-controlled, randomized, double-blind, parallel-group study to confirm the superiority of caplacizumab to placebo in non-Japanese patients with acquired TTP, using the time to normalization of platelet count as the primary endpoint. As for the Japanese clinical study, it was expected that 20 study sites would be available for enrollment of patients with acquired TTP and approximately 0.5 patients would be enrolled every year at each study site. The study plan was developed as follows for the feasibility purpose. In Study ALX0681-C301, time to normalization of platelet count, the primary endpoint, varied widely (0.6-18.8 days in the placebo group, 0.6-9.8 days in the caplacizumab group), which suggested that it was inappropriate to use the same endpoint as that in Study ALX0681-C301. Instead, the rate of TTP relapse throughout the study period was selected as the primary endpoint from among the secondary endpoints in Study ALX0681-C301, because the endpoint occurred in a certain number of subjects in the placebo group and was suggested to be related to disease aggravation and the risk of death (*Am J Hematol.* 2018;93:E73-5). Introducing a concurrent control group was considered at the planning of Study ALX0681-C202. However, results of Study ALX0681-C301 had shown that, if a placebo-controlled study was planned with the TTP relapse rate as the primary

endpoint, 44 subjects would be required to enroll in each group (88 subjects in total)[29] in order to confirm the superiority of caplacizumab to placebo in achieving in the primary endpoint. This was considered infeasible with only approximately 10 patients expected to be enrolled per year. Instead, the study was conducted as an open-label, uncontrolled study with the success criteria specified in advance, after evaluating the availability of the data of Study ALX0681-C301 evaluated beforehand. The target size of Study ALX0681-C202 was determined to be 15 evaluable subjects (PP population) from the feasibility point of view. Due to the limited number of subjects, appropriate evaluation of TTP relapse would be difficult if there were many premature discontinuation cases before the first normalization of platelet count. Therefore, subjects who received the study drug according to the study protocol and completed the follow-up period or subjects who showed TTP relapse, excluding subjects with serious protocol deviations, were included in the PP population, and the population was handled as the main efficacy analysis population.

PMDA's view:
Given the seriousness and rarity of acquired TTP, it is unavoidable that Study ALX0681-C202 was conducted as an uncontrolled study with the objectively evaluable efficacy endpoint and with the roughly acceptable success criteria, and that the development plan was to use the data of Study ALX0681-C301 as the supporting evidence. Although a decrease in TTP relapse rate, the parameter employed as the primary endpoint for Study ALX0681-202, has a clinical significance, because of the limitation to the assessment of TTP relapse rate in the uncontrolled study conducted in only a limited number of subjects, multiple secondary endpoints including the time to normalization of platelet count (primary endpoint in Study ALX0681-C301) were compared with those in Study ALX0681-C301 to collectively evaluate the efficacy of caplacizumab [for feasibility of extrapolating the data of Study ALX0681-C301 and the efficacy of caplacizumab, see Sections "7.R.2.2 Feasibility of extrapolating foreign clinical data" and "7.R.2.4 Efficacy in Japanese clinical study"]. Given the applicant's explanation, it is inevitable that the PP population was used as the main analysis population in Study ALX0681-202. However, data should be collectively evaluated, including the results of analyses in all subjects receiving caplacizumab.

7.R.2.2 Feasibility of extrapolating foreign clinical data

The applicant's explanation about the justification for using the data of the foreign clinical study to support the efficacy of caplacizumab in Japanese patients with acquired TTP:
There is no clinically significant difference in PK or PD of caplacizumab between Japanese and non-Japanese subjects [see Section "6.R.1 Difference in PK and PD between Japanese and non-Japanese subjects]. Related guidelines of Japan and foreign countries do not show a significant difference in the pathology of acquired TTP, definition of the disease, diagnostic criteria, or treatment method, except that caplacizumab is not approved in Japan (*Blood*. 2021;137:1855-61, *J Thromb Haemast*. 2020;18:2496-502, and Consensus report on the diagnosis and management of thrombotic thrombocytopenic purpura 2020). These facts suggest that there is no clear difference between Japan and foreign countries affecting the efficacy evaluation of caplacizumab from either intrinsic or extrinsic

[29] Throughout the period of Study ALX0681-C301, TTP relapsed in 38% of subjects in the placebo group and in 13% of subjects in the caplacizumab group. By assuming that TTP would relapse in a similar percentage in each group of Study ALX0681-C202, 44 subjects in each group were required to confirm the superiority at the two-sided significance level of 5% with the statistical power of 80%.

ethnic factors. Studies ALX0681-C301 and ALX0681-C202 were conducted under the identical conditions affecting TTP relapse rate, including inclusion/exclusion criteria, the rule for PE and administration of concomitant drugs such as immunosuppressants, and criteria for caplacizumab discontinuation. Despite the difference in the study design such as the period of daily PE and the longest permitted extended treatment period after the daily PE period, only 1 subject received caplacizumab for more than 4 weeks, suggesting that the effect of the difference on the comparability of these studies is limited. From the above results, the applicant considers that it is acceptable to use the data of Study ALX0681-C301 in explaining the efficacy of caplacizumab in Japanese patients with acquired TTP, based on the similarity of the data of Study ALX0681-C202.

PMDA's view:
Given the applicant's explanation about the mechanism of action of caplacizumab, the extent of the effect of the difference in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese subjects, and the effect of the difference in study design between Study ALX0681-C301 and Study ALX0681-C202 on the efficacy evaluation, there are no factors that forbid the use of the data of Study ALX0681-C301 in explaining the efficacy of caplacizumab in Japanese patients with acquired TTP. The data of this foreign study can be used to explain the usefulness of caplacizumab in Japanese patients if data of Japanese and foreign clinical studies show similar tendencies. Extrapolability of the data of Study ALX0681-C301 is discussed continuously, also taking account of the similarity of the data of the Japanese and foreign clinical studies [see Section "7.R.2.4 Efficacy in Japanese clinical study"].

7.R.2.3 Efficacy in foreign clinical study

The applicant's explanation about the efficacy of caplacizumab in Study ALX0681-C301:
The objective of the treatment of acquired TTP is to suppress platelet aggregation in microvessels and thrombus formation as early as possible in order to avoid serious complications such as organ ischemia, cerebral stroke, and myocardial infarction caused by thrombus formation within microvessels in the whole body. Accordingly, in Study ALX0681-C301, the time to normalization of platelet count was used as the primary endpoint, with platelet count as the index for the decrease in platelet consumption. The median time [95% CI] to normalization of platelet count was 2.88 [2.68, 3.56] days in the placebo group and 2.69 [1.89, 2.83] days in the caplacizumab group, showing a statistically significant reduction in the caplacizumab group compared to the placebo group, with the hazard ratio [95% CI] of the rate of achieving platelet count normalization in the caplacizumab group relative to the placebo group being 1.55 [1.095, 2.195].

Results of the main secondary endpoints were as shown in Table 27. The frequency of ITT-related events (TTP-related death, TTP relapse, or one or more serious thromboembolic events) during the study drug administration period was lower in the caplacizumab group than in the placebo group, and the frequency of each event in the caplacizumab group was also lower than, or similar to, the frequency in the placebo group, suggesting the possibility that caplacizumab prevents the occurrence of these clinically significant events.

Refractory TTP was observed only in the placebo group and not in the caplacizumab group. Subjects in the caplacizumab group showed a tendency of rapid normalization of markers of organ injuries (LDH,

cardiac troponin I [cTnI], and serum creatinine), suggesting the possibility of preventing refractory TTP and aggravation of organ injury.

On the basis of the above, the applicant considers that results of Study ALX0681-C301 demonstrated a clinically significant effect of caplacizumab.

PMDA asked the applicant to explain the reason why, in Study ALX0681-C301, the observed time to normalization of platelet count, the primary endpoint, was different from the assumption at the planning of the study and to explain the clinical significance of the between-group difference.

The applicant's explanation:
At the time of planning the clinical study, the time to normalization of platelet count in the placebo group was estimated to be 7 days, taking account of the published report (*Journal of Clinical Apheresis.* 1998;13:133-41) and information obtained in clinical practice such as opinions of medical experts. In the placebo group of Study ALX0681-C301, platelet count returned to the normal level within a shorter time than expected. This may have been due to the strictly controlled study procedures including the procedure of PE. So far, there are no approved drugs that specifically target inhibition of thrombogenesis in microvessels in patients with acquired TTP. In Study ALX0681-C301, the time to achieve the primary endpoint was statistically significantly shorter in the caplacizumab group than in the placebo group, and the rate of achieving normal platelet count in the caplacizumab group was 1.55 times the rate in the placebo group. These results suggest that caplacizumab has a clinically significant effect in rapidly preventing thrombogenesis and the progress to organ injuries.

PMDA's view:
Taking account of the applicant's explanation about the relationship between the objective of the treatment and the efficacy endpoint, it was appropriate that, in Study ALX0681-C301, the time to normalization of platelet count was used as the primary endpoint. The study demonstrated the clinically significant efficacy of caplacizumab, given the following observations: (a) The superiority of caplacizumab to placebo in the primary endpoint was demonstrated; (b) although the between-group difference was smaller than expected at the study planning stage, results of the secondary endpoints suggested improvement of TTP-associated critical events by caplacizumab, such as decrease in the rate of subjects showing TTP-related death, TTP relapse, or serious thromboembolic events, decreased rate of the occurrence of refractory TTP, and reduction in the time to normalization of markers of organ injuries; and (c) these results suggest that caplacizumab is expected to decrease the days of PE and total volume of PE.

7.R.2.4 Efficacy in Japanese clinical study

The applicant's explanation about the efficacy of caplacizumab in Study ALX0681-C202:
In Study ALX0681-C202, the rate of TTP relapse throughout the study period (PP population), the primary endpoint, was 6.7% (1 of 15 subjects), achieving the prespecified success criterion (≤20%). This success criterion was defined based on the rate of TTP relapse throughout the study period in the placebo group of Study ALX0681-C301 (38.4%, double-blind administration period) and on the opinion of the medical experts, according to the following assumptions: By assuming the rate of TTP relapse in

Japanese patients with acquired TTP untreated with caplacizumab to be 30%, and by assuming the rate of TTP relapse in patients receiving caplacizumab in this study to be 15% (relative risk reduction rate 50%) taking account of the risk reduction rate of TTP relapse in Study ALX0681-C301 (approximately 67%), the number of patients with relapse is calculated to be 2.25 among 15 subjects (target number). Accordingly, the success criterion of ≤20% (corresponding to ≤3 of 15 subjects) was defined. Since subjects who discontinued the study were excluded from the PP population which is the primary population for evaluation, sensitivity analysis also was conducted in the mITT population which included all subjects receiving caplacizumab. Results confirmed that the rate of TTP relapse throughout the study period was 4.8% (1 of 21 subjects) which was similar to the rate in the PP population, and that, in 6 subjects who discontinued the study, TTP relapse did not occur either during the study drug administration or during the follow-up period after the study discontinuation.

Table 34 shows the comparison of the results of the primary endpoint and the secondary endpoints between Japanese and foreign clinical studies. Results of the Japanese clinical study were similar to those in the caplacizumab group of the foreign Study ALX0681-C301.

Table 34. Efficacy in Study ALX0681-C301 (double-blind administration period) and Study ALX0681-C202

Efficacy endpoints	Study ALX0681-C301 (double-blind administration period, ITT population)		Study ALX0681-C202 (PP population)
	Placebo (n = 73)	Caplacizumab (n = 72)	(n = 15)
Time (days) to normalization of platelet count	2.88 [2.68, 3.56] (n = 73)	2.69 [1.89, 2.83] (n = 72)	2.79 [1.758, 3.588] (n = 15)
TTP relapse rate throughout the study period	38.4 (28/73)	12.7 (9/71)	6.7 (1/15)
TTP relapse rate during the study drug administration period	38.4 (28/73)	4.2 (3/71)	6.7 (1/15)
TTP relapse rate during the follow-up period	0 (0/73)	9.1 (6/66)	0 (0/15)
Percentage of subjects with TTP-related events during the study drug administration period	49.3 (36/73)	12.7 (9/71)	6.7 (1/15)
TTP-related death[a]	4.1 (3/73)	0 (0/71)	0 (0/15)
TTP relapse	38.4 (28/73)	4.2 (3/71)	6.7 (1/15)
Serious thromboembolic events that occurred during study drug administration[b]	8.2 (6/73)	8.5 (6/71)	0 (0/15)
Percentage of subjects with refractory TTP[c]	7.0 (5/73)	0 (0/71)	0 (0/15)
Time (days) to normalization of organ injury markers (LDH, cTnI, and serum creatinine)	3.36 [1.88, 7.71] (n = 66)	2.86 [1.93, 3.86] (n = 66)	2.65 [0.977, 4.980] (n = 15)
Days of PE during the study drug administration period	7.0 (3-46) (n = 73)	5.0 (1-35) (n = 71)	5 (3-11) (n = 15)
Total volume of PE (L) during the study drug administration period	26.94 (4.0-254.0) (n = 73)	18.06 (5.3-102.2) (n = 71)	24.60 (13.4-50.0) (n = 15)

Incidence (%) (number of subjects with events/number of subjects analyzed), Median [95% CI] (number of subjects analyzed), Median (minimum-maximum) (number of subjects analyzed)

a Adverse events with death outcome that were classified as "clinically significant TTP-related events" and regarded as "death caused by TTP" and/or "TTP-related" by the investigator.

b Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

c Despite 5 PEs and treatment with corticosteroid, a persistent increase in platelet count was not observed, or platelet count was <50 × 10^9/L with a persistent increase in LDH (>1.5 times the upper limit of normal).

PMDA asked the applicant to explain whether the comparability between Japanese and foreign clinical studies is ensured, based on the characteristics of subjects enrolled in Studies ALX0681-C301 and ALX0681-C202, use status of the standard treatment, etc.

The applicant's explanation:

Table 35 shows the patient characteristics in Studies ALX0681-C301 and ALX0681-C202. No significant difference was observed between the Japanese and the foreign clinical studies in the patient characteristics and the use status of the standard treatment, except for a past history of TTP (first onset or relapsed), the number of times of relapses, severity, vWF:Ag level, and cumulative dose of corticosteroid. Regarding the standard treatment, the percentage of subjects receiving in combination with rituximab during the post-daily PE period was higher in Study ALX0681-C202 (73.3% [11 of 15 subjects]) than in Study ALX0681-C301 (33.8% [22 of 65 subjects]).

Table 35. Comparison of patient characteristics and use status of the standard treatment between Study ALX0681-C301 and Study ALX0681-C202

		Study ALX0681-C301 (double-blind administration period, ITT population)		Study ALX0681-C202 (PP population)
		Placebo (n = 73)	Caplacizumab (n = 72)	(n = 15)
Time from diagnosis with TTP[a]		0.06 (0.0-30.4) (n = 73)	0.01 (0.0-20.1) (n = 71)	1.0 (1-299) (n = 15)
Past history of TTP	First onset	46.6 (34/73)	66.7 (48/72)	80.0 (12/15)
	Relapse	53.4 (39/73)	33.3 (24/72)	20.0 (3/15)
Number of TTP relapse	1	28.8 (21/73)	11.1 (8/72)	20.0 (3/15)
	2	9.6 (7/73)	12.5 (9/72)	0 (0/15)
	>2	15.1 (11/73)	9.7 (7/72)	0 (0/15)
ADAMTS13	<10%	90.3 (65/72)	81.7 (58/71)	100 (15/15)
	≥10%	9.7 (7/72)	18.3 (13/71)	0 (0/15)
Severity	Very severe	34.2 (25/73)	41.7 (30/72)	60.0 (9/15)
	Less severe	65.8 (48/73)	58.2 (42/72)	40.0 (6/15)
Baseline RICO (%)		135.04 ± 68.443 (n = 64)	123.46 ± 53.401 (n = 66)	134.97 ± 58.37 (n = 15)
Baseline vWF:Ag level (%)		174.52 ± 79.754 (n =64)	159.49 ± 52.381 (n = 65)	198.57 ± 77.66 (n = 15)
GCS score at randomization	≤12	6.9 (5/72)	8.5 (6/71)	13.3 (2/15)
	13-15	93.1 (67/72)	91.5 (65/71)	86.7 (13/15)
Rate of corticosteroid co-administration throughout the study period		100.0 (71/71)	98.6 (69/70)	100.0 (15/15)
Duration of corticosteroid use during the study drug administration period (days)		32.0 (1-78)	34.0 (1-65)	45.0 (34-90)
Cumulative dose of corticosteroid during the study drug administration period (mg)		1770 (100-8440)	1970 (60-23125)	5475 (1352.8-10721.6)
Rate of rituximab co-administration throughout the study period		49.3 (35/71)	40.0 (28/70)	73.3 (11/15)
Rate of the immunosuppressant co-administration throughout the study period		5.6 (4/71)	14.3 (10/70)	20.0 (3/15)

Median (maximum-minimum), Percentage (number of subjects/number of subjects analyzed), Mean ± SD (number of subjects analyzed)
a Study ALX0681-C301, years; Study ALX0681-C202, days

Results of the analysis of subpopulations suggest that a past history of TTP (first onset or relapse), severity, and rituximab co-administration are unlikely to affect the efficacy of caplacizumab [see Section "7.R.2.5 Factors affecting the efficacy of caplacizumab" for efficacy of caplacizumab, classified by a past history of TTP (first onset or relapse) and use/no-use of rituximab in combination]. Table 36 shows the results of subpopulation analysis on the number of relapse of TTP in Study ALX0681-C301, showing generally more favorable results in the caplacizumab group than in the placebo group in all subpopulations and being unlikely to affect the efficacy evaluation of caplacizumab, although there are limitations to the interpretation of the results because of the small number of subjects analyzed. Although the baseline vWF:Ag level was higher in Japanese patients with TTP, suppression of RICO was observed in both studies [see Section "6.2.2 Studies in patients"], suggesting that the high baseline vWF:Ag level

does not significantly affect the efficacy of caplacizumab. Table 37 shows the results of the subpopulation analysis of the effect of corticosteroid in Study ALX0681-C301 and Study ALX0681-C202. In all subpopulations of Study ALX0681-C301, generally more favorable effects were observed in the caplacizumab group than in the placebo group, suggesting that the difference in the cumulative dose of corticosteroid is unlikely to affect the efficacy of caplacizumab. On the basis of the above, the applicant considers that the differences in the patient characteristics and in the use status of the standard treatment between the Japanese and foreign clinical studies are unlikely to affect the comparability of these studies.

Table 36. Efficacy in Study ALX0681-C301, by the number of times of TTP relapse (double-blind administration period, ITT population)

Number of times of TTP relapse	1		≥2	
	Placebo (n = 21)	Caplacizumab (n = 8)	Placebo (n = 18)	Caplacizumab (n = 16)
Time to normalization of platelet count (days) [95% CI]	2.90 [1.766, 3.888]	2.74 [0.803, 2.903]	2.85 [2.697, 3.478]	2.71 [1.628, 2.785]
Hazard ratio [95% CI]	1.06 [0.437, 2.556]		2.20 [1.040, 4.646]	
Percentage of subjects with TTP-related events during the study drug administration period	42.9 (9/21)	12.5 (1/8)	44.4 (8/18)	12.5 (2/16)
TTP-related death[a]	0 (0/21)	0 (0/8)	5.6 (1/18)	0 (0/16)
TTP relapse	33.3 (7/21)	0 (0/8)	33.3 (6/18)	6.3 (1/16)
Serious thromboembolic events during the study drug administration[b]	9.5 (2/21)	12.5 (1/8)	5.6 (1/18)	6.3 (1/16)
TTP relapse rate throughout the study period	33.3 (7/21)	0 (0/8)	33.3 (6/18)	18.8 (3/16)
TTP relapse rate during the follow-up period	0 (0/13)	0 (0/8)	0 (0/10)	12.5 (2/16)
Percentage of subjects with refractory TTP[c]	4.8 (1/21)	0 (0/8)	5.6 (1/18)	0 (0/16)
Duration of PE during the study drug administration period (days)	7.0 (3-23)	5.0 (3-13)	7.0 (3-26)	5.0 (3-7)
Total plasma volume (L) during the study drug administration period	27.40 (9.0-124.1)	20.64 (10.6-39.0)	22.55 (7.5-91.0)	17.18 (7.9-27.1)

Incidence % (number of subjects with events/number of subjects analyzed), Median (minimum-maximum)

a Adverse events with death outcome that were classified as “clinically significant TTP-related events” and regarded as “death caused by TTP” and/or “TTP-related” by the investigator.

b Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

c Platelet count did not double and LDH exceeded the upper limit of normal after the 4-day standard treatment.

Table 37. Efficacy by cumulative dose of corticosteroid in Study ALX0681-C301 (double-blind administration period) and in Study ALX0681-C202

	Study ALX0681-C301 (double-blind administration period, ITT population)				Study ALX0681-C202 (PP population)	
Cumulative dose of corticosteroid throughout the study period	Less than median[a]		Not less than median[a]		Less than median[b]	Not less than median[b]
	Placebo (n = 40)	Caplacizumab (n = 35)	Placebo (n = 33)	Caplacizumab (n = 37)	(n = 7)	(n = 8)
Time to normalization of platelet count (days) [95% CI]	2.77 [2.438, 3.556]	2.65 [1.815, 2.828]	3.00 [2.697, 3.849]	2.72 [1.864, 2.930]	2.79 [1.692, 3.647]	2.95 [0.876, 3.982]
Hazard ratio [95% CI]	1.41 [0.854, 2.317]		1.70 [1.033, 2.802]		—	—
Percentage of subjects with TTP-related events during the study drug administration period	35.0 (14/40)	11.8 (4/34)	66.7 (22/33)	13.5 (5/37)	0 (0/7)	12.5 (1/8)
TTP-related death[c]	5.0 (2/40)	0 (0/34)	3.0 (1/33)	0 (0/37)	0 (0/7)	0 (0/8)
TTP relapse	22.5 (9/40)	5.9 (2/34)	57.6 (19/33)	2.7 (1/37)	0 (0/7)	12.5 (1/8)
Serious thromboembolic events that occurred during study drug administration[d]	10.0 (4/40)	5.9 (2/34)	6.1 (2/33)	10.8 (4/37)	0 (0/7)	0 (0/8)
TTP relapse rate throughout the study period	22.5 (9/40)	14.7 (5/34)	57.6 (19/33)	10.8 (4/37)	0 (0/7)	12.5 (1/8)
TTP relapse rate during the follow-up period	0 (0/27)	10.0 (3/30)	0 (0/12)	8.3 (3/36)	0 (0/7)	0 (0/8)
Percentage of subjects with refractory TTP[e]	5.0 (2/40)	0 (0/34)	3.0 (1/33)	0 (0/37)	0 (0/7)	0 (0/8)
Days of PE during the study drug administration period	6.0 (3-14)	5.0 (1-35)	10.0 (3-46)	5.0 (3-13)	5.0 (4-7)	5.5 (3-11)
Total plasma volume (L) during the study drug administration period	19.60 (4.0-71.5)	16.47 (5.3-102.2)	34.50 (9.0-254.0)	20.44 (9.0-49.6)	23.04 (13.4-29.4)	26.76 (17.2-50.0)

Incidence % (number of subjects with events/number of subjects analyzed); Median (minimum-maximum); -, Not calculated.

a 1862.50 mg

b 5475.00 mg

c Adverse events with death outcome that were classified as "clinically significant TTP-related events" and regarded as "death caused by TTP" and/or "TTP-related" by the investigator.

d Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

e Study ALX0681-C301: Platelet count did not double and LDH exceeded the upper limit of normal after the 4-day standard treatment. Study ALX0681-C202: Despite 5 PEs and treatment with corticosteroid, a persistent increase in platelet count was not observed, or platelet count was $<50 \times 10^9$/L with a persistent increase in LDH (>1.5 times the upper limit of normal),

PMDA's view:

TTP relapse rate throughout the study period (6.7%) was below the pre-specified efficacy threshold (≤20%), although precise efficacy evaluation is difficult because Study ALX0681-C202 was conducted as an uncontrolled study. Given the limited feasibility of the Japanese clinical study due to the small number of patients eligible for the study, it is unavoidable to evaluate the efficacy from the comparison of the point estimate with the efficacy threshold pre-defined based on the information available from Study ALX0681-C301, etc. It is thus acceptable to evaluate the efficacy based on the above threshold, given the applicant's explanation about the justification on the evaluation method. PMDA also confirmed that the sensitivity analysis in the mITT population showed results similar to those in the PP population.

Regarding the comparison with Study ALX0681-C301, although there were some differences in the characteristics of patients enrolled in the Japanese and the foreign clinical studies and in the use status of the standard treatment, the results of the subpopulation analysis show that these differences are unlikely to significantly affect the evaluation of the efficacy of caplacizumab. From the comparison of the primary endpoint and the secondary endpoints, Study ALX0681-C202 showed the efficacy similar to that observed in the caplacizumab group of Study ALX0681-C301.

From the above discussion, PMDA concludes that it is possible to evaluate the usefulness of caplacizumab in Japanese patients with the results of Study ALX0681-C301 also taken into account, and that caplacizumab is expected to be effective in Japanese patients with acquired TTP as in non-Japanese patients with acquired TTP.

7.R.2.5 Factors affecting the efficacy of caplacizumab

The applicant's explanation about the effects of patient characteristics on the efficacy of caplacizumab: Tables 38 and 39 show the efficacy, classified by a past history of TTP (first onset or relapse) and baseline ADAMTS13 activity (<10%, ≥10%), in Studies ALX0681-C301 and ALX0681-C202. In Study ALX0681-C202, there are limitations to the interpretation of the results due to the small number of subjects, whereas in Study ALX0681-C301, more favorable results were obtained in the caplacizumab group than in the placebo group in all subpopulations studied.

Table 38. Efficacy classified by past history of TTP (first onset or relapse) in Study ALX0681-C301 (double-blind administration period) and in Study ALX0681-C202

	Study ALX0681-C301 (double-blind administration period, ITT population)				Study ALX0681-C202 (PP population)	
Past history of TTP	First onset		Relapse		First onset (n = 12)	Relapse (n = 3)
	Placebo (n = 34)	Caplacizumab (n = 48)	Placebo (n = 39)	Caplacizumab (n = 24)		
Time (days) to normalization of platelet count	2.89 [2.59, 3.69]	2.64 [1.82, 2.87]	2.88 [2.53, 3.74]	2.71 [1.82, 2.83]	2.60 [1.692, 3.647]	3.46 [2.537, -]
Hazard ratio [95% CI]	1.67 [1.025, 2.722]		1.64 [0.951, 2.828]		—	—
Percentage of subjects with TTP-related events during the study drug administration period	55.9 (19/34)	12.8 (6/47)	43.6 (17/39)	12.5 (3/24)	8.3 (1/12)	0 (0/3)
TTP relapse rate throughout the study period	44.1 (15/34)	12.8 (6/47)	33.3 (13/39)	12.5 (3/24)	8.3 (1/12)	0 (0/3)
TTP relapse rate during the study drug administration period	44.1 (15/34)	4.3 (2/47)	33.3 (13/39)	4.2 (1/24)	8.3 (1/12)	0 (0/3)
TTP relapse rate during the follow-up period	0 (0/16)	9.5 (4/42)	0 (0/23)	8.3 (2/24)	0 (0/12)	0 (0/3)
Percentage of subjects with refractory TTP[a]	2.9 (1/34)	0 (0/48)	5.1 (2/39)	0 (0/24)	0 (0/12)	0 (0/3)
Days of PE during the study drug administration period	8.5 (3-46)	5.0 (1-35)	7.0 (3-26)	5.0 (3-13)	5.0 (3-11)	5.0 (5-7)
Total plasma volume (L) during the study drug administration period	28.27 (4.0-254.0)	18.00 (5.3-102.2)	24.13 (7.5-124.1)	18.76 (7.9-39.0)	24.48 (13.4-50.0)	24.60 (20.3-29.4)

Incidence % (number of subjects with events/number of subjects analyzed); Median (minimum-maximum); -, Not calculated.

a Study ALX0681-C301: Platelet count did not double and LDH exceeded the upper limit of normal after the 4-day standard treatment. Study ALX0681-C202: Despite 5 PEs and treatment with corticosteroid, a persistent increase in platelet count was not observed, or platelet count was $<50 \times 10^9$/L with a persistent increase in LDH (>1.5 times the upper limit of normal).

Table 39. Efficacy classified by baseline ADAMTS13 activity (<10%, ≥10%) in Study ALX0681-C301 (double-blind administration period) and in Study ALX0681-C202

	Study ALX0681-C301 (double-blind administration period, ITT population)				Study ALX0681-C202 (mITT population)	
Baseline ADAMTS13 activity	<10%		≥10%		<10%	≥10%
	Placebo (n = 65)	Caplacizumab (n = 58)	Placebo (n = 7)	Caplacizumab (n = 13)	(n = 18)	(n = 3)
Time (days) to normalization of platelet count	2.88 [2.67, 3.74]	2.70 [1.93, 2.83]	3.53 [1.88, 7.79]	1.89 [0.79, 4.69]	3.47 [1.884, 3.765]	— [2.725, —]
Hazard ratio [95% CI]	1.70 [1.162, 2.489]		1.52 [0.649, 4.919]		—	
Percentage of subjects with TTP-related events during the study drug administration period	53.8 (35/65)	15.5 (9/58)	14.3 (1/7)	0 (0/13)	11.1 (2/18)	33.3 (1/3)
TTP relapse rate throughout the study period	41.5 (27/65)	13.8 (8/58)	14.3 (1/7)	7.7 (1/13)	5.6 (1/18)	0 (0/3)
TTP relapse rate during the study drug administration period	41.5 (27/65)	5.2 (3/58)	14.3 (1/7)	0 (0/13)	5.6 (1/18)	0 (0/3)
TTP relapse rate during the follow-up period	0 (0/33)	9.4 (5/53)	0 (0/6)	7.7 (1/13)	0 (0/18)	0 (0/3)
Percentage of subjects with refractory TTP[a]	4.6 (3/65)	0 (0/58)	0 (0/7)	0 (0/13)	0 (0/18)	0 (0/3)
Days of PE during the study drug administration period	8 (3-46)	5 (1-35)	6 (3-11)	4 (2-13)	5.5 (3-20)	7.0 (5-15)
Total plasma volume (L) during the study drug administration period	28.13 (4.0-254.0)	18.37 (5.3-102.2)	20.50 (10.7-29.1)	14.55 (7.9-39.7)	25.56 (13.4-53.7)	28.99 (20.2-59.4)

Incidence % (number of subjects with events/number of subjects analyzed), Median (min-max.)

a Study ALX0681-C301: Platelet count did not double and LDH exceeded the upper limit of normal after the 4-day standard treatment. Study ALX0681-C202: Despite 5 PEs and treatment with corticosteroid, a persistent increase in platelet count was not observed, or platelet count was $<50 \times 10^9$/L with a persistent increase in LDH (>1.5 times the upper limit of normal).

The above results show that caplacizumab is expected to be effective in all patient populations regardless of a past history of TTP (first onset or relapse) or baseline ADAMTS13 activity (<10%, ≥10%).

In both Japanese and foreign clinical studies, efficacy and safety were investigated under the standard treatment (PE and corticosteroid) in combination with caplacizumab, and use of immunosuppressants such as rituximab was permitted according to the standard treatment in each region. Efficacy classified by use/non-use of rituximab in combination was compared throughout the study period (Table 40). In Study ALX0681-C301, more favorable results were observed in the caplacizumab group than in the placebo group, regardless of use/non-use of rituximab in combination, suggesting the efficacy of caplacizumab in both patient populations.

Table 40. Efficacy classified by use/non-use of rituximab in combination in Study ALX0681-C301 (double-blind administration period) and Study ALX0681-C202

	Study ALX0681-C301 (double-blind administration study, ITT population)				Study ALX0681-C202 (PP population)	
Rituximab co-administration throughout the study period	No		Yes		No (n = 4)	Yes (n = 11)
	Placebo (n = 38)	Caplacizumab (n = 44)	Placebo (n = 35)	Caplacizumab (n = 28)		
Time (days) to normalization of platelet count [95% CI]	2.89 [2.598, 3.849]	2.69 [1.815, 2.848]	2.78 [2.591, 3.615]	2.67 [2.452, 2.903]	3.71 [1.692, —]	2.54 [1.758, 3.487]
Hazard ratio [95% CI]	1.50 [0.937, 2.414]		1.66 [0.978, 2.816]		—	
Percentage of subjects with TTP-related events during the study drug administration period	34.2 (13/38)	7.0 (3/43)	65.7 (23/35)	21.4 (6/28)	0 (0/4)	9.1 (1/11)
TTP-related death[a]	7.9 (3/38)	0 (0/43)	0 (0/35)	0 (0/28)	0 (0/4)	0 (0/11)
TTP relapse	23.7 (9/38)	2.3 (1/43)	54.3 (19/35)	7.1 (2/28)	0 (0/4)	9.1 (1/11)
Serious thromboembolic events that occurred during study drug administration[b]	5.3 (2/38)	4.7 (2/43)	11.4 (4/35)	14.3 (4/38)	0 (0/4)	0 (0/11)
TTP relapse rate throughout the study period	23.7 (9/38)	9.3 (4/43)	54.3 (19/35)	17.9 (5/28)	0 (0/4)	9.1 (1/11)
TTP relapse rate during the follow-up period	0 (0/23)	7.7 (3/39)	0 (0/16)	11.1 (3/27)	0 (0/4)	0 (0/11)
Percentage of subjects with refractory TTP[c]	2.6 (1/38)	0 (0/43)	5.7 (2/35)	0 (0/28)	0 (0/4)	0 (0/11)
Days of PE during the study drug administration period	6.0 (3-25)	5.0 (1-35)	10.0 (3-46)	5.0 (3-16)	6.0 (5-7)	5.0 (3-11)
Total plasma volume (L) during the study drug administration period	20.73 (4.0-115.9)	18.00 (5.3-102.2)	31.91 (8.4-254.0)	19.13 (6.9-51.1)	25.20 (18.6-31.7)	24.60 (13.4-50.0)

Incidence % (number of subjects with events/number of subjects analyzed); Median (minimum-maximum); -, Not calculated.

a Adverse events with death outcome that were classified as "clinically significant TTP-related events" and regarded as "death caused by TTP" and/or "TTP-related" by the investigator.

b Events considered to be myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, etc.

c Study ALX0681-C301: Platelet count did not double and LDH exceeded the upper limit of normal after the 4-day standard treatment. Study ALX0681-C202: Despite 5 PEs and treatment with corticosteroid, a persistent increase in platelet count was not observed, or platelet count was $<50 \times 10^9$/L with a persistent increase in LDH (>1.5 times the upper limit of normal).

On the basis of the review of the results in subpopulations in Study ALX0681-C301 submitted by the applicant, PMDA concluded that caplacizumab is expected to be effective regardless of a past history of TTP (first onset or relapse), ADAMTS13 activity (<10%, ≥10%), and use/non-use of rituximab in combination.

7.R.3 Safety

On the basis of the following reviews, PMDA concluded that the safety of caplacizumab in patients with acquired TTP is clinically acceptable, given its efficacy observed in Section "7.R.2 Efficacy."

7.R.3.1 Incidences of adverse events in Japanese and foreign clinical studies

The applicant's explanation:

Table 41 shows the incidences of adverse events in Studies ALX0681-C301, ALX0681-C202, and ALX-0681-2.1/10.

Table 41. Incidences of adverse events in Japanese and foreign clinical studies

		Study ALX0681-C301 (double-blind administration period)		Study ALX0681-C202	Study ALX-0681-2.1/10 (single-blind study period)	
Treatment		Placebo (n = 73)	Caplacizumab (n = 71)	n = 21	Placebo (n = 37)	Caplacizumab (n = 35)
Exposure period (median [minimum-maximum]) (days)		23.0 (2-66)	35.0 (1-65)	35.0 (7-69)	37.0 (2-90)	36.0 (3-77)
All adverse events		97.3 (71)	97.2 (69)	100.0 (21)	100.0 (37)	97.1 (34)
Severity	Mild	37.0 (27)	39.4 (28)	28.6 (6)	97.3 (36)	88.6 (31)
	Moderate	27.4 (20)	36.6 (26)	47.6 (10)	83.8 (31)	77.1 (27)
	Severe	32.9 (24)	21.1 (15)	23.8 (5)	37.8 (14)	51.4 (18)
Serious adverse events		53.4 (39)	39.4 (28)	23.8 (5)	51.4 (19)	57.1 (20)
Adverse events resulting in death		4.1 (3)	1.4 (1)	0 (0)	5.4 (2)	0 (0)
Adverse events leading to discontinuation of the study drug		12.3 (9)	7.0 (5)	9.5 (2)	5.4 (2)	11.4 (4)

Incidence % (number of subjects with events)

In Study ALX0681-C301, the incidences, severity, etc., of adverse events did not differ between the treatment groups. In Study ALX-0681-2.1/10, the incidences of severe adverse events and adverse events leading to discontinuation of the study drug were higher in the caplacizumab group than in the placebo group. The main severe event was TTP (13.5% in the placebo group, 31.4% in the caplacizumab group). A causal relationship to the study drug was denied for adverse events leading to discontinuation of the study drug except anaemia/hypertransaminasaemia/metrorrhagia/epistaxis/gingival bleeding/ecchymosis/haematoma, and transaminases increased in 1 subject each in the caplacizumab group.

Death occurred in 1 patient with acquired TTP (cerebral ischaemia) in the caplacizumab group in Study ALX0681-C301 (double-blind administration period), which occurred during the follow-up period (6 days after the end of the study drug administration) and was concluded to be TTP-related death. Its causal relationship to the study drug was denied. In Study ALX0681-C202, death occurred in 1 patient (lower gastrointestinal haemorrhage) after the end of the study (33 days after the end of caplacizumab administration), but its causal relationship to the study drug was denied.

In Studies ALX0681-C301 and ALX-0681-2.1/10, mucocutaneous bleeding-associated adverse events such as epistaxis and gingival bleeding were observed more frequently in the caplacizumab group than in the placebo group, as expected from the mechanism of action of caplacizumab. Except for these events, the safety profile of caplacizumab was generally favorable. The incidence of adverse events in Study ALX0681-C202 was similar to that in Study ALX0681-C301, showing no safety concerns unique to Japanese patients.

PMDA's view:
The incidences of adverse events in the Japanese and foreign clinical studies suggest no clinically significant safety concerns with caplacizumab except for haemorrhage-related events. Neither are there any concerns unique to Japanese patients with acquired TTP. The bleeding risk caused by caplacizumab is discussed further in the next section.

7.R.3.2 Bleeding risk

(a) Evaluation of bleeding risk

The applicant's explanation about the bleeding risk caused by caplacizumab:

Thrombocytopenia is a typical symptom during the acute phase of acquired TTP, showing a bleeding tendency. Since caplacizumab inhibits the binding of vWF with platelets, thereby interfering with platelet adhesion and aggregation, caution should be exercised against the occurrence of haemorrhage during the treatment with caplacizumab. Table 42 shows the incidences of haemorrhage-related events[30] observed in Studies ALX0681-C301, ALX0681-C202, and ALX-0681-2.1/10.

Table 42. Incidences of haemorrhage-related events[a] in each clinical study

	Study ALX0681-C301			Study ALX0681-C202	Study ALX-0681-2.1/10 (single-blind study period)	
	Double-blind administration period		Open-label administration period			
	Placebo (n = 73)	Caplacizumab (n = 71)	n = 28	(n = 21)	Placebo (n = 37)	Caplacizumab (n = 35)
All haemorrhage-related events	47.9 (35)	64.8 (46)	78.6 (22)	33.3 (7)	37.8 (14)	54.3 (19)
Haemorrhage-related events resulting in death	1.4 (1)	0 (0)	0 (0)	0 (0)	2.7 (1)	0 (0)
Serious haemorrhage-related events	1.4 (1)	14.1 (10)	3.6 (1)	4.8 (1)	5.4 (2)	5.7 (2)
Moderate haemorrhage-related events	4.1 (3)	19.7 (14)	17.9 (5)	4.8 (1)	8.1 (3)	20.0 (7)
Severe haemorrhage-related events	1.4 (1)	4.2 (3)	0 (0)	4.8 (1)	2.7 (1)	2.9 (1)
Haemorrhage-related events leading to discontinuation of the study drug	1.4 (1)	2.8 (2)	0 (0)	4.8 (1)	2.7 (1)	2.9 (1)
Haemorrhage-related events leading to treatment interruption	0 (0)	5.6 (4)	3.6 (1)	4.8 (1)	0 (0)	5.7 (2)

Incidence % (number of subjects with events)

a Studies ALX0681-C301 and ALX0681-C202: Standardised MedDRA queries (MedDRA SMQ) "haemorrhage (narrow)" (except Medical Dictionary for Regulatory Activities Preferred Term [MedDRA PT] "TTP")
Study ALX-0681-2.1/10: Post-hoc identification from MedDRA PTs in the applicant's medical review

In Study ALX0681-C301 (double-blind administration period), main haemorrhage-related events with a higher incidence in the caplacizumab group than in the placebo group were epistaxis (2.7% in the placebo group, 32.4% in the caplacizumab group) and gingival bleeding (1.4%, 18.3%). Serious haemorrhage-related events observed in the caplacizumab group were epistaxis in 4 subjects, gingival bleeding, upper gastrointestinal haemorrhage, haematemesis, subarachnoid haemorrhage, menorrhagia, gastric ulcer haemorrhage, and haemorrhagic ovarian cyst in 1 subject each. Except for gastric ulcer haemorrhage and haemorrhagic ovarian cyst, a causal relationship to the study drug could not be ruled out for other 9 events in 8 subjects. All of the events resolved before the end of the study in each subject. Severe haemorrhage-related events observed in the caplacizumab group were epistaxis, gingival bleeding, and upper gastrointestinal haemorrhage in 1 subject each. Their causal relationship to the study drug could not be ruled out, and caplacizumab administration was discontinued or interrupted. The outcome was "recovered." Haemorrhage-related events frequently observed during the open-label administration period were catheter site haemorrhage (28.6%), epistaxis (17.9%), and gingival bleeding (14.3%). A serious haemorrhage-related event (upper gastrointestinal haemorrhage) was observed in 1

[30] Studies ALX0681-C301 and ALX0681-C202: MedDRA SMQ "haemorrhages (narrow)" (except MedDRA PT "TTP")
Study ALX-0681-2.1/10: Post-hoc identification from MedDRA PTs based on the medical review of the applicant

of 28 subjects, but resolved without interruption of the study drug administration. There were no haemorrhage-related events resulting in death, severe haemorrhage-related events, or haemorrhage-related events leading to discontinuation of the study drug.

Among haemorrhage-related events observed in Study ALX0681-C202, events for which a causal relationship to the study drug could not be ruled out were epistaxis and gastrointestinal haemorrhage in 2 subjects each, and injection site haemorrhage, pulmonary alveolar haemorrhage, wound haemorrhage, and haemorrhage subcutaneous in 1 subject each. Among them, pulmonary alveolar haemorrhage was a serious haemorrhage-related event for which a causal relationship to caplacizumab could not be ruled out. This patient[24)] had a past history of old myocardial infarction, etc. (orally treated with acetylsalicylic acid until pulmonary alveolar haemorrhage was noticed) and was complicated with dermatomyositis, hepatic dysfunction, etc., accompanied by interstitial pneumonia. Caplacizumab was discontinued because of pulmonary alveolar haemorrhage on Day 25 (post-daily PE period). The incidence of haemorrhage-related events, etc., did not significantly differ between the Japanese and the foreign clinical studies, showing a similar bleeding risk in both study regions.

Main haemorrhage-related events frequently observed in Study ALX-0681-2.1/10 (single-blind study period) were epistaxis (10.8% in the placebo group, 31.4% in the caplacizumab group), gingival bleeding (5.4%, 14.3%), contusion (5.4%, 11.4%), petechiae (0%, 11.4%), and haematoma (10.8%, 11.4%). Serious haemorrhage-related events observed in the caplacizumab group were subarachnoid haemorrhage/retinal haemorrhage and metrorrhagia in 1 subject each. A causal relationship to the study drug could not be ruled out for subarachnoid haemorrhage and metrorrhagia and administration of the study drug was discontinued or interrupted. The outcome was “recovered.” Metrorrhagia in 1 subject of the caplacizumab group was the only severe haemorrhage-related event and the only haemorrhage-related event leading to treatment discontinuation.

In the Japanese and foreign clinical studies, in case of a serious or severe haemorrhage, an interruption of the study drug should be considered and the administration should be resumed only after the haemorrhage had stopped. In addition to the standard anti-bleeding treatment, rescue treatment with human plasma-derived vWF-containing coagulation factor VIII product or with recombinant blood coagulation factor VIII product (both are off-label use in Japan) were permitted. No patients received these rescue therapies in Study ALX0681-C202, whereas combined vWF/blood coagulation factor VIII product was administered to 1 subject who had serious epistaxis in Study ALX0681-C301 and in 1 subject who showed serious haematuria in Study ALX0681-C302/LTS16371.

After the launch of overseas marketing ([redacted], 20[redacted] to [redacted], 20[redacted]), there were reports[31)] of incidences of major bleeding[32)] including fatal or life-threatening haemorrhage and haemorrhage in critical sites or organs (e.g., cerebral haemorrhage, pulmonary haemorrhage), which led to the conclusion that a new

[31)] Most of subjects with fatal or life-threatening haemorrhage were those co-administered with acetylsalicylic acid and heparin (including low-molecular-weight heparin).

[32)] Criteria of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH SSC Criteria) 1) Fatal haemorrhage; 2) haemorrhage from critical sites or organs; 3) anemia with hemoglobin ≤20 g/L (1.24 mmol/L), or haemorrhage requiring transfusion of ≥2 units of whole blood or red cells

precaution against major bleeding is essential, resulting in the revision of the package insert in approved countries including the US and Europe.

On the basis of the above information, “Clinically Significant Adverse Reactions” and “Important Precautions” sections in the package insert will include the following advice: (a) Haemorrhage including fatal or life-threatening haemorrhage may occur; (b) patients’ clinical conditions should be monitored carefully; and (c) if a clinically significant haemorrhage occur, caplacizumab should be interrupted and clinically appropriate measures should be taken in order to normalize hemostatic imbalance upon consultation with a hematology specialist as necessary. At the same time, information on the incidences of haemorrhage after the Japanese and foreign clinical studies and the overseas marketing launch will be provided to healthcare professionals. Haemorrhage will be specified as an important identified risk in the risk management plan, and information on the incidences will be collected continuously, including the exploration of risk factors after the market launch.

PMDA’s view:
Haemorrhage-related events were the adverse events most frequently observed in clinical studies of caplacizumab. Caution should be paid to bleeding risk during the treatment with caplacizumab. The comparison of the incidences of haemorrhage-related events between Japanese and foreign clinical studies does not show any tendency of a higher bleeding risk after treatment with caplacizumab in Japanese patients with acquired TTP than in non-Japanese patients with acquired TTP, suggesting that the content of the precautions against haemorrhage proposed by the applicant is appropriate as a whole. Details of the precautions will be discussed in sections below.

(b) Characteristics of patients with a high bleeding risk and appropriateness of raising precautions
PMDA asked the applicant to investigate factors characteristic to patients who had haemorrhage-related events (death, serious adverse events, in particular) and to explain the sufficiency of the proposed precautions.

The applicant’s explanation:
Patients who had serious or moderate/severe haemorrhage-related events in Japanese and foreign clinical studies were investigated for characteristic factors. No particular tendency was observed in age, past illness, platelet count, coagulation parameters, or use/non-use of antithrombogenic drugs, although there are limitations to the interpretation of the results because of the scarcity of patients who had these events.

The incidences of haemorrhage-related events, classified by age (≥65 years, <65 years) and body weight (not less than median weight [82.8 kg], less than median weight [82.8 kg]) in Study ALX0681-C301 (double-blind administration period) were investigated. No significant difference was noted between subpopulations.

After the launch of overseas marketing ([redacted], 20[redacted] to [redacted], 20[redacted]), there were reports of occurrences of major bleeding including fatal or life-threatening haemorrhage in patients co-administered with an anticoagulant or a drug with a platelet aggregation-inhibitory effect, which led to the conclusion that a

new precaution against major bleeding is essential in this group of patients, resulting in the revision of the package insert in approved countries including the US and Europe.

Since comorbidities and co-administration of anticoagulants and/or antiplatelet drugs may possibly affect bleeding risk, caution should be provided in the package insert that physicians are advised to carefully determine caplacizumab administration upon evaluating the therapeutic benefit and possible risk of caplacizumab in patients who have an underlying disease with coagulation disorder such as hemophilia, severe hepatic impairment, or high bleeding risk due to administration of anticoagulants and/or antiplatelet drugs. In the Japanese and foreign clinical studies, the following patients were excluded from subjects: Patients with clinically significant active or with high risk of haemorrhage (except thrombocytopenia); and patients requiring uninterrupted chronic treatment with an anticoagulant for safety reasons. In these patient groups as well, acquired TTP is a fatal disease even under the standard treatment, and restricting the administration of caplacizumab may increase the risk of death due to the delay in recovery, resistance acquisition to the antecedent treatment, progressive ischemia, or organ injury. Rather than uniformly contraindicating caplacizumab in these groups of patients, whether to use caplacizumab should be determined for each patient based on careful assessment of the therapeutic benefits and possible risks of caplacizumab. Thus the following precautions will be included in the package insert: (a) Major haemorrhage including fatal or life-threatening haemorrhage associated with caplacizumab is reported in patients co-administered with a drug with a platelet aggregation-inhibitory effect or an anticoagulant, (b) careful administration is required in patients in whom caplacizumab may increase the bleeding risk and patients with clinically significant active haemorrhage, and (c) if clinically significant haemorrhage occur, caplacizumab administration should be interrupted and adequate clinical measures should be taken to promptly normalize hemostatic imbalance upon consultation with a hematology specialist as necessary.

PMDA's view:
Attention should be paid to bleeding risk in all subjects receiving caplacizumab. Although Japanese and foreign clinical studies have not identified characteristics of patients with evidently increased risk of bleeding, enhanced bleeding risk is potentially assumed in patients with an increased bleeding risk such as patients with coagulation disorder and haemorrhage disorder and in patients requiring treatment with an antithrombogenic drug. It is therefore appropriate that the applicant propose to advise in the package insert that whether to use caplacizumab should be carefully determined upon evaluating the therapeutic benefit and possible risk of caplacizumab. As for patients with clinically significant active haemorrhage, the condition requiring discontinuation of caplacizumab once manifest (a population excluded from clinical studies), whether caplacizumab should be contraindicated will be finalized, taking account of comments raised in the Expert Discussion.

(c) Timing of the onset of haemorrhage
The applicant's explanation about the timing of the onset of haemorrhage-related events caused by caplacizumab:
Table 43 shows the incidences of first-onset haemorrhage-related events in Study ALX0681-C301 (double-blind administration period) and Study ALX0681-C202. During the daily PE period, thrombocytopenia and haemorrhage-related events associated with PE technique were observed, but the

risk did not increase with the prolongation of the treatment period. Caution should be exercised against haemorrhage regardless of the period of the treatment with caplacizumab.

Table 43. Incidences of first-onset haemorrhage-related events by period

		Study ALX0681-C301 (double-blind administration period)							
		Daily PE period		Post-daily PE period		Extended treatment period		Follow-up period	
		Placebo	Caplacizumab	Placebo	Caplacizumab	Placebo	Caplacizumab	Placebo	Caplacizumab
All haemorrhage-related events		26.0 (19/73)	38.0 (27/71)	32.8 (21/64)	47.7 (31/65)	0 (0/6)	36.4 (8/22)	5.1 (2/39)	12.1 (8/66)
Severity	Mild	23.3 (17/73)	26.8 (19/71)	29.7 (19/64)	33.8 (22/65)	0 (0/6)	31.8 (7/22)	5.1 (2/39)	12.1 (8/66)
	Moderate	1.4 (1/73)	9.9 (7/71)	3.1 (2/64)	12.3 (8/65)	0 (0/6)	0 (0/22)	0 (0/39)	0 (0/66)
	Severe	1.4 (1/73)	1.4 (1/71)	0 (0/64)	1.5 (1/65)	0 (0/6)	4.5 (1/22)	0 (0/39)	0 (0/66)
Serious events		1.4 (1/73)	5.6 (4/71)	0 (0/64)	9.2 (6/65)	0 (0/6)	4.5 (1/22)	0 (0/39)	0 (0/66)
Events leading to discontinuation of the study drug		1.4 (1/73)	0 (0/71)	0 (0/64)	1.5 (1/65)	0 (0/6)	4.5 (1/22)	0 (0/39)	0 (0/66)

		Study ALX0681-C202			
		Daily PE period	Post-daily PE period	Extended treatment period	Follow-up period
All haemorrhage-related events		19.0 (4/21)	26.3 (5/19)	14.3 (1/7)	4.8 (1/21)
Severity	Mild	14.3 (3/21)	21.1 (4/19)	14.3 (1/7)	4.8 (1/21)
	Moderate	4.8 (1/21)	0 (0/19)	0 (0/7)	0 (0/21)
	Severe	0 (0/21)	5.3 (1/19)	0 (0/7)	0 (0/21)
Serious events		0 (0/21)	5.3 (1/19)	0 (0/7)	0 (0/21)
Events leading to discontinuation of the study drug		0 (0/21)	5.3 (1/19)	0 (0/7)	0 (0/21)

Incidence % (number of subjects with events/number of subjects analyzed

PMDA's view:

Currently, the timing particularly requiring attention against caplacizumab-induced haemorrhage has not been identified. Attention should be paid to the occurrence of haemorrhage throughout the period of treatment with caplacizumab.

7.R.3.3 Hypersensitivity reactions

The applicant's explanation about the risk of hypersensitivity reactions caused by caplacizumab:

In Study ALX0681-C301 (double-blind administration period), hypersensitivity reactions[33)] were observed in 30.1% (22 of 73) of subjects in the placebo group and in 33.8% (24 of 71) of subjects in the caplacizumab group. Main events were urticaria (6.8% in the placebo group, 16.9% in the caplacizumab group), rash (12.3%, 7.0%), and anaphylactic transfusion reactions (4.1%, 1.4%). Most of hypersensitivity reactions (19.2% [14 of 73 subjects] in the placebo group, 22.5% [16 of 71 subjects] in the caplacizumab group) occurred during the first daily PE period. There was no drug-induced anaphylaxis for which a causal relationship to caplacizumab could not be ruled out. Hypersensitivity reactions for which a causal relationship to the study drug could not be ruled out were observed in 1.4%

33) MedDRA SMQ "hypersensitivity (narrow)," "anaphylactic reaction (narrow)," and "angioedema (narrow)"

(1 of 73) of subjects in the placebo group (rash) and in 5.6% (4 of 71) of subjects in the caplacizumab group (injection site rash/injection site urticaria, injection site rash, injection site hypersensitivity, and urticaria in 1 subject each). Serious hypersensitivity reactions were observed in 4.1% (3 of 73) of subjects in the placebo group and in 1.4% (1 of 71) of subjects in the caplacizumab group, but their causal relationship to the study drug was denied. During the open-label administration period, hypersensitivity reactions were observed in 35.7% (10 of 28) of subjects. Serious hypersensitivity reaction (rash erythematous) in 1 subject was moderate in severity, and its causal relationship to the study drug could not be ruled out. The outcome was "improved" while the treatment with the study drug was continued.

In Study ALX0681-C202, hypersensitivity reactions[33)] were observed in 57.1% (12 of 21) of subjects (urticaria in 4 subjects, allergic transfusion reaction in 3 subjects, rash in 2 subjects, allergic transfusion reaction/rash/drug hypersensitivity, dermatitis acneiform/continuous infusion-related reaction, and injection site rash in 1 subject each). Injection site rash in 1 subject which occurred on Day 17 after the start of caplacizumab administration (during the first daily PE period) was considered to be causally related to the study drug. Many of hypersensitivity reactions (42.9% [9 of 21 subjects]) occurred during the daily PE period. No serious or severe hypersensitivity reactions were observed throughout the study period.

In Study ALX-0681-2.1/10, hypersensitivity reactions[33)] were observed in 18.9% (7 of 37) of subjects in the placebo group and in 28.6% (10 of 35) of subjects in the caplacizumab group. A serious hypersensitivity reaction was observed in 2.9% (1 of 35) of subjects in the caplacizumab group (dermatitis allergic), which was moderate in severity and its causal relationship to the study drug or PE could not be ruled out. The event resolved while the treatment with the study drug was continued without interruption.

In Study ALX0681-C302/LTS16371, hypersensitivity reactions[33)] were observed in 3 of 13 subjects who had shown relapse of TTP and received caplacizumab again. Two events of injection site hypersensitivity (mild in severity) in 1 patient were considered to be causally related to the study drug.

After the market launch in overseas countries ([redacted], 20[redacted] to [redacted], 20[redacted]), anaphylactic reaction was reported in 1 patient who received caplacizumab in combination with PE for the treatment of acute acquired TTP. The anaphylactic reaction was highly likely to be due to PE with frozen fresh plasma (FFP), judging from the timing of its onset.

As shown above, although information obtained from Japanese and foreign clinical studies or from post-marketing data does not strongly suggest the relationship between caplacizumab and serious hypersensitivity reactions or anaphylactic reaction, information on the incidences of related adverse events will be provided in the package insert, and serious hypersensitivity reactions will be defined as an important potential risk in the risk management plan and information on their incidences will be collected after the market launch.

PMDA's view:

Currently, no clear risk of hypersensitivity reactions related to caplacizumab administration has been detected in the Japanese and foreign clinical studies or in the overseas post-marketing safety information. However, since caplacizumab is a protein product, it is appropriate that the applicant plans to provide information on the incidences of related adverse events and antibody production in the package insert and to collect the information on the incidences of hypersensitivity reactions continuously after the market launch.

7.R.3.4 ADA

The applicant's explanation about the incidences of ADA and its effect:

In Studies ALX0681-C301, ALX0681-C202, ALX-0681-2.1/10, and ALX0681-C302/LTS16371, pre-Ab was detected in 17.1% to 56.7% of subjects and drug-induced TE-ADA was detected in 3.1% to 14.3% of subjects. TE-NAb was positive in 0% to 12% of subjects according to the measurement based on pharmacological action and in 2.7% to 14.3% of subjects according to the measurement by epitope analysis. The effect of ADA on PK of caplacizumab was investigated using the final PK-PD model [see Section "6.2.3 PK-PD analysis"]. ADA of any type, pre-Ab, and TE-ADA were not identified as significant covariates for CL or Vc, but the possible effect of ADA on PK cannot be excluded because of the limited number of TE-ADA positive subjects. Table 44 shows the incidences[34)] of pre-Ab and drug-induced TE-ADA, classified by presence/absence of hypersensitivity reactions throughout the study period of Studies ALX0681-C301 and ALX0681-C202. No serious adverse events were observed in subjects positive for drug-induced TE-ADA. No clear relationship was observed between the occurrence of hypersensitivity reaction and pre-Ab or drug-induced TE-ADA, although cautions are necessary in the interpretation of the results because of the limited number of subjects positive for drug-induced TE-ADA.

Table 44. Incidences of ADA by presence/absence of hypersensitivity reaction

		Study ALX0681-C301 (double-blind administration period)				Study ALX0681-C202	
pre-Ab	Drug-induced TE-ADA	Occurrence of ≥1 hypersensitivity reaction[a]		No hypersensitivity reaction[a]		Occurrence of ≥1 hypersensitivity reaction[a]	No hypersensitivity reaction[a]
		Placebo (n = 27)	Caplacizumab (n = 27)	Placebo (n = 46)	Caplacizumab (n = 44)	(n = 12)	(n = 9)
−	−	40.7 (11)	25.9 (7)	19.6 (9)	38.6 (17)	50.0 (6)	55.6 (5)
+	−	51.9 (14)	66.7 (18)	69.6 (32)	54.5 (24)	25.0 (3)	44.4 (4)
−	+	0 (0)	3.7 (1)	2.2 (1)	2.3 (1)	16.7 (2)	0 (0)
+	+	0 (0)	0 (0)	0 (0)	0 (0)	8.3 (1)	0 (0)

Incidence % (number of subjects with events)

a MedDRA SMQ "hypersensitivity (narrow)," "anaphylaxis (narrow)," and "angioedema (narrow)"

34) In Studies ALX0681-C202, ALX0681-C301, and ALX0681-C302/LTS16371, incidences of ADA in subjects available for samples at ≥1 time point after administration was classified as follows:
- Pre-Ab-negative/drug-induced TE-ADA negative: No ADA-positive sample
- Pre-Ab-positive/drug-induced TE-ADA negative: All ADA-positive samples are negative by revised ADA measurement
- Pre-Ab-negative/drug-induced TE-ADA positive: All ADA-positive samples are positive by revised ADA measurement
- Pre-Ab-positive/drug-induced TE-ADA positive: ADA-positive samples are a mixture of positive and negative by revised ADA measurement.
- Uncertain
- Missing data

The subpopulation analysis of efficacy by presence/absence of pre-Ab and drug-induced TE-ADA and by presence/absence of TE-NAb[35)] in Studies ALX0681-C301 and ALX0681-C202 was performed and the results (Table 45) showed that, although cautions are necessary for the interpretation of the results because of the limited number of subjects positive for drug-induced TE-ADA, similar to subjects who were pre-Ab negative/drug-induced TE-ADA negative after caplacizumab administration, most of subjects who were pre-Ab negative/drug-induced TE-ADA positive and subjects who were pre-Ab positive/drug-induced TE-ADA positive also achieved normalization of platelet count, demonstrating that production of these antibodies does not affect the efficacy of caplacizumab.

Table 45. Time to normalization of platelet count by presence/absence of ADA expression in Study ALX0681-C301 (double-blind administration period)

	pre-Ab	Drug-induced TE-ADA	Placebo (n = 73)	Caplacizumab (n = 71)
ADA	−	−	2.88 [1.81, 3.82] (n = 20)	2.67 [1.71, 2.94] (n = 24)
	+	−	2.78 [1.94, 3.89] (n = 46)	2.70 [1.82, 3.69] (n = 42)
	−	+	1.94 (n = 1)	0.79, 1.81 (n = 2)
	pre-dose NAb	TE-NAb	Placebo (n = 73)	Caplacizumab (n = 71)
Assay based on pharmacological action	−	−	2.89 [1.93, 3.86] (n = 36)	2.69 [1.78, 2.96] (n = 59)
	+	−	1.94 (n = 1)	1.76, 2.87 (n = 2)
	−	+	− (n = 0)	1.81 (n = 1)
Assay based on epitope analysis	−	−	2.83 [1.89, 3.89] (n = 63)	2.69 [1.78, 2.95] (n = 59)
	+	−	1.94, 2.89 (n = 2)	2.87 [1.68, 4.69] (n = 6)
	−	+	3.53 (n = 1)	0.79 (n = 1)
	+	+	− (n = 0)	1.81 (n = 1)

Median (first quartile, third quartile) (number of subjects analyzed)

In the ITO population of Study ALX0681-C302/LTS16371, pre-Ab was positive in 20.7% (6 of 29) of untreated subjects and 26.7% (20 of 75) of treated subjects, while drug-induced TE-ADA was not observed in untreated subjects but detected in 10.7% (8 of 75) of treated subjects. In 2 subjects who showed TE-ADA expression after the start of the initial dose of caplacizumab and, after the end of caplacizumab administration, received caplacizumab again to the relapse of TTP, drug-induced TE-ADA expression was observed around the same time with TTP relapse. The re-administration of caplacizumab led to normalization of platelet count, and no relapse occurred during the period of the caplacizumab administration.

These results show that the measurement of ADA is no required routinely in the clinical setting. Information on the percentage of caplacizumab treated patients with drug-induced TE-ADA production and on neutralizing activity will be included in the package insert.

[35)] In Studies ALX0681-C202, ALX0681-C301, and ALX0681-C302/LTS1637, ADA-positive subjects were classified as follows based on NAb production before and after the study drug administration:
- Pre-dose NAb negative/TE-NAb negative: No NAb-positive samples
- Pre-dose NAb negative/TE-NAb positive: NAb negative at baseline and positive at ≥1 time point after caplacizumab administration
- Pre-dose NAb positive/TE-NAb negative: NAb positive at baseline and negative at all time points after caplacizumab administration (or antibody titer did not increase after administration [in Study ALX0681-C301 only])
- Pre-dose NAb positive/TE-NAb positive: NAb positive at baseline and at ≥1 time point after caplacizumab administration (or antibody titer increased after caplacizumab administration or the maximum increase in antibody titer from the titer before administration is higher than the minimum significant ratio (MSR) [only in Study ALX0681-C301]).
- Missing data

PMDA's view:
Because of the small number of subjects who were positive for drug-induced TE-ADA in the Japanese and foreign clinical studies, the effect of ADA production on PK, efficacy, and safety of caplacizumab was evaluated in this limited number of subjects. Nevertheless, no tendency of ADA-induced decrease in the efficacy of caplacizumab was observed in the Japanese and foreign clinical studies, and ADA-positive subjects do not show a clear tendency of an increase in hypersensitivity reactions. From these results, there are no concerns associated with ADA production in the clinical use of caplacizumab. Information on percentage of subjects with TE-ADA and neutralizing antibody production in clinical studies should be provided in the package insert.

7.R.4 Indication and intended population

7.R.4.1 Patients with ADAMTS13 activity of ≥10%

The applicant's explanation:
If decreased platelet count of unknown cause and hemolytic anemia are detected, ADAMTS13 activity is measured. If ADAMTS13 activity has markedly decreased to <10%, diagnosis of TTP is made, and if autoantibody against ADAMTS13 is positive, diagnosis of acquired TTP is made (Consensus report on the diagnosis and management of thrombotic thrombocytopenic purpura 2020). On the other hand, the clinical diagnosis of acquired TTP in the Japanese and foreign clinical studies was based on severe thrombocytopenia, hemolytic anemia, etc., of unknown cause, and ADAMTS13 activity of <10% was not defined as an inclusion criterion.

In Study ALX0681-C301, baseline ADAMTS13 activity was found to be ≥10% after the start of the study drug administration in 9.7% (7 of 73) of subjects in the placebo group and in 18.3% (13 of 71) of subjects in the caplacizumab group. In 7 subjects (4 in the placebo group, 3 in the caplacizumab group), diagnosis of acquired TTP could not be confirmed based on the available information such as a past history of acquired TTP and ADAMTS13 activity, and the study was terminated prematurely in 5 subjects (3 in the placebo group, 2 in the caplacizumab group) at the discretion of the physicians. In the 7 subjects without definite diagnosis of TTP, the median time to the normalization of platelet count was 3.53 days in the placebo group and 4.69 days in the caplacizumab group. Onset of TTP was not observed throughout the study period. In Study ALX0681-C301, there was no difference in the efficacy and safety of caplacizumab between subjects with ADAMTS13 activity of <10% and subjects with ADAMTS13 activity of ≥10%. In Study ALX0681-C202, baseline ADAMTS13 activity was ≥10% in 3 of 21 subjects and all of them discontinued the study because of adverse events or at the discretion of the physician and were not included in the PP population. In 2 of them, the disease was eventually concluded not to be acquired TTP. In Study ALX0681-C202, which was an uncontrolled study with limitations to the evaluation of efficacy and safety, onset of TTP was not observed during the period of study drug administration in 3 subjects with ADAMTS13 activity of ≥10%. Haemorrhage-related events (pulmonary alveolar haemorrhage[24)]/wound haemorrhage/large intestinal ulcer/rectal ulcer and gastrointestinal haemorrhage/haemoglobin decreased in 1 subject each) were observed in 2 subjects.

Since prompt intervention is critical for the treatment of acquired TTP because of the seriousness of the disease and for the purpose of improved outcome, it is expected that, in the clinical setting, PE and caplacizumab administration are started before the result of ADAMTS13 activity is obtained. As

described in ISTH Guideline (*J Thromb Haemost.* 2020;18:2496-502), when ADAMTS13 activity is found to be ≥10% after the start of caplacizumab administration, the physician should decide whether to continue caplacizumab administration by taking into account the conditions of individual patients (ADAMTS13 activity, past illness, trend of the recovery of platelet count, presence/absence of clinical symptoms related to acquired TTP), and bleeding risk.

PMDA's view:
Taking into account that ADAMTS13 activity of <10% is gaining international consensus as a diagnostic criterion for acquired TTP (*J Thromb Haemost*. 2017;15:312-22), it is expected that most of the patients intended for the treatment with caplacizumab in the clinical setting are patients with ADAMTS13 activity of <10%. On the other hand, since acquired TTP is a serious disease requiring urgent treatment and any delay in the start of treatment worsens the outcome (*Ann Hematol*. 1995;70:319–23), there may be cases where therapeutic intervention is required before the availability of the results of the ADAMTS13 activity test which takes several days at the current situation. In clinical studies, patients with ADAMTS13 activity of ≥10% were eligible, and no clear difference was observed in the efficacy of caplacizumab among subject groups stratified by ADAMTS13 activity [see Section "7.R.2.5 Factors affecting the efficacy of caplacizumab]. However, given the quite limited number of subjects studied and the mechanism of action of caplacizumab, whether to continue caplacizumab administration should be carefully determined by the physician when ADAMTS13 activity data of the patient become available, by taking account of the patient conditions and therapeutic benefits and possible risks of caplacizumab.

7.R.4.2 Patients with secondary acquired TTP

PMDA asked the applicant to explain whether patients with secondary acquired TTP (autoimmune disease, drug-induced disease) are intended for the treatment with caplacizumab.

The applicant's explanation:
Patients with secondary acquired TTP show a marked decrease in ADAMTS13 activity and presence of autoantibody against ADAMTS13, and had accumulation of ULvWF multimers and platelet thrombosis within microvessels. These features are not different from those of the primary acquired TTP, and treated with PE and the standard therapy with immunosuppressants, in addition to the treatment of the causative disease and/or removal of the causative drug (*J Thromb Haemost.* 2017;15:312-22). In the Japanese and foreign clinical studies, there were no rules to exclude patients with autoimmune disease or drug-induced thrombotic microangiopathy and, as a result, subjects who possibly met the definition of the secondary acquired TTP in Japan (*J Thromb Haemost*. 2017;15:312-22) were enrolled, and caplacizumab was administered to 4 subjects in Study ALX0681-C301 (undifferentiated connective tissue disease, rheumatoid arthritis, Sjogren's syndrome, and Basedow's disease with hypothyroidism in 1 subject each), 1 subject in Study ALX0681-C202 (Sjogren syndrome) and 1 subject in Study ALX-0681-2.1/10 (mixed connective-tissue disease). All of them showed normalization of platelet count, without relapse of TTP during the administration period. Although it is difficult to evaluate the efficacy and safety of caplacizumab in patients with secondary acquired TTP based on the use experience in these limited number of subjects, patients with acquired TTP can be considered appropriate for the treatment of caplacizumab regardless of the etiology of the disease, given the mechanism of thrombosis in the microvessels of patients with secondary acquired TTP and the mechanism of action of caplacizumab.

PMDA's view:
In light of the explanation of the applicant, patients diagnosed with acquired TTP with ADAMTS13 activity of <10% can be considered appropriate for the treatment with caplacizumab, regardless of the etiology.

On the basis of the subjects investigated and safety and efficacy observed in the Japanese and foreign clinical studies, and on the results of reviews in Sections "7.R.2.5 Factors affecting the efficacy of caplacizumab," "7.R.4.1 Patients with ADAMTS13 activity of ≥10%," and "7.R.4.2 Patients with secondary acquired TTP," PMDA concluded that the indication for caplacizumab should be "acquired thrombotic thrombocytopenic purpura." The appropriateness of the above conclusion and the indication will be finalized, also taking account of comments raised in the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Dosage regimen in adults

The applicant's explanation about the rationale for proposing the dosage regimen in adults:
The proposed dosage and administration of caplacizumab for acquired TTP was determined to achieve the decrease in vWF activity (RICO <20%) in order to inhibit the binding of platelets with vWF. Study ALX0681-C301 showed the expected efficacy with acceptable safety, demonstrating the appropriateness of the above dosage regimen.

The exposure to caplacizumab tends to be slightly higher in Japanese patients than in non-Japanese patients, due perhaps to the differences in body weight and the vWF:Ag level, while PD was considered not to be significantly different at the exposure estimated from the selected dosage regimen. Using the pooled data of the foreign clinical studies in non-Japanese patients with acquired TTP (Study ALX-0681-2.1/10 and Study ALX0681-C301), the plasma caplacizumab concentrations at the end of PE and at the last visit after PE were stratified into quartiles. Results showed that the time to the normalization of platelet count was similar among 4 quartile groups, suggesting that the exposure to caplacizumab, achieved after administration at the dosage regimen specified in clinical studies, is within the range of plateau of the exposure-response curve. The incidence of adverse events including haemorrhage-related events did not show any clear tendency of an increase with the increase in the exposure, demonstrating acceptable safety profile. These results show that the difference in the exposure to caplacizumab between Japanese and non-Japanese patients is not clinically significant, demonstrating the appropriateness of using the same dosage regimen in Japanese patients with acquired TTP as that in non-Japanese patients with acquired TTP.

PMDA's view:
No dose-finding study was conducted using an appropriate endpoint in patients with acquired TTP. Also, clinical significance of restricting RICO to "<20%" as the target of PD in dose setting is unclear [see Section "6.R.2.1 Rationale for the proposed dosage regimen in clinical studies in patients with acquired TTP]. However, clinically significant efficacy of caplacizumab was observed in Study ALX0681-C301 and the safety was acceptable based on the efficacy [see Sections "7.R.2.3 Efficacy in foreign clinical study" and "7.R.3 Safety"], from which the appropriateness of using caplacizumab for the treatment of

acquired TTP at the dosage regimen specified in the above study has been demonstrated. Given the explanation of the applicant, there is no clinically significant difference in PK and PD of caplacizumab between Japanese and non-Japanese patients [see Section "6.R.1 Difference in PK and PD between Japanese and non-Japanese subjects"]. Results of Study ALX0681-C202 conducted using the same dosage regimen as in Study ALX0681-C301, together with the results of Study ALX0681-C301, suggest the efficacy of caplacizumab in Japanese patients with acquired TTP with acceptable safety [see Sections "7.R.2.4 Efficacy in Japanese clinical study" and "7.R.3 Safety"]. On the basis of the above results, the following dosage regimen which was confirmed to demonstrate efficacy and safety in clinical studies should be used as the dosage regimen of caplacizumab for Japanese patients with acquired TTP: caplacizumab 10 mg is administered intravenously prior to PE followed by a 10 mg subcutaneous injection after completion of PE on Day 1. From Day 2, caplacizumab 10 mg is administered subcutaneously, once daily.

7.R.5.2 Treatment period after the end of daily PE

The applicant's explanation about the period of caplacizumab administration after the end of daily PE:
After recovery from the first onset of TTP in patients with acquired TTP, TTP becomes aggravated during the next 30 days in 50% of patients, and TTP relapses in the future in 30% to 50% of patients, and that TTP relapse increases the risk of death (*Am J Hematol*. 2018;93:E73-5). The corticosteroid included in the standard therapy is started/continued during the daily PE period and, after the end of the daily PE, is tapered off, resulting in the loss of the efficacy. There is a high need for treatment to suppress the risk of TTP relapse after the end of the daily PE. During 30 days after the end of the daily PE period, there is a high risk of new platelet thrombosis within microvessels that may lead to TTP relapse and organ injuries, and the period is considered to be required for treatment continuation of caplacizumab. In order to avoid this risk, in the Japanese and foreign clinical studies, caplacizumab was administered not only during the daily PE period but also for 30 days after the end of the daily PE period.

The applicant's explanation about the necessity of continued administration after the daily PE period and the post-daily PE period (30 days):
In the foreign phase II study (Study ALX-0681-2.1/10) which did not specify the continued administration period after the end of the post-daily PE period, TTP relapse occurred in 22.2% (8 of 36) of subjects in the caplacizumab group during the follow-up period (as of 1 month after the end of administration), and ADAMTS13 activity was <10% at around the end of the treatment with the study drug in 7 of 8 patients with relapse. Among subjects with TTP relapse during the study drug administration period (post-PE period) (28.2% [11 of 39 subjects] in the placebo group, 8.3% [3 of 36 subjects] in the caplacizumab group), many of them available with ADAMTS13 activity data showed the activity of <10% at around the time of relapse. In contrast, in subjects without TTP relapse, ADAMTS13 activity exceeded 10% at around the end of the study drug administration. Taking these results into account, in Studies ALX0681-C301 and ALX0681-C202, subjects were allowed to continue caplacizumab administration for the maximum of 4 and 8 weeks, respectively, after the end of the post-

daily PE period, depending on the risk factors of TTP relapse.[36)] As a result, TTP relapse was observed in 9.1% (6 of 66) of subjects during the follow-up period of Study ALX0681-C301 (double-blind administration period) and in none of the subjects during the follow-up period of Study ALX0681-C202. In these clinical studies, the rate of TTP relapse after the end of treatment with caplacizumab was lower than the rate in Study ALX-0681-2.1/10, suggesting the clinical significance of continued caplacizumab administration in patients with persisting symptoms and signs of acquired TTP.

In Study ALX0681-C301, 6 of 47 subjects in the placebo group and 22 of 69 subjects in the caplacizumab group during the double-blind administration period, as well as 8 of 28 subjects in the open label administration period, proceeded to the extended treatment period of 24.5 (4-28) days (median [minimum-maximum]), 21.5 (0-30) days, and 27.5 (7-29) days, respectively. Among the subjects who proceeded to the extended treatment period, 4 subjects in the placebo group, 16 subjects in the caplacizumab group, and 4 subjects in the open-label administration period showed ADAMTS13 activity of <10%. Of these, 0 of 4 subjects in the placebo group, 5 of 16 subjects in the caplacizumab group, and 1 of 4 subjects in the open-label administration period showed ADAMTS13 activity of ≥10% during the extended treatment period. Among subjects who proceeded to the extended treatment period with ADAMTS13 activity of <10%, 0 of 4 subjects in the placebo group, 4 of 16 subjects in the caplacizumab group, and 1 of 4 subjects in the open-label administration period showed TTP relapse during the extended treatment period, and 3 of 4 subjects in the caplacizumab group and 1 of 1 subject in the open-label administration period showed ADAMTS13 activity of <10% at the latest relapse. During the extended treatment period of Study ALX0681-C301, the incidences of adverse events were similar to those during the post-daily PE period (30 days after the end of daily PE), showing no safety concerns unique to the extended treatment.

In Study ALX0681-C202, 7 of 21 subjects proceeded to the extended treatment period of 14.0 (11-36) days (median [minimum-maximum]). At the end of the post-daily PE period, ADAMTS13 activity was <10% in 4 of 7 subjects, but increased to ≥10% within 2 weeks of the extended treatment in all of them. Throughout the subsequent study period, ADAMTS13 activity was maintained at ≥10% with no TTP relapse observed. The incidences of adverse events during the extended treatment period of Study ALX0681-C202 were similar to those during the post-PE period (30 days), with no safety concerns unique to the extended treatment.

Thus, patients with ADAMTS13 activity of <10% at the end of the post-daily PE period (30 days after the end of daily PE) are highly likely to remain at a high risk of TTP relapse. During the period of high risk of TTP relapse suspected from ADAMTS13 activity of <10% or other symptoms/signs of acquired TTP, suppression of the relapse is expected by the continued administration of caplacizumab. Caplacizumab suppresses vWF-mediated platelet adhesion but does not contribute to the removal, or suppression of production of, autoantibody against ADAMTS13 which is frequently observed in acquired TTP. It is therefore essential to optimize the immunosuppressive therapy against acquired TTP

[36)] The study drug was administered over an extended period if subjects had ADAMTS13 activity of <10%, autoantibody against ADAMTS13, or showed clinical symptoms of TTP. The extended period was 4 weeks at the maximum in Study ALX0681-C301 and 8 weeks at the maximum in Study ALX0681-C202. In parallel with the study drug administration, the immunosuppressive therapy was optimized, including a dose increase or resumption of corticosteroid, or the start or continuation of other immunosuppressants such as rituximab. If ADAMTS13 activity showed a tendency of a continuous increase above 10% or other clinical signs of TTP improved, the continued administration of the study drug was stopped.

after the end of PE, in addition to treatment with caplacizumab. As for the safety in the long-term administration of caplacizumab, there are no particular concerns associated with the extended treatment of caplacizumab, in light of the incidences of adverse events during the extended treatment period of the Japanese and foreign clinical studies. The data of the administration period in Japanese and foreign clinical studies suggest that, in most of the patients, the administration will be completed after the daily PE period or the 30-day post-daily PE period in the clinical setting as well. However, it is likely that caplacizumab is administered to patients with more diverse characteristics in the clinical setting than in clinical studies, suggesting the undeniable possibility that caplacizumab has to be administered for a period exceeding the longest period experienced in clinical studies (the longest period in Study ALX0681-C202 was 69 days, for instance). Therefore, whether to continue administration after the end of the post-daily PE period should be determined for each patient by the physician with ADAMTS13 activity of <10% as the main criterion, together with the collective judgment of the conditions of the patient such as presence/absence of autoantibody against ADAMTS13 and persistence of signs and symptoms of acquired TTP.

PMDA's view:
Caplacizumab treatment period with the PE period and 30 days after the PE period as a general rule, is acceptable for the following reasons: (a) The risk of TTP relapse is high during a certain period after the end of the daily PE period; and (b) the efficacy and safety of caplacizumab was demonstrated in the Japanese and foreign clinical studies administering caplacizumab during the daily PE period and the post-daily PE period (30 days after the end of the daily PE). Also, the following findings suggest the usefulness of extended treatment of caplacizumab in patients with persisting signs and symptoms of acquired TTP at the end of the post-daily PE period (e.g., persistent decrease in ADAMTS13 activity): (a) Results in Japanese and foreign clinical studies showed that in patients who required the extended treatment according to the judgment of the physician based on the ADAMTS13 activity (<10%), presence of autoantibody against ADAMTS13, or other signs/symptoms of acquired TTP, the risk of TTP relapse tended to decrease during 1 month after the end of caplacizumab administration, although there are limitations to the interpretation of the results because of the comparison between different studies; and (b) there was no significant difference between the safety profile during the extended treatment period and the safety profile during the post-daily PE period, showing no increase in the risk related to the extended treatment period. The duration of extended treatment with caplacizumab should be determined by the collective judgment of the physician based on the clinical symptoms of acquired TTP, persistence of decreased ADAMTS13 activity, occurrences of adverse events, etc. Uniform criteria for discontinuation and administration period should not be applied. The applicant's plan to include the following Precautions Concerning Dosage and Administration in the package insert is generally appropriate: "Caplacizumab administration may be continued until the signs/symptoms of acquired TTP (e.g., persistent decrease in ADAMTS13 activity) disappear."

On the other hand, attention should be paid to bleeding risk during the treatment with caplacizumab. Whether to continue caplacizumab administration should be determined by taking into account the balance of the risk of TTP relapse and the bleeding risk. Also, physicians should be advised the following statement not to continue the treatment with caplacizumab without careful consideration: Caplacizumab should be discontinued when symptoms have improved and signs of acquired TTP (e.g., persistent

decrease in ADAMTS13 activity) have disappeared. As for the upper limit of the extended treatment period after the post-daily PE study (30 days), Study ALX0681-C202 use the upper limit at 8 weeks which was longer than 4 weeks employed in Study ALX0681-C301. However, in Study ALX0681-C202, the administration period exceeded 4 weeks in only 1 subject (36 days) and, as a result, there is only extremely limited safety information available on the long-term administration of caplacizumab. The maximum extended treatment period should be 4 weeks as a general rule. PMDA thus concludes that physicians should be advised in the package insert not to continue caplacizumab administration for >4 weeks beyond the post-daily PE period (30 days) without careful consideration, and that information on the actual administration period in Studies ALX0681-C301 and ALX0681-C202 should be provided to healthcare professionals.

7.R.5.3 Actions taken against TTP relapse

(a) TTP relapse during caplacizumab administration

The applicant's explanation about the actions taken in case of TTP relapse during caplacizumab administration:

In Study ALX0681-C301 (double-blind administration period), TTP relapse occurred in 2 of 3 subjects in the caplacizumab group during the study drug administration period, and caplacizumab administration was resumed under the open-label conditions [see Section "7.2.1 Foreign phase III study" for the dosage regimen]. In 1 of 2 subjects who restarted the dosage regimen, improvement of TTP was observed and the treatment was well tolerated.[37)] In Study ALX0681-C202, the caplacizumab regimen was resumed in 1 subject who showed TTP relapse during the treatment with caplacizumab. Improvement of TTP was observed and the treatment was well tolerated. Studies ALX0681-C301 and ALX0681-C202 had stipulated that caplacizumab should be discontinued in case of 2 or more TTP relapses during the study drug administration period. As a consequence, no data are available on the resumption of caplacizumab dosage regimen after the second or further TTP relapse during caplacizumab administration.

The above results suggest the usefulness of resuming the caplacizumab regimen against the first TTP relapse during caplacizumab administration, whereas caplacizumab may not be effective against the second and further relapses of TTP during caplacizumab administration. Therefore, the package insert will include the precaution that caplacizumab should be discontinued in case of the second or further TTP relapse during the caplacizumab administration period.

(b) TTP relapse after the end of caplacizumab administration

The applicant's explanation about the measures taken against TTP relapse after the end of caplacizumab administration:

In Study ALX0681-C302/LTS16371 in subjects who had completed ALX0681-C301, improvement of TTP was observed in 9 subjects who restarted caplacizumab regimen after TTP relapse. Neither severe thromboembolic events nor death occurred in these subjects, showing no safety concerns unique to resumption of the dosage regimen.

[37)] One subject who did not show improvement was diagnosed with TTP aggravation on Day 24 of caplacizumab administration (PE was completed on Day 5) and resumed PE and received caplacizumab for 1 month under open-label conditions, but diagnosis of the second TTP relapse was made and caplacizumab administration was discontinued. ADAMTS13 activity was 60% at the second relapse of TTP.

These results suggest the usefulness of treatment with caplacizumab against the relapse of TTP after the end of caplacizumab administration without tendency of an increase in any particular risk compared to that in the use of caplacizumab against the initial treatment for TTP. It is therefore unnecessary to restrict the resumption, or the number of times of caplacizumab regimen against TTP relapse after the end of the initial dosage regimen of caplacizumab.

PMDA's view:
In Studies ALX0681-C301 and ALX0681-C202, a limited number of subjects restarted caplacizumab regimen against TTP relapse that occurred during caplacizumab administration period, and some of them showed improvement of TTP after resumption of caplacizumab administration together with the standard therapy. They did not show any significant increase in the risk of haemorrhage-related events after the resumption of caplacizumab regimen. On the basis of the above, as stipulated in clinical studies, it is acceptable to treat the first relapse of TTP during the caplacizumab administration period by resumption of caplacizumab regimen together with daily PE therapy and an appropriate immunosuppressive treatment. On the other hand, since there are no data on caplacizumab administration against the second or further TTP relapse during the caplacizumab administration period, the benefit of further caplacizumab administration to patients poorly responsive to caplacizumab is unclear. The applicant's proposal not to resume caplacizumab regimen to the second or further TTP relapse during the caplacizumab administration period is appropriate. Against TTP relapse after the end of caplacizumab administration in Study ALX0681-C302/LTS16371, resumption of the caplacizumab regimen in a limited number of subjects together with the standard treatment improved TTP without a significant increase in the risk such as haemorrhage-related events. Any specific restriction or precaution for resumption of caplacizumab regimen against different TTP episodes is unnecessary currently. Because of the limited information related to the resumption of caplacizumab regimen in clinical studies, information on safety, etc., in re-administration of caplacizumab should be collected continuously after the market launch.

7.R.5.4 Measures for missed doses

The applicant's explanation about the measures for missed dose of caplacizumab:
For the treatment of acquired TTP, it is extremely important to maintain pharmacological activity of caplacizumab by daily administration and uninterrupted treatment. It is desirable to promptly administer caplacizumab when a missed dose is noticed. On the other hand, because of the PK characteristics of caplacizumab ($t_{1/2}$ following a single subcutaneous administration is 52.8 hours), the interval of multiple administration was ≥12 hours in Japanese and foreign clinical studies in patients with acquired TTP, and a missed dose noticed within 12 hours before the next dose was skipped to receive the next dose as planned, because of safety concerns due to the accumulated exposure. Although no clear relationship has been noticed between the exposure to caplacizumab and safety [see Section 7.R.5.1 Dosage regimen in adults], because of no experience of multiple administration within 12 hours after the end of the PE period, similar precautions in clinical settings should be provided as those exercised in clinical studies. In contrast, during the PE period, missed doses should be administered promptly because the drug is eliminated from the body by PE.

PMDA's view:

Given the explanation of the applicant, the following measures are appropriate, as stipulated in clinical studies: (a) Missed dose during the PE period should be administered promptly when noticed, and the next dose should be given as scheduled; (b) missed dose after the end of PE period should be administered promptly when noticed within 12 hours after the scheduled dose, and the next dose should also be given as scheduled; and (c) if noticed >12 hours after the scheduled dose, the missed dose should be skipped and the administration should be resumed from the next scheduled timing.

7.R.5.5 Administration in children aged ≥12 years weighing ≥40 kg

The applicant's explanation about the appropriateness of including patients with acquired TTP aged ≥12 years weighing ≥40 kg in the target population for caplacizumab:

Results of the simulation using PK-PD model suggested that when patients with acquired TTP aged ≥12 years weighing ≥40 kg received caplacizumab according to the same dosage regimen as that recommended for adult patients, the efficacy and safety similar to those in adults would be achieved [see Section "6.R.2.2 Rationale for the dosage regimen in children aged ≥12 years weighing ≥40 kg"].

TTP occurs mostly in adults and less frequently in adolescents (*Nelson Textbook of Pediatrics*. 19th edition), and the annual incidence of TTP in children is 0.09×10^6/year which is approximately 3% of the incidences in adults (2.88×10^6/year) (*Pediatr Blood Cancer*. 2013;9999:1-7). Although there are no Japanese or foreign guidelines which provide clear definition and diagnostic criteria for acquired TTP in children, in clinical settings, diagnosis and classification of the disease in children are carried out similarly as in adults, according to the textbook (*Nelson Textbook of Pediatrics*. 19th edition) and the diagnostic method in the Information Center for Specific Pediatric Chronic Diseases, Japan (https://www.shouman.jp/disease/instructions/09_14_025 [as of April 22, 2022]). Although there are only limited data on primary acquired TTP in children, according to the registry data in Japan,[38)] the clinical characteristics and the outcome in 14 patients with acquired TTP aged ≤15 years (1.6-14 years) and 181 adult patients with primary acquired TTP are as shown in Table 46, suggesting that the pathophysiological characteristics in children are similar to those in adults (*Presse Med*. 2012;41:e137-55). Thus, it is appropriate to diagnose and classify the disease according to the classic 5 signs (thrombocytopenia, hemolytic anemia, renal impairment, pyrexia, perturbed neuropsychiatric symptoms), ADAMTS13 activity, and presence or absence of inducing causes such as underlying diseases.

[38)] The registry data on 283 patients diagnosed with acquired TTP from 1998 through 2008 in Nara Medical University

Table 46. Clinical characteristics and outcome of primary acquired TTP in adults and children (modified from *Presse Med*. 2012;41:e137-55)

		Children (n = 14)	Adults (n = 181)
Age of onset		11 [1.6, 14]	57 [41, 65]
Percentage of female patients		35.7	55.2
Clinical symptoms	Platelet count ($\times 10^9$/L)	15 [8, 24]	10 [7, 17]
	Hemoglobin (g/dL)	8.0 [5.6, 8.8]	7.5 [6.3, 8.8]
	Renal impairment	71.4	75.7
	Serum creatinine (mg/dL)	0.5 [0.3, 0.9]	1.0 [0.7, 1.3]
	Neurologic symptoms	71.4	79.6
	Pyrexia (≥37.0°C)	92.9	69.6
PE period (days)		5.5 (3.0-17.5)	—
Mortality due to TTP episode		7.1	15.5

Median (first quartile, third quartile)

Adult patients undergo the standard treatment with PE and immunosuppressant therapy, whereas there are no guidelines containing clear description of the standard treatment for pediatric patients, and the Japanese guidelines state that cautions are required for the dosage regimen in children because of the scant experience (Consensus report on the diagnosis and management of thrombotic thrombocytopenic purpura 2020). According to the Japanese registry data, all 6 patients with acquired TTP aged ≥12 and ≤15 years received PE and treatment with corticosteroid, with 3 of the 6 patients receiving immunosuppressants and 1 of the 6 patients receiving transfusion of frozen fresh plasma (*Presse Med*. 2012;41:e137-55). On the basis of these situations, pediatric patients with acquired TTP aged ≥12 years are considered to undergo similar therapeutic management as that in adult patients.

TTP relapse after the first-line treatment is reported in pediatric patients as in adults, and the mortality is 0.9% to 9% despite the intervening therapy (*Pediatr Blood Cancer.* 2013;60:1676-82, *Presse Med*. 2012;41:e137-55, *Lancet Haematol*. 2016;3:e537-46).

The Japanese and foreign guidelines stipulate that PE discontinuation and dose reduction of corticosteroid should be considered based on platelet count and ADAMTS13 activity (Consensus report on the diagnosis and management of thrombotic thrombocytopenic purpura 2020, *J Thromb Haemost*. 2020;18:2496-502), indicating that platelet count and ADAMTS13 activity are important indices of the progression of acquired TTP, both in adults and in children.

Thus, adults and children aged ≥12 years are similar in the mechanism of the onset of acquired TTP, pathophysiological characteristics, diagnosis and classification, disease course, and the index for disease progression.

In Studies ALX-0681-2.1/10 and ALX0681-C301, the clinical study protocols were revised during the course of the studies to allow enrollment of patients with acquired TTP aged ≥12 and <18 years and those aged ≥2 and <18 years, respectively. However, no pediatric patients were enrolled in either study due to the rarity of the disease. In Europe, caplacizumab was approved for use in children aged ≥12 years weighing ≥40 kg in June 2020 according to the method of Modeling & Simulation based on PK-PD analysis without data of children treated with caplacizumab because of the difficulty in collecting information on pediatric patients treated with caplacizumab in clinical studies.

PMDA asked the applicant to explain the details of the program for collecting information on administration in children after the market launch in foreign countries and post-marketing safety measures taken in foreign countries, such as precautions for administration in children.

The applicant's explanation:
In Europe, no specific information-collecting program on pediatric use is conducted other than the usual pharmacovigilance activities after the market launch. In the US, a consultation with Food and Drug Administration (FDA) was made on the appropriateness of including in the labeling the explanation about administration in pediatric patients aged ≥2 and <18 years according to the method of Modeling & Simulation based on PK-PD analysis. FDA required collection of data of efficacy, safety, etc., including platelet count in pediatric patients with acquired TTP. Sanofi is conducting a retrospective observation study in order to collect information on the efficacy and safety of caplacizumab in children with acquired TTP. Sanofi is also planning to develop caplacizumab in pediatric patients with acquired TTP in the US. According to the registry data in the UK (25 study sites, May 2018 to January 2020), the outcome in 85 patients with acquired TTP receiving caplacizumab was TTP relapse in 6% (5 of 85 patients) and death in 6% (5 of 85 patients) of the entire population; and 4 deaths and no TTP relapse among 4 children (3-17 years). All 4 children had received caplacizumab in combination with corticosteroid and rituximab (*Blood.* 2021;137:1731-40).

Regarding the safety in children, a non-clinical toxicity study in juvenile (corresponding to adolescent period [approximately 8-16 years] in humans) and mature cynomolgus monkeys [see Section "5.2 Repeated-dose toxicity"] detected no pathological changes in any organs except for bleeding tendency caused by an excessive pharmacological effect. In the reproductive and developmental toxicity evaluation in mature cynomolgus monkeys [see Section "5.5 Reproductive and developmental toxicity"], no findings related to caplacizumab administration were observed in the parameters of male and female fertility, showing no safety concerns with caplacizumab administration in children aged ≥12 years. After marketing in foreign countries[39] ([redacted], 20[redacted] to [redacted], 20[redacted]), 99 adverse drug reactions were reported in 43 patients aged <18 years (25 events in 11 patients aged ≤11 years, 32 events in 17 patients aged 12-15 years, 42 events in 15 patients aged 16-17 years). Among them, 6 events in 6 patients aged ≤11 years, 11 events in 10 patients aged 12 to 15 years, and 7 events in 7 patients aged 16 to 17 years were considered to be related to off-label use during the period (or in regions) without approval for pediatric use. A total of 5 serious adverse drug reactions were observed in 3 patients aged ≤11 years, which were epistaxis/off-label use/incorrect dose administered, hospitalization (platelet count low), and haematemesis (followed by abdominal distension). The main adverse drug reaction reported was haemorrhage event (epistaxis). The outcome of 40 adverse drug reactions reported in patients aged ≤15 years (except those due to off-label use) was "resolved" for 10 events, "resolving" for 2 events, "not resolved" for 3 events, no report for 6 events, and unknown outcome for 19 events. Thus, the above information together with the findings so far obtained from non-clinical studies and in adults suggests that there are currently no safety concerns unique to children, except for bleeding risk supposedly due to the mechanism of action of caplacizumab.

[39] The cumulative exposure to caplacizumab corresponds to 221 person-years regardless of age. In Europe, caplacizumab was approved for use in children with acquired TTP aged ≥12 years weighing ≥40 kg on June 9, 2020.

PMDA's view:

There is some rationality in the applicant's explanation that the same dosage regimen as that in adults may be applicable to children aged ≥12 years weighing ≥40 kg based on the assumption that the PK-PD model of caplacizumab in adults is applicable to patients of this group [see Section "6.R.2.2 Rationale for the dosage regimen in children aged ≥12 years weighing ≥40 kg"]. However, since caplacizumab was not administered to children aged ≥12 years weighing ≥40 kg in clinical studies, there is no evidence supporting the above assumption and no information available on the efficacy and safety of the dosage regimen, precluding the judgment of the validity of extrapolating the dosage regimen in adults to children.

Under ordinary circumstances, PK, PD, efficacy, and safety data of caplacizumab in children with acquired TTP should be collected before the application, and the evidence supporting the above assumption, as well as the efficacy and safety of the dosage regimen should be explained. However, taking account of the following situations, it is acceptable to include children with acquired TTP aged ≥12 years weighing ≥40 kg in the intended patients for treatment with caplacizumab at the same dosage regimen as in adults, on the premise that information on the efficacy, safety, PK., etc., of caplacizumab are collected in children after the market launch.

- There is no significant difference between children aged ≥12 years and adults in the mechanism of development of acquired TTP, pathophysiological characteristics, diagnosis, disease course, and index for disease progression. Also, since the coagulation system is considered to have matured in children aged ≥12 years, the response to drug therapy is unlikely to differ significantly between adults and children.
- Acquired TTP is a serious disease which may result in death even under the standard therapy, and there is no approved drug with the same positioning as that of caplacizumab.
- During the process of caplacizumab development, measures were taken to obtain the data of pediatric subjects by allowing enrollment of children with acquired TTP in the foreign phase II and III studies, but no children could be enrolled in studies. Thus, given the extremely small number of patients with TTP aged <18 years, it appears to be quite infeasible to obtain a certain amount of data from a clinical study in children aged ≥12 years weighing ≥40 kg.
- Findings obtained from non-clinical toxicity studies and from adults with acquired TTP treated with caplacizumab do not suggest that administration of caplacizumab to children would cause any safety concerns unique to children, except for bleeding risk due to the mechanism of action of caplacizumab.
- No safety concerns unique to children have been reported in children with acquired TTP treated with caplacizumab after the market launch in foreign countries.

On the basis of reviews in Sections 7.R.5.1 to 7.R.5.5 above, PMDA concludes that "Dosage and Administration" and "Precautions Concerning Dosage and Administration" should be described as shown below. PMDA will draw a final conclusion, taking account of comments raised in the Expert Discussion.

Dosage and Administration

In adults and in children aged ≥12 years weighing ≥40 kg, 10 mg of caplacizumab is administered intravenously prior to plasma exchange followed by a 10 mg subcutaneous injection after completion of

plasma exchange on the first day of treatment. During the subsequent plasma exchange period, 10 mg of caplacizumab is administered subcutaneously, once daily, after the daily plasma exchange. After the plasma exchange period, 10 mg is administered subcutaneously once daily for 30 days.

Treatment with caplacizumab may be extended beyond 30 days after the plasma exchange period depending on the condition of the patient.

Precautions Concerning Dosage and Administration

- Caplacizumab should be administered in combination with the standard therapy consisting of plasmapheresis and an appropriate immunosuppressant, with reference to the latest information including clinical practice guidelines etc.
- Caplacizumab administration should be started at the same time with plasma exchange, whenever possible. The initial dose of caplacizumab should be completed not less than 15 minutes before the start of the plasma exchange.
- If symptoms or signs of acquired thrombotic thrombocytopenic purpura (e.g., persisting decreased ADAMTS13 activity) are observed on Day 30 after the end of the plasma exchange period, caplacizumab may be continued until the symptoms or signs of acquired thrombotic thrombocytopenic purpura (e.g., persisting decreased ADAMTS13 activity) disappear, together with the optimized immunotherapy. The caplacizumab administration period should be determined in each patient, by taking account of the risk of relapse of acquired thrombotic thrombocytopenic purpura and the risk of haemorrhage. The treatment with caplacizumab should not be continued without careful consideration when caplacizumab is administered beyond 30 days after the plasma exchange period. The maximum extended treatment period is 4 weeks as a general rule.
- Missed dose during the plasma exchange period should be administered promptly when noticed. Missed dose after the end of plasma exchange period may be administered when noticed within 12 hours after the scheduled dose. If noticed >12 hours after the scheduled dose, the missed dose should be skipped and the administration should be resumed from the next scheduled timing.
- Caplacizumab should be discontinued in case of the second or further relapses of acquired thrombotic thrombocytopenic purpura during the caplacizumab administration period.

7.R.6 Self-injection (subcutaneous injection)

The applicant's explanation about the self-injection (subcutaneous injection) of caplacizumab:
In Studies ALX0681-C301, ALX0681-C302/LTS16371, and ALX0681-C202, subjects or caregivers who learned the methods for the preparation and self-injection (subcutaneous injection) of the study drug during the hospitalization period were allowed to self-inject the study drug after discharge from the post-daily PE period.

The number of subjects who self-injected at least 1 dose of the study drug was as follows: 87 of 97 subjects in the caplacizumab group in Study ALX0681-C301, 12 of 13 subjects in Study ALX0681-C302/LTS16371, and 9 of 21 subjects in Study ALX0681-C202. As for the safety of self-injection, the

incidence of adverse events with self-injection at home[40)] in Study ALX0681-C301 (double-blind administration period) was 80.8% (42 of 52 subjects) in the placebo group and 73.0% (46 of 63 subjects) in the caplacizumab group which was similar to the incidence in the injection at study sites[41)] (84.9% [62 of 73 subjects] in the placebo group, 81.7% [58 of 71 subjects] in the caplacizumab group). The incidence was also similar between self-injection at home and injection at study sites for serious adverse events (26.9% in the placebo group and 12.7% in the caplacizumab group in the self-injection at home; 34.2% in the placebo group and 15.5% in the caplacizumab group in the injection at study sites) and for adverse events leading to discontinuation of the study drug (1.9% in the placebo group and 3.2% in the caplacizumab group in the self-injection at home; 11.0% in the placebo group and 4.2% in the caplacizumab group in the injection at study sites). No device-related malfunctions were observed in any of the foreign clinical studies. In Study ALX0681-C202, 5 adverse events (dry skin, pruritus, ALT increased, skin laceration, arthralgia) were observed in 4 of 9 subjects after self-injection at home.[40)] All of them were mild or moderate in severity. There were no adverse events which were serious or led to discontinuation of the study drug. No device-related malfunctions were reported. The above results suggest that clinical problems are unlikely to occur when patients with acquired TTP self-inject caplacizumab after mastering the method for the preparation and subcutaneous injection of caplacizumab under hospitalized conditions. After the market launch of caplacizumab, leaflets for patients explaining the method for self-injection will be provided to assist proper use of caplacizumab.

PMDA's view:
Given the explanation of the applicant, it is appropriate that patients self-inject caplacizumab (subcutaneous injection) on the premise that, as is the case with the clinical studies, physicians have provided guidance for self-injection together with providing precautions and information material, and have confirmed that the subject is able to self-inject caplacizumab.

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing investigations of caplacizumab:
Haemorrhage is a major risk related to the pharmacological action of caplacizumab, and multiple haemorrhage-related events for which a causal relationship to caplacizumab could not be ruled out occurred in Japanese and foreign clinical studies. Characteristic factors affecting the occurrence of caplacizumab-induced serious haemorrhage-related events in clinical practice should be investigated. In addition, taking account of the risk suggested by clinical studies and of missing information, a use-result survey covering all patients treated with caplacizumab will be conducted, with the aim of investigating the incidence of serious hypersensitivity reactions, use in patients with severe hepatic impairment, safety in re-administration, etc. The survey period will be approximately 3 years to allow rapid collection of post-marketing information and prompt provision of the collected information. As for the sample size of this all-case surveillance, it is assumed that there are approximately 500 patients with acquired TTP per year in Japan. However, given that whether to use caplacizumab in clinical settings is decided based on various factors such as patient conditions, the number of patients with acquired TTP treated with

40) Adverse events that occurred during the period from the study drug administration at home up to (a) the time of study drug administration at the study site or (b) the time of the last dose of the study drug (whichever occurred first) in subjects who received at least 1 dose of the study drug at home.
41) Adverse events that occurred during the period from the study drug administration at the study site up to (a) the time of study drug administration at home or (b) the time of the last dose of the study drug (whichever occurred first) in subjects who received at least 1 dose of the study drug at the study site.

caplacizumab is estimated to be approximately 20 per year, approximately 60 within 3 years. This number of patients allows the detection of the risk of 1.6-fold increase in haemorrhage-related events with a probability of 80%, assuming that (a) at least 1 case of serious haemorrhage-related event for which a causal relationship to caplacizumab could not be ruled out in Study ALX0681-C202 (incidence 4.76%) is collected at 90% probability; (b) the incidence of haemorrhage-related events is 50% as was the case with Study ALX0681-C202; and (c) 50% of patients have risk factors for haemorrhage-related events. As for the children aged ≥12 years weighing ≥40 kg, it is estimated that there are only approximately 20 children with acquired TTP aged ≥12 years per year, but those with body weight of ≥40 kg to be selected for caplacizumab administration will be further limited to 1 patient at most per year. Because of the difficulty in estimating the number of pediatric cases collected, the target sample size will not be determined. Instead, at the time point when the target sample size is reached in the entire use-result survey including adults, termination of enrollment of pediatric patients will be considered. In administering caplacizumab to children in clinical settings, data of RICO and vWF:Ag level, if measured in clinical practice, will be collected in addition to safety and efficacy information as in adults. Since PK will be determined only when requested at the discretion of clinical physicians, the PK data obtained may not necessarily be within the range predicted by PK-PD analysis.

PMDA's view:
Because of the limited number of patients investigated in the Japanese clinical study on caplacizumab, the applicant should collect information on the characteristics of patients using caplacizumab, safety, etc., until data from a certain number of patients have been gathered so that information is provided to ensure proper use of caplacizumab. The applicant's plan to conduct a use-results survey on all patients treated with caplacizumab after the market launch is appropriate. Since haemorrhage-related events occurred frequently in clinical studies, information on the incidences of haemorrhage-related adverse events in clinical use of caplacizumab should be collected, and factors for bleeding risk should be explored. In patients receiving caplacizumab in combination with a drug with the bleeding risk-enhancing effect, information in caplacizumab administration should be collected including the reason for the co-administration, type of antithrombogenic drug, dose, timing of coadministration, and incidence of haemorrhage-related adverse events. It is therefore necessary to re-examine the planned sample size and survey period that allow the detection of bleeding risk factors, etc. Administration in pediatric patients aged ≥12 years weighing ≥40 kg should be included in the missing information in the risk management plan because of no use experience in clinical studies, and pharmacovigilance activities should be conducted to collect information on PK, efficacy, and safety in caplacizumab administration. Details of the post-marketing investigations will be finalized upon discussion with the Expert Discussion, including the appropriateness of identification and risk classification of safety specifications, pharmacovigilance activities, and risk minimization activities, based on the "Risk Management Guidance" (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012).

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 ongoing. Results and the conclusion of 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 ongoing. Results and the conclusion of 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 caplacizumab has efficacy in the treatment of acquired thrombotic thrombocytopenic purpura, and that caplacizumab has acceptable safety in view of its benefits. Caplacizumab is a recombinant single-chain, bivalent monoclonal antibody against vWF. Caplacizumab is clinically meaningful because it offers a new treatment option for patients with acquired thrombotic thrombocytopenic purpura. Further investigations are needed on the indication, target patient population for treatment with caplacizumab, dosage and administration, cautionary statements in the package insert, specific methods for collecting information after the market launch, etc.

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

Review Report (2)

August 9, 2022

Product Submitted for Approval

Brand Name	Cablivi Injection 10 mg
Non-proprietary Name	Caplacizumab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	February 10, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Clinical positioning

The following conclusion of PMDA was supported by the expert advisors:

Caplacizumab acts by a novel mechanism of action, i.e., suppression of thrombogenesis in microvessels by inhibiting the binding of platelets and ULvWF. Japanese and foreign clinical studies demonstrated the clinically significant efficacy and tolerable safety of caplacizumab. It is of clinical significance to make caplacizumab available for clinical practice as a novel treatment option for acquired TTP regardless of first onset or relapse whereby the administration is initiated as a combination therapy with the standard treatment (daily PE therapy and immunosuppressive therapy with corticosteroid, etc.) and is continued for a certain period after the end of daily PE.

1.2 Efficacy

The following conclusions of PMDA were supported by the expert advisors:

(a) It is inevitable that, for the development of caplacizumab, the Japanese phase II/III study (Study ALX0681-C202) was conducted as an uncontrolled study supplemented with the data of the foreign phase III study (Study ALX0681-C301), taking account of the following into account: (1) Acquired TTP is serious but rare; (2) it is possible to establish objectively assessable efficacy endpoints and generally acceptable success criteria; and (3) there is no clinically significant difference in the intrinsic or extrinsic ethnic factors between Japanese and non-Japanese subjects.

(b) Collective assessment of the results of Study ALX0681-C202 with those in the caplacizumab group of Study ALX0681-C301 shows that, in addition to the TTP relapse rate, the primary endpoint of Study

ALX0681-C202, multiple secondary points including the time to normalization of platelet count (the primary endpoint in Study ALX0681-C301) may be used for interpreting the usefulness of caplacizumab in Japanese patients.

Regarding the efficacy in Study ALX0681-C301, some expert advisors commented that the between-group difference in the median time to normalization of platelet count [95% CI], the primary endpoint, was small (2.88 [2.68, 3.56] days in the placebo group, 2.69 [1.89, 2.83] days in the caplacizumab group), raising doubts about the clinical significance of treatment with caplacizumab. The following comments were raised regarding the above comments: (a) Given the seriousness of the disease, it is of clinical significance that the platelet count is normalized earlier than by the standard therapy, even if only slightly; and (b) favorable results were observed in the caplacizumab group not only in the time to normalization of platelet count, but also in the occurrence of clinically significant events, such as TTP-related death and TTP relapse (secondary endpoints), indicating clinically significant efficacy of caplacizumab looking overall. On the basis of these opinions, the expert advisors reached the agreement that caplacizumab has clinically significant efficacy.

The following conclusions of PMDA were supported by the expert advisors:
In Japanese patients with acquired TTP as well, caplacizumab is expected to show clinically significant efficacy as demonstrated in Study ALX0681-C301, based on the following findings:
(a) In Study ALX0681-C202, incidence of TTP relapse throughout the study period, the primary endpoint, was below the pre-defined threshold for efficacy, although accurate efficacy assessment is difficult because of the uncontrolled study in the limited number of patients, and
(b) Comparison with Study ALX0681-C301 showed some difference in the patient characteristics enrolled in Japanese and foreign clinical studies and in some of the use status of the standard therapy, but these differences are unlikely to affect the assessment of the efficacy of caplacizumab, judging from the results of the subpopulation analysis presented, and comparison of the results of the primary endpoint and the secondary endpoints [see Table 34 of the "Review Report (1)] showed similar efficacy results in Study ALX0681-C202 as those in the caplacizumab group of Study ALX0681-C301.

1.3 Safety

The expert advisors supported the PMDA's conclusion that caplacizumab should be contraindicated in patients with clinically serious active haemorrhage. The expert advisors commented that since caplacizumab may possibly be particularly useful in patients with active haemorrhage (except patients with clinically serious active haemorrhage), its use should be permitted in this patient group as well, with the caution that caplacizumab should be administered carefully with the understanding that it may aggravate the haemorrhage. PMDA explained that, in the "Precautions concerning Patients with Specific Backgrounds" section of the package insert, physicians will be advised to carefully decide whether to use caplacizumab based on the assessment of the therapeutic benefits and risk in patients with active haemorrhage (except patients with clinically serious active haemorrhage) and monitor the patient carefully if caplacizumab is administered. The expert advisors supported the explanation of PMDA.

PMDA further assessed the appropriateness of the precautions by taking account of the following: (a) Acquired TTP is a disease with a high risk of haemorrhage due to decreased platelet count; (b)

caplacizumab may also be used in patients with clinically nonserious active haemorrhage or with a high risk of haemorrhage upon assessment of therapeutic benefits and risks; and (c) major haemorrhage including fatal cases for which a causal relationship to caplacizumab could not be ruled out was reported in multiple patients after the market launch in foreign countries. Consequently, PMDA proposed to include the following cautionary statement in the "Warning" section of the package insert: "Caplacizumab may lead to serious haemorrhage, possibly resulting in death. Whether to use caplacizumab should be decided carefully with consideration given to bleeding risk." This proposal was supported by the expert advisors.

Regarding caplacizumab administration in patients with hepatic or renal impairment, the following conclusions of PMDA were supported by the expert advisors: (a) Currently, it is unnecessary to include precautions for these patients in the package insert from the aspect of PK and PD; and (b) in patients with severe hepatic impairment accompanied by coagulation disorder, physicians should be advised in the package insert to carefully decide whether to use caplacizumab based on the assessment of therapeutic benefits and risks, because bleeding risk may increase. These conclusions of PMDA were supported by the expert advisors.

1.4 Indication and target population

PMDA's conclusion that the indication of caplacizumab should be "acquired thrombotic thrombocytopenic purpura" was supported by the expert advisors.

Regarding the target population for treatment with caplacizumab, PMDA concluded that when ADAMTS13 activity data become available after the start of the treatment, whether to continue caplacizumab administration should be assessed carefully by the physician by taking account of the conditions of the patient and the therapeutic benefit/risk of caplacizumab. To this conclusion, the expert advisors commented that since prompt treatment is required for acquired TTP, there may be cases where treatment intervention is necessary before the results of the ADAMTS13 activity test become available. However, caplacizumab administration should be discontinued when baseline ADAMTS13 activity is found to be ≥10%. PMDA requested the applicant to make the above points clear in the information materials for healthcare professionals, and confirmed that the request was handled appropriately. Regarding the secondary acquired TTP, the expert advisors supported the PMDA's conclusion that patients diagnosed with acquired TTP regardless of the cause can be considered for treatment with caplacizumab.

1.5 Dosage and administration

The expert advisors supported the conclusion of PMDA that the dosage regimen of caplacizumab in adult patients with acquired TTP should be "10 mg of caplacizumab is administered intravenously prior to PE, followed by a 10 mg subcutaneous injection after completion of PE on the first day of treatment. From Day 2, 10 mg of caplacizumab is administered subcutaneously, once daily."

The expert advisors also supported the conclusions of PMDA to provide the following precautions: (a) The caplacizumab administration period after the end of the daily PE should be 30 days as a general rule; (b) the administration may be continued after the end of the above administration, as necessary; (c)

the extended treatment period should be 4 weeks at the maximum as a rule, and the administration should not be continued without careful consideration, i.e., the administration should be discontinued if clinical symptoms have improved or signs of acquired TTP (e.g., persistent decrease in ADAMTS13 activity) have disappeared.

Regarding the dosage regimen of caplacizumab in children aged ≥12 years weighing ≥40 kg, the expert advisors commented that (a) the simulation by the PK-PD model is a method commonly used and the results obtained are generally acceptable; and (b) although in ordinary circumstances, the appropriateness of the dosage regimen should be justified based on clinical data, there is a certain rationality in the justification of the dosage regimen, given the theoretical discussion based on the allometry, disease pathology, physiology, and pharmacology. On the basis of these comments, the expert advisors supported the following conclusion of PMDA: Caplacizumab may be administered to children aged ≥12 years weighing ≥40 kg at the same dosage regimen as that for adults, given that no safety concerns unique to children have been reported in children treated with caplacizumab after the market launch in foreign countries. The expert advisors also supported the following conclusion of PMDA: Since there is no use experience in children in Japan currently, information on PK, efficacy, and safety of caplacizumab in children treated with caplacizumab should be collected after the market launch to confirm the appropriateness of the above assumption.

On the basis of the above, PMDA concluded that the Dosage and Administration and the Precautions Concerning Dosage and Administration should be described as shown below:

Dosage and Administration

In adults and in children aged ≥12 years weighing ≥40 kg, 10 mg of caplacizumab is administered intravenously prior to plasma exchange, followed by a 10 mg subcutaneous injection after completion of plasma exchange on the first day of treatment. During the subsequent plasma exchange period, 10 mg of caplacizumab is administered subcutaneously, once daily, after the daily plasma exchange. After the plasma exchange period, 10 mg is administered subcutaneously once daily for 30 days.

Treatment with caplacizumab may be extended beyond 30 days after the plasma exchange period depending on the condition of the patient.

Precautions Concerning Dosage and Administration

- Caplacizumab should be administered in combination with plasmapheresis and the standard therapy with an appropriate immunosuppressant, with reference to the latest information including clinical practice guidelines etc.
- Caplacizumab administration should be started with plasma exchange, whenever possible. The initial dose of caplacizumab should be completed not less than 15 minutes before the start of the plasma exchange.
- Missed dose during the plasma exchange period should be administered promptly when noticed. Missed dose after the end of plasma exchange period may be administered when noticed within 12 hours after the scheduled dose. If noticed >12 hours after the scheduled dose, the missed dose should be skipped and the administration should be resumed from the next scheduled timing.

- If symptoms or signs of acquired thrombotic thrombocytopenic purpura (e.g., persisting decreased ADAMTS13 activity) are observed on Day 30 after the end of the plasma exchange period, caplacizumab may be continued until the disappearance of the symptoms or signs of acquired thrombotic thrombocytopenic purpura (e.g., persisting decreased ADAMTS13 activity), together with the optimized immunotherapy. The caplacizumab administration period should be determined in each patient, by taking account of the risk of relapse of acquired thrombotic thrombocytopenic purpura and the risk of haemorrhage. The treatment with caplacizumab should not be continued without careful consideration when caplacizumab is administered beyond 30 days after the plasma exchange period. The maximum extended treatment period is 4 weeks as a general rule.
- Caplacizumab should be discontinued in case of the second or further relapses of acquired thrombotic thrombocytopenic purpura during the caplacizumab administration period.

1.6 Post-marketing investigations

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for caplacizumab should include the safety specification presented in Table 47, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 48, and a use-results survey (all-case surveillance) presented in Table 49.

Table 47. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Haemorrhage	• Serious hypersensitivity reaction • Haemorrhage in combination with an antithrombotic agent	• Use in patients with hepatic impairment • Safety in re-administration • Use in children aged ≥12 years weighing ≥40 kg
Efficacy specification		
None		

Table 48. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	• Disseminate data gathered through early post-marketing phase vigilance • Organize and disseminate information materials for healthcare professionals (a proper use guide for Cablivi) • Organize and disseminate information materials for patients (brochure for patients: For patients who start treatment with Cablivi, patient safety card)

Table 49. Outline of the use-results survey (all-case surveillance) (draft)

Objective	To investigate safety and efficacy in clinical use
Survey method	Central registry system (all-case surveillance)
Population	All patients treated with caplacizumab
Observation period	From the initial dose of caplacizumab up to 3 months after the end of the treatment
Planned sample size	100 patients (safety analysis population) All children receiving caplacizumab during 8 years of the registration period are included even after the planned sample size has been reached.
Main survey items	Haemorrhage, hypersensitivity reactions, patient characteristics (sex, age, past history/comorbidity, first onset/recurrent of TTP, prior caplacizumab treatment, ADAMTS13 activity, etc.), use of caplacizumab, concomitant treatments (treatment for TTP [PE, corticosteroid, rituximab, etc.], antithrombogenic agents, etc.), PK (children only), etc.

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 compliance 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 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and dosage and administration, with approval conditions shown below. Since the product is an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or as a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Acquired thrombotic thrombocytopenic purpura

Dosage and Administration

In adults and in children aged ≥12 years weighing ≥40 kg, 10 mg of caplacizumab is administered intravenously prior to plasma exchange, followed by a 10 mg subcutaneous injection after completion of plasma exchange on the first day of treatment. During the subsequent plasma exchange period, 10 mg of caplacizumab is administered subcutaneously, once daily, after the daily plasma exchange. After the plasma exchange period, 10 mg is administered subcutaneously once daily for 30 days.

Treatment with caplacizumab may be extended beyond 30 days after the plasma exchange period depending on the condition of the patient.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a certain number of patients have been gathered to understand the characteristics of patients using the product. The applicant is also required to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

List of Abbreviations

ADA	Anti-caplacizumab antibody
ADAMTS13	a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13
A/G ratio	Albumin/globulin ratio
aHUS	Atypical hemolytic uremic syndrome
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	AUC from time zero to 24 hours
$AUC_{0\text{-}\infty}$	AUC from time zero to infinite time
$AUC_{0\text{-last}}$	AUC from time zero to the last measurable time
$AUC_{ss,\tau}$	AUC during a dosing interval at steady state
CAL	Cells at the limit of *in vitro* cell age
CEX-HPLC	Cation exchange high-performance liquid chromatography
CI	Confidence interval
CL	Total body clearance
CL/F	Apparent total body clearance
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CRCL	Creatinine clearance
$C_{ss,\,max}$	Maximum plasma concentration at steady state
$C_{ss,\,min}$	Minimum plasma concentration at steady state
CT	Computed tomography
cTnI	Cardiac troponin I
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
ELISA	Enzyme-linked immunosorbent assay
EPC	End of production cells
FDA	Food and Drug Administration
FFP	Frozen fresh plasma
FVIII: C	Factor VIII procoagulant activity
GCS	Glasgow coma scale
GPIb-IX-V	Platelet glycoprotein Ib-IX-V receptor
HCP	Host Cell Protein
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
[redacted]	[redacted]
HUVEC	Human Umbilical Vein Endothelial Cells
IC_{50}	Half maximal inhibitory concentration
ICH Q5B Guidelines	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D Guidelines	"Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)

ICH S6 (R1) Guidelines	"Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1, dated March 23, 2012)
IPTG	Isopropyl-beta-D-1-thiogalactopyranoside
ISTH	The International Society on Thrombosis and Haemostasis
ITO	Intent-to-observe
ITT	Intent-to-treat
JP	Japanese Pharmacopoeia
K_D	Dissociation constant
LDH	Lactate dehydrogenase
LDPE	Low density polyethylene
[redacted]	[redacted]
MCB	Master cell bank
MedDRA PT	Medical Dictionary for Regulatory Activities Preferred Term
MedDRA SOC	Medical Dictionary for Regulatory Activities System Organ Class
mITT	Modified intent-to-treat
NAb	Neutralizing antibody
NSAIDs	Non-Steroidal Anti-inflammatory Drug
PBS	Phosphate buffered saline
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PE	Plasma exchange
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per protocol
PPG	Polypropylene glycol
pre-Ab	Pre-existing antibodies
PT	Prothrombin time
Q	Drug inter-compartmental clearance
RH	Relative humidity
RICO	Ristocetin cofactor activity
RIPA	Ristocetin-induced platelet aggregation
Rituximab	Rituximab (genetical recombination)
RNA	Ribonucleic acid
RP-HPLC	Reverse phase high-performance liquid chromatography
SDS	Sodium dodecyl sulfate
SE-HPLC	Size exclusion high-performance liquid chromatography
SMQ	Standardised MedDRA queries
SPR	Surface plasmon resonance
$t_{1/2}$	Elimination half-life
TE-ADA	Treatment-emergent anti-caplacizumab antibody
TE-NAb	Treatment-emergent neutralizing antibody
TK	Toxicokinetic
t_{max}	Time to reach peak concentration
TTP	Thrombotic thrombocytopenic purpura
ULvWF	Ultra large von Willebrand factor
V	Volume of distribution
V_C	Volume of central compartment

VKA	Vitamin K antagonist
V_p	Volume of peripheral compartment
vWF	von Willebrand factor
vWF: Ag	von Willebrand factor antigen
vWFpp	von Willebrand factor propeptide
V_z	Apparent volume of distribution based on terminal phase
WCB	Working cell bank
γ-GTP	Gamma-glutamyl transpeptidase