Report on the Deliberation Results

March 6, 2024

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

Brand Name	Adzynma Intravenous 1500
Non-proprietary Name	Apadamtase Alfa (Genetical Recombination)/Cinaxadamtase Alfa (Genetical Recombination) (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	August 16, 2023

Results of Deliberation

In its meeting held on February 29, 2024, 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 classified as a 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. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of cases will be collected, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 7, 2024
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Adzynma Intravenous 1500
Non-proprietary Name	Apadamtase Alfa (Genetical Recombination)/Cinaxadamtase Alfa (Genetical Recombination)※
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	August 16, 2023
Dosage Form/Strength	Lyophilized powder to be reconstituted before injection: Each vial contains 1590 international units (IU) of apadamtase alfa (genetical recombination)/cinaxadamtase alfa (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Apadamtase Alfa is a recombinant human von Willebrand factor-cleaving protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13: ADAMTS-13, EC 3.4.24.87), which is produced in CHO cells. Apadamtase Alfa is a glycoprotein (molecular weight: ca. 173,000) consisting of 1353 amino acid residues. Cinaxadamtase Alfa is a recombinant human von Willebrand factor-cleaving protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13: ADAMTS-13, EC 3.4.24.87) analog (Q23R), which is produced in CHO cells. Cinaxadamtase Alfa is a glycoprotein (molecular weight: ca. 173,000) consisting of 1353 amino acid residues.

※ The active ingredient of the product is a mixture of Apadamtase Alfa (Genetical Recombination) and Cinaxadamtase Alfa (Genetical Recombination).

Structure

Apadamtase alfa (genetical recombination)

Amino acid sequence:

AAGGILHLEL LVAVGPDVFQ AHQEDTERYV LTNLNIGAEL LRDPSLGAQF
RVHLVKMVIL TEPEGAPNIT ANLTSSLLSV CGWSQTINPE DDTDPGHADL
VLYITRFDLE LPDGNRQVRG VTQLGGACSP TWSCLITEDT GFDLGVTIAH
EIGHSFGLEH DGAPGSGCGP SGHVMASDGA APRAGLAWSP CSRRQLLSLL
SAGRARCVWD PPRPQPGSAG HPPDAQPGLY YSANEQCRVA FGPKAVACTF
AREHLDMCQA LSCHTDPLDQ SSCSRLLVPL LDGTECGVEK WCSKGRCRSL
VELTPIAAVH GRWSSWGPRS PCSRSCGGGV VTRRRQCNNP RPAFGGRACV
GADLQAEMCN TQACEKTQLE FMSQQCARTD GQPLRSSPGG ASFYHWGAAV
PHSQGDALCR HMCRAIGESF IMKRGDSFLD GTRCMPSGPR EDGTLSLCVS
GSCRTFGCDG RMDSQQVWDR CQVCGGDNST CSPRKGSFTA GRAREYVTFL
TVTPNLTSVY IANHRPLFTH LAVRIGGRYV VAGKMSISPN TTYPSLLEDG
RVEYRVALTE DRLPRLEEIR IWGPLQEDAD IQVYRRYGEE YGNLTRPDIT
FTYFQPKPRQ AWVWAAVRGP CSVSCGAGLR WVNYSCLDQA RKELVETVQC
QGSQQPPAWP EACVLEPCPP YWAVGDFGPC SASCGGGLRE RPVRCVEAQG
SLLKTLPPAR CRAGAQQPAV ALETCNPQPC PARWEVSEPS SCTSAGGAGL
ALENETCVPG ADGLEAPVTE GPGSVDEKLP APEPCVGMSC PPGWGHLDAT
SAGEKAPSPW GSIRTGAQAA HVWTPAAGSC SVSCGRGLME LRFLCMDSAL
RVPVQEELCG LASKPGSRRE VCQAVPCPAR WQYKLAACSV SCGRGVVRRI
LYCARAHGED DGEEILLDTQ CQGLPRPEPQ EACSLEPCPP RWKVMSLGPC
SASCGLGTAR RSVACVQLDQ GQDVEVDEAA CAALVRPEAS VPCLIADCTY
RWHVGTWMEC SVSCGDGIQR RRDTCLGPQA QAPVPADFCQ HLPKPVTVRG
CWAGPCVGQG TPSLVPHEEA AAPGRTTATP AGASLEWSQA RGLLFSPAPQ
PRRLLPGPQE NSVQSSACGR QHLEPTGTID MRGPGQADCA VAIGRPLGEV
VTLRVLESSL NCSAGDMLLL WGRLTWRKMC RKLLDMTFSS KTNTLVVRQR
CGRPGGGVLL RYGSQLAPET FYRECDMQLF GPWGEIVSPS LSPATSNAGG
CRLFINVAPH ARIAIHALAT NMGAGTEGAN ASYILIRDTH SLRTTAFHGQ
QVLYWESESS QAEMEFSEGF LKAQASLRGQ YWTLQSWVPE MQDPQSWKGK
EGT

Main disulfide bonds:

C81-C134, C128-C207, C168-C191, C237-C263, C248-C273, C258-C292, C286-297, C322-C359, C326-C364, C337-C349, C376-C413, C409-C448, C434-C453, C458-C474, C471-C481, C621-C625, C621-C663/C668, C625-C663/C668, C636-C650, C663-C668, C680-C725/C730, C684-C725/C730, C695-C711, C742-C757, C785-C790, C830-C872/C877, C834-C872/C877, C845-C859, C888-C933/C938, C892-C933/C938, C903-C921, C950-C993/C998, C954-C993/C998, C965-C981, C1010-C1051/C1056, C1014-C1501/C1506, C1025-C1039, C1118-C1139, C1162-C1180, C1225-C1251

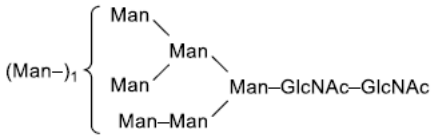
Glycosylation sites:

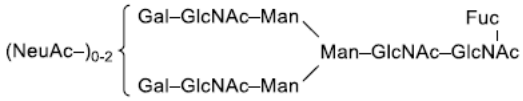
N68, N72, T304, W313, S325, N478, N505, N540, N593, S624, N633, S683, N754, S789, T800, S808, W810, S812, T815, S833, S891, S953, S1013, T1061, S1063, S1096, N1161, N1280

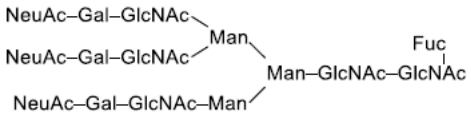
Main proposed carbohydrate structures

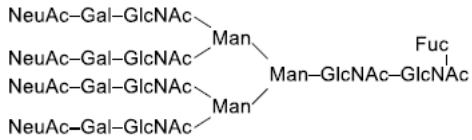
N-linked glycosylation:

N68, N72, N478, N505, N540, N593, N633, N754, N1161, N1280



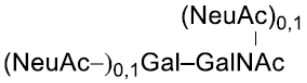




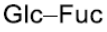


O-linked glycosylation:

T304, S789, T800, S808, S812, T815, T1061, S1063, S1096



S325, S624, S683, S833, S891, S953, S1013



C-linked glycosylation:

W313, W810

Man, Mannose; GlcNAc, *N*-acetylglucosamine; NeuAc, *N*-acetylneuraminic acid; Gal, galactose; Fuc, fucose

Molecular formula: $C_{6286}H_{9802}N_{1860}O_{1918}S_{100}$ (protein moiety)

Molecular weight: ca.173,000

Cinaxadamtase alfa (genetical recombination)

Amino acid sequence:

AAGGILHLEL LVAVGPDVFQ AHREDTERYV LTNLNIGAEL LRDPSLGAQF
RVHLVKMVIL TEPEGAPNIT ANLTSSLLSV CGWSQTINPE DDTDPGHADL
VLYITRFDLE LPDGNRQVRG VTQLGGACSP TWSCLITEDT GFDLGVTIAH
EIGHSFGLEH DGAPGSGCGP SGHVMASDGA APRAGLAWSP CSRRQLLSLL
SAGRARCVWD PPRPQPGSAG HPPDAQPGLY YSANEQCRVA FGPKAVACTF
AREHLDMCQA LSCHTDPLDQ SSCSRLLVPL LDGTECGVEK WCSKGRCRSL
VELTPIAAVH GRWSSWGPRS PCSRSCGGGV VTRRRQCNNP RPAFGGRACV
GADLQAEMCN TQACEKTQLE FMSQQCARTD GQPLRSSPGG ASFYHWGAAV
PHSQGDALCR HMCRAIGESF IMKRGDSFLD GTRCMPSGPR EDGTLSLCVS
GSCRTFGCDG RMDSQQVWDR CQVCGGDNST CSPRKGSFTA GRAREYVTFL
TVTPNLTSVY IANHRPLFTH LAVRIGGRYV VAGKMSISPN TTYPSLLEDG
RVEYRVALTE DRLPRLEEIR IWGPLQEDAD IQVYRRYGEE YGNLTRPDIT
FTYFQPKPRQ AWVWAAVRGP CSVSCGAGLR WVNYSCLDQA RKELVETVQC
QGSQQPPAWP EACVLEPCPP YWAVGDFGPC SASCGGGLRE RPVRCVEAQG
SLLKTLPPAR CRAGAQQPAV ALETCNPQPC PARWEVSEPS SCTSAGGAGL
ALENETCVPG ADGLEAPVTE GPGSVDEKLP APEPCVGMSC PPGWGHLDAT
SAGEKAPSPW GSIRTGAQAA HVWTPAAGSC SVSCGRGLME LRFLCMDSAL
RVPVQEELCG LASKPGSRRE VCQAVPCPAR WQYKLAACSV SCGRGVVRRI
LYCARAHGED DGEEILLDTQ CQGLPRPEPQ EACSLEPCPP RWKVMSLGPC
SASCGLGTAR RSVACVQLDQ GQDVEVDEAA CAALVRPEAS VPCLIADCTY
RWHVGTWMEC SVSCGDGIQR RRDTCLGPQA QAPVPADFCQ HLPKPVTVRG
CWAGPCVGQG TPSLVPHEEA AAPGRTTATP AGASLEWSQA RGLLFSPAPQ
PRRLLPGPQE NSVQSSACGR QHLEPTGTID MRGPGQADCA VAIGRPLGEV
VTLRVLESSL NCSAGDMLLL WGRLTWRKMC RKLLDMTFSS KTNTLVVRQR
CGRPGGGVLL RYGSQLAPET FYRECDMQLF GPWGEIVSPS LSPATSNAGG
CRLFINVAPH ARIAIHALAT NMGAGTEGAN ASYILIRDTH SLRTTAFHGQ
QVLYWESESS QAEMEFSEGF LKAQASLRGQ YWTLQSWVPE MQDPQSWKGK
EGT

Main disulfide bonds, glycosylation sites, and main proposed carbohydrate structures are the same as in apadamtase alfa (genetical recombination).

Molecular formula: $C_{6287}H_{9806}N_{1862}O_{1917}S_{100}$ (protein moiety)

Molecular weight: ca. 173,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 555 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022, 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 congenital 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 conditions.

Indication

Congenital thrombotic thrombocytopenic purpura

Dosage and Administration

The product vial should be reconstituted with 5 mL of the diluent provided, and the reconstituted solution should be infused intravenously slowly at a rate of 2 to 4 mL/min.

For routine prophylaxis, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg every other week. The prophylactic dosing frequency may be adjusted to 40 IU/kg once weekly according to the patient's condition.

For on-demand treatment of an acute event, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg once daily from Day 3.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of cases will be collected, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

December 26, 2023

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	Adzynma Intravenous 1500
Non-proprietary Name	Apadamtase Alfa (Genetical Recombination)/Cinaxadamtase Alfa (Genetical Recombination)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	August 16, 2023
Dosage Form/Strength	Lyophilized powder to be reconstituted before injection: Each vial contains 1590 IU of apadamtase alfa (genetical recombination)/cinaxadamtase alfa (genetical recombination).

Proposed Indication

Congenital thrombotic thrombocytopenic purpura

Proposed Dosage and Administration

The product vial should be reconstituted with 5 mL of the diluent provided, and the reconstituted solution should be infused intravenously slowly at a rate of 2 to 4 mL/min.

Routine prophylaxis

The usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg (body weight) every other week. The prophylactic dosing frequency may be adjusted to 40 IU/kg (body weight) once weekly based on prior prophylactic dosing regimen or clinical response.

On-demand treatment

Usually, for adults and adolescents aged ≥12 years, an initial dose of 40 IU/kg (body weight) should be administered on Day 1 for management etc. of the symptoms of thrombotic thrombocytopenic purpura. A subsequent dose of 20 IU/kg (body weight) should be administered on Day 2, and an additional daily dose of 15 IU/kg (body weight) should be administered from Day 3 until 2 days after the symptoms have resolved.

Table of Contents

List of Abbreviations

See Appendix.

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

von Willebrand factor (VWF) mediates platelet adhesion to subendothelial connective tissue at sites of vascular injury. VWF is a large glycoprotein that plays an important role in primary hemostasis and is synthesized principally by vascular endothelial cells. Newly synthesized VWF forms ultralarge (UL) multimers, and once secreted into blood, ULVWF multimers are cleaved by a disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 (ADAMTS13), a specific VWF cleaving protease. The platelet-binding activity of VWF depends on the size of its multimers, and ADAMTS13 cleaves ULVWF multimers with high platelet-binding activity to smaller units and thereby reduces the platelet binding properties of VWF.

Thrombotic thrombocytopenic purpura (TTP) results from severe deficiency of ADAMTS13 activity, leading to accumulation of ULVWF multimers in blood and their conformational change induced by high shear stress in the microvasculature, resulting in spontaneous formation of platelet-rich microthrombi, thrombocytopenia due to platelet consumption, ischemic damage to multiple organs, etc. TTP is classified into congenital and acquired forms. Congenital TTP is caused by mutations in the *ADAMTS13* gene, and acquired TTP is caused by the production of autoantibodies against ADAMTS13.

The active ingredient of the product is a recombinant ADAMTS13 (rADAMTS13) in-licensed by Baxter from the Chemo-Sero-Therapeutic Research Institute. A cell line expressing rADAMTS13 was developed by Baxter. rADAMTS13 consists of a mixture of Native rADAMTS13 Q97 with a glutamine residue at position 97 (apadamtase alfa [genetical recombination]) and Variant rADAMTS13 R97 with an arginine residue at position 97 (cinaxadamtase alfa [genetical recombination]).

Baxter initiated the clinical development of rADAMTS13 in 2014, which was taken over by Baxalta in 2015, Shire in 2018, and the applicant in 2020. The applicant has recently filed a marketing application for the indication of "congenital thrombotic thrombocytopenic purpura" based on the results of global studies. Outside Japan, rADAMTS13 was approved for "congenital thrombotic thrombocytopenic purpura" in the US in November 2023, and the EU application is under review as of November 2023.

rADAMTS13 received an orphan drug designation (Orphan Drug Designation No. 555 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) with the intended indication of "thrombotic thrombocytopenic purpura" as of December 16, 2022.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The coding sequence of ADAMTS13 cloned from [redacted] of [redacted] was inserted into an expression vector to generate the expression construct for rADAMTS13. The expression construct was transfected into a Chinese hamster ovary (CHO) cell line, and a clone most suitable for the manufacture of rADAMTS13 was selected and used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and end of production cells (EPC) were characterized and subjected to purity tests in accordance with the ICH Q5A (R1), ICH Q5B, and ICH Q5D guidelines. No viral or non-viral adventitious agents were detected other than endogenous retrovirus-like particles, which are known to be present in rodent cell lines, in any of the tests conducted. Although the coding sequence for the desired product of the expression construct had been verified by [redacted] performed during early development, the analyses of the MCB, WCB, and EPC by [redacted] detected the presence of a mutant containing a substitution of adenine for guanine at position 290 of the coding sequence in all samples, and it was found during the ongoing global phase III study (Study 281102) that rADAMTS13 consists of a mixture of native rADAMTS13 with a glutamine residue at position 97 (Native rADAMTS13 Q97, apadamtase alfa [genetical recombination]) and a variant of rADAMTS13 with an arginine residue at position 97 (Variant rADAMTS13 R97, cinaxadamtase alfa [genetical recombination]) [see Sections "2.1.5.1 Structure and properties" and "2.R.1 Variant rADAMTS13 R97"]. Except for [redacted] of Variant rADAMTS13 R97 to Native rADAMTS13 Q97 [redacted], genetic stability during production was demonstrated.

The MCB and WCB are stored at ≤[redacted]°C. There is no plan for generating a new MCB or WCB.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of cell expansion, production culture, harvest, ultrafiltration/diafiltration, virus inactivation ([redacted]), [redacted] chromatography, [redacted] filtration, [redacted] chromatography, [redacted] chromatography, and filling/testing/storage.

Cell expansion at final scale, production culture, harvest, virus inactivation ([redacted]), [redacted] chromatography, [redacted] filtration, [redacted] chromatography, and [redacted] chromatography have been defined as critical steps.

Process validation of the commercial-scale drug substance manufacturing process has been performed.

2.1.3 Safety evaluation of adventitious agents

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

The MCB, WCB, and EPC were subjected to purity tests [see Section "2.1.1 Generation and control of cell substrate"]. Pre-harvest unprocessed bulk at commercial scale was subjected to test for mycoplasma, *in vitro* virus tests, test for mouse minute virus (MMV), sterility test, and transmission electron microscopy. None of the tests revealed contamination with viral or nonviral adventitious agents. These tests excluding sterility test and transmission electron microscopy for pre-harvest unprocessed bulk are included as in-process controls.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

Table 1. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})				
	X-MuLV	BVDV	PRV	Reo 3	MMV
Virus inactivation ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] filtration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>15.7	>10.6	>4.5	4.7	>5.6

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, Process C, the proposed commercial process). The drug product derived from the drug substance manufactured by Process A was used in a phase I study, and the drug products derived from the drug substances manufactured by Process B or C were used in phase III studies.

- Process A→Process B: change of [redacted] and optimization of [redacted]
- Process B→Process C: changes of [redacted] and [redacted], and optimization of [redacted]
- Process C→the proposed commercial process: optimization of [redacted]

For these process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as shown in Table 2.

Table 2. Characterization attributes

Primary/higher order structure	extinction coefficient, amino acid sequence, N-terminal amino acid sequence, post-translational modifications ([redacted], [redacted], and [redacted]), disulfide bonds, secondary structure, tertiary structure, thermal stability
Physicochemical properties	charge variants, molecular weight, size variants
Carbohydrate structure	monosaccharide composition, sialic acid, N-glycan profile, O-glycan profile, glycosylation sites
Biological properties	rADAMTS13 activity, [redacted], [redacted]

The main analyses of quality attributes are shown below.

- rADAMTS13 activity was determined by [redacted] using [redacted], [redacted], and [redacted], in addition to [redacted] using [redacted] (a test system for the potency of the drug substance and the drug product [rADAMTS13 activity and [redacted]]).
- [redacted], [redacted], and [redacted] were demonstrated to be comparable with [redacted].
- [redacted], [redacted], and [redacted] of Native rADAMTS13 Q97 were compared with those of Variant

rADAMTS13 R97. Except for the presence of a mutation, comparable results were obtained. [redacted] assessment indicated no generation of novel [redacted] as a result of [redacted].

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization etc., Related Substance A and Related Substance B (Related Substance A/B) and Related Substance C were considered product-related impurities. No product-related substances have been identified. Among the product-related impurities, Related Substance A/B is controlled by the drug substance and drug product specifications, and Related Substance C is controlled by the manufacturing process.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, Impurity A, Impurity B, Impurity C, Impurity D, and Impurity E were considered process-related impurities. Host cell DNA, Impurity A, Impurity B, Impurity D, and Impurity E were demonstrated to be adequately removed by the manufacturing process, and HCP is controlled by the drug substance specification. Impurity C is [redacted], and its concentration is controlled by the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of appearance, identity ([redacted], Western blotting, and peptide map), pH, purity (size exclusion liquid chromatography [SEC] and HCP), N-glycan profile, Variant rADAMTS13 R97 ([redacted]), microbial limits, bacterial endotoxin, and biological activity (rADAMTS13 activity and [redacted]). Identity (peptide map) was included in the specifications in the course of regulatory review.

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

Table 3. Overview of primary stability studies on drug substance

	Manufacturing process	Number of batches	Storage conditions	Testing period	Storage package
Long-term	Proposed commercial process	3	[redacted]°C-[redacted]°C	24 months[a]	Polyethylene terephthalate glycol copolyester bottle and high-density polyethylene cap
Forced degradation	Process C	4	[redacted] ± [redacted]°C	[redacted] weeks	
Photostability	Process C	1	An overall illumination of not less than 1.2 million lux·hr and an integrated near ultraviolet energy of not less than 200 W·h/m^2		

a: ongoing through [redacted] months.

Under the long-term condition, no significant changes in quality attributes occurred throughout the testing period.

In the forced degradation study, increases in [redacted] and [redacted] in [redacted] and a decrease in [redacted] were observed.

Photostability data showed that the drug substance is photosensitive.

Based on the above, a shelf life of 24 months has been proposed for the drug substance when stored in a polyethylene terephthalate glycol copolyester bottle with a high-density polyethylene cap, protected from light, at [redacted]°C to [redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder to be reconstituted before injection. Each 10-mL glass vial contains 1590 IU of rADAMTS13 and the following excipients: sodium chloride, calcium chloride dihydrate, L-histidine, D-mannitol, sucrose, polysorbate 80, hydrochloric acid, and sodium hydroxide. An overage is used to ensure that 1500 IU of rADAMTS13 can be withdrawn after reconstitution with 5 mL of water for injection.

The drug product is packaged and distributed as a combination product. One vial of rADAMTS13 is co-packaged with 5.4 mL of water for injection (Japanese Pharmacopoeia) in a 6-mL glass vial as a diluent and a reconstitution device (Notification Number: 27B1X00150000002).

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of formulation, sterilizing filtration, sterile filling, lyophilization/crimping, visual inspection/storage/testing, and labeling/packaging/storage/testing.

Sterilizing filtration, sterile filling, and lyophilization/crimping have been defined as critical steps.

The manufacturing process for the diluent consists of preparation of water for injection, filtration, filling, sterilization, visual inspection/storage/testing, and labeling/packaging/storage/testing.

Sterilization has been defined as a critical step.

Process validation of each commercial-scale manufacturing process has been performed.

2.2.3 Manufacturing process development

The following are major changes made to the drug product manufacturing process during development (Process I, Process II, Process III, Process IV, Process V, and the proposed commercial process). The drug product produced by Process II was used in a phase I study, and the drug products produced by Process III, IV, or V were used in phase III studies.

- Process I→Process II: change of [redacted] and optimization of [redacted]
- Process II→Process III: changes of [redacted], [redacted], and [redacted], and optimization of [redacted]
- Process III→Process IV: optimization of [redacted]
- Process IV→Process V: optimization of [redacted]

- Process V→the proposed commercial process: change of [redacted] and optimization of [redacted]

For these process changes, comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, reconstitution time, identity ([redacted] and Western blotting), pH, osmolality, residual moisture, purity (SEC), foreign insoluble matter, insoluble particulate matter, sterility, bacterial endotoxin, biological activity (rADAMTS13 activity and [redacted]), and assay ([redacted]).

2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 4.

Table 4. Overview of primary stability studies on drug product

	Number of batches	Storage conditions	Testing period	Storage package
Long-term	2 [a]	5 ± 3°C	36 months	Glass vial and regular butyl rubber stopper
	2 [b]		24 months[c]	
	2 [a]	30 ± 2°C/65 ± 5%RH	36 months	
	2 [b]		24 months[c]	
Accelerated	2 [a]	40 ± 2°C/75 ± 5%RH	6 months	
	2 [b]		6 months	
Photostability	1 [b]	An overall illumination of not less than 1.2 million lux·hr and an integrated near ultraviolet energy of not less than 200 W·h/m^2, 25 ± 2°C/60 ± 5%RH		

a: The drug product produced by [redacted] from the drug substance manufactured by [redacted]
b: The drug product produced by the proposed commercial process from the drug substance manufactured by the proposed commercial process
c: Ongoing through [redacted] months.

Under the long-term condition (5 ± 3°C), [redacted] tended to increase.

Under the long-term condition (30 ± 2°C/65 ± 5%RH), [redacted] tended to increase, and [redacted] in [redacted] tended to increase.

Under the accelerated condition, [redacted] tended to increase, [redacted] in [redacted] tended to increase, and [redacted] tended to decrease.

Photostability data showed that the drug product is photosensitive.

Based on the above, a shelf life of 24 months has been proposed for the drug product when primary packaged in a glass vial with a regular butyl rubber stopper and stored in a carton to protect from light, at 2°C to 8°C.

2.3 Quality control strategy

Based on the following studies etc., the method of control of the quality attributes of rADAMTS13 through the combination of the control of process parameters, in-process controls, and the specifications was developed

[for the control of product-related impurities and process-related impurities, see Sections "2.1.5.2 Product-related substances/Product-related impurities" and "2.1.5.3 Process-related impurities"].

- Identification of critical quality attributes (CQAs):

  The following CQAs were identified based on the information obtained during the development of rADAMTS13, the relevant knowledge, etc.

  The CQAs of the drug substance: amino acid sequence, [redacted], disulfide bonds, higher-order structure, N-glycan profile, N-linked glycosylation sites, O-glycan profile, [redacted], [redacted], [redacted], [redacted], HCP, host cell DNA, [redacted], appearance, potency (rADAMTS13 activity and [redacted]), pH, [redacted], [redacted], [redacted], [redacted], foreign insoluble matter, viruses, microbial contamination, bacterial endotoxin, and mycoplasma

  The CQAs of the drug product: disulfide bonds, higher-order structure, [redacted], [redacted], appearance, potency (rADAMTS13 activity and [redacted]), pH, residual moisture, reconstitution time, L-histidine, mannitol, sucrose, sodium chloride, calcium chloride, polysorbate 80, insoluble particulate matter, foreign insoluble matter, microbial contamination, bacterial endotoxin, and elemental impurities

- Process characterization

  The operating ranges of process parameters were determined, and the process parameters that impact CQAs and process performance indicators were identified through process risk assessment and characterization studies.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.R.1 Variant rADAMTS13 R97

The applicant's explanation about Variant rADAMTS13 R97:

During the ongoing global phase III study (Study 281102), sequencing of the expression construct for rADAMTS13 using a more sensitive technique using [redacted] confirmed the presence of a mutation in the coding sequence for the desired protein, which could not be detected by the classical gene analysis approach ([redacted]) [see Section "2.1.1 Generation and control of cell substrate"]. Characterization of rADAMTS13 revealed that rADAMTS13 consists of a mixture of Native rADAMTS13 Q97 with a glutamine residue at position 97 (apadamtase alfa [genetical recombination]) and Variant rADAMTS13 R97 with an arginine residue at position 97 (cinaxadamtase alfa [genetical recombination]). The test results showed that the quality attributes are comparable between Native rADAMTS13 Q97 and Variant rADAMTS13 R97 except for the presence of a mutation, demonstrating that heterogeneity of the gene sequence does not affect the quality of rADAMTS13 [see Section "2.1.5.1 Structure and properties"]. Furthermore, since the results from process characterization showed that [redacted] affects [redacted] of Variant

rADAMTS13 R97, quality consistency can be secured through the control of this parameter within the appropriate range and the control of [redacted] of Variant rADAMTS13 R97 in rADAMTS13 by the drug substance specification.

Based on the applicant's explanation that the presence of Variant rADAMTS13 R97 is unlikely to affect the efficacy and safety of rADAMTS13, and that quality consistency is secured, PMDA concluded that the presence of Variant rADAMTS13 R97 in rADAMTS13 is acceptable.

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 Activity on VWF in plasma from different animal species (CTD 4.2.1.1-1 [Reference data])

The ability of rADAMTS13 to cleave VWF in plasma from ADAMTS13 knockout mouse, rat, guinea pig, cynomolgus monkey, and minipig was evaluated by Western blotting using anti-human VWF antibody. rADAMTS13 cleaved VWF in plasma from all species.

3.1.2 *In vivo* studies

3.1.2.1 Prophylactic efficacy in TTP mouse model (CTD 4.2.1.1-2, 4.2.1.1-3)

rADAMTS13 (1, 5, 40, 80, or 200 U/kg) or vehicle[1)] was prophylactically administered intravenously, immediately followed by IV injection of recombinant human von Willebrand factor (rhVWF) (2000 RCoU/kg)[2)] in ADAMTS13 knockout mice (5/sex/group) (Day 0). On Day 1, platelet counts and serum lactate dehydrogenase (LDH) concentrations were determined, and histopathological assessment was performed. The percentage of platelet count on Day 1 relative to baseline (median [1st quartile, 3rd quartile]) was 3.4% [2.6%, 4.0%] in the vehicle group and those in the rADAMTS13 1, 5, 40, 80, and 200 U/kg groups were 6.5% [4.7%, 19.6%], 68.5% [66.6%, 69.9%], 98.9% [90.3%, 102.8%], 99.9% [94.0%, 104.5%], and 88.2% [83.1%, 96.7%], respectively. Platelet counts were significantly higher at all dose levels of rADAMTS13 compared to vehicle. The serum LDH level on Day 1 (median [1st quartile, 3rd quartile]) was 1997.5 [1829.0, 2473.0] U/L in the vehicle group and those in the rADAMTS13 1, 5, 40, 80, and 200 U/kg groups were 290.5 [207.0, 359.0], 184.5 [142.0, 244.0], 216.0 [141.0, 326.0], 176.0 [157.0, 211.0], and 210.0 [174.0, 277.0] U/L, respectively. Serum LDH levels were significantly lower at all dose levels of rADAMTS13 compared to vehicle. As to histopathological findings in the kidney, acute tubular necrosis and increased severity of tubular casts observed in the vehicle group were absent in all dose groups of rADAMTS13. As to histopathological findings in the heart, compared to acute myocardial necrosis, acute myocarditis, and acute myocardial hemorrhage observed in the vehicle group, a dose-dependent decrease in the severity of those findings was observed in animals treated with rADAMTS13, and the incidences of acute myocardial necrosis and acute myocarditis were reduced at ≥80 U/kg of rADAMTS13.

[1)] A buffer containing sodium, calcium, chloride, histidine, mannitol, sucrose, and polysorbate 80

[2)] Challenge of ADAMTS13 knockout mice with rhVWF led to the development of TTP-like symptoms such as thrombocytopenia, decreased hematocrit, and increased LDH. Compared with ADAMTS13 knockout mice untreated with rhVWF, platelet counts were reduced by approximately 33% after 5 minutes and by approximately 95% after 9 hours (*Blood*. 2012;119:6128-35).

rADAMTS13 (200 U/kg) or vehicle[1)] was prophylactically administered intravenously followed by IV injection of rhVWF (2000 RCoU/kg) (Day 0) in ADAMTS13 knockout mice (5/sex/group). rADAMTS13 was administered at 5 minutes or 3, 24, 48, 72, or 120 hours before administration of rhVWF, or vehicle was administered at 5 minutes before administration of rhVWF. On Day 1, platelet counts and serum LDH concentrations were determined, and histopathological assessment was performed. The percentage of platelet count on Day 1 relative to baseline (mean ± standard deviation [SD]) was 2.8 ± 0.9% in the vehicle group and those when rADAMTS13 was administered at 5 minutes or 3, 24, 48, 72, or 120 hours before administration of rhVWF were 106.4 ± 18.2%, 95.5 ± 7.3%, 103.4 ± 7.8%, 101.0 ± 49.4%, 79.7 ± 13.2%, and 19.2 ± 16.4%, respectively. Platelet counts were significantly higher in the rADAMTS13 group than in the vehicle group, across all treatment intervals. The serum LDH level (mean ± SD) on Day 1 was 1922.3 ± 319.1 U/L in the vehicle group and those when rADAMTS13 was administered at 5 minutes or 3, 24, 48, 72, or 120 hours before administration of rhVWF were 155.4 ± 35.3, 161.4 ± 49.1, 143.7 ± 51.9, 143.5 ± 25.0, 204.3 ± 200.4, and 227.2 ± 187.0 U/L, respectively. Serum LDH levels were significantly lower in the rADAMTS13 group than in the vehicle group, across all treatment intervals. As to histopathological findings in the kidney, acute tubular necrosis and increased severity of tubular casts observed in the vehicle group were absent in animals treated with rADAMTS13. As to histopathological findings in the heart, acute myocardial necrosis, acute myocarditis, and acute myocardial hemorrhage observed in the vehicle group were absent when rADAMTS13 was administered at 5 minutes or 3 hours before administration of rhVWF. When rADAMTS13 was administered at ≥24 hours before administration of rhVWF, acute myocardial necrosis, acute myocarditis, and acute myocardial hemorrhage were observed. The prolongation of the treatment interval between rADAMTS13 and rhVWF caused an increase in the severity of those findings, but their severity was still lower in rADAMTS13-treated animals than in the vehicle group.

3.1.2.2 Therapeutic efficacy in TTP mouse model (CTD 4.2.1.1-4 [Reference data], 4.2.1.1-5 [Reference data])

ADAMTS13 knockout mice (5/sex/group) received therapeutic treatment with intravenous rADAMTS13 (200 U/kg) at 15, 30, or 180 minutes after IV injection of rhVWF (2000 RCoU/kg) or intravenous vehicle[1)] at 15 minutes after IV injection of rhVWF (2000 RCoU/kg) (Day 0). On Day 1, platelet counts and serum LDH concentrations were determined, and histopathological assessment was performed. The percentage of platelet count on Day 1 relative to baseline (mean ± SD) was 7.2 ± 5.0% in the vehicle group and those when rADAMTS13 was administered at 15, 30, or 180 minutes after administration of rhVWF were 110.4 ± 35.0%, 115.3 ± 37.5%, and 84.3 ± 11.9%, respectively. Platelet counts were significantly higher in the rADAMTS13 group than in the vehicle group, across all treatment intervals. The serum LDH level (mean ± SD) on Day 1 was 1700.9 ± 231.2 U/L in the vehicle group, and those when rADAMTS13 was administered at 15, 30, or 180 minutes after administration of rhVWF were 148.9 ± 36.2, 198.6 ± 69.6, and 353.8 ± 99.0 U/L, respectively. Serum LDH levels were significantly lower in the rADAMTS13 group than in the vehicle group, across all treatment intervals. As to histopathological findings in the kidney, acute tubular necrosis observed in the vehicle group was absent in animals treated with rADAMTS13. As to histopathological findings in the heart, acute myocardial necrosis and hemorrhage observed in the vehicle group had a low severity grade when rADAMTS13 was administered at 15 or 30 minutes after administration of rhVWF.

ADAMTS13 knockout mice (5/sex/group) received therapeutic treatment with intravenous rADAMTS13 (1, 5, 40, 80, or 200 U/kg) or vehicle[1)] at 16 minutes after IV injection of rhVWF (2000 RCoU/kg) (Day 0). On Day 1, platelet counts were determined. Platelet counts were significantly higher in the rADAMTS13 40, 80, and 200 U/kg groups than in the vehicle group.

3.1.2.3 Effects on formation and resolution of microvascular thrombosis (CTD 4.3-1: *Arterioscler Thromb Vasc Biol*. 2019;39:1817-30 [Reference data])

In ADAMTS13 knockout mice (3 males and 2 females/group), (1) rADAMTS13 (320 U/kg) or vehicle (0.9% [w/v] sodium chloride solution) was administered intravenously at 10 minutes prior to IV injection of fluorescently labeled anti-platelet antibody and rhVWF (2000 U/kg), or (2) rADAMTS13 (320 U/kg) was administered intravenously at 30 to 60 minutes after IV injection of fluorescently labeled anti-platelet antibody and rhVWF (2000 U/kg). The formation and resolution of microvascular thrombosis in the brain were evaluated by real-time monitoring under fluorescent microscope. While platelet aggregation indicative of microvascular thrombosis was detected in the brain microvasculature in mice injected with rhVWF, prophylactic treatment with rADAMTS13 protected mice from microvascular thrombosis in the brain after rhVWF challenge, and therapeutic treatment with rADAMTS13 resolved microvascular thrombi in the brain of mice after rhVWF challenge.

3.2 Secondary pharmacodynamics

3.2.1 Bleeding risks with rADAMTS13 in combination with anti-thrombotic drugs (CTD 4.3-6, *Blood Coagul Fibrinolysis*. 2022;33:56-60 [Reference data])

rADAMTS13 (3111 U/kg) or anti-thrombotic drugs (enoxaparin 30 mg/kg or acetylsalicylic acid 30 mg/kg) were administered intravenously alone, rADAMTS13 was administered intravenously in combination with anti-thrombotic drugs, or vehicle (0.9% [w/v] sodium chloride solution) was administered intravenously, in male rats (6/group). At 5 minutes after administration, the tail tip of each rat was cut, and blood loss was assessed. There were no significant differences in the blood loss between the rADAMTS13 alone group and the vehicle group. There were no significant differences in the blood loss between the rADAMTS13 + anti-thrombotic drug group and the anti-thrombotic drug alone group.

3.3 Safety pharmacology

The results of safety pharmacology studies are shown in Table 5.

Table 5. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Doses (U/kg)	Route of administration	Findings	CTD
CNS	Cynomolgus monkey (4/sex)	Clinical observations	200, 1790 [a]	IV	No effects[b]	4.2.3.1-1
	Rat (SD) (10/sex/group)	Clinical observations	0,[c] 800, or 1820[d] QD for 30 days + 2-week recovery period	IV	No effects[e]	4.2.3.2-4
	Cynomolgus monkey (5/sex/group)	Clinical observations	0,[c] 80, 200, or 400 QW for 4 weeks + 2-week recovery period	IV	No effects[f]	4.2.3.2-7
Cardiovascular		Blood pressure, heart rate, ECG (telemetry)				
Respiratory		Respiratory rate				

a: rADAMTS13 was administered at 200 U/kg on Day 1, followed by a 14-day washout period before administering 1790 U/kg on Day 15.
b: ADAs were detected (2 of 8 animals at 200 U/kg). No neutralizing ADAs were detected.
c: A buffer containing sodium, calcium, chloride, histidine, mannitol, sucrose, and polysorbate 80
d: IU/kg
e: ADAs were detected (1/10 in the 800 IU/kg group, 3/10 in the 1820 IU/kg group; All were detected on the last day of the 2-week recovery period). Although neutralizing ADAs were detected in all of ADA-positive animals in the 1820 IU/kg group, animals evaluated for TK did not show lower ADAMTS13 activity. The applicant explained that the effect of neutralizing ADAs on ADAMTS13 activity was considered limited in rats [see Section "4.1.2 Repeated-dose studies"].
f: ADAs were detected (4/10 in the 80 U/kg group, 7/10 in the 200 U/kg group, 10/10 in the 400 U/kg group). Among ADA-positive animals, 1/4 in the 80 U/kg group, 6/7 in the 200 U/kg group, and 8/10 in the 400 U/kg group had neutralizing ADA and lower ADAMTS13 activity, but most animals developed neutralizing ADA after the last dose of rADAMTS13 at Week 4. The applicant explained that safety pharmacology assessment was not affected.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacologic action of rADAMTS13 in congenital TTP

The applicant's explanation about the physiological function of ADAMTS13 and the pharmacologic action of rADAMTS13 in congenital TTP:

ADAMTS13 is a VWF-cleaving protease and forms VWF fragments with low platelet-binding activity. ULVWF multimers with high platelet-binding activity result in spontaneous formation of platelet-rich microthrombi in the microvasculature. Thus, ADAMTS13 is considered to prevent thrombosis by cleaving ULVWF multimers (*Blood.* 2019;133:1644-51, *Blood*. 2008;112:1713-9, etc.). Congenital TTP is caused by deficiency and dysfunction of ADAMTS13 due to autosomal recessive mutations in the *ADAMTS13* gene, leading to accumulation of ULVWF multimers in plasma.

Given that *in vivo* studies demonstrated the following points, etc., the use of rADAMTS13 as prophylactic or on-demand enzyme replacement therapy in patients with congenital TTP is expected to prevent and treat TTP symptoms such as thrombocytopenia and microvascular thrombosis.

- Prophylactic administration of rADAMTS13 in ADAMTS13 knockout mice prevented the development of TTP-like symptoms such as thrombocytopenia after rhVWF challenge [see Section "3.1.2.1 Prophylactic efficacy in TTP mouse model"].
- Therapeutic administration of rADAMTS13 in ADAMTS13 knockout mice tended to improve TTP-like symptoms such as thrombocytopenia and microvascular thrombosis after rhVWF challenge [see Sections "3.1.2.2 Therapeutic efficacy in TTP mouse model" and "3.1.2.3 Effects on formation and resolution of microvascular thrombosis"].

PMDA's conclusion:

Given that the structure and function of rADAMTS13 are comparable to those of endogenous ADAMTS13 [see Section "2.1.5.1 Structure and properties"] and based on the results of *in vivo* studies, rADAMTS13 is expected to prevent and treat TTP symptoms in patients with congenital TTP.

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

The pharmacokinetics (PK) of rADAMTS13 were evaluated based on ADAMTS13 activity in plasma.

ADAMTS13 activity in mouse, rat, and monkey plasma was determined by a fluorogenic assay using fluorescence resonance energy transfer substrate composed of 73 amino acids from the A2 domain of von Willebrand factor (FRETS-VWF73). The lower limit of quantitation (LLOQ) was 0.050 U/mL in non-clinical studies in mice, rats, and monkeys (CTD 4.2.2.2-1, 4.2.2.2-2, 4.2.3.1-1, 4.2.3.2-5, 4.2.3.2-7) and 0.1 IU/mL in a non-clinical study in rats (CTD 4.2.3.2-4).[3)]

Anti-drug antibodies (ADAs) in rat and monkey plasma were detected by an enzyme-linked immunosorbent assay (ELISA).

Neutralizing ADAs to rADAMTS13 in plasma were assessed by a modified Bethesda method using a fluorogenic assay using FRETS-VWF73 substrate. One Bethesda unit (BU) was defined as the ADA titer that reduces ADAMTS13 activity by 50%. In all animal species, ADAs were considered neutralizing if the inhibitor titer was ≥2 BU/mL.

Unless otherwise specified, PK parameters are expressed as the mean or the mean ± SD.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.2-2, 4.2.3.1-1)

Table 6 shows the PK parameters of ADAMTS13 activity following a single intravenous administration of rADAMTS13 in male and female ADAMTS13 knockout mice.

ADAs etc. were not assessed.

Table 6. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13 in ADAMTS13 knockout mice

Dose (U/kg)	C_{max} (U/mL)	t_{max} (h)	$AUC_{0-\infty}$ (U·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V (mL/kg)
40	0.478	0.083	5.07	10.0	8.3	113.1
80	1.025	0.083	11.6	15.9	7.0	134.9
200	2.440	0.083	30.8	17.3	7.6	161.4

5/sex/time point

[3)] Pooled normal human plasma was defined to have an ADAMTS13 activity of 1 U/mL, which corresponds to 1.104 IU/mL of WHO International Standard for ADAMTS13.

Table 7 shows the PK parameters of ADAMTS13 activity following a single intravenous administration of rADAMTS13 in male and female rats.

ADAs etc. were not assessed.

Table 7. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13 in rats

Dose (U/kg)	C_{max} (U/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (U·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V (mL/kg)
80	1.447 (8.7)	0.083	25.9 (4.22)	16.7 (10.4)	2.9 (9.1)	66.3 (6.0)
200	3.738 (8.0)	0.083	77.6 (1.38)	25.6 (13.9)	2.4 (7.4)	72.6 (7.0)
400	7.114 (8.1)	0.083	170 (0.63)	24.0 (16.4)	2.0 (7.7)	59.6 (9.2)

5/sex, Geometric mean (Coefficient of variation %)
a: Median

Table 8 shows the PK parameters of ADAMTS13 activity following escalating intravenous doses of 200 and 1790 U/kg of rADAMTS13 (a 14-day washout period) in male and female monkeys.

Two of 8 animals developed ADA, but not neutralizing ADA.

Table 8. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13 in monkeys

Dose (U/kg)	Sex	C_{max} (U/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (U·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V (mL/kg)
200	M	3.954 (17.0)	0.083	86.4 (1.25)	25.2 (27.6)	2.1 (8.7)	66.8 (21.0)
	F	4.402 (7.4)	0.292	78.4 (1.37)	24.0 (15.0)	2.4 (7.9)	66.5 (11.8)
1790	M	33.988 (3.6)	0.083	949 (0.11)	31.1 (10.4)	1.7 (8.4)	69.5 (6.2)
	F	32.002 (13.5)	0.083	717 (0.15)	25.1 (32.0)	2.3 (5.6)	73.7 (21.9)

4/sex, Geometric mean (Coefficient of variation %)
a: Median

4.1.2 Repeated-dose studies (CTD 4.2.3.2-4, 4.2.3.2-5, 4.2.3.2-7)

Table 9 shows the PK parameters of ADAMTS13 activity following intravenous administration of rADAMTS13 QD for 30 days in male and female rats.

Table 9. PK parameters of ADAMTS13 activity following repeated intravenous administration of rADAMTS13 in rats

Dose (IU/kg)	Sampling time point (Day)	C_{max} (IU/mL)	AUC_{0-24h} (IU·h/mL)
800	1	15.08	195.8
	30	33.74	436.1
1820	1	40.62	482.6
	30	108.5	1153

2-6/sex/time point

rADAMTS13 800 or 1820 IU/kg QD was administered intravenously for 30 days in male and female rats (5/sex). By Day 44, 1 of 10 animals in the 800 IU/kg group and 3 of 10 animals in the 1820 IU/kg group tested positive for ADA, of which 3 animals in the 1820 U/kg group developed neutralizing ADA.

Table 10 shows the PK parameters of ADAMTS13 activity following intravenous administration of rADAMTS13 Q3D for 26 weeks in male and female rats.

Table 10. PK parameters of ADAMTS13 activity following repeated intravenous administration of rADAMTS13 in rats

Dose (U/kg)	Sex	Sampling time point (Day)	C_{max} (U/mL)	$AUC_{0\text{-}72h}$ (U·h/mL)
80	M	1	1.47	28.7
		91	1.91	39.7
		181	2.31	55.8
	F	1	1.14	18.6
		91	1.68	31.6
		181	1.85	27.3
200	M	1	3.87	82.2
		91	7.79	129
		181	5.92	157
	F	1	3.68	55.9
		91	4.65	103
		181	4.85	97.0
400	M	1	6.91	142
		91	10.2	231
		181	10.0	268
	F	1	6.46	106
		91	7.66	181
		181	9.12	177

3/sex/time point

rADAMTS13 80, 200, or 400 U/kg Q3D was administered intravenously for 26 weeks in male and female rats (5/sex). By Week 30, 1 of 10 animals in the 200 U/kg group and 2 of 10 animals in the 400 U/kg group tested positive for ADA, but not neutralizing ADA.

The applicant's explanation:
Based on the incidences of neutralizing ADAs in repeated-dose toxicity studies in rats (CTD 4.2.3.2-2, 4.2.3.2-4, 4.2.3.2-5) and given that there was no trend towards markedly lower ADAMTS13 activity after repeated dosing compared to the first dose in these toxicity studies, the effect of neutralizing ADAs on ADAMTS13 activity is considered limited in rats.

Table 11 shows the PK parameters of ADAMTS13 activity following intravenous administration of rADAMTS13 QW for 28 days in male and female monkeys.

Table 11. PK parameters of ADAMTS13 activity following repeated intravenous administration of rADAMTS13 in monkeys

Dose (U/kg)	Sex	Sampling time point (Day)	C_{max} (U/mL)	$AUC_{0\text{-}70h}$ (U·h/mL)
80	M	1	1.590 (5.1)	22.4 (6.01)
		29	1.020 (97.8)	7.02 (72.1)
	F	1	1.614 (35.5)	38.4 (2.84)
		29	1.134 (40.3)	5.87 (48.9)
200	M	1	4.766 (6.8)	93.5 (1.18)
		29	1.095 (176.7)	10.7, 94.1 [a]
	F	1	3.791 (10.3)	96.0 (1.16)
		29	0.538 (424.1)	0.20, 85.8 [a]
400	M	1	8.067 (3.9)	175 (0.60)
		29	5.527 (72.2)	20.9 (15.2)
	F	1	9.377 (6.6)	189 (0.56)
		29	5.184 (57.5)	18.0 (17.0)

3/sex, Geometric mean (Coefficient of variation %)
a: Individual values are listed.

By Day 46, 4 of 10 animals in the 80 U/kg group, 7 of 10 animals in the 200 U/kg group, and 10 of 10 animals in the 400 U/kg group tested positive for ADA, of which 1 animal in the 80 U/kg group, 6 animals in the 200 U/kg group, and 8 animals in the 400 U/kg group developed neutralizing ADA.

The applicant explained that lower ADAMTS13 activity after repeated dosing in monkeys was considered attributed to the development of neutralizing ADA in a large proportion of the animals.

4.2 Distribution

No tissue distribution study of rADAMTS13 was conducted.

The applicant's explanation:
In single intravenous dose studies in mice, rats, and monkeys, the V values of ADAMTS13 activity were 113.1 to 161.4, 59.6 to 72.6, and 66.5 to 73.7 mL/kg, respectively, which were slightly higher than their respective plasma volumes (50, 31.2, and 44.8 mL/kg, respectively) (*Pharm Res*. 1993;10:1093-5), but the distribution of rADAMTS13, a large protein with a high molecular weight, should be limited to the vascular space.

4.2.1 Placental transfer (CTD 4.2.3.5.1-1 [Reference data])

Following a single intravenous administration of rADAMTS13 3200 U/kg in pregnant rats on gestation day 21 (n = 6), the serum concentrations of ADAMTS13 protein at 30 minutes post-dose were 19.62 to 37.09 µg/mL in the dams and 0.01 to 0.12 µg/mL in the fetuses. Following a single intravenous administration of vehicle as a negative control, ADAMTS13 protein was not detected in maternal or fetal serum.

4.3 Metabolism and excretion

No metabolism or excretion studies of rADAMTS13 were conducted.

The applicant's explanation about the metabolism and excretion of rADAMTS13:
As with other exogenous proteins, rADAMTS13 is considered to be degraded through regular protein catabolism into its amino acids. Milk excretion of rADAMTS13 was not studied, and the possibility that

rADAMTS13 is excreted into human milk cannot be ruled out. Meanwhile, since limited milk excretion of rADAMTS13, a large protein with a high molecular weight, is inferred (*The Showa University Journal Of Medical Sciences.* 2013;73:301-6), and its oral bioavailability should be low, there should be little effect on breastfed infants. However, as the potential risks to breastfed infants cannot be excluded, the package insert will advise that the decision to continue or discontinue breastfeeding should take into account the therapeutic benefits of rADAMTS13 and the benefits of breastfeeding nutrition.

4.R Outline of the review conducted by PMDA

PMDA's view:

Although apart from a placental transfer study, no non-clinical distribution, metabolism, or excretion studies of rADAMTS13 were conducted, these can be inferred from the existing information. Based on the submitted data and the applicant's explanation, the non-clinical pharmacokinetics of rADAMTS13 were adequately evaluated. The precautionary statement regarding the use of rADAMTS13 in breastfeeding women in the package insert presented by the applicant, is also appropriate.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

Although no single-dose toxicity studies were conducted, the acute toxicity of rADAMTS13 was assessed based on the results of a dose-escalation toxicity study in cynomolgus monkeys (Table 12). No toxicity findings were observed up to the highest dose tested, and the approximate lethal dose of rADAMTS13 could not be determined.

Table 12. Overview of dose-escalation toxicity study

Test system	Route of administration	Dose (U/kg)	Noteworthy findings	Approximate lethal dose (U/kg)	Attached document CTD
Male and female cynomolgus monkeys	IV	200, 1790 [a]	No toxicity findings ADAs were detected (2 of 8 animals at 200 U/kg)[b]	>1790	4.2.3.1-1

a: rADAMTS13 was administered at 200 U/kg on Day 1, followed by a 14-day washout period before administering 1790 U/kg on Day 15.
b: No neutralizing ADAs were detected.

5.2 Repeated-dose toxicity

Five-day, 28-day, 30-day, or 26-week repeated-dose toxicity studies in rats and a 4-week repeated-dose toxicity study in cynomolgus monkeys were conducted (Table 13). No rADAMTS13-related toxicity was observed in the repeated-dose toxicity studies in rats, and ADAMTS13 activity exposures (C_{max} = 9.56 U/mL, AUC_{last} = 223 U·h/mL) at the no-observed-adverse-effect-level (NOAEL) (400 U/kg) in the 26-week repeated-dose toxicity study in rats were 8.5-fold and 14-fold, respectively, the predicted steady-state ADAMTS13 activity exposures ($C_{max,\ ss}$ = 1.12 IU/mL, estimated AUC_{last}[4)] = 15.6 IU·h/mL) in humans following prophylactic administration of rADAMTS13 40 IU/kg Q2W.

[4)] Steady-state $C_{ave,\ ss}$ in humans following prophylactic administration of rADAMTS13 40 IU/kg Q2W multiplied by t_{last} for the non-clinical study

Since the incidence of ADAs was high in cynomolgus monkeys, and lower ADAMTS13 activity was observed in animals with neutralizing ADAs, a long-term toxicity study was conducted in rats only. In the 4-week repeated-dose toxicity study in cynomolgus monkeys, the high incidence or titer of cross-reactive neutralizing ADAs to endogenous monkey ADAMTS13 led to TTP-like findings such as thrombopenia and hemolytic anemia secondary to decreased ADAMTS13 activity.

Table 13. Overview of repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (U/kg)	Noteworthy findings	NOAEL (U/kg)	Attached document CTD
Male and female rats (SD)	IV	5 days (QD) + 2-week recovery period	0,[a] 80, 200, 400	Died or euthanized moribund: 200 (1 of 5 females in the recovery group)[b] No toxicity findings No ADAs were detected.	400	4.2.3.2-1
Male and female rats (SD)	IV	28 days (Q3D) + 2-week recovery period	0,[a] 80, 400, 800	No toxicity findings ADAs were detected (1/10 in the 80 U/kg group, 3/10 in the 400 U/kg group, 7/10 in the 800 U/kg group)[c]	800	4.2.3.2-2
Male and female rats (SD)	IV	30 days (QD) + 2-week recovery period	0,[a] 800, 1820 [d]	No toxicity findings ADAs were detected (1/10 in the 800 IU/kg group, 3/10 in the 1820 IU/kg group)[e]	1820	4.2.3.2-4
Male and female rats (SD)	IV	26 weeks (Q3D) + 4-week recovery period	0,[a] 80, 200, 400	Died or euthanized moribund: 80 (1 of 10 males), 200 (1 of 10 males), 400 (2 of 10 males)[b] No toxicity findings ADAs were detected (1/10 in the 200 U/kg group, 2/10 in the 400 U/kg group)[f]	400	4.2.3.2-5
Male and female cynomolgus monkeys	IV	4 weeks (QW) + 2-week recovery period	0,[a] 80, 200, 400	≥200: thrombopenia (female) 400: hemolytic anemia, bilirubinemia, increased LDH, extramedullary hematopoiesis, medial thickening in small vessels in the heart, proteinaceous casts in the kidneys (all in females)[g] ADAs were detected (4/10 in the 80 U/kg group, 7/10 in the 200 U/kg group, 10/10 in the 400 U/kg group)[h]	400	4.2.3.2-7

a: A buffer containing sodium, calcium, chloride, histidine, mannitol, sucrose, and polysorbate 80
b: These were considered unlikely related to rADAMTS13.
c: Among ADA-positive animals, 1/1 in the 80 U/kg group, 3/3 in the 400 U/kg group, and 3/7 in the 800 U/kg group had neutralizing ADAs, but animals evaluated for TK did not show lower ADAMTS13 activity.
d: IU/kg
e: All of ADA-positive animals in the 1820 IU/kg group had neutralizing ADAs, but animals evaluated for TK did not show lower ADAMTS13 activity.
f: No neutralizing ADAs were detected, and animals evaluated for TK did not show lower ADAMTS13 activity.
g: All findings were considered secondary to decreased ADAMTS13 activity due to the development of neutralizing ADAs.
h: Among ADA-positive animals, 1/4 in the 80 U/kg group, 6/7 in the 200 U/kg group, and 8/10 in the 400 U/kg group had neutralizing ADAs and showed lower ADAMTS13 activity.

5.3 Genotoxicity

Since rADAMTS13 is a biotechnology-derived pharmaceutical, no genotoxicity studies were conducted in accordance with the ICH S6 (R1) guideline.

5.4 Carcinogenicity

Since rADAMTS13 is a biotechnology-derived pharmaceutical, no carcinogenicity studies were conducted in accordance with the ICH S6 (R1) guideline.

The applicant's explanation:
Since administration of rADAMTS13 is endogenous enzyme replacement therapy, and repeated-dose toxicity

studies showed no findings indicative of its carcinogenic potential, the risk of cancer associated with the clinical use of rADAMTS13 is low.

5.5 Reproductive and developmental toxicity

Fertility and embryo-fetal development and pre- and postnatal development studies were conducted in rats (Table 14).

The applicant's explanation:
Due to lack of rADAMTS13 activity in cleaving VWF in rabbit plasma (CTD 4.2.3.2-6), high incidences of ADAs and neutralizing ADAs, and lower ADAMTS13 activity, rabbits are not a relevant species for reproductive and developmental toxicity studies.

Although the target population for rADAMTS13 includes adolescents aged ≥12 years, no juvenile animal studies were conducted. The applicant explained that given the following points, there should be no major differences in rADAMTS13 susceptibility between adults and adolescents aged ≥12 years.

- Although plasma ADAMTS13 levels are markedly lower in neonates than in younger adults, neonatal levels reach adult levels by 6 months of age (*Blood*. 2001;98:2730-6).
- The only known physiological substrate of ADAMTS13 is VWF (*Blood*. 2008;112:1713-9). Plasma VWF levels in full-term neonates are higher than those in adults, but gradually decrease during the first 6 months after birth and mature to a molecular weight pattern similar to that of adults at 3 weeks of age (*Thromb Res*. 2007;119 Suppl 1:S4-S5).

No rADAMTS13-related toxicity findings were observed. ADAMTS13 activity exposures (C_{max} = 4.41 U/mL, AUC_{last} = 97.6 U·h/mL) at the NOAEL (400 U/kg) in the reproductive and developmental toxicity studies were 3.9-fold and 8.4-fold, respectively, the predicted steady-state ADAMTS13 activity exposures ($C_{max, ss}$ = 1.12 IU/mL, estimated AUC_{last}[4)] = 11.7 IU·h/mL) in humans following prophylactic administration of rADAMTS13 40 IU/kg Q2W.

Table 14. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Dose (U/kg)	Noteworthy findings	NOAEL (U/kg)	Attached document CTD
Fertility and embryo-fetal development	Female rat (SD)	IV	From 2 weeks prior to mating through gestation day 16 (Q3D)	0,[a] 80, 200, 400	Dams: No toxicity findings Embryo-fetal: No toxicity findings No ADAs were detected.	Maternal general toxicity: 400 Maternal reproductive toxicity: 400 Embryo-fetal development: 400	4.2.3.5.1-2
Pre- and postnatal development	Female rat (SD)	IV	From gestation day 7 through lactation day 21 (Q3D)	0,[a] 80, 200, 400	Dams: No toxicity findings F1 offspring: Died or euthanized moribund: 80 (1 of 22 animals), 200 (1 of 24 animals)[b] No toxicity findings No ADAs were detected.	Maternal general toxicity: 400 Maternal reproductive toxicity: 400 F1 offspring: 400	4.2.3.5.3-1

a: A buffer containing sodium, calcium, chloride, histidine, mannitol, sucrose, and polysorbate 80
b: These were considered unlikely related to rADAMTS13.

5.6 Local tolerance

The local tolerance of rADAMTS13 was evaluated in rabbits that received rADAMTS13 via intravenous, intra-arterial, paravenous, or subcutaneous routes (Table 15). No findings indicative of local irritation were observed via any route of administration.

There were no rADAMTS13-related findings at the injection sites also in repeated-dose toxicity studies in rats and cynomolgus monkeys.

Table 15. Overview of local tolerance studies

Test system	Route of administration	Duration of dosing	Dose	Noteworthy findings	Attached document CTD
Male and female rabbits (NZW)	IV, intra-arterial, paravenous	Single dose	0[a] or 311 U/mL of rADAMTS13 was administered. Injection volumes were 5 mL for IV and IA and 0.5 mL for PV.	No findings indicative of local irritation	4.2.3.6-1
Male rabbit (NZW)	SC	Single dose	0[a] or 300 IU/mL of rADAMTS13 was administered. Injection volume was 1 mL.	No findings indicative of local irritation	4.2.3.6-2

a: A buffer containing sodium, calcium, chloride, histidine, mannitol, sucrose, and polysorbate 80

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there were no findings relevant to the clinical use of rADAMTS13 from non-clinical toxicological evaluation.

5.R.1 Assessment of male fertility

The effect of rADAMTS13 on male fertility was not evaluated in reproductive and developmental toxicity studies. PMDA asked the applicant to explain the effect of rADAMTS13 on male fertility.

The applicant's explanation:
The structure and function of rADAMTS13 are comparable to those of endogenous ADAMTS13 in human plasma [see Section "2.1.5.1 Structure and properties"]. ADAMTS13 is present in the blood only and has a high affinity for VWF unfolded by high shear stress etc. (*Blood*. 2008;112:1713-9), and no other physiological substrates of rADAMTS13 have been identified (*Nat Commun*. 2019;10:3781). Moreover, sperm evaluation (motility, morphology, sperm cell count), reproductive organ weights, and histopathological examination of the male reproductive organs in a 26-week repeated-dose toxicity study in rats showed no rADAMTS13-related effects. Based on the above, the applicant concluded that there is no possibility that rADAMTS13 affects male fertility, and that a separate reproductive and developmental toxicity study for male fertility is unnecessary.

PMDA's conclusion:
Although a separate reproductive and developmental toxicity study for male fertility was not conducted, given the applicant's explanation about the properties etc. of rADAMTS13, rADAMTS13 is very unlikely to affect male fertility.

5.R.2 Toxicologic evaluation of rADAMTS13 based on submitted non-clinical toxicity studies

rADAMTS13 consists of a mixture of two protein species: Native rADAMTS13 Q97 (apadamtase alfa [genetical recombination]) and Variant rADAMTS13 R97 (cinaxadamtase alfa [genetical recombination]). PMDA asked the applicant to explain whether the toxicity of each protein species was adequately evaluated based on the submitted toxicity study data.

The applicant's explanation:
The test article batches used in the submitted toxicity studies contained 30.2% to 37.7% of Native rADAMTS13 Q97 and 62.3% to 69.8% of Variant rADAMTS13 R97.[5)] Even at the lowest relative contents of Native rADAMTS13 Q97 and Variant rADAMTS13 R97 (30.2% and 62.3%, respectively), exposures based on ADAMTS13 activity of each protein species at the NOAELs in the submitted non-clinical toxicity studies were 2.5 to 67-fold and 5.2 to 138-fold the predicted steady-state ADAMTS13 activity exposure (AUC) in humans following administration of rADAMTS13 40 IU/kg Q2W using the drug product containing 100% Native rADAMTS13 Q97 or 100% Variant rADAMTS13 R97, respectively. Thus, adequate exposures to each protein species were achieved in the toxicity studies.

Based on the applicant's explanation, PMDA concluded that the non-clinical toxicity of apadamtase alfa (genetical recombination) or cinaxadamtase alfa (genetical recombination) was adequately evaluated based on the submitted data.

[5)] The relative contents of Native rADAMTS13 Q97 and Variant rADAMTS13 R97 in the test article batches used in a 30-day repeated-dose toxicity study in rats, a pilot reproductive and developmental toxicity study in rats (CTD 4.2.3.5.1-1), and a subcutaneous local tolerance study in rabbits are unknown.

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

The PK of rADAMTS13 were evaluated based on ADAMTS13 activity in plasma.

Unless otherwise specified, PK parameters are expressed as the mean or the mean ± SD.

6.1 Summary of biopharmaceutic studies and associated analytical methods

During the product development, changes were made to the drug substance and/or drug product manufacturing processes: the drug product produced by Process II (the drug substance manufactured by Process A)→the drug product produced by Process III (the drug substance manufactured by Process B); the drug product produced by Process III (the drug substance manufactured by Process B)→the drug product produced by Process IV (the drug substance manufactured by Process B); the drug product produced by Process IV (the drug substance manufactured by Process B)→the drug product produced by Process V (the drug substance manufactured by Process C); and the drug product produced by Process V (the drug substance manufactured by Process C)→the to-be-marketed drug product. For all of these process changes, comparability of quality attributes between pre-change and post-change drug products/substances has been demonstrated [see Sections "2.1.4 Manufacturing process development" and "2.2.3 Manufacturing process development"]. The data obtained from the PK-II period of a global phase III study (Study 281102) demonstrated the bioequivalence between the drug product produced by Process IV and the drug product produced by Process V [see Section "6.1.1 Comparison between the drug product produced by Process IV and the drug product produced by Process V"]. The drug product produced by Process II was used in a global phase I study (Study 281101). The drug product produced by Process III, the drug product produced by Process IV, and the drug product produced by Process V were used in a global phase III study (Study 281102). The drug product produced by Process V was used in a global phase IIIb extension study (Study TAK-755-3002).

In Study 281101, ADAMTS13 activity in plasma was determined by a fluorogenic assay using FRETS-VWF73 substrate and an ELISA using a recombination fusion protein of VWF73 peptide and glutathione-(*S*)-transferase as a substrate, and the LLOQs were 0.05 and 0.0073 U/mL, respectively.[3)] In Studies 281102 and TAK-755-3002, ADAMTS13 activity in plasma was determined by a fluorogenic assay using FRETS-VWF73 substrate, and the LLOQ was 0.065 IU/mL.

ADAs in plasma were detected by an ELISA.

Neutralizing ADAs to rADAMTS13 or plasma-derived ADAMTS13 were assessed by a modified Bethesda method using a fluorogenic assay using FRETS-VWF73 substrate. One BU was defined as the ADA titer that reduces ADAMTS13 activity by 50%. ADAs were considered neutralizing if the inhibitor titer was >0.6 BU/mL. Unless the investigator considered that assessment of neutralizing ADAs was necessary, only ADA-positive samples were to be assessed for neutralizing ADAs to rADAMTS13 or plasma-derived ADAMTS13. If samples were considered positive for neutralizing ADAs, the samples were to be retested 2 to 4 weeks later.

Only if the samples were considered positive for neutralizing ADAs again, the samples were determined to be positive for neutralizing ADAs.

6.1.1 Comparison between the drug product produced by Process IV and the drug product produced by Process V (Study 281102, CTD 5.3.5.1-1, ongoing since October 2017 [data cutoff date of August 12, 2022])

In the PK-II period of Study 281102, subjects received a single intravenous dose of rADAMTS13 40 IU/kg using the drug product produced by Process IV or the drug product produced by Process V in a crossover fashion (a washout period of 14 days) to compare the PK of ADAMTS13 activity [see Figure 1 in Section "7.2.1 Global phase III study"]. The geometric least-square mean ratios of the C_{max} and $AUC_{0-\infty}$ of ADAMTS13 activity for the drug product produced by Process V vs. the drug product produced by Process IV [90% confidence interval (CI)] were 1.0181 [0.9676, 1.0713] and 1.0024 [0.9413, 1.0675], respectively. Table 16 shows the PK parameters of ADAMTS13 activity following a single intravenous administration of rADAMTS13 40 IU/mL using the drug product produced by Process V. The time with ADAMTS13 activity of ≥10% was 5.8 ± 1.2 days.

Table 16. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13 (Drug product produced by Process V)

N	C_{max} (IU/mL)	t_{max} [a] (h)	C_{ave} (IU/mL)	$AUC_{0-\infty}$ [b] (IU·h/mL)	$t_{1/2}$ (h)	CL [b] (mL/h)	V_{ss} [b] (mL)
23	1.15 ± 0.252	0.33	0.30 ± 0.066	57.57 ± 13.872	47.80 ± 13.697	53.7 ± 12.8	3295 ± 620

a: Median
b: N = 22

6.2 Clinical pharmacology

6.2.1 Patient studies

6.2.1.1 Single intravenous dose study in patients with congenital TTP (Study 281101, CTD 5.3.3.2-1, September 2014 to February 2016)

Table 17 shows the PK parameters of ADAMTS13 activity following a single intravenous administration of rADAMTS13 at 5, 20, or 40 U/kg in Japanese and non-Japanese patients with congenital TTP.

Table 17. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13

Dose (U/kg)	N	C_{max} (U/mL)	t_{max} [a] (h)	$AUC_{0-\infty}$ (U·h/mL)	$t_{1/2}$ (h)	CL (mL/h)	V_{ss} (mL)
5	3	0.080 ± 0.018	1.00	—	—	—	—
20	3	0.415 ± 0.149	0.33	19.5 ± 4.89	45.1 ± 21.2	72.8 ± 24.5	4240 ± 1230
40	7	0.957 ± 0.140	0.37	54.5 ± 14.9	60.5 ± 13.5	65.2 ± 24.2	5300 ± 1030

—, Not calculated
a: Median

No ADAs were detected in any of the subjects.

6.2.1.2 Comparison between rADAMTS13 and standard of care (Study 281102, CTD 5.3.5.1-1, ongoing since October 2017 [data cutoff date of August 12, 2022])

In the PK-I period of Study 281102, subjects received a single intravenous dose of rADAMTS13 40 IU/kg or standard of care (SoC) in a crossover fashion (a washout period of 14 days) to compare the PK of ADAMTS13 activity [see Figure 1 in Section "7.2.1 Global phase III study"]. Table 18 shows the PK parameters of ADAMTS13 activity following a single intravenous administration of rADAMTS13 40 IU/kg or SoC.

Table 18. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13 40 IU/kg or SoC

	N	C_{max} (IU/mL)	t_{max} [a] (h)	AUC_{all} [b] (IU·h/mL)	$t_{1/2}$ (h)	CL (mL/h)	V_{ss} (mL)
rADAMTS13 40 IU/kg	34	1.01 ± 0.240	0.33	44.40 ± 11.124	47.12 ± 11.397	61.6 ± 14.2[c]	3844 ± 898[c]
SoC	36	0.19 ± 0.106	3.44	10.60 ± 8.136[c]	62.66 ± 28.281[d]	39.2, 88.7[e]	2850, 8140[e]

a: Median
b: $AUC_{0-\infty}$ after treatment with SoC was calculated for 2 subjects only.
c: N = 32, d: N = 23, e: Individual values are listed.

6.2.1.3 PPK analysis (CTD 5.3.3.5-1)

Using 2462 ADAMTS13 activity levels from 65 subjects in a global phase I study (Study 281101), a global phase III study (Study 281102), and a global phase IIIb extension study (Study TAK-755-3002) in patients with congenital TTP, a PPK analysis was performed. The PK of ADAMTS13 activity following administration of rADAMTS13 (the drug product produced by Process IV or the drug product produced by Process V), SOC (fresh frozen plasma [FFP] or solvent/detergent [S/D]-treated plasma), or factor VIII/VWF concentrates were described by a 2-compartment model with first-order elimination. In the case of SoC, the PK of ADAMTS13 activity were modelled taking account of ADAMTS13 activity levels measured prior to administration.

The distribution of the major demographics and baseline characteristics of patients included in the PPK analysis was as follows: age (4 patients aged <6 years, 4 patients aged 6 to <12 years, 6 patients aged 12 to <18 years, 51 patients aged ≥18 years); sex (26 male patients and 39 female patients); race (40 White patients, 2 Black patients, 11 Asian patients, 1 patient with multiple race, 11 patients with unknown race); ethnicity (1 Hispanic/Latino patient, 54 non-Hispanic/Latino patients, 10 patients with unknown ethnicity); blood type (22 patients with blood type O, 24 patients with blood type A, 10 patients with blood type B, 8 patients with blood type AB, 1 patient with unknown blood type); body weight (68.7 [18.3, 130] kg (median [min., max.]); height (165 [99.0, 190] cm); BMI (24.2 [14.6, 52.5] kg/m^2); body surface area (1.77 [0.723, 2.50] m^2); platelet count (205 [20.0, 442] [×10^9/L]); hematocrit (0.390 [0.242, 0.517] g/L); hemoglobin (133 [81.0, 167] g/L); ALT (13.0 [5.00, 53.9] U/L); AST (18.0 [11.0, 189] U/L); albumin (46.0 [38.0, 63.1] g/L); ALP (75.0 [30.0, 356] U/L); bilirubin (0.468 [0.175, 3.74] mg/dL); CL_{cr} (106 [31.3, 219] mL/min); and eGFR (95.8 [23.5, 464] mL/min/1.73 m^2). Allometric scaling was applied to the base model, based on the assumption that CL, Q (intercompartmental clearance), V_c, and V_p are proportional to a power of body weight (with the exponents fixed to 0.75 for CL and Q and 1 for V_c and V_p). As to intrinsic factors, the above demographic and baseline characteristics were tested as potential covariates. Except for body weight, no intrinsic factors had significant effects on CL, Q, V_c, or V_p, and no additional covariates were incorporated in the model. As to extrinsic factors, the effects of rADAMTS13 drug product (the drug product produced by Process IV, the drug product produced

by Process V) and treatment type (rADAMTS13, SoC or factor VIII/VWF concentrates) on the relative ADAMTS13 activity were added to the PPK model.

The population mean PK parameter estimates from the final model (relative standard error %) were as follows: CL was 0.0398 L/h (10.7%), Q was 0.0456 L/h (12.1%), V_c was 2.69 L (4.99%), and V_p was 3.71 L (51.4%). The relative ADAMTS13 activity estimate was reduced by 7.37% following administration of the drug product produced by Process IV, by 39.0% following administration of SoC, or by 93.3% following administration of factor VIII/VWF concentrates, as compared to the drug product produced by Process V.

Using the final model and the data from patients included in the PPK analysis, the following simulations were performed.

- Table 19 shows the predicted PK parameters of ADAMTS13 activity following intravenous administration of rADAMTS13 (the drug product produced by Process V) 40 IU/kg or SoC (10 IU/kg as ADAMTS13 activity) Q2W or QW in Japanese and non-Japanese patients with congenital TTP.

Table 19. Predicted PK parameters of ADAMTS13 activity following administration of rADAMTS13 or SoC in Japanese and non-Japanese patients with congenital TTP

	Dosing frequency	$C_{max, ss}$ (IU/mL)		$C_{ave, ss}$ (IU/mL)		Time with ADAMTS13 activity of ≥10% (days)	
		Japanese (N = 7)	Non-Japanese (N = 58)	Japanese (N = 7)	Non-Japanese (N = 58)	Japanese (N = 7)	Non-Japanese (N = 58)
rADAMTS13 40 IU/kg	Q2W	1.03 ± 0.253	1.13 ± 0.273	0.180 ± 0.0245	0.221 ± 0.104	7.85 ± 1.34	9.13 ± 2.60
	QW	1.14 ± 0.260	1.27 ± 0.316	0.359 ± 0.0488	0.436 ± 0.188	7.00 ± 0	6.98 ± 0.162
SoC	Q2W	0.150 ± 0.0358	0.165 ± 0.0388	0.0272 ± 0.00370	0.0335 ± 0.0158	0.539 ± 0.283	0.861 ± 0.874
	QW	0.167 ± 0.0368	0.187 ± 0.0457	0.0544 ± 0.00738	0.0661 ± 0.0286	0.814 ± 0.281	1.34 ± 1.41

- Table 20 shows the predicted PK parameters of ADAMTS13 activity by age group (<6 years, 6 to <12 years, 12 to <18 years, ≥18 years) following intravenous administration of rADAMTS13 (the drug product produced by Process V) 40 IU/kg Q2W or QW in patients with congenital TTP.

Table 20. Predicted PK parameters of ADAMTS13 activity by age group

Age group	N	$C_{max, ss}$ (IU/mL)		$C_{ave, ss}$ (IU/mL)		Time with ADAMTS13 activity of ≥10% (days)	
		Q2W	QW	Q2W	QW	Q2W	QW
<6 years	4	0.901 ± 0.120	0.978 ± 0.129	0.135 ± 0.0154	0.270 ± 0.0308	5.48 ± 0.800	6.69 ± 0.616
6-11 years	4	1.13 ± 0.193	1.25 ± 0.204	0.186 ± 0.0332	0.372 ± 0.0660	8.19 ± 2.19	7.00 ± 0
12-17 years	6	0.995 ± 0.113	1.10 ± 0.115	0.174 ± 0.00896	0.348 ± 0.0179	7.45 ± 0.447	7.00 ± 0
≥18 years	51	1.15 ± 0.288	1.30 ± 0.328	0.230 ± 0.107	0.454 ± 0.193	9.51 ± 2.48	7.00 ± 0.000586

6.2.1.4 ER analysis (CTD 5.3.3.5-1)

Using the event count data for thrombocytopenia, microangiopathic hemolytic anemia, etc., obtained from the modified full analysis set (mFAS) (6 patients aged <12 years, 4 patients aged 12 to <18 years, 31 patients aged ≥18 years) in Periods 1 and 2 of the prophylactic cohort in a global phase III study in patients with congenital TTP (Study 281102) and individual $C_{ave, ss}$ values (the average values in Period 1 or 2) predicted from the PPK model [see Section "6.2.1.3 PPK analysis"], exposure-response (ER) analyses were performed.

Thrombocytopenia event counts were described by the Poisson model with random effect and sigmoidal E_{max} drug effect. Microangiopathic hemolytic anemia event counts were described by the Poisson model with random effect and linear drug effect. Age was tested as a potential covariate, but was not included as a covariate in either model.

Based on the ER analyses for thrombocytopenia and microangiopathic hemolytic anemia event counts, the predicted probability of being thrombocytopenia event-free (count = 0) or microangiopathic hemolytic anemia event-free (count = 0) following administration of rADAMTS13 40 IU/kg Q2W or QW, or SoC (10 IU/kg as ADAMTS13 activity) in patients with congenital TTP is shown in Table 21 or Table 22, respectively.

Table 21. Predicted probability of being thrombocytopenia event-free

$C_{ave, ss}$ distribution	SoC		rADAMTS13 Q2W (40 IU/kg)		rADAMTS13 QW (40 IU/kg)	
	$C_{ave, ss}$ (IU/mL)	Probability of count 0 (%)	$C_{ave, ss}$ (IU/mL)	Probability of count 0 (%)	$C_{ave, ss}$ (IU/mL)	Probability of count 0 (%)
5%tile	0.0155	12.2	0.130	70.8	0.239	71.6
10%tile	0.0184	18.3	0.137	70.9	0.256	71.6
25%tile	0.0277	38.3	0.155	71.2	0.288	71.7
50%tile	0.0398	54.6	0.176	71.3	0.332	71.7
75%tile	0.0491	60.9	0.206	71.5	0.351	71.7
90%tile	0.0863	69.0	0.249	71.6	0.424	71.8
95%tile	0.121	70.6	0.396	71.7	0.427	71.8

Table 22. Predicted probability of being microangiopathic hemolytic anemia event-free

$C_{ave, ss}$ distribution	SoC		rADAMTS13 Q2W (40 IU/kg)		rADAMTS13 QW (40 IU/kg)	
	$C_{ave, ss}$ (IU/mL)	Probability of count 0 (%)	$C_{ave, ss}$ (IU/mL)	Probability of count 0 (%)	$C_{ave, ss}$ (IU/mL)	Probability of count 0 (%)
5%tile	0.0155	68.3	0.130	80.9	0.239	88.6
10%tile	0.0184	68.7	0.137	81.5	0.256	89.5
25%tile	0.0277	69.9	0.155	83.0	0.288	91.0
50%tile	0.0398	71.4	0.176	84.6	0.332	92.7
75%tile	0.0491	72.6	0.206	86.6	0.351	93.4
90%tile	0.0863	76.7	0.249	89.1	0.424	95.4
95%tile	0.121	80.1	0.396	94.7	0.427	95.5

6.2.2 Intrinsic factor pharmacokinetic studies

6.2.2.1 PK of rADAMTS13 in patients with hepatic or renal impairment

No clinical pharmacology studies to assess the effects of hepatic or renal impairment on the PK of rADAMTS13 were conducted.

The applicant's explanation:

According to the PPK analysis, baseline eGFR did not have a significant effect on the PK parameter (CL) of ADAMTS13 activity [see Section "6.2.1.3 PPK analysis"]. In addition, given the molecular weight of rADAMTS13 (173 kDa) and its distribution, metabolism, and excretion characteristics [see Section "4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA"], decreased hepatic or renal function is unlikely to affect the PK of rADAMTS13.

6.R Outline of the review conducted by PMDA

6.R.1 PK differences between Japanese and non-Japanese populations

The applicant's explanation:

Given the following points, race or ethnicity has no effects on the PK of ADAMTS13 activity.

- In a global phase III study (Study 281102), there were no major differences in the PK parameters of ADAMTS13 activity following a single intravenous administration of rADAMTS13 40 IU/kg between Japanese and non-Japanese patients (Table 23).

Table 23. PK parameters of ADAMTS13 activity following single intravenous administration of rADAMTS13 40 IU/kg in Japanese or non-Japanese patients

	N	C_{max} (IU/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (IU·h/mL)	$t_{1/2}$ (h)	CL (mL/h)	V_{ss} (mL)
Japanese	5	1.05 ± 0.30	0.33	53.88 ± 9.78[b]	49.69 ± 18.37	50 ± 10[b]	3480 ± 480[b]
Non-Japanese	29	1.00 ± 0.23	0.33	49.46 ± 11.27[c]	46.68 ± 10.17	60 ± 10[c]	3900 ± 940[c]

a: Median, b: N = 4, c: N = 28

- According to simulations using the PPK model, the predicted PK parameters ($C_{max, ss}$, $C_{ave, ss}$, time with ADAMTS13 activity of ≥10%) of ADAMTS13 activity following repeated intravenous administration of rADAMTS13 were similar between Japanese and non-Japanese patients [see Section "6.2.1.3 PPK analysis"].
- In the PPK analysis based on the data from a global phase I study (Study 281101) and global phase III studies (Study 281102 and Study TAK-755-3002) in patients with congenital TTP, race or ethnicity was not identified as a significant covariate on the PK of ADAMTS13 activity [see Section "6.2.1.3 PPK analysis"].

PMDA's conclusion:

Based on the applicant's explanation, there were no major differences in the PK of ADAMTS13 activity following administration of rADAMTS13 between Japanese and non-Japanese patients.

6.R.2 Rationale for the dosing regimens in a global phase III study

The applicant's explanation about the rationale for the dosing regimens of rADAMTS13 in a global phase III study (Study 281102):

The relationship between acute TTP events/isolated TTP manifestations including thrombocytopenia and microangiopathic hemolytic anemia and ADAMTS13 activity has not been well investigated, and its correlation is unclear (*J Clin Med.* 2023;12:3365). On the other hand, since congenital TTP is caused by severe deficiency of ADAMTS13 activity (ADAMTS13 activity of <10%) due to mutations in the *ADAMTS13* gene, the cause of the disease can be addressed directly by replacing the missing ADAMTS13 enzyme to achieve normal levels of ADAMTS13 activity (50%-150%) as soon as possible. Thus, the dosing regimens of rADAMTS13 for the prevention and on-demand treatment of acute TTP events should be chosen based on the goal to achieve the C_{max} of ADAMTS13 activity within the normal range.

The dosing regimen for the prophylactic cohort for the prevention of acute TTP events in Study 281102 was chosen as follows:

In a global phase I study (Study 281101), the C_{max} of ADAMTS13 activity following a single intravenous administration of rADAMTS13 40 IU/kg was approximately 1 IU/mL (100%), and rADAMTS13 was considered to provide higher ADAMTS13 activity exposure relative to FFP. Simulations based on the PK parameters of ADAMTS13 activity obtained from this study (Table 17) predicted that the C_{max} of ADAMTS13 activity following intravenous administration of rADAMTS13 40 IU/kg Q2W was 0.9 to 1.25 IU/mL (90%-125%), suggesting that ADAMTS13 activity exposures within the normal range (50%-150%) can be achieved. Thus, a dose of 40 IU/kg of rADAMTS13 was chosen for the prophylactic cohort, and the Q2W or QW dosing frequency was chosen based on the SoC frequency.

The dosing regimen for the on-demand cohort for the on-demand treatment of acute TTP events in Study 281102 was chosen as follows:

If an acute TTP event occurs, it is important to achieve normal levels of ADAMTS13 activity as soon as possible and maintain them until resolution. Since acute/subacute TTP events often occur with triggering factors such as infections, and duration of the event is associated with increased risk of disease exacerbation, it is recommended that in patients with acquired TTP, plasma exchange should continue for at least 48 hours after the initial normalization of platelet count (*Renal Replacement Therapy*. 2023;9:25, *Blood*. 2021;137:733-42, etc.). A similar treatment strategy should be employed also for patients with congenital TTP, and treatment with rADAMTS13 should continue until 2 days after the acute TTP event has resolved. Simulations based on the data from Study 281101 suggested that administration of rADAMTS13 at a dose of 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg QD from Day 3 through Day 5 can maintain the mean C_{max} of ADAMTS13 activity across all time points within the normal range (>0.8 IU/mL [80%]). Thus, in the on-demand cohort, if an acute TTP event occurred, rADAMTS13 was to be administered at a dose of 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg QD from Day 3 until 2 days after the event had resolved.

In the PK-I period of Study 281102, following a single intravenous administration of rADAMTS13 40 IU/kg or SoC, the C_{max} values of ADAMTS13 activity were 1.01 and 0.19 IU/mL, respectively, and the AUC_{all} values were 44.4 and 10.6 IU·h/mL, respectively. rADAMTS13 administration resulted in approximately 5-fold higher ADAMTS13 activity exposures as compared with SoC administration (Table 18). In the PPK analysis, the predicted C_{max} following administration of rADAMTS13 40 IU/kg Q2W or QW was approximately 1 IU/mL (100%) (Table 19). The ER analyses showed that thrombocytopenia and microangiopathic hemolytic anemia event counts are correlated with the C_{ave} of ADAMTS13 activity and suggested that exposures (C_{ave}) associated with high probabilities of being thrombocytopenia event-free and microangiopathic hemolytic anemia event-free are achieved (Table 21 and Table 22). Thus, the dosing regimen of rADAMTS13 for the prophylactic cohort was sufficient to prevent acute TTP events.

In the on-demand cohort of Study 281102, the C_{max} of ADAMTS13 activity ranged from 0.1 to 0.4 IU/mL in the SoC group. Meanwhile, in both of 2 patients[6)] in the rADAMTS13 group, the C_{max} of ADAMTS13 activity reached 0.8 IU/mL (>80%) fast, the profile of the C_{max} of ADAMTS13 activity was largely similar to the results of the above simulations, and rADAMTS13 showed favorable efficacy and safety. Thus, the dosing regimen of rADAMTS13 for the on-demand cohort was appropriate for on-demand treatment of acute TTP events.

PMDA's view:
The dosing regimens of rADAMTS13 for the prevention and on-demand treatment of acute TTP events were chosen based on the goal to achieve the C_{max} of ADAMTS13 activity within the normal range. However, according to the currently available findings, the clinical significance of achieving the C_{max} of ADAMTS13 activity above a target threshold for the prevention and on-demand treatment of acute TTP events is unclear.

On the other hand, given the following points, the dosing regimens of rADAMTS13 chosen for the prophylactic and on-demand cohorts of a global phase III study in patients with congenital TTP (Study 281102) are rational to a certain extent, from the standpoint of ADAMTS13 activity exposure.

- Routine prophylaxis
  In the prophylactic cohort of Study 281102, rADAMTS13 administration resulted in higher ADAMTS13 activity exposures as compared with SoC administration. "ADAMTS13 activity of <10%" is a diagnostic criterion for TTP, and the time with ADAMTS13 activity of ≥10% was longer with rADAMTS13 than with SoC (Table 19). rADAMTS13 is expected to provide higher ADAMTS13 activity over time than SoC.
- On-demand treatment
  The dosing regimen of rADAMTS13 was chosen based on the goal to increase ADAMTS13 activity as soon as possible and maintain ADAMTS13 activity within or near the normal range until the acute event has resolved. Actually, ADAMTS13 activity profiles, which were largely as expected, were seen in 2 patients enrolled in the rADAMTS13 group of the on-demand cohort of Study 281102.

Since the relationship between ADAMTS13 activity exposure and the clinical efficacy and safety of rADAMTS13 is unclear, the appropriateness of the recommended dosing regimens of rADAMTS13 should continue to be discussed, taking also account of the actual dosing regimens used in clinical studies and the efficacy and safety results [see Section "7.R.6 Dosage and administration"].

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

The applicant submitted 3 studies presented in Table 24 as the main efficacy and safety clinical studies [for PK, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

[6)] Patients received rADAMTS13 according to the on-demand dosing regimen tested, for 4 or 6 days.

Table 24. Overview of main clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects	Dosing regimen	Main endpoints
Evaluation	Global	281101	I	Patients with congenital TTP	N = 16[a]	Single IV administration of rADAMTS13 at 5, 20, or 40 U/kg	Safety PK
	Global	281102 (ongoing)	III	Patients with congenital TTP	[Prophylactic cohort] N = 48[b] [On-demand cohort] N = 5[b]	[PK-I period] Single IV administration of SoC[c] or rADAMTS13 40 IU/kg in a crossover fashion (a 14-day washout period) [PK-II period] Single IV administration of rADAMTS13 40 IU/kg using the drug product produced by Process IV (the drug substance manufactured by Process B) or the drug product produced by Process V (the drug substance manufactured by Process C) in a crossover fashion (a 14-day washout period) [PK-III period] Single IV administration of rADAMTS13 40 IU/kg [Prophylactic cohort] Periods 1 and 2: IV administration of SoC[c] or rADAMTS13 40 IU/kg Q2W or QW for 6 months in a crossover fashion Period 3: IV administration of rADAMTS13 40 IU/kg Q2W or QW for 6 months [On-demand cohort] IV administration of SoC[c] or rADAMTS13 at 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg QD from Day 3 until 2 days after acute TTP event had resolved	Efficacy Safety PK
	Global	TAK-755-3002 (ongoing)	IIIb	Patients with congenital TTP	[Prophylactic cohort] N = 36[a] [On-demand cohort] N = 0[a]	[Prophylactic cohort] IV administration of rADAMTS13 40 IU/kg Q2W or QW [On-demand cohort] IV administration of rADAMTS13 at 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg QD from Day 3 until 2 days after acute TTP event had resolved	Safety Efficacy

a: Number of enrolled subjects
b: Number of randomized subjects
c: SoC was to be administered using the dosing regimen recommended by the investigator.

7.1 Global phase I study (Study 281101, CTD 5.3.3.2-1, September 2014 to February 2016)

An open-label, uncontrolled study was conducted at 13 sites in Japan and overseas to evaluate the safety and PK of rADAMTS13 following a single intravenous administration of 5, 20, or 40 U/kg of rADAMTS13 in patients with congenital TTP [target sample size, 14 subjects (3 in the 5 U/kg cohort, 3 in the 20 U/kg cohort, 8 in the 40 U/kg cohort)].

Key inclusion criteria

Patients with congenital TTP aged 12 to 65 years were eligible if the following criteria were met. Pregnant or breastfeeding women were excluded.

- Patients with a documented diagnosis of hereditary ADAMTS13 deficiency confirmed by molecular genetic testing and ADAMTS13 activity[7] <6%, documented in patient history or at screening
- Cryoprecipitate, FFP, or other ADAMTS13 containing products interfering with ADAMTS13 PK had to be paused at least 10 days prior to infusion of study drug.
- Patients not displaying any severe TTP signs at screening. Patients presenting with minor, but stable laboratory abnormalities (LDH not higher than 3 times the ULN or platelet count not lower than 100,000/μl) at screening were allowed to be enrolled.
- Patients ≥18 years of age had a Karnofsky score ≥60%, and patients <18 years of age had a Lansky score ≥70%.

Among 16 enrolled subjects (3 in the 5 U/kg cohort, 4 in the 20 U/kg cohort, 9 in the 40 U/kg cohort), 15 subjects who received study drug (3 in the 5 U/kg cohort, 3 in the 20 U/kg cohort, 9 in the 40 U/kg cohort) were included in the safety analysis set. One subject in the 20 U/kg cohort discontinued the study due to failure to receive study drug within the protocol-specified timeframe.

The incidences of adverse events were 100% (3 of 3 subjects) in the 5 U/kg cohort, 66.7% (2 of 3 subjects) in the 20 U/kg cohort, and 77.8% (7 of 9 subjects) in the 40 U/kg cohort. Adverse events reported by more than 1 subject were headache (33.3% [1 of 3 subjects], 33.3% [1 of 3 subjects], 0% [0 of 9 subjects]), dizziness (33.3% [1 of 3 subjects], 0% [0 of 3 subjects], 11.1% [1 of 9 subjects]), and nasopharyngitis (33.3% [1 of 3 subjects], 0% [0 of 3 subjects], 22.2% [2 of 9 subjects]).

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

7.2 Phase III study

7.2.1 Global phase III study (Study 281102, CTD 5.3.5.1-1, ongoing since October 2017 [data cutoff date of August 12, 2022: interim analysis])

A randomized, open-label, controlled study was conducted at 34 sites in Japan and overseas to compare the efficacy and safety of rADAMTS13 with SoC in patients with congenital TTP [target sample size, 57 subjects[8] (48 in the prophylactic cohort [36 subjects aged ≥18 years, 12 subjects aged <18 years (4 subjects aged 12 to <18 years, 4 subjects aged 6 to <12 years, 4 subjects aged <6 years), 9 in the on-demand cohort [6 subjects aged ≥18 years, 3 subjects aged <18 years])]. The study was voluntarily halted from November 2017 until July 2019 because rADAMTS13 was found to consist of a mixture of Native rADAMTS13 Q97 (apadamtase alfa [genetical recombination]) and Variant rADAMTS13 R97 (cinaxadamtase alfa [genetical recombination]).

[7] In patients receiving prophylactic therapy with SoC, the levels of ADAMTS13 activity may exceed 6% at screening.
[8] In the initial version of the protocol (as of February 13, 2017), the target sample size was 24 to 40 subjects (including ≥9 subjects aged <18 years) in the prophylactic cohort and 6 to 20 subjects in the on-demand cohort, based on feasibility. Then, the protocol was amended multiple times, taking account of the precision of predicting event rates, patient enrollment rate, etc., and the final target sample size was 48 subjects in the prophylactic cohort and 9 subjects in the on-demand cohort (Protocol Version 11 [as of February 24, 2021]).

The study included two cohorts: patients who received treatment to prevent acute TTP events (prophylactic cohort) and those who received treatment only if an acute TTP event occurred (on-demand cohort). Age-staggered enrollment was planned for the prophylactic cohort of the study (≥18 years, 12 to <18 years, 6 to <12 years, <6 years) (an older age cohort enrolled first, then sequentially moving to the next lower age cohort).[9)]

Key inclusion criteria for the prophylactic and on-demand cohorts

Patients with congenital TTP ≤70 years of age were eligible if the following criteria were met. In the prophylactic cohort, eligibility was to be determined after patients underwent a minimum washout period of 1 week from their last prophylactic infusion of SoC.

- Patients with a documented diagnosis of hereditary ADAMTS13 deficiency confirmed by molecular genetic testing and ADAMTS13 activity[10)] <10%, documented in patient history or at screening
- Patients not displaying any severe TTP signs (platelet count <100,000/μL and elevation of LDH >2 × ULN) at screening (prophylactic cohort only)
- Patients were currently on a prophylactic dosing regimen or had a documented history of at least one TTP event and an ability to tolerate SoC prophylactic dosing (prophylactic cohort only).
- Patients ≥16 years of age had a Karnofsky score ≥70%, and patients <16 years of age had a Lansky score ≥80%.

Key exclusion criteria

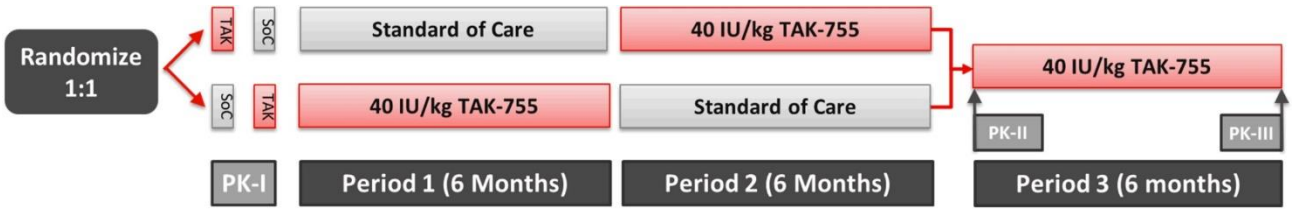
- Patients who had been diagnosed with any other TTP-like disorder, including acquired TTP
- Patients who had experienced an acute TTP episode within 30 days prior to screening (prophylactic cohort only)
- Patients who had a medical history or presence of a functional ADAMTS13 inhibitor at screening
- If female, patients who were pregnant or lactating at the time of enrollment

Patients enrolled in the prophylactic cohort were randomized to receive rADAMTS13 or SoC for 6 months (Period 1) and then crossed over to the alternate treatment for 6 months[11)] (Period 2) to evaluate the efficacy and safety of prophylactic rADAMTS13 or SoC. All patients received rADAMTS13 for 6 months (Period 3)[12)] to evaluate the efficacy and safety of prophylactic rADAMTS13 (Figure 1).

Prior to Period 1, the PK (ADAMTS13 activity) following a single intravenous administration of rADAMTS13 or SoC were assessed (the PK-I period, crossover design). After Period 2, some patients received a single intravenous infusion of the drug product produced by Process IV (the drug substance manufactured by Process B) or the drug product produced by Process V (the drug substance manufactured by Process C), and the comparability of the PK (ADAMTS13 activity) between these drug products was assessed (the PK-II period,[13)]

[9)] In Protocol Version 11 (as of February 24, 2021), age-staggered enrollment was abolished for patients aged <12 years, based on the recommendations from the data monitoring committee, taking account of safety information etc. from patients aged ≥12 years.
[10)] In patients receiving prophylactic therapy with SoC, the levels of ADAMTS13 activity may exceed 10% at screening.
[11)] If patients could not move to the next period after 6 months of treatment for practical or medical reasons, Period 1 or 2 could be extended to 7 months. For patients enrolled prior to the study halt in November 2017, Period 1 could be extended to up to 24 months until the study was resumed.
[12)] Patients were to continue in Study 281102 until enrollment in Study TAK-755-3002 began.
[13)] Patients who received the drug product produced by Process IV (the drug substance manufactured by Process B) in the PK-I period (patients screened before September 30, 2021) were included.

crossover design). After the last dose of rADAMTS13 in Period 3, the PK after long-term exposure to rADAMTS13 were assessed (the PK-III period[14]) [for PK in the PK-I period, see Section "6.2.1.2 Comparison between rADAMTS13 and standard of care" and for PK in the PK-II period, see Section "6.1.1 Comparison between the drug product produced by Process IV and the drug product produced by Process V"].



TAK-755 = rADAMTS13, SoC = standard of care

Figure 1. Study 281102 design of prophylactic cohort

Prior to the start of the PK-I period, patients were randomized in a 1:1 ratio to receive SoC in Period 1 and rADAMTS13 in Period 2 (the SoC-rADAMTS13 group) or rADAMTS13 in Period 1 and SoC in Period 2 (the rADAMTS13-SoC group).

In the prophylactic cohort, SoC was to be administered using the dosing regimen recommended by the investigator,[15] and rADAMTS13 40 IU/kg (± 4 IU/kg) Q2W or QW[16] was to be administered. If any of the following criteria was met, the dose or dosing frequency of SoC was to be increased, and the dosing frequency of rADAMTS13 was to be changed from Q2W to QW.

- One acute TTP event
- Two separate occurrences of laboratory deviations:
  - Drop in platelet count of ≥25% of baseline or a platelet count <150,000/μL, OR
  - Elevation of LDH >1.5 × of baseline or >1.5 × ULN
- Three separate occurrences of TTP-related signs or symptoms, with or without changes in platelet count or LDH
  - Neurological symptoms (e.g., confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR
  - Abdominal pain; OR
  - An increase of serum creatinine >1.5 × baseline

Subjects experiencing an acute TTP event during the prophylaxis period were to receive SoC or rADAMTS13 using the dosing regimen for the on-demand cohort (described later). The investigators were able to elect to treat a subacute TTP event (during the prophylaxis period) with 1 or 2 additional daily doses of SoC or rADAMTS13 40 IU/kg.

[14] Patients who received the drug product produced by Process V (the drug substance manufactured by Process C) in the PK-I period (patients screened after October 1, 2021), patients aged <12 years, patients treated with QW regimen, and patients in the on-demand cohort who received the drug product produced by Process V (the drug substance manufactured by Process C) and moved to the prophylactic cohort were included, and other patients who received the drug product produced by Process V (the drug substance manufactured by Process C) in Period 3 could opt to join.
[15] The recommended dosing frequency was Q2W or QW, and Q3W was accepted, but not recommended.
[16] The dosing frequency was QW for subjects who had received their prior SoC QW, or Q2W for all other subjects.

If the investigator suspected that patients were undergoing an acute TTP event, the patients were to be enrolled in the on-demand cohort and randomized in a 1:1 ratio to receive SoC or rADAMTS13. After enrollment, if suspected acute TTP events were not confirmed by central laboratory data (platelet count and LDH), i.e., the acute TTP event definition (Table 25) was not met, those events were to be excluded from the efficacy analyses.

The definitions of TTP events and TTP manifestations in the study are shown in Table 25.

Table 25. Definitions of TTP events and TTP manifestations

Criteria	Acute TTP event	Subacute TTP event	Isolated TTP manifestations
	Both of (1) and (2)	At least 2 of (1)(2)(3): at least 1 of which must include (1) or (2)	Any of (1)(2)(3)
(1) Thrombocytopenia	Drop in platelet count ≥50% of baseline or a platelet count <100,000/μL	Drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/μL	
(2) Microangiopathic hemolytic anemia	Elevation of LDH >2 × of baseline or >2 × ULN	Elevation of LDH >1.5 × of baseline or >1.5 × ULN	
(3) TTP-related clinical signs/symptoms		● Renal dysfunction [a] ● Neurological symptoms [b] ● Abdominal pain[c] ● Other TTP manifestations[d]	

For each patient, if multiple symptoms on the same day met the definition of the same TTP manifestation (examples: more than 1 event of headache or a drop in platelet count at multiple blood sampling time points), only 1 symptom was counted. However, if multiple symptoms on the same day met the definitions of different TTP manifestations (examples: a drop in platelet count and headache), each of the symptoms was counted.
a: Increase of serum creatinine >1.5 × baseline
b: Events in the MedDRA SOC "nervous system disorders," events in the MedDRA HLGT "vision disorders," and MedDRA PT "irritability"
c: Events in the MedDRA HLT "gastrointestinal and abdominal pains (excluding oral and throat)"
d: Adverse events considered related to TTP (or possibly related to TTP) other than thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological symptoms, and abdominal pain

In the on-demand cohort, SoC was to be administered using the dosing regimen recommended by the investigator, and rADAMTS13 was to be administered at a dose of 40 IU/kg (± 4 IU/kg) on Day 1, 20 IU/kg (± 2 IU/kg) on Day 2, and 15 IU/kg (± 1.5 IU/kg) QD from Day 3 until 2 days after the acute TTP event had resolved.[17] After resolution of the acute TTP events, patients could opt to complete the study or enter the prophylactic cohort.[18]

In the initial version of the protocol (as of February 13, 2017), an interim analysis was to be performed after 24 patients in the prophylactic cohort had completed Period 2. After the initiation of the study, the protocol was amended multiple times. In the end, an interim analysis of all patients enrolled in the prophylactic and on-demand cohorts was to be performed after a total of 30 patients aged ≥12 years in the prophylactic cohort had completed Period 3 (data cutoff date) (Protocol Version 11 [as of February 24, 2021]).

(1) Prophylactic cohort

[Overall population]

All of 48 randomized subjects (26 in the SoC-rADAMTS13 group, 22 in the rADAMTS13-SoC group) received study drug and were included in the safety analysis set. After excluding 1 subject who was found to have acquired TTP, 47 subjects (25 subjects, 22 subjects) were included in the full analysis set (FAS). Among

[17] Acute TTP event resolution was defined as platelet count ≥150,000/μL or platelet count within 25% of baseline, and elevation of LDH ≤1.5 × baseline or ≤1.5 × ULN.
[18] If patients elected to enter the prophylactic cohort, they were to receive the same treatment as their randomized on-demand treatment in Period 1.

the FAS, 46 subjects (25 subjects, 21 subjects) after excluding 1 subject who was enrolled before the study halt and randomized to the rADAMTS13-SoC group, but received SoC followed by rADAMTS13 due to unavailability of rADAMTS13 were included in the mFAS. The mFAS was used as the primary efficacy population. For patients enrolled prior to the study halt, if they were randomized to the SoC-rADAMTS13 group and treated with SoC beyond the protocol-specified 6-month period because rADAMTS13 was not available, only the data from Period 1 between the first dose and the Month 6 visit and the data from Period 2 and beyond were to be used in the efficacy analyses.

As of the data cutoff date, among the 48 randomized subjects[19)] (26 subjects [19 subjects aged ≥18 years, 3 subjects aged 12 to <18 years, 4 subjects aged <12 years], 22 subjects [17 subjects aged ≥18 years, 1 subject aged 12 to <18 years, 4 subjects aged <12 years]), 32 subjects (16 subjects [14 subjects, 2 subjects, 0 subjects], 16 subjects [15 subjects, 1 subject, 0 subjects]) completed the study, and 14 subjects (8 subjects [3 subjects, 1 subject, 4 subjects], 6 subjects [2 subjects, 0 subjects, 4 subjects]) were still on the study. Two subjects discontinued the study (2 subjects aged ≥18 years, 0 subjects), and the reasons for discontinuations were a diagnosis with acquired TTP (1 subject) and an allergic reaction to SoC (the other subject[19)]). As of the data cutoff date, the durations of the observation periods in the prophylactic cohort of the mFAS (median [min., max.]) were 0.54 [0.1, 1.0] years (42 patients) in all patients while receiving SoC during Periods 1 and 2 combined, 0.54 [0, 0.6] years (43 patients) in all patients while receiving rADAMTS13 during Periods 1 and 2 combined, 0.54 [0, 1.3] years (35 patients) in all patients while receiving rADAMTS13 during Period 3, 0.54 [0.1, 1.0] years (38 patients) in patients aged ≥12 years while receiving SoC during Periods 1 and 2 combined, 0.55 [0, 0.6] years (37 patients) in patients aged ≥12 years while receiving rADAMTS13 during Periods 1 and 2 combined, and 0.54 [0, 1.3] years (35 patients) in patients aged ≥12 years while receiving rADAMTS13 during Period 3. Subacute TTP events prompted administration of 6 supplemental doses of study drug in 2 of 42 patients on SoC in Periods 1 and 2 (all patients aged ≥12 years), no subacute TTP events occurred in patients on rADAMTS13 (0 of 43 patients) in Periods 1 and 2, and subacute TTP events prompted administration of 4 supplemental doses of study drug in 1 of 35 patients on rADAMTS13 in Period 3 (all patients aged ≥12 years). The initial dosing frequency of rADAMTS13 was Q2W in 78% (28 of 36) of patients and QW in 22% (8 of 36) of patients.

The primary efficacy endpoint of the incidence rate of acute TTP events in the prophylactic cohort is shown in Table 26. As of the data cutoff date for the interim analysis, efficacy evaluation was to be conducted for all patients and patients aged ≥12 years.

[19)] One patient (≥18 years of age) discontinued the study from the prophylactic cohort due to the principal investigator's decision following an allergic reaction to SoC (S/D-treated plasma). Then, the patient was re-enrolled in the prophylactic cohort, receiving different SoC (factor VIII/VWF concentrates). This patient was double-counted. This patient completed treatment in the on-demand cohort (SoC group) and moved to the prophylactic cohort.

Table 26. Incidence rate of acute TTP events in the prophylactic cohort (mFAS, Overall population)

	Periods 1 and 2 combined		Period 1		Period 2		Period 3
All patients	SoC (N = 42)	rADAMTS13 (N = 43)	SoC (N = 24)	rADAMTS13 (N = 21)	rADAMTS13 (N = 22)	SoC (N = 18)	rADAMTS13 (N = 35)
	0.04 ± 0.266 1 (1)	0 0 (0)	0.07 ± 0.352 1 (1)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)
Patients aged ≥12 years	SoC (N = 38)	rADAMTS13 (N = 37)	SoC (N = 21)	rADAMTS13 (N = 17)	rADAMTS13 (N = 20)	SoC (N = 17)	rADAMTS13 (N = 35)
	0.05 ± 0.280 1 (1)	0 0 (0)	0.08 ± 0.376 1 (1)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)

Upper row, Mean annualized event rate ± SD (events/year); Lower row, Number of subjects with event (Number of events)
Although annualized acute TTP event rates were planned to be calculated from a generalized linear mixed-effects model, non-model-based estimates of annualized event rates (number of events/duration of observation period [years]) are presented due to the sparse number of events.

Regarding safety, Table 27 shows the incidence of all adverse events and adverse events reported by ≥5% of subjects on either study drug in Periods 1 and 2 in the prophylactic cohort.

Table 27. Incidence of all adverse events and adverse events reported by ≥5% of subjects on either study drug in Periods 1 and 2 in the prophylactic cohort (Safety analysis set, Overall population)

	Periods 1 and 2		Period 3
	SoC (N = 44)	rADAMTS13 (N = 45)	rADAMTS13 (N = 36)
Any adverse event	84.1 (37)	71.1 (32)	72.2 (26)
Main events			
Headache	22.7 (10)	24.4 (11)	25.0 (9)
Migraine	6.8 (3)	13.3 (6)	11.1 (4)
Nasopharyngitis	11.4 (5)	13.3 (6)	8.3 (3)
Diarrhoea	2.3 (1)	13.3 (6)	5.6 (2)
Upper respiratory tract infection	2.3 (1)	11.1 (5)	2.8 (1)
Lethargy	6.8 (3)	8.9 (4)	11.1 (4)
Nausea	4.5 (2)	8.9 (4)	11.1 (4)
Dizziness	0 (0)	8.9 (4)	11.1 (4)
COVID-19	4.5 (2)	8.9 (4)	8.3 (3)
Platelet count decreased	11.4 (5)	6.7 (3)	0 (0)
Abdominal pain	9.1 (4)	4.4 (2)	11.1 (4)
Cough	6.8 (3)	4.4 (2)	8.3 (3)
Oropharyngeal pain	11.4 (5)	4.4 (2)	2.8 (1)
Vomiting	9.1 (4)	4.4 (2)	2.8 (1)
Arthralgia	6.8 (3)	4.4 (2)	2.8 (1)
Pruritus	6.8 (3)	4.4 (2)	2.8 (1)
Fatigue	15.9 (7)	2.2 (1)	8.3 (3)
Thrombocytopenia	9.1 (4)	2.2 (1)	2.8 (1)
Iron deficiency	6.8 (3)	2.2 (1)	2.8 (1)
Tachycardia	6.8 (3)	2.2 (1)	0 (0)
Urticaria	13.6 (6)	0 (0)	5.6 (2)
Rash	9.1 (4)	0 (0)	2.8 (1)
Drug hypersensitivity	9.1 (4)	0 (0)	0 (0)
Myalgia	6.8 (3)	0 (0)	0 (0)

Incidence % (n)

In the prophylactic cohort, no deaths were reported. The incidences of serious adverse events were 15.9% (7 of 44 subjects) (thrombocytopenia; pyrexia; seasonal allergy; platelet count decreased; headache; urinary retention; and sinus disorder [1 subject each]) with SoC and 2.2% (1 of 45 subjects) (tachycardia) with rADAMTS13 in Periods 1 and 2 and 11.1% (4 of 36 subjects) (congenital thrombocytopenia[20]; abdominal pain; pneumonia; and ovarian cyst [1 subject each]) with rADAMTS13 in Period 3. All those events were considered unrelated to study drug, except for pyrexia reported with SoC in Periods 1 and 2. An adverse event

[20] Relapse or recurrence of the primary disease triggered by COVID-19 infection

leading to study drug discontinuation occurred in 1 of 44 subjects receiving SoC (2.3%) (rash) in Periods 1 and 2, and the event was considered related to study drug.

In the PK-I period, the incidences of all adverse events were 40.9% (9 of 22 subjects) following the first infusion of SoC, 30.4% (7 of 23 subjects) following the first infusion of rADAMTS13, 13.0% (3 of 23 subjects) following the second infusion of SoC, and 28.6% (6 of 21 subjects) following the second infusion of rADAMTS13. Adverse events reported by more than 1 subject following the first or second infusion of rADAMTS13 were headache (13.6% [3 of 22 subjects] after the first infusion of SoC, 13.0% [3 of 23 subjects] after the first infusion of rADAMTS13, 8.7% (2 of 23 subjects) after the second infusion of SoC, 19.0% [4 of 21 subjects] after the second infusion of rADAMTS13). No deaths were reported. The incidences of serious adverse events were 4.5% (1 of 22 subjects) (road traffic accident and upper limb fracture) following the first infusion of SoC and 4.8% (1 of 21 subjects) (hyperthyroidism) following the second infusion of rADAMTS13, and all those events were considered unrelated to study drug.

In the PK-II period, the incidences of all adverse events were 11.1% (3 of 27 subjects) (nausea; blood LDH increased; and disturbance in attention and hypothyroidism) with the drug product produced by Process IV and 20.0% (5 of 25 subjects) (enterocolitis; hypertension; abdominal pain lower and genital infection; vulvovaginal candidiasis and migraine; and cystitis) with the drug product produced by Process V, and all those events were considered unrelated to study drug. There were no deaths or serious adverse events.

In the PK-III period, no adverse events were reported.

[Japanese subgroup]
In the prophylactic cohort, 5 randomized subjects (3 in the SoC-rADAMTS13 group, 2 in the rADAMTS13-SoC group) (all subjects ≥18 years of age) were included in the safety analysis set, FAS, and mFAS. As of the data cutoff date, all of the 5 randomized subjects (3 subjects, 2 subjects) completed the study, and no subjects discontinued the study. As of the data cutoff date, the durations of the observation periods in the prophylactic cohort of the mFAS (median [min., max.]) were 0.55 [0.5, 0.6] years (5 patients) in patients while receiving SoC in Periods 1 and 2 combined, 0.58 [0.6, 0.6] years (5 patients) in patients while receiving rADAMTS13 during Periods 1 and 2 combined, and 0.59 [0.5, 0.6] years (5 patients) in patients while receiving rADAMTS13 in Period 3. No patients received supplemental doses to treat a subacute TTP event. The initial dosing frequency of rADAMTS13 was Q2W in 80% (4 of 5) of patients and QW in 20% (1 of 5) of patients.

As to the primary efficacy endpoint, no acute TTP events occurred in the prophylactic cohort.

Regarding safety, the incidence of all adverse events in the prophylactic cohort is shown in Table 28.

Table 28. Incidence of all adverse events in the prophylactic cohort
(Safety analysis set, Japanese subgroup)

	Periods 1 and 2		Period 3
	SoC (N = 5)	rADAMTS13 (N = 5)	rADAMTS13 (N = 5)
Any adverse event	80.0 (4)	80.0 (4)	60.0 (3)
Events			
Upper respiratory tract infection	20.0 (1)	40.0 (2)	0 (0)
Anaemia	0 (0)	20.0 (1)	0 (0)
Aphthous ulcer	0 (0)	20.0 (1)	0 (0)
Tooth abscess	0 (0)	20.0 (1)	0 (0)
Arthropod bite	0 (0)	20.0 (1)	0 (0)
Prurigo	0 (0)	20.0 (1)	0 (0)
Urticaria	20.0 (1)	0 (0)	40.0 (2)
Stomatitis	20.0 (1)	0 (0)	20.0 (1)
Malaise	20.0 (1)	0 (0)	20.0 (1)
Gastric polyps	0 (0)	0 (0)	20.0 (1)
Ischaemic enteritis	0 (0)	0 (0)	20.0 (1)
Nausea	0 (0)	0 (0)	20.0 (1)
Blood bilirubin increased	20.0 (1)	0 (0)	0 (0)
Thrombocytopenia	20.0 (1)	0 (0)	0 (0)
Abdominal pain	20.0 (1)	0 (0)	0 (0)
Vomiting	20.0 (1)	0 (0)	0 (0)
Drug hypersensitivity	20.0 (1)	0 (0)	0 (0)
Rhinitis	20.0 (1)	0 (0)	0 (0)
Blood LDH increased	20.0 (1)	0 (0)	0 (0)
Haptoglobin decreased	20.0 (1)	0 (0)	0 (0)
Arthralgia	20.0 (1)	0 (0)	0 (0)
Hand dermatitis	20.0 (1)	0 (0)	0 (0)
Purpura	20.0 (1)	0 (0)	0 (0)

Incidence % (n)

In the prophylactic cohort, there were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

(2) On-demand cohort

[Overall population]

All of 5 randomized subjects[21)] (3 in the SoC group, 2 in the rADAMTS13 group) (all subjects ≥18 years of age) received study drug and were included in the safety analysis set, FAS, and mFAS. mFAS was used as the primary efficacy population. As of the data cutoff date for the interim analysis, among the 5 randomized subjects (3 subjects, 2 subjects), 2 subjects (0 subjects, 2 subjects) ended their participation in the study, and 3 subjects (3 subjects, 0 subjects) moved to the prophylactic cohort, after the completion of the on-demand treatment. Among the 5 randomized subjects, 2 subjects[21)] (1 subject, 1 subject) had an acute TTP event that met the protocol definition (Table 25).

Regarding efficacy, 1 patient in the rADAMTS13 group had a confirmed acute TTP event, which resolved [17)] without requiring the use of another ADAMTS13-containing agent (100% [1 of 1 patient]). The times to resolution for the confirmed acute TTP events as assessed by the investigator were 1.5 days (1 patient) in the SoC group and 3.0 days (1 patient) in the rADAMTS13 group.

[21)] One patient (≥18 years of age) was enrolled in the rADAMTS13 group of the on-demand cohort and then re-enrolled in the SoC group of the on-demand cohort. This patient was double-counted, i.e., 1 each in the rADAMTS13 and SoC groups of the on-demand cohort. Then, this patient moved to the prophylactic cohort.

Regarding safety, the incidence of all adverse events in the on-demand cohort was 100% (3 of 3 subjects) (pruritus, paraesthesia, nausea, headache, and hypoaesthesia; pruritus and tooth abscess; and thrombocytopenia and blood LDH increased [1 subject each]) in the SoC group, and no adverse events were reported in the rADAMTS13 group. There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

[Japanese subgroup]
No Japanese patients were enrolled in the on-demand cohort.

7.2.2 Global phase IIIb extension study (Study TAK-755-3002, CTD 5.3.5.2-1, ongoing since April 2021 [data cutoff date of August 12, 2022: interim analysis])

An open-label, uncontrolled study was conducted at 36 sites in Japan and overseas to evaluate the long-term safety and efficacy of rADAMTS13 in patients with congenital TTP who had completed prophylactic treatment in Study 281102 (rollover patients) and naïve patients with congenital TTP (non-rollover patients) (target sample size, ≥77 subjects [57 rollover patients, ≥20 non-rollover patients]). Non-rollover patients were defined as patients who had not participated in Study 281102 (including patients who had completed Study 281101, but had not participated in Study 281102 and patients who had received rADAMTS13 as part of an expanded access program[22)]) or patients who had participated in Study 281102, but had withdrawn due to an allergic reaction to SoC. The duration of the study was 3 years, or until [redacted] time point of [redacted] time point.

The study included the prophylactic cohort and the on-demand cohort (patients who experienced an acute TTP event). Non-rollover patients could be enrolled in the prophylactic cohort by age cohort (≥18 years, 12 to <18 years, 6 to <12 years, <6 years) after enrollment of the respective age cohort in the prophylactic cohort of Study 281102 had been completed. Enrollment in the on-demand cohort was to be started after patient enrollment in the on-demand cohort of Study 281102 had been completed.

The key inclusion and exclusion criteria were similar to those for Study 281102 [see Section "7.2.1 Global phase III study"].

The dosing regimen of rADAMTS13 in the prophylactic cohort is shown below.

- Rollover patients: rADAMTS13 was administered using the same dosing regimen as that used at the completion of Period 3 in the prophylactic cohort of Study 281102 (40 IU/kg [± 4 IU/kg] Q2W or QW).
- Non-rollover patients (excluding patients enrolled from an expanded access program):
  - In patients receiving FFP or S/D-treated plasma QW, rADAMTS13 40 IU/kg (± 4 IU/kg) QW was administered.
  - In patients receiving factor VIII/VWF concentrates QW or more frequently, rADAMTS13 40 IU/kg (± 4 IU/kg) Q2W or QW was administered, per the investigator's decision.

[22)] Individual patient requests (compassionate use) and named patient program. As of the data cutoff date for the interim analysis, no relevant patients were enrolled in the study.

- In other cases, rADAMTS13 40 IU/kg (± 4 IU/kg) Q2W was administered.

- Patients enrolled from an expanded access program could continue treatment with rADAMTS13 using the same dosing regimen as that used at the completion of the expanded access program.

If any of the following criteria was met, the dosing frequency of rADAMTS13 was to be changed from Q2W (or less frequent than QW) to QW.

- One acute TTP event within the past 6 months.
- Two separate occurrences of laboratory deviations within the past 6 months:
  - Drop in platelet count of ≥25% of baseline or a platelet count <150,000/μL, OR
  - Elevation of LDH >1.5 × of baseline or >1.5 × ULN
- Three separate occurrences of TTP-related signs or symptoms, with or without changes in platelet count or LDH, within the past 12 months
  - Neurological symptoms (e.g., confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR
  - Abdominal pain; OR
  - An increase of serum creatinine >1.5 × baseline

If none of the following occurred within the past 6 months, the dosing frequency of rADAMTS13 could be changed from QW (or more frequent than Q2W) to Q2W, per the investigator's decision.

- Acute TTP event
- Laboratory deviations
  - Drop in platelet count of ≥25% of baseline or a platelet count <150,000/μL
  - Elevation of LDH >1.5 × of baseline or >1.5 × ULN
- TTP-related signs or symptoms (neurological symptoms, abdominal pain, an increase of serum creatinine >1.5 × baseline, etc.)

Subjects experiencing an acute TTP event during prophylaxis were to receive rADAMTS13 using the dosing regimen for the on-demand cohort (described later). The investigators were able to elect to treat a subacute TTP event (during prophylaxis) with 1 or 2 additional doses of rADAMTS13 ≤40 IU/kg.

If the investigator suspected that patients were undergoing an acute TTP event, the patients were to be enrolled in the on-demand cohort. After enrollment, if suspected acute TTP events were not confirmed by central laboratory data (platelet count and LDH), i.e., the acute TTP event definition (Table 25) was not met, those events were to be excluded from the efficacy analyses.

The definitions of TTP events and TTP manifestations in the study were the same as those in Study 281102 [see Table 25].

In the on-demand cohort, rADAMTS13 was to be administered at a dose of 40 IU/kg (± 4 IU/kg) on Day 1, 20 IU/kg (± 2 IU/kg) on Day 2, and 15 IU/kg (± 1.5 IU/kg) QD from Day 3 until 2 days after the acute TTP event

had resolved.[17] After resolution of the acute TTP events, patients could opt to complete the study or enter the prophylactic cohort.

An interim analysis was to be performed after a total of 30 patients aged ≥12 years in the prophylactic cohort of Study 281102 had completed the study (data cutoff date). As of the data cutoff date, no patients were enrolled in the on-demand cohort. Thus, the results in the prophylactic cohort are described below.

[Overall population]
All of 36 enrolled subjects (29 rollover patients [28 patients aged ≥18 years, 1 patient aged 12 to <18 years], 7 non-rollover patients [7 patients aged ≥18 years]) received rADAMTS13 and were included in the safety analysis set and FAS. The FAS was used as the primary efficacy population. As of the data cutoff date, 35 patients (28 patients, 7 patients) were still on the study, and 1 patient discontinued the study (1 patient aged ≥18 years, 0 patients) due to pregnancy. The initial dosing frequency of rADAMTS13 was Q2W in 69.0% (20 of 29) of rollover patients and 85.7% (6 of 7) of non-rollover patients and QW in 31.0% (9 of 29) of rollover patients and 14.3% (1 of 7) of non-rollover patients. As of the data cutoff date, the total durations of rADAMTS13 exposure (median [min., max.]) in the safety analysis set were 7.6 [0, 15.8] months in rollover patients and 1.9 [0.5, 4.7] months in non-rollover patients. Three patients experienced subacute TTP events, which prompted administration of 5 supplemental doses of rADAMTS13.

Regarding efficacy, no acute TTP events occurred in the prophylactic cohort.

Regarding safety, all adverse events and adverse events reported by more than 1 subject in the prophylactic cohort are shown in Table 29.

Table 29. All adverse events and adverse events reported by more than 1 subject in the prophylactic cohort (Safety analysis set, Overall population)

	Rollover patients (N = 29)	Non-rollover patients (N = 7)
Any adverse event	62.1 (18)	28.6 (2)
Main events		
COVID-19	37.9 (11)	0 (0)
Headache	31.0 (9)	14.3 (1)
Migraine	13.8 (4)	14.3 (1)
Fatigue	13.8 (4)	0 (0)
Dizziness	10.3 (3)	14.3 (1)
Abdominal pain	10.3 (3)	14.3 (1)
Oropharyngeal pain	10.3 (3)	0 (0)
Anxiety	10.3 (3)	0 (0)
Nasopharyngitis	6.9 (2)	0 (0)
Upper respiratory tract infection	6.9 (2)	0 (0)
Lethargy	6.9 (2)	0 (0)
Diarrhoea	6.9 (2)	0 (0)
Pyrexia	6.9 (2)	0 (0)
Visual impairment	6.9 (2)	0 (0)
Back pain	6.9 (2)	0 (0)
Gastroenteritis	3.4 (1)	14.3 (1)
Feeling hot	0 (0)	28.6 (2)

Incidence % (n)

There were no deaths or adverse events leading to rADAMTS13 discontinuation.

Serious adverse events occurred in 3 of 29 rollover patients (10.3%) (thrombocytopenia; Campylobacter infection; and COVID-19), but all those events were considered unrelated to rADAMTS13.

[Japanese subgroup]
All of 5 enrolled subjects (all rollover patients) were included in the safety analysis set and FAS and were still on the study.

Regarding safety, the incidence of adverse events was 80.0% (4 of 5 subjects) (pericoronitis, acute sinusitis, COVID-19, dizziness, and bone contusion; AST increased; viral gastroenteritis, COVID-19, fatigue, platelet count decreased, and ALT increased; and infectious enterocolitis [1 subject each]).

There were no deaths or adverse events leading to rADAMTS13 discontinuation.

A serious adverse event occurred in 1 subject (COVID-19), but the event was considered unrelated to rADAMTS13.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of rADAMTS13:
Congenital TTP is a rare life-threatening autosomal recessive disease. It is a platelet-mediated thrombotic disorder of the microcirculation throughout the body caused by severe deficiency of ADAMTS13 activity due to mutations in the *ADAMTS13* gene.

In patients with congenital TTP, severe deficiency of ADAMTS13 activity leads to accumulation of ULVWF multimers with high platelet-binding activity in blood, resulting in spontaneous formation of platelet-rich microthrombi in the microvasculature, thrombocytopenia due to platelet consumption, ischemic damage to multiple organs, etc. (*N Engl J Med*. 2006;354:1927-35, *Am J Med*. 1989;87:9N-15N, etc.). The clinical presentation of congenital TTP lies on a spectrum of severity ranging from patients who can be followed untreated to patients with chronic, recurring TTP manifestations which include thrombocytopenia, haemolytic activity, headache, abdominal pain, fatigue or lethargy, bruising, joint pain, muscular pain, forgetfulness, and confusion and patients with severe acute TTP episodes resulting from transient or irreversible organ ischemia such as stroke, myocardial infarction, and renal dysfunction leading to renal failure. Patients with congenital TTP exhibit heterogeneous clinical courses (*Patient*. 2019;12:503-12). There are 2 peaks in the initial presentation of congenital TTP: in newborns/childhood and during pregnancy (*Blood*. 2021;137:3563-75, *Blood Adv*. 2022;6:750-9, *J Thromb Haemost.* 2020;18:2929-41). Infections, trauma, excessive alcohol intake, etc. are known risk factors for acute exacerbation of congenital TTP (*Blood.* 2021;137:3563-75, *Blood*. 2019;133:1644-51).

Current standard therapy for congenital TTP involves ADAMTS13 replacement through prophylactic or on-demand infusions of plasma-derived products. Some patients require regular prophylactic infusions, and others require on-demand infusions for acute exacerbation of TTP (Clinical guide for thrombotic thrombocytopenic purpura 2023, *J Thromb Haemost*. 2020;18:2496-502). The following issues and limitations have been pointed out for plasma-based therapies.

- The plasma ADAMTS13 activity immediately after the infusion of a plasma-derived product has been reported to be up to approximately 25%, and plasma-derived products provide inadequate ADAMTS13 replacement and limited efficacy (*J Clin Apher*. 2019;34:13-20).
- Allergic and hypersensitivity reactions are known to occur, which are treatment-limiting. These reactions are sometimes severe despite premedication with corticosteroids and antihistamines (*J Clin Apher*. 2001;16:134-8, *Br J Haematol*. 2021;194:444-52).
- Infusions of 10 to 15 mL/kg over 2 to 4 hours are often required to achieve the ADAMTS13 replacement needed to control symptoms, which is burdensome to patients.

On the other hand, rADAMTS13 is a recombinant ADAMTS13 product, which can provide consistent and adequate ADAMTS13 replacement. The results from a global phase III study suggested the efficacy of rADAMTS13 as prophylactic or on-demand ADAMTS13 replacement therapy and identified no safety or tolerability issues. Thus, rADAMTS134 can prevent/reduce and improve acute TTP events and TTP manifestations, avoiding hypersensitivity reactions. In addition, rADAMTS13 is more convenient than plasma-derived products because of its reduced infusion volume (0.13 mL/kg) and infusion time (several minutes). Thus, compared with standard therapy, rADAMTS13 will become a safer and simpler treatment option for patients with congenital TTP.

PMDA's view:

In Japan, there are no drugs approved for the indication of congenital TTP. As standard therapy for congenital TTP, FFP is administered prophylactically or for on-demand treatment of an acute episode, with dosage adjustment according to the patient's platelet count or clinical response, but there are issues such as infectious agent transmission and allergic reactions including anaphylaxis (Clinical guide for thrombotic thrombocytopenic purpura 2023, Guideline for the Use of Blood Products [March 2019, Pharmaceutical Safety and Environmental Health Bureau, MHLW]). The results of a global phase III study suggested that the efficacy of rADAMTS13 is not lower than that of plasma-derived products in preventing acute TTP events when administered as routine prophylaxis and in treating acute TTP events when administered as on-demand treatment, and showed that rADAMTS13 has acceptable safety [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. Thus, offering rADAMTS13 as an alternative treatment option to plasma-derived products to medical practice has its high significance.

7.R.2 Development strategy for rADAMTS13

The applicant's explanation about the development strategy for rADAMTS13:

Both adult and pediatric patients were to be enrolled in Study 281102 because the target disease is ultra-rare. As the primary basis to seek approval for the adult indication as early as possible, an interim analysis was

planned to be performed based on the patient accrual status in the initial version of the protocol (as of February 13, 2017). Taking account of the precision of predicting event rates, patient enrollment rate, etc., the target sample size and the timing of an interim analysis in the prophylactic cohort of Study 281102 were changed multiple times after the initiation of the study. In the end, in order to seek approval for congenital TTP in patients aged ≥12 years, an interim analysis was to be performed based on the data when ≥30 patients aged ≥12 years had completed prophylactic treatment (Protocol Version 11 [as of February 24, 2021]). This interim analysis for efficacy was to be performed for all patients including those aged <12 years and patients aged ≥12 years.

Actually, an interim analysis was performed after 32 patients aged ≥12 years in the prophylactic cohort had completed Period 3. Based on the results of this analysis, a marketing application for rADAMTS13 in adult patients and adolescent patients aged ≥12 years with congenital TTP was filed in Japan. As of the data cutoff date for Study 281102, 6 patients aged ≥12 years (5 patients aged ≥18 years, 1 patient aged 12 to <18 years) were still on prophylactic treatment. All of these 6 patients completed Period 3 by [redacted], 20[redacted]. An application for rADAMTS13 in pediatric patients aged <12 years with congenital TTP is also planned to be submitted based on the results of the final analysis of Study 281102.

PMDA asked the applicant to present the efficacy and safety data from 6 patients aged ≥12 years who were still on prophylactic treatment in Study 281102 and then provide a justification for evaluation based on the results of an interim analysis.

The applicant's explanation:
Regarding efficacy, in 2 patients aged ≥18 years who had not completed Period 2 (Periods 1 and 2 were important for comparison with SoC) as of the data cutoff date23) (both in the SoC-rADAMTS13 group), no acute TTP events or subacute TTP events occurred between the data cutoff date and the completion of Period 2.

Regarding safety in the 6 patients, 10 adverse events occurred in 2 patients between the data cutoff date and the completion of Period 3, but none of them were considered related to rADAMTS13. All those adverse events were mild or moderate in severity, and there were no adverse events leading to treatment interruption or discontinuation. In Period 3, 1 serious adverse event occurred in 1 patient (clostridial gastroenteritis). The event was considered unrelated to rADAMTS13 and resolved following treatment.

Based on the above, in patients aged ≥12 years in the prophylactic cohort of Study 281102, the efficacy and safety conclusions based on the results of the interim analysis are not affected by the efficacy and safety data obtained after the interim analysis data cutoff date.

23) All of the 6 patients were included in the efficacy population (mFAS) as of the interim analysis data cutoff date, and 4 patients had completed Period 2 (Periods 1 and 2 were important for comparison with SoC) as of the interim analysis data cutoff date.

PMDA's view:

With regard to the development strategy for rADAMTS13, at least the following points were not appropriate.

- The applicant claimed that the objective of an interim analysis of Study 281102 was to seek approval for patients aged ≥12 years with congenital TTP as early as possible, and that they planned to evaluate the efficacy and safety of rADAMTS13 in adult patients and adolescent patients aged ≥12 years based on the results of the interim analysis for regulatory submission. However, the objective of an interim analysis or the definition of the primary analysis population was not pre-specified in the protocol etc.
- Statistical hypothesis testing or evaluation based on the pre-defined success criteria was not planned for the prophylactic cohort of Study 281102. rADAMTS13 efficacy and safety evaluation based on more limited data at the time of the interim analysis could lead to a more uncertain evaluation, compared with the time of the final analysis, and the possibility that evaluation at the time of the interim analysis bring about a different interpretation of the results from that at the time of the final analysis also cannot be ruled out.

On the other hand, in addition to the following points, there are no drugs approved for congenital TTP, the currently used plasma-derived products have issues such as infectious agent transmission and allergic reactions, and offering an alternative treatment to plasma-derived products as soon as possible has its high significance. Given these points, for the present application for adults and adolescents aged ≥12 years, it was unavoidable to evaluate the efficacy and safety of rADAMTS13 in patients with congenital TTP, based on the results of the interim analysis of patients aged ≥12 years.

- In the statistical analysis plan, a subgroup of patients aged ≥12 years was a pre-specified population for an interim analysis. Taking also account of rADAMTS13 development history etc., it can be inferred to a certain extent that the efficacy and safety of rADAMTS13 in adults and adolescents aged ≥12 years were planned to be evaluated based mainly on the results of this interim analysis.
- Given the applicant's explanation about the efficacy and safety of rADAMTS13 in 6 patients aged ≥12 years who had not completed prophylactic treatment as of the interim analysis data cutoff date, the efficacy and safety of rADAMTS13 in adults and adolescents aged ≥12 years at the time of the final analysis of this study can be inferred to a certain extent from the results of the interim analysis.

7.R.3 Efficacy

7.R.3.1 Efficacy of routine prophylaxis

7.R.3.1.1 Justification for Study 281102 design

The applicant's explanation about the appropriateness of evaluating the efficacy of rADAMTS13 in the prophylactic cohort based on the results of Study 281102:

The infusion volume and time of rADAMTS13 are different from those of SoC, and in patients receiving SoC, premedication with corticosteroids and antihistamines may be needed to manage hypersensitivity reactions. Thus, Study 281102 was conducted in an open-label manner. The efficacy endpoints of TTP events and some of clinical signs or symptoms of TTP (thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction) were assessed based on laboratory measures using the pre-specified time points and reference ranges. Thus, these are considered objective endpoints.

A crossover design was employed because it allows for intra-patient comparison to exclude imbalances in patient characteristics between the treatment groups when comparing the efficacy of rADAMTS13 with SoC in a limited number of patients. An ER analysis and platelet count simulations using the quantitative systems pharmacology (QSP) model suggested the carry-over effect of rADAMTS13 or SoC received in Period 1, i.e., the residual protective effect against acute TTP events for 2 to 3 weeks after switching treatment in Period 2. However, the results of a sensitivity analysis excluding the data collected during the first 14 days of each Period in which the carry-over effect was expected, and the results from Period 1 only [see Section "7.R.3.1.2 Results in prophylactic cohort of Study 281102"] also showed a trend in favor of rADAMTS13 compared with SoC, as with the results of the primary analysis of Periods 1 and 2 combined. Based on the above, the efficacy of rADAMTS13 can be evaluated based on the data from Periods 1 and 2 combined in the crossover study.

The primary endpoint in the prophylactic cohort was the incidence rate of acute TTP events, defined by thrombocytopenia and microangiopathic hemolytic anemia. The occurrence of an acute TTP event (acute exacerbation) is assessed based mainly on the clinical symptoms in clinical practice (*J Thromb Haemost*. 2017;15:312-22, *Blood*. 2021;137:3563-75), whereas objective laboratory (platelet count and LDH) criteria were used for standardized assessment in Study 281102. Platelet counts directly reflect platelet thrombogenesis, i.e., the center of pathophysiology of TTP, and a lower limit of normal of 150,000/μL is commonly used. In immune-mediated TTP, a platelet count of <100,000/μL is generally used as a criterion for an acute TTP event (*Int J Hematol*. 2023;118:529-46). Given these points etc., the laboratory results were assessed based on a relative drop in platelet count (≥50% or ≥25% drop from baseline) and an absolute value (<100,000/μL or <150,000/μL). LDH reflects the state of microangiopathic hemolytic anemia, and the criteria were established based on the International Working Group consensus report on immune-mediated TTP. The consensus report recommends that clinical response to treatment of immune-mediated TTP should be defined as platelet count >150,000/μL and LDH <1.5 times ULN (*Blood*. 2021;137:1855-61), etc.

Congenital TTP is a rare disease. There are limited data on the natural history of congenital TTP. No controlled studies evaluated the efficacy of standard therapy, i.e., plasma-derived products. Given these points etc., statistical hypothesis testing or evaluation based on the pre-defined success criteria was not planned for Study 281102,[24)] and it was decided to evaluate the efficacy of rADAMTS13 comprehensively, based on the efficacy, safety, and PK data as well as the primary endpoint.

PMDA's view:
Though Study 281102 was conducted in an open-label manner, as the primary efficacy endpoint in the prophylactic cohort of acute TTP events was a laboratory-based objective endpoint, the efficacy of rADAMTS13 can be evaluated to a certain extent. However, it should be noted that as the incidences of TTP

[24)] At the time of planning the study, the assumed incidence rate of acute TTP events with SoC was 1.65/year (*Clin J Am Soc Nephrol*. 2015;10:2002-12), and a ≥50% decrease in annualized event rate with rADAMTS13 compared with SoC was expected. A sample size of 146 to 220 patients (73-110/group) would be required to provide ≥90% power at a two-sided significance level of 0.05 to demonstrate the superiority of rADAMTS13 over SoC in preventing acute TTP events with a treatment duration of 6 to 12 months. However, assessment based on statistical hypothesis testing was considered difficult in terms of patient accrual.

manifestations (neurological symptoms, abdominal pain, etc.) based on adverse events and adverse events, etc., are subjective assessments, bias cannot be excluded.

A crossover design cannot be justified because the carry-over effect of rADAMTS13 or SoC received in Period 1 after switching treatment in Period 2 in the prophylactic cohort was suggested. The efficacy of rADAMTS13 should be evaluated focusing on the results from Period 1, instead of the results from Periods 1 and 2 combined.

The primary endpoint for Study 281102 focused on thrombocytopenia and microangiopathic hemolytic anemia, which are important for diagnosis, among the classic TTP pentad. The laboratory thresholds that define thrombocytopenia and microangiopathic hemolytic anemia are appropriate in terms of assessing a drop in platelet count that can lead to serious hemorrhage and clinically relevant microangiopathic hemolytic anemia.

There are a limited number of patients with congenital TTP in Japan and overseas, and the primary endpoint of the incidence rate of acute TTP events in the prophylactic cohort was also expected to be low, etc. Thus, it was unavoidable to plan no statistical hypothesis testing for efficacy evaluation of rADAMTS13, and the efficacy of rADAMTS13 should be evaluated comprehensively, including the incidence rates of acute TTP events, subacute TTP events, and TTP manifestations, etc.

7.R.3.1.2 Results in prophylactic cohort of Study 281102

(1) Efficacy in the overall population

The applicant's explanation about the efficacy of routine prophylaxis with rADAMTS13:

Table 30 shows the incidence rates of TTP events and TTP manifestations in Study 281102, and Table 31 shows patient characteristics in the SoC-rADAMTS13 group and the rADAMTS13-SoC group of the study.

Table 30. Incidence rates of TTP events and TTP manifestations in Study 281102
(mFAS, Overall population, Patients aged ≥12 years)

	Period 1		Period 2		Period 3
	SoC (N = 21)	rADAMTS13 (N = 17)	rADAMTS13 (N = 20)	SoC (N = 17)	rADAMTS13 (N = 35)
Acute TTP events	0.08 ± 0.376 1 (1)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)
Subacute TTP events	0.45 ± 1.013 4 (5)	0 0 (0)	0 0 (0)	0 0 (0)	0.07 ± 0.291 2 (2)
Thrombocytopenia	5.06 ± 6.738 11 (49)	1.62 ± 3.342 4 (15)	2.02 ± 5.102 5 (15)	2.91 ± 4.299 8 (26)	1.44 ± 4.501 9 (16)
Microangiopathic hemolytic anemia	1.82 ± 3.521 9 (13)	0.54 ± 1.241 3 (5)	0.19 ± 0.584 2 (2)	0.78 ± 2.227 2 (7)	0.53 ± 0.829 11 (11)
Renal dysfunction	0.45 ± 1.455 2 (5)	0 0 (0)	0.76 ± 2.069 3 (8)	0 0 (0)	0.06 ± 0.378 1 (3)
Neurological symptoms	1.02 ± 2.842 4 (12)	1.26 ± 4.345 2 (12)	0.57 ± 1.855 2 (6)	1.76 ± 6.004 3 (17)	1.06 ± 2.587 8 (23)
Abdominal pain	0.43 ± 0.964 4 (5)	0.20 ± 0.832 1 (2)	0.19 ± 0.854 1 (2)	0.22 ± 0.926 1 (2)	0.22 ± 1.069 2 (4)
Other TTP manifestations[a]	1.40 ± 2.344 8 (16)	0.53 ± 1.066 4 (5)	0.37 ± 1.282 2 (4)	0.90 ± 1.584 6 (8)	0.36 ± 1.395 4 (9)

Upper row, Mean annualized event rate ± SD (events/year); Lower row, Number of subjects with event (Number of events)
a: All symptoms considered related to congenital TTP other than thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological symptoms, and abdominal pain

Table 31. Patient characteristics in the SoC-rADAMTS13 group and the rADAMTS13-SoC group of Study 281102 (mFAS, Overall population, Patients aged ≥12 years)

		SoC-rADAMTS13 (N = 21)	rADAMTS13-SoC (N = 17)
Age (years)[a]		29.0 [12, 58]	42.0 [13, 54]
Sex	Male	42.9 (9)	35.3 (6)
	Female	57.1 (12)	64.7 (11)
Race	Asian	14.3 (3)	11.8 (2)
	Caucasian	66.7 (14)	82.4 (14)
	Multiple	4.8 (1)	0 (0)
	Unknown	14.3 (3)	5.9 (1)
Prior treatments for congenital TTP	FFP	66.7 (14)	70.6 (12)
	S/D-treated plasma	14.3 (3)	29.4 (5)
	Factor VIII/VWF concentrates	14.3 (3)	0 (0)
	Unknown	4.8 (1)	0 (0)
Prior or concurrent conditions related to ischemic organ damage	Yes	42.9 (9)	58.8 (10)
	No	57.1 (12)	41.2 (7)
TTP event in the 12 months before enrollment	Acute TTP event only	14.3 (3)	11.8 (2)
	Subacute TTP event only	9.5 (2)	5.9 (1)
	Acute and subacute TTP events	0 (0)	5.9 (1)
	None	76.2 (16)	76.5 (13)
Platelet count at baseline (/μL)[a]		193,000 [118,000, 344,000]	225,000 [95,000, 361,000]
LDH at baseline (U/L)[a]		171.0 [129, 419]	161.0 [129, 224]

Proportion % (n)
a: Median [Min., Max.]

One patient had 1 acute TTP event while receiving prophylaxis with SoC during Period 1, but no patients had an acute TTP event while receiving prophylaxis with rADAMTS13. At the time of planning the study, the assumed incidence rate of acute TTP events in patients receiving prophylaxis with SoC was 1.65/year based on the publication (*Clin J Am Soc Nephrol*. 2015;10:2002-12). However, the incidence rate of acute TTP events with SoC in Study 281102 was 0.05/year, which was lower than assumed at the time of planning the study. The following points may be the causes for the lower than assumed incidence rate of acute TTP events.

- According to the recent data from the international hereditary TTP registry (*Blood*. 2021;137:3563-75), the annual incidence rate of acute TTP events [95% CI] with regular plasma prophylaxis was 0.36 [0.29, 0.44].
- While the occurrence of an acute TTP event (acute exacerbation) is assessed based mainly on the clinical symptoms in clinical practice, the acute TTP event definition in Study 281102 was more conservative because the laboratory criteria related to thrombocytopenia and microangiopathic hemolytic anemia had to be rigorously met.
- Although pregnancy is a major trigger of acute TTP events, pregnant women were excluded from Study 281102.

Five subacute TTP events occurred in 4 patients receiving SoC in Period 1, but no subacute TTP events occurred in patients receiving rADAMTS13. As to the incidence rates of isolated TTP manifestations, except for neurological symptoms, the incidence rates of thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, abdominal pain, and other TTP manifestations were lower with rADAMTS13 than with SoC in Period 1. The incidence rate of renal dysfunction, defined by increase of serum creatinine, was higher with rADAMTS13 than with SoC in Period 2. However, since an increase of serum creatinine was slightly higher than 1.5 × baseline and below ULN in most cases, and the reported maximum level was 1.1 × ULN, these increases of serum creatinine were not clinically relevant. In Period 3 of Study 281102 and rollover patients in

Study TAK-755-3002, the incidence rates of acute and subacute TTP events and isolated TTP manifestations did not tend to increase over time following long-term exposure to rADAMTS13.

The incidence rates of TTP events and TTP manifestations were reviewed by type of prior treatment for congenital TTP (FFP, S/D-treated plasma, factor VIII/VWF concentrates), by prior or concurrent conditions related to ischemic organ damage (stroke, transient ischemic attack, cardiac infarction, renal dysfunction, etc.), and by the occurrence of TTP event in the 12 months before enrollment (acute TTP event only, subacute TTP event only, acute and subacute TTP events, no TTP events). The trend was not clearly different across all subgroups.

(2) Efficacy by age group

The applicant's explanation about the appropriateness of grouping patients aged ≥12 years together for efficacy evaluation:

In addition to the following points, the PK of ADAMTS13 activity following body weight-based intravenous dosing of rADAMTS13 were similar among the different age groups [see Section "6.2.1.3 PPK analysis"]. Thus, patients aged ≥18 years and patients aged 12 to <18 years can be grouped together for efficacy evaluation.

- The trigger for diagnosis of congenital TTP is known to differ according to age, which is attributable to differences in the factors associated with increases in VWF levels, such as physiological changes at birth and during pregnancy and infections in childhood. Patients in all age groups share the condition of the absence of cleavage of ULVWF multimers due to severe hereditary deficiency of ADAMTS13 activity.
- The occurrence of TTP events and the symptoms including chronic ischemic organ damage are considered similar between adult and pediatric patients. According to the international hereditary TTP registry, the incidence rate of TTP events has been reported to be higher in children aged <10 years than in patients aged >40 years, but TTP episodes are observed across varying age groups (*Blood*. 2021;137:3563-75), and similar treatments are used in adults and children (*Blood*. 2019;133:1644-51).
- Although plasma ADAMTS13 levels are markedly lower in neonates than in younger adults, neonatal levels reach adult levels by 6 months of age (*Blood*. 2001;98:2730-6).
- The only known physiological substrate of ADAMTS13 is VWF (*Blood*. 2008;112:1713-9). Plasma VWF levels in full-term neonates are higher than those in adults, but gradually decrease during the first 6 months after birth and mature to a molecular weight pattern similar to that of adults at 3 weeks of age (*Thromb Res*. 2007;119 Suppl 1:S4-S5). Thus, there should be no major differences in rADAMTS13 susceptibility between adolescents aged ≥12 years and adults (*Blood*. 2008;112:1713-9).

Table 32 shows the incidence rates of TTP events and TTP manifestations by age group (≥18 years, 12 to <18 years). Although there are limitations to the interpretation of the results due to the limited number of patients aged 12 to <18 years, these patients exhibited no clearly different trend from that of patients aged ≥18 years.

Table 32. Incidence rates of TTP events and TTP manifestations by age group in Study 281102
(mFAS, Overall population, Patients aged ≥12 years)

	≥18 years			12 to <18 years		
	Periods 1 and 2 combined		Period 3	Periods 1 and 2 combined		Period 3
	SoC (N = 34)	rADAMTS13 (N = 33)	rADAMTS13 (N = 31)	SoC (N = 4)	rADAMTS13 (N = 4)	rADAMTS13 (N = 4)
Acute TTP events	0.05 ± 0.296 1 (1)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)
Subacute TTP events	0.28 ± 0.819 4 (5)	0 0 (0)	0.08 ± 0.309 2 (2)	0 0 (0)	0 0 (0)	0 0 (0)
Thrombocytopenia	4.14 ± 5.855 17 (67)	1.72 ± 4.249 8 (24)	1.56 ± 4.767 8 (15)	3.73 ± 6.200 2 (8)	2.78 ± 5.569 1 (6)	0.54 ± 1.077 1 (1)
Microangiopathic hemolytic anemia	1.41 ± 3.177 9 (18)	0.39 ± 0.995 5 (7)	0.54 ± 0.826 10 (10)	0.89 ± 1.029 2 (2)	0 0 (0)	0.49 ± 0.982 1 (1)
Renal dysfunction	0.28 ± 1.155 2 (5)	0.46 ± 1.638 3 (8)	0.07 ± 0.401 1 (3)	0 0 (0)	0 0 (0)	0 0 (0)
Neurological symptoms	1.51 ± 4.721 7 (29)	0.99 ± 3.393 4 (18)	1.20 ± 2.723 8 (23)	0 0 (0)	0 0 (0)	0 0 (0)
Abdominal pain	0.38 ± 0.988 5 (7)	0.22 ± 0.879 2 (4)	0.24 ± 1.135 2 (4)	0 0 (0)	0 0 (0)	0 0 (0)
Other TTP manifestations[a]	1.31 ± 2.105 14 (24)	0.50 ± 1.235 6 (9)	0.40 ± 1.478 4 (9)	0 0 (0)	0 0 (0)	0 0 (0)

Upper row, Mean annualized event rate ± SD (events/year); Lower row, Number of subjects with event (Number of events)
a: All symptoms considered related to congenital TTP other than thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological symptoms, and abdominal pain

Based on the above, the results of Study 281102 showed the clinically meaningful efficacy of routine prophylaxis with rADAMTS13 in congenital TTP patients aged ≥12 years.

(3) Efficacy in the Japanese subgroup

PMDA asked the applicant to explain the efficacy of rADAMTS13 in Japanese patients with congenital TTP, along with the intrinsic and extrinsic ethnic factors assessed for participation of Japan in Study 281102.

The applicant's explanation:

A global phase I study (Study 281101) and simulations using the PPK model, etc., showed no major differences in the PK of ADAMTS13 activity between Japanese and non-Japanese populations [see Section "6.R.1 PK differences between Japanese and non-Japanese populations"]. Although ≥200 *ADAMTS13* gene mutations have been reported, no clear ethnic differences have been observed (*Haematologia*. 2019;104:2107-15).

When the Japanese and foreign guidelines (*Int J Hematol*. 2017;106:3-15, *Br J Haematol.* 2012;158:323-35) were compared, the definition of and diagnostic criteria for congenital TTP were similar. While there are no drugs approved for the treatment of congenital TTP in Japan or overseas, the both guidelines recommend regular prophylactic or on-demand infusions of ADAMTS13-containing plasma products. While the use of FFP is recommended in Japan, S/D-treated plasma (unapproved in Japan) and factor VIII/VWF concentrates containing ADAMTS13 in addition to FFP are recommended overseas. Although there are differences in the types of drugs available between Japan and overseas, all drugs aim to replace the missing ADAMTS13. Neither guideline defines the characteristics of patients eligible for routine prophylaxis or treatment intervention for acute TTP events, but improvement of isolated TTP manifestations and the prevention of organ damage such as renal dysfunction should be associated with better outcomes in patients with congenital TTP in both Japan and overseas. Thus, there should be no clear intrinsic or extrinsic ethnic differences between Japanese and non-Japanese populations that can affect the efficacy evaluation of rADAMTS13.

Taking account of the above, Study 281102 was conducted. In the Japanese subgroup of patients aged ≥12 years in this study, all patients were women aged ≥18 years and received prior treatment with FFP. There were no major differences in patient characteristics between the Japanese subgroup and the overall population. Table 33 shows the incidence rates of TTP events and TTP manifestations in the overall population and Japanese subgroup of Study 281102 (Periods 1 and 2 combined and Period 3). No acute or subacute TTP events occurred in Japanese patients receiving rADAMTS13. As to the incidence rates of isolated TTP manifestations, the Japanese subgroup showed a similar trend to that of the overall population.

Table 33. Incidence rates of TTP events and TTP manifestations in the overall population and Japanese subgroup of Study 281102 (mFAS, Patients aged ≥12 years)

	Overall population			Japanese subgroup		
	Periods 1 and 2 combined		Period 3	Periods 1 and 2 combined		Period 3
	SoC (N = 38)	rADAMTS13 (N = 37)	rADAMTS13 (N = 35)	SoC (N = 5)	rADAMTS13 (N = 5)	rADAMTS13 (N = 5)
Acute TTP events	0.05 ± 0.280 1 (1)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)
Subacute TTP events	0.25 ± 0.778 4 (5)	0 0 (0)	0.07 ± 0.291 2 (2)	0.74 ± 1.651 1 (2)	0 0 (0)	0 0 (0)
Thrombocytopenia	4.10 ± 5.806 19 (75)	1.84 ± 4.329 9 (30)	1.44 ± 4.501 9 (16)	3.32 ± 4.954 2 (9)	0.68 ± 1.518 1 (2)	0 0 (0)
Microangiopathic hemolytic anemia	1.36 ± 3.019 11 (20)	0.35 ± 0.946 5 (7)	0.53 ± 0.829 11 (11)	0.37 ± 0.826 1 (1)	0 0 (0)	0.34±0.763 1 (1)
Renal dysfunction	0.25 ± 1.094 2 (5)	0.41 ± 1.551 3 (8)	0.06 ± 0.378 1 (3)	1.11 ± 2.477 1 (3)	1.37 ± 3.067 1 (4)	0 0 (0)
Neurological symptoms	1.35 ± 4.483 7 (29)	0.88 ± 3.214 4 (18)	1.06 ± 2.587 8 (23)	0 0 (0)	0 0 (0)	0 0 (0)
Abdominal pain	0.34 ± 0.940 5 (7)	0.20 ± 0.832 2 (4)	0.22 ± 1.069 2 (4)	0.37 ± 0.826 1 (1)	0 0 (0)	0 0 (0)
Other TTP manifestations[a]	1.17 ± 2.030 14 (24)	0.45 ± 1.175 6 (9)	0.36 ± 1.395 4 (9)	1.11 ± 2.477 1 (3)	0 0 (0)	0.34 ± 0.763 1 (1)

Upper row, Mean annualized event rate ± SD (events/year); Lower row, Number of subjects with event (Number of events)
a: All symptoms considered related to congenital TTP other than thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological symptoms, and abdominal pain

Based on the above, the efficacy of rADAMTS13 observed in the overall population of Study 281102 is expected also in Japanese patients with congenital TTP.

PMDA's view:

Although efficacy evaluation based on the results of Study 281102 has limitations, rADAMTS13 is a recombinant ADAMTS13 and aims to replace the severely deficient ADAMTS13 activity in congenital TTP. In addition, given the following points, rADAMTS13 is expected to prevent acute TTP episodes to a certain extent in patients who require regular ADAMTS13 replacement. Taking account of the applicant's explanation and the results of subgroup analysis, patients aged ≥18 years and patients aged 12 to <18 years can be grouped together for efficacy evaluation.

- In Study 281102, the primary endpoint of acute TTP events was a laboratory-based objective endpoint. Only 1 patient had 1 acute TTP event while receiving prophylaxis with SoC, and evaluation has limitations, but its incidence rate with rADAMTS13 was not higher than that with SoC.
- In Study 281102, though it should be noted that some endpoints were based on subjective assessments, the incidence rates of subacute TTP events and individual TTP manifestations were generally lower with rADAMTS13 than with SoC.

- In the PPK analysis using the data from Studies 281101, 281102, and TAK-755-3002, except for body weight, no intrinsic factors had significant effects on the PK of ADAMTS13 activity [see Section "6.2.1.3 PPK analysis"], and administration of rADAMTS13 is expected to increase ADAMTS13 activity, irrespective of patient characteristics etc.

Regarding the efficacy of rADAMTS13 in Japanese patients, since the number of Japanese patients enrolled in Study 281102 was limited, and no acute or subacute TTP events occurred in patients receiving rADAMTS13, it is difficult to assess the consistency of the results between the Japanese subgroup and the overall population. However, there was no clear concern about differences in the incidence rates of isolated TTP manifestations in Study 281102 (Periods 1 and 2 combined and Period 3) between Japanese and non-Japanese populations, based on the obtained data. In addition, given that assessment prior to the study also showed no rADAMTS13 efficacy-related intrinsic or extrinsic ethnic differences between Japanese and non-Japanese populations, the results from the overall population of Study 281102 can be utilized to explain the efficacy of rADAMTS13 in Japanese patients, and routine prophylaxis with rADAMTS13 is expected to prevent acute TTP episodes also in Japanese congenital TTP patients aged ≥12 years.

7.R.3.2 Efficacy of on-demand treatment

The applicant's explanation about the efficacy of on-demand treatment with rADAMTS13:

In Study 281102, patients who experienced an acute TTP event were to be enrolled in the on-demand cohort, where rADAMTS13 was compared with SoC, i.e., plasma-derived products, in an open-label manner. As of the data cutoff date for an interim analysis, 5 patients had been enrolled. In the on-demand cohort, subjects were provisionally enrolled if an investigator suspected the subject was undergoing an acute TTP event, pending central laboratory (platelet count and LDH) confirmation (the central laboratory values met the acute TTP event definition). Thus, the event was a suspected acute TTP event until confirmed by laboratory data. Some suspected acute TTP events were not confirmed by central laboratory data (the central laboratory values did not meet the acute TTP event definition) and were excluded from the efficacy analyses. In the 5 patients enrolled in the on-demand cohort, 2 acute TTP events and 4 suspected acute TTP events occurred. Of the 5 patients, 2 patients (1 acute TTP event, 1 suspected acute TTP event) were randomized to receive rADAMTS13 and 3 patients (1 acute TTP event, 3 suspected acute TTP events) were randomized to receive SoC. The same patient [21)] had 2 acute TTP events. This patient was enrolled twice with different patient IDs in the on-demand cohort and randomized to the rADAMTS13 group after the first event and the SoC group after the second event.

Figure 2 shows laboratory parameters over time in the 2 patients randomized to receive rADAMTS13 in the on-demand cohort.

A 2[redacted]-year-old [redacted] patient[21)] (a) had a platelet count of 25,000/μL and LDH of 625 U/L (ULN 246 U/L), which was considered an acute TTP event. The patient had petechiae mainly over the chest, arms, and lower limbs, and hematomas with a maximum diameter of 5 cm on the lower limb, all of which were considered related to TTP. rADAMTS13 was administered at a dose of 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg on Days 3 and 4 (a total of 4 doses). After administration of rADAMTS13, platelets increased, and LDH decreased.

On Day 4, the platelet count was 152,000/μL, and LDH was 296 U/L, and petechiae and hematomas also resolved. Thus, the acute TTP event was considered resolved,[17] and treatment with rADAMTS13 ended on the same day.

A 2[redacted]-year-old [redacted] patient (b) had a platelet count of 84,000/μL (a local laboratory value), but LDH was 202 U/L, and an elevation of LDH >2 × ULN (250 U/L) was not observed. Thus, this was considered a suspected acute TTP event. rADAMTS13 was administered at a dose of 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg on Days 3 to 6 (a total of 6 doses). After administration of rADAMTS13, the platelet count increased to 187,000/μL on Day 4. Thus, the suspected acute TTP event was considered resolved,[17] and the patient received rADAMTS13 until 2 days after resolution.

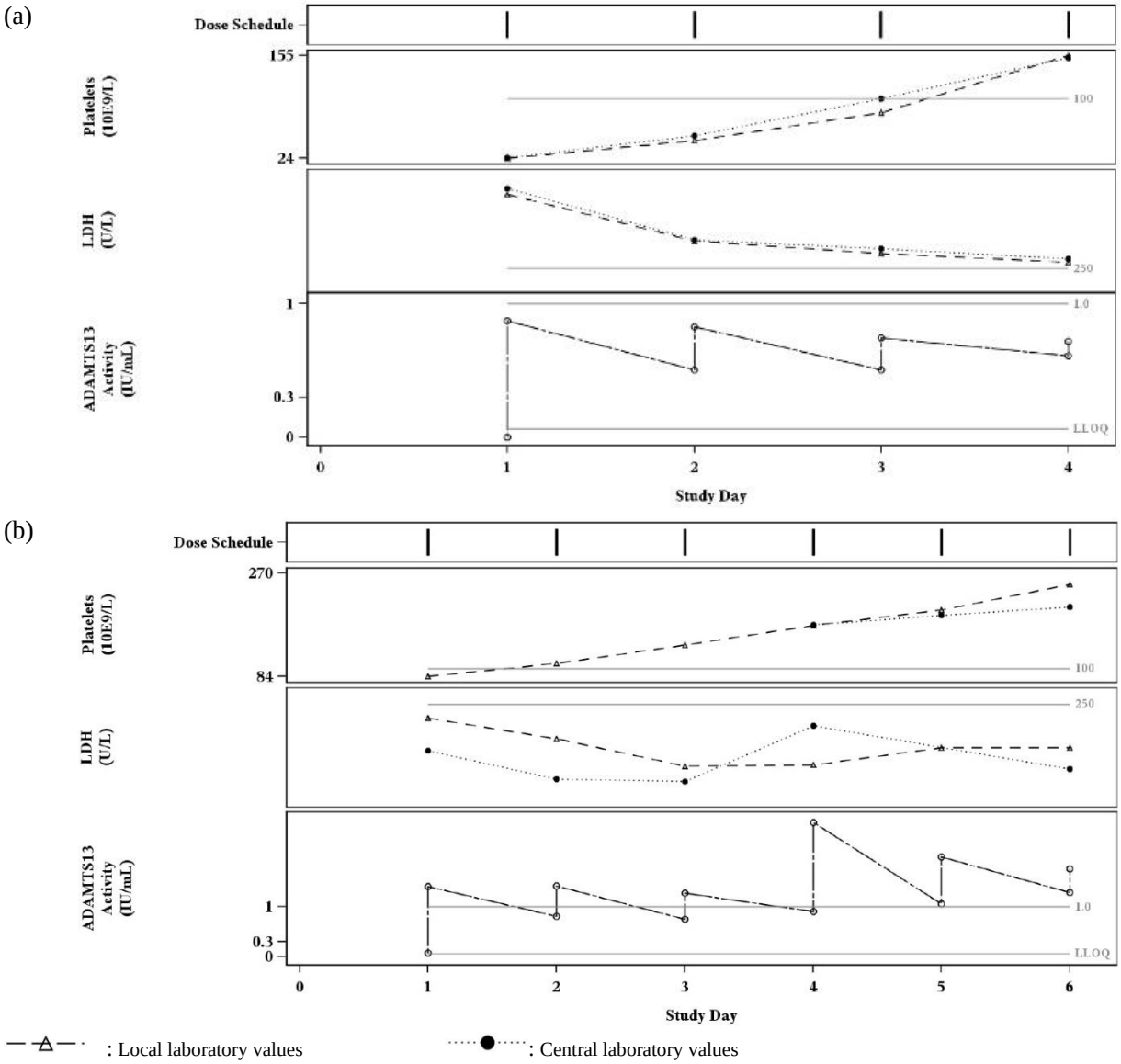


Figure 2. Laboratory parameters over time in the rADAMTS13 group in the on-demand cohort of Study 281102

Figure 3 shows laboratory parameters over time in the 3 patients randomized to receive SoC in the on-demand cohort.

A 2[redacted]-year-old [redacted] patient[21)] (a) had 1 acute TTP event and 1 suspected acute TTP event. The patient had a platelet count of 20,000/μL and LDH of 627 U/L (ULN 246 U/L), which was considered an acute TTP event. The patient received FFP on Days 1 to 3. As LDH on Day 3 was 337 U/L, which was ≤1.5 × ULN, the investigator considered that the acute TTP event had resolved. However, as the platelet count was 67,000/μL, treatment ended without meeting the definition of acute TTP event resolution.[17)] Thirty-six days after the last dose of FFP, the patient had a platelet count of 23,000/μL and LDH of 652 U/L (both local laboratory values) again, which was considered a suspected acute TTP event, and the patient received FFP on Days 1 and 2. Since the platelet count was 101,000/μL, and LDH was 323 U/L (both local laboratory values) on Day 3, the investigator considered that the suspected acute TTP event had resolved, but treatment ended without meeting the definition of acute TTP event resolution.17) Then, the patient moved to the prophylactic cohort.

A 3[redacted]-year-old [redacted] patient[19)] (b) had a platelet count of 20,000/μL (a local laboratory value) and LDH of 412 U/L (ULN 225 U/L), which was considered a suspected acute TTP event. The patient received S/D-treated plasma on Days 1 to 3. Since the platelet count was 261,000/μL, and LDH was 235 U/L 3 days after the end of treatment, the suspected acute TTP event was considered resolved.[17)] Then the patient moved to the prophylactic cohort, but discontinued the study due to an allergic reaction to SoC.

A 2[redacted]-year old [redacted] patient (c) had a platelet count of 65,000/μL and LDH of 211 U/L (ULN 200 U/L) (both local laboratory values), which was considered a suspected acute TTP event. The patient received S/D-treated plasma on Days 1 to 4. Since the platelet count was 150,000/μL (a local laboratory value), and LDH was 225 U/L on Day 4, the investigator considered that the acute TTP event had resolved. However, as the central laboratory platelet count was 137,000/μL, treatment ended without meeting the definition of acute TTP event resolution.[17)] Then the patient moved to the prophylactic cohort.

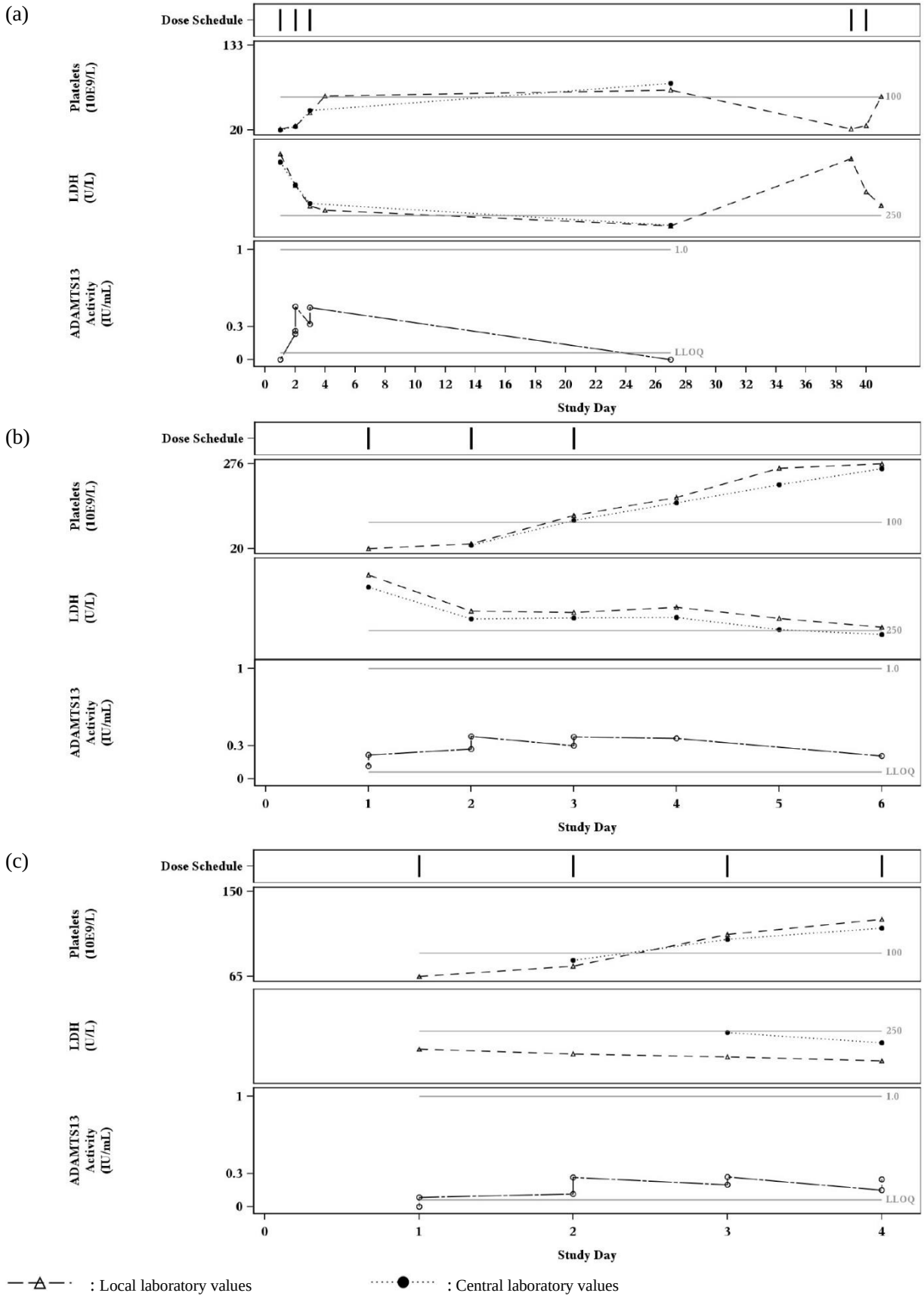
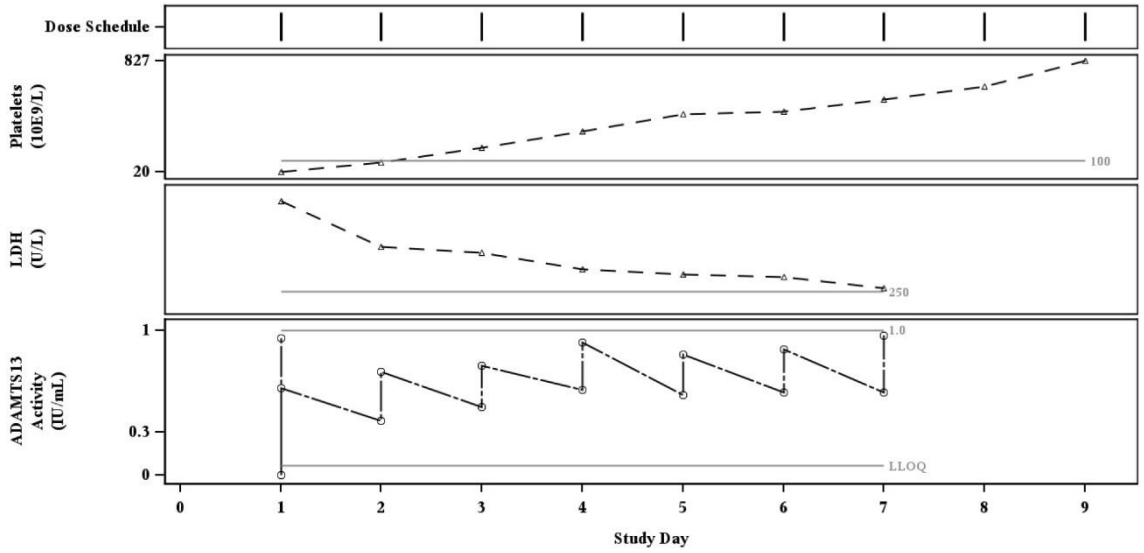


Figure 3. Laboratory parameters over time in the SoC group in the on-demand cohort of Study 281102

Other than the patients enrolled in the on-demand cohort of Study 281102, 1 patient received rADAMTS13 using the dosing regimen for the on-demand cohort. In Study TAK-755-3002, no patients were enrolled in the on-demand cohort. However, 1 non-rollover patient enrolled in the prophylactic cohort (a 2[redacted]-year-old [redacted]) was confirmed to have had an acute TTP event based on baseline laboratory results, which were known after initiating the dosing of rADAMTS13, and then received rADAMTS13 using the dosing regimen for the on-demand cohort. Figure 4 shows laboratory parameters over time in this patient. The platelet count at baseline was 20,000/μL, and LDH at baseline was 1027 U/L (ULN 350 U/L), and rADAMTS13 was administered at a dose of 40 IU/kg on Day 1 (the first prophylactic dose), 20 IU/kg on Day 2, and 15 IU/kg on Days 3 to 9 (a total of 9 doses). After administration of rADAMTS13, the platelet count increased to 195,000/μL on Day 3, and LDH decreased to 282 U/L on Day 7. The acute TTP event was considered resolved, and the patient received rADAMTS13 until 2 days after resolution.



—△— : Local laboratory values

Figure 4. Laboratory parameters over time in patient who received rADAMTS13 for an acute TTP event in the prophylactic cohort of Study TAK-755-3002

As described above, though the type and severity of TTP manifestations differed from patient to patient, platelet count and LDH met the definition of acute TTP event resolution within 7 days after the initiation of rADAMTS13 dosing in all patients who received on-demand treatment with rADAMTS13 per the investigator's decision based on the symptoms/signs.

PMDA's view:

The number of patients enrolled in the on-demand cohort of Study 281102 was limited, and only 1 patient each in the rADAMTS13 and SoC groups (the same patient) had an acute TTP event meeting the definition and were included in the efficacy population. Thus, there are limitations to efficacy evaluation of rADAMTS13 based on the data from the on-demand cohort of Study 281102. On the other hand, taking also account of the following points, the efficacy of rADAMTS13 is expected also for the on-demand treatment of an acute event.

- In Studies 281102 and TAK-755-3002, 2 patients received rADAMTS13 for an acute TTP event or a suspected acute TTP event. After administration of rADAMTS13, platelets increased, and LDH decreased in both patients.
- rADAMTS13 aims to replace the severely deficient ADAMTS13 activity in congenital TTP. Administration of rADAMTS13 increased ADAMTS13 activity fast and maintained ADAMTS13 activity within or near the normal range until the acute TTP event had resolved.
- The efficacy of rADAMTS13 not lower than that of SoC was suggested in the prophylactic cohort [see Section "7.R.3.1 Efficacy of routine prophylaxis"].

7.R.4 Safety

PMDA's conclusion:

Based on the incidence of adverse events in Japanese and foreign clinical studies for the present application and the following considerations, given the efficacy of rADAMTS13 shown in Section "7.R.3 Efficacy," rADAMTS13 has clinically acceptable safety in patients with congenital TTP.

7.R.4.1 Incidence of adverse events in clinical studies

The applicant's explanation about the incidence of adverse events in clinical studies of rADAMTS13:

(1) Routine prophylaxis

Table 34 shows the incidence of adverse events in the prophylactic cohort of Study 281102. The incidences of adverse events in all categories were lower with rADAMTS13 than with SoC. There were no deaths or adverse events leading to rADAMTS13 discontinuation. In Period 1, 1 serious adverse event (sinus disorder) occurred in 1 subject receiving rADAMTS13, but was considered unrelated to rADAMTS13. The majority of adverse events reported with rADAMTS13 were mild to moderate in severity. In Period 3, 4 subjects had 5 serious adverse events, and 5 subjects had 10 severe adverse events. All those events were considered unrelated to rADAMTS13 and resolved without discontinuation or interruption of rADAMTS13.

Table 34. Incidence of adverse events in the prophylactic cohort of Study 281102 (Safety analysis set, Patients aged ≥12 years)

	Overall population					Japanese subgroup				
	Period 1		Period 2		Period 3	Period 1		Period 2		Period 3
	SoC (N = 23)	rADAMTS13 (N = 17)	rADAMTS13 (N = 22)	SoC (N = 17)	rADAMTS13 (N = 36)	SoC (N = 3)	rADAMTS13 (N = 2)	rADAMTS13 (N = 3)	SoC (N = 2)	rADAMTS13 (N = 5)
All adverse events	91.3 (21)	82.4 (14)	72.7 (16)	88.2 (15)	72.2 (26)	66.7 (2)	100 (2)	66.7 (2)	100 (2)	60.0 (3)
Adverse events considered related to study drug	39.1 (9)	11.8 (2)	9.1 (2)	64.7 (11)	2.8 (1)	33.3 (1)	0 (0)	0 (0)	50.0 (1)	0 (0)
Serious adverse events	21.7 (5)	5.9 (1)	0 (0)	5.9 (1)	11.1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe adverse events	13.0 (3)	5.9 (1)	9.1 (2)	17.6 (3)	13.9 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	4.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment interruption	8.7 (2)	0 (0)	0 (0)	29.4 (5)	0 (0)	33.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence % (n)

In the prophylactic cohort of pooled Studies 281102 and TAK-755-3002,[25)] among adverse events occurring within 24 hours after study drug administration, those reported by more than 1 subject receiving SoC or rADAMTS13 were headache, urticaria, nausea, abdominal pain, rash, nasopharyngitis, COVID-19, feeling hot, allergic transfusion reaction, cough, drug hypersensitivity, fatigue, infusion related hypersensitivity reaction, pruritus, seasonal allergy, tachycardia, and thrombocytopenia.

Among 6 subjects who had not completed prophylactic treatment as of the data cutoff date for an interim analysis (5 subjects aged ≥18 years, 1 subject aged 12 to <18 years), 2 subjects experienced 10 adverse events between the data cutoff date and the completion of Period 3, but all those events were considered unrelated to rADAMTS13. All those events were mild or moderate in severity, and there were no adverse events leading to study drug discontinuation or interruption. In Period 3, 1 subject had 1 serious adverse event (clostridial gastroenteritis). The event was considered unrelated to rADAMTS13 and resolved following treatment. Based on the above, as to the prophylactic cohort of Study 281102, the interpretation of the safety results based on the interim analysis remains unchanged, even taking account of the safety data obtained after the interim analysis.

Regarding the long-term safety of rADAMTS13, Table 35 shows the incidence of adverse events with rADAMTS13 by duration of treatment in the prophylactic cohort, according to a pooled analysis of Studies 281102 and TAK-755-3002.[25)] There were no particular concerns. There were no adverse events leading to study drug discontinuation or interruption. The incidence rates of all adverse events were 1110.2/100 subject-years (48 subjects) with SoC and 934.1/100 subject-years (54 subjects) with rADAMTS13 in the overall

[25)] By the prophylactic cohort or the on-demand cohort, patients in the prophylactic cohort during rADAMTS13 treatment in Study 281102 and patients in the prophylactic cohort of Study TAK-755-3002 for rADAMTS13, and patients in the prophylactic cohort during SoC treatment in Study 281102 for SoC were included in the analysis. The total duration of exposure to study drug (median [min., max.]) and the total exposure to study drug in the prophylactic cohort were 195.5 [1, 626] days and 27.6 subject-years, respectively, for SoC and 454.5 [12, 1118] days and 68.3 subject-years, respectively, for rADAMTS13. The total duration of exposure to study drug in the on-demand cohort was 3.0 [3, 4] days (3 subjects) for SoC and 5.0 [4, 6] days (2 subjects) for rADAMTS13.

population and 648.1/100 subject-years with SoC and 284.0/100 subject-years with rADAMTS13 in the Japanese subgroup.

Table 35. Incidence of adverse events with rADAMTS13[a] by duration of treatment in the prophylactic cohort (Pooled analysis of Studies 281102 and TAK-755-3002, Safety analysis set, Patients aged ≥12 years)

		<6 months (N = 46)	6 to <12 months (N = 37)	12 to <18 months (N = 33)	18 to <24 months (N = 22)	24 to <30 months (N = 17)	30 to <36 months (N = 4)	≥36 months (N = 2)
All adverse events		73.9 (34)	64.9 (24)	57.6 (19)	68.2 (15)	70.6 (12)	50.0 (2)	50.0 (1)
Adverse events considered related to study drug		15.2 (7)	2.7 (1)	3.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events		2.2 (1)	8.1 (3)	12.1 (4)	0 (0)	5.9 (1)	0 (0)	0 (0)
Adverse events by severity	Severe	8.7 (4)	10.8 (4)	12.1 (4)	13.6 (3)	11.8 (2)	25.0 (1)	0 (0)
	Moderate	26.1 (12)	32.4 (12)	15.2 (5)	27.3 (6)	17.6 (3)	0 (0)	50.0 (1)
	Mild	39.1 (18)	21.6 (8)	30.3 (10)	27.3 (6)	41.2 (7)	25.0 (1)	0 (0)

Incidence % (n)
a: The cumulative periods of patient participation in Studies 281102 and TAK-755-3002, starting from the first dose of rADAMTS13 in Study 281102 or TAK-755-3002, were included in the analysis.

Regarding safety in Japanese patients, there were no major differences in the safety profile of rADAMTS13 between the overall population and the Japanese subgroup in Studies 281102 and TAK-755-3002 (Table 34), and no particular risk tended to increase in Japanese patients.

Regarding safety by age group, during rADAMTS13 prophylaxis in the prophylactic cohort of pooled Studies 281102 and TAK-755-3002,[25)] 2 of 4 subjects aged 12 to <18 years experienced 22 adverse events, and the most common adverse events were headache, abdominal pain, dyspepsia, and seasonal allergy. In the patients aged 12 to <18 years, no serious or severe adverse events, adverse events leading to study drug discontinuation or interruption, or adverse events considered related to rADAMTS13 were reported. Based on the above, the safety profile of rADAMTS13 was similar between patients aged ≥18 years and patients aged 12 to <18 years.

At present, the following safety information other than the clinical study data has been obtained, but this information does not affect the safety assessment of rADAMTS13.

- Among 9 patients with congenital TTP who received rADAMTS13 through individual patient requests (compassionate use[26)]), 1 patient had 1 adverse event considered related to rADAMTS13 (flatulence).
- Three patients with congenital TTP who participated in a named patient program[27)] had 10 serious adverse events (hypotension, tachycardia, and loss of consciousness after FFP infusion; menorrhagia; thrombocytopenia, decreased platelet count [13,000-14,000/μL], pyrexia, anaemia, catarrh, and acute hemolytic event), but all those events were considered unrelated to rADAMTS13.

(2) On-demand treatment

All patients in the on-demand cohort of Study 281102 were aged ≥18 years, and no Japanese patients were enrolled. All of the subjects in the SoC group (3 subjects) had adverse events, of which nausea (1 event, 1

[26)] Patients with life-threatening congenital TTP who responded inadequately or were intolerant to current SoC and who were ineligible to enter a clinical study of rADAMTS13 were able to receive rADAMTS13 through compassionate use. Between July 2020 and December 2022, 9 patients with congenital TTP aged between 36 hours and 72 years received rADAMTS13 through compassionate use.

[27)] The program provided access to rADAMTS13 to patients with congenital TTP who responded inadequately or were intolerant to current SoC during the period between the completion of a clinical study of rADAMTS13 and the availability of marketed product.

subject) and pruritus (1 event, 1 subject) were considered related to study drug. In these 3 subjects, no deaths, serious adverse events, or adverse events leading to study drug discontinuation or interruption were reported. Except for 2 adverse events reported by 1 subject (thrombocytopenia and blood LDH increased), all those events were mild or moderate in severity. Two subjects in the rADAMTS13 group received 4 or 6 doses of rADAMTS13 and experienced no adverse events.

In Study TAK-755-3002, no patients were enrolled in the on-demand cohort, but 1 non-rollover patient enrolled in the prophylactic cohort (a 2[redacted]-year-old [redacted]) was found to have had an acute TTP event based on baseline laboratory results, which were known after initiating the dosing of rADAMTS13, and received a total of 9 doses using the dosing regimen for the on-demand cohort. This patient experienced 3 adverse events (nausea, feeling hot, and thrombocytosis) by Day 7. Those events were considered related to study drug, but were non-serious and mild and resolved. This patient started prophylaxis (QW) as planned and was still on the study as of the data cutoff date.

As described above, routine prophylaxis with rADAMTS13 or on-demand treatment of an acute event in patients with congenital TTP showed favorable safety and tolerability profiles. Especially in prophylactic treatment, the overall incidence of adverse events was lower with rADAMTS13 than with SoC.

PMDA's conclusion:
Based on the incidence of adverse events in a global phase III study etc., there were no clinically relevant safety concerns associated with rADAMTS13 or clinically relevant differences between Japanese and non-Japanese populations. In the following sections, adverse events of special interest are investigated.

7.R.4.2 Hypersensitivity reactions (including shock and anaphylaxis)

The applicant's explanation about the incidence of hypersensitivity reaction-related adverse events:
During rADAMTS13 prophylaxis in the prophylactic cohort of Study 281102, 5 subjects had 5 hypersensitivity reaction-related events,[28)] but all those events were non-serious and considered unrelated to rADAMTS13. There were no adverse events leading to rADAMTS13 discontinuation or interruption. In Study TAK-755-3002, there were no hypersensitivity reaction-related events associated with rADAMTS13. In these studies, no patients received premedication to prevent allergic reactions during rADAMTS13 treatment.

On the other hand, during prophylaxis with SoC in the prophylactic cohort of Study 281102, 16 subjects had 24 hypersensitivity reaction-related events. All those events were non-serious, of which 22 events were considered related to SoC. The main adverse events were urticaria, drug hypersensitivity, rash, allergic transfusion reaction, and infusion-related hypersensitivity. Six adverse events led to SoC discontinuation or interruption. The reported events were 23 mild or moderate events and 1 severe event (urticaria).

[28)] Adverse events in the MedDRA SMQ "hypersensitivity" (narrow)

In the on-demand cohort of Study 281102, no hypersensitivity reaction-related events were reported in the SoC or rADAMTS13 group.

In Studies 281102 and TAK-755-3002, there were no shock or anaphylaxis-related events.[29])

Based on the above, hypersensitivity reaction-related events were very rare with rADAMTS13, and the risk of hypersensitivity reaction-related events should be low with rADAMTS13 than with SoC. While there were no shock or anaphylaxis-related events in Studies 281102 and TAK-755-3002, rADAMTS13 is a protein product, and the possibility that serious hypersensitivity symptoms such as anaphylactic shock occur also cannot be ruled out. Thus, a relevant precautionary statement will be included in the CLINICALLY SIGNIFICANT ADVERSE REACTIONS section of the package insert, and relevant information will be provided using information materials for healthcare professionals. Post-marketing information on its incidence will be collected.

PMDA's view:
The applicant's measures (Although the incidence of hypersensitivity reaction-related events was lower with rADAMTS13 than with SoC in Study 281102, and there was no shock or anaphylaxis, given that as with other protein products, hypersensitivity-related events such as anaphylactic shock are anticipated, and that the number of patients included in clinical studies was limited, etc., a relevant precautionary statement will be included in the package insert, and post-marketing information will be collected.) are appropriate.

7.R.4.3 Immunogenicity

The applicant's explanation about the immunogenicity of rADAMTS13 [for testing procedure etc., see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods"]:
In Studies 281102 and TAK-755-3002, 7 subjects were ADA-positive. However, 1 subject tested positive for ADAs also at baseline, and ADAs were not induced by rADAMTS13. In the 6 subjects, the antibody titer did not rise over time. Except for 1 subject diagnosed with acquired TTP, no subjects tested positive for neutralizing antibodies. There was no temporal relationship between ADA positivity and TTP events/hypersensitivity reaction-related events. Given these points etc., ADA positivity was not clinically meaningful. Since ADAMTS-13 activity was not determined in most of the ADA-positive subjects, it was difficult to assess the effect of ADA formation on ADAMTS-13 activity.

According to a pooled analysis of Studies 281102 and TAK-755-3002,[25)] the incidence of ADAs by duration of treatment in patients receiving rADAMTS13 in the prophylactic cohort is shown in Table 36. The incidence of ADAs was increased in patients who received prophylaxis with rADAMTS13 for ≥18 months, which may have been attributed to the limited number of patients analyzed who received rADAMTS13 for ≥18 months and higher assay sensitivity in Study TAK-755-3002 than in Study 281102.

[29)] Adverse events in the MedDRA SMQs "anaphylactic reaction" (narrow) and "anaphylactic/anaphylactoid shock conditions" (narrow)

Table 36. Incidence of ADAs to rADAMTS13 by duration of treatment in patients receiving rADAMTS13[a] in the prophylactic cohort
(Pooled analysis of Studies 281102 and TAK-755-3002, Safety analysis set, Patients aged ≥12 years)

	<6 months (N = 41)	6 to <12 months (N = 36)	12 to <18 months (N = 33)	18 to <24 months (N = 21)	24 to <30 months (N = 14)	Entire period (N = 41)
ADA-positive	4.9 (2)[b]	2.8 (1)	6.1 (2)	14.3 (3)	21.4 (3)	17.1 (7)[b]

Incidence % (n)
a: The cumulative periods of patient participation in Studies 281102 and TAK-755-3002, starting from the first dose of rADAMTS13 in Study 281102 or TAK-755-3002, were included in the analysis.
b: Including a patient who was diagnosed with acquired TTP after enrollment

Based on the above, although there were no particular concerns about ADA formation in the clinical studies, as rADAMTS13 is a recombinant protein, and the development of neutralizing antibodies to rADAMTS13 can lead to lack of efficacy of rADAMTS13, etc., information on the incidences of ADAs and neutralizing antibodies in clinical studies will be provided using the package insert, and post-marketing information will be collected.

PMDA's view:
Given the applicant's explanation, the possibility that ADA formation has a clinically relevant impact on the efficacy and safety of rADAMTS13 has not been suggested. Meanwhile, since the development of neutralizing antibodies can lead to lack of efficacy of rADAMTS13 etc., the applicant's measures (Information on the incidence of ADAs in clinical studies will be provided using the package insert, and post-marketing information will be collected.) are appropriate.

7.R.4.4 Use in pregnant women

The applicant's explanation about the use of rADAMTS13 during pregnancy:
Pregnancy is a known trigger of acute TTP episodes, and adult-onset congenital TTP is often diagnosed during pregnancy. Especially, TTP episodes associated with pregnancy are known to significantly affect not only the mother, but also the fetus. The fetal death rate in pregnancies without prophylactic FFP infusions is as high as 50%. Thus, prophylactic FFP infusions are recommended during pregnancy (Clinical guide for thrombotic thrombocytopenic purpura 2023).

In a fertility and embryo-fetal development study in female rats, no toxicity findings were observed in the dams, and there were no effects on fertility, at exposures of up to 3.9-fold and 8.4-fold the C_{max} and AUC, respectively, in humans at the recommended clinical dose of rADAMTS13 [see Section "5.5 Reproductive and developmental toxicity"]. Drugs with a molecular weight of >1 kDa cross the placenta very poorly (*Clin Pharmacokinet*. 2004;43:487-514). As a large protein with a molecular weight of 173 kDa, rADAMTS13 is expected to have only limited access to a conceptus and interaction with intracellular organelles, including DNA.

Although pregnant women were excluded from clinical studies of rADAMTS13 in patients with congenital TTP, 3 patients with congenital TTP were exposed to rADAMTS13 during pregnancy in Study TAK-755-3002 or through compassionate use[26)] as follows.

- One rollover patient (2[redacted] years) in Study TAK-755-3002 was found to be pregnant approximately 3 months after entering Study TAK-755-3002 (approximately 1 week after the last dose of rADAMTS13) and discontinued the study. The patient had a first trimester miscarriage approximately 2 months after study discontinuation. This was considered unrelated to rADAMTS13 by the principal investigator.
- One patient (2[redacted] years) under a compassionate use program, in the third trimester of pregnancy, experienced recurrent stroke, mild thrombocytopenia, and mild elevation of LDH and was diagnosed with congenital TTP. A previous pregnancy resulted in intra-uterine fetal death and stroke. Thrombocytopenia was refractory to daily plasmapheresis. The patient received rADAMTS13 40 IU/kg QW, starting at 33 weeks of gestation. With increasing ADAMTS13 activity, thrombocytopenia resolved rapidly. At 37 weeks of gestation, the patient delivered a healthy baby by cesarean section, but the birth weight of the baby was 1,865 g, i.e., a small-for-gestational-age infant (<1 percentile). No adverse events occurred during treatment with rADAMTS13, and the mother continues on rADAMTS13 Q2W.
- One patient (2[redacted] years) under a compassionate use program experienced a stroke and her first acute TTP event during her second trimester of pregnancy. The patient achieved remission after daily plasmapheresis, but shortly afterwards had a second acute TTP event, with a rapid decrease in ADAMTS13 activity, a drop in platelet count, and elevation of LDH. Following administration of rADAMTS13 40 IU/kg QW, ADAMTS13 activity levels normalized fast, and thrombocytopenia resolved. Then, the patient delivered a healthy baby at 29 weeks of gestation. No adverse events occurred during treatment with rADAMTS13.

Based on the above, though the use of rADAMTS13 in pregnant women has raised no safety concerns at present, pregnant women were excluded from clinical studies, and the safety of rADAMTS13 in pregnant women has not been established. On the other hand, since ADAMTS13 replacement through infusions of rADAMTS13 is highly likely needed during pregnancy in clinical practice, the package insert will advise that rADAMTS13 may be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.

PMDA's view:

Patients often present with an adult onset of overt congenital TTP during pregnancy. TTP episodes during pregnancy are associated with a serious fetal outcome, and prophylactic enzyme replacement therapy is essential (Clinical guide for thrombotic thrombocytopenic purpura 2023, *J Thromb Haemost.* 2020;18:2496-502). Thus, enzyme replacement therapy with rADAMTS13 is highly likely needed during pregnancy. The applicant's measures (Although there should be little concern about the reproductive and developmental toxicity of rADAMTS13 via placental transfer, given that no safety data from pregnant women and infants have been obtained from clinical studies, the package insert will advise that rADAMTS13 may be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.) are acceptable. Information on the use of rADAMTS13 during pregnancy in clinical studies or under a compassionate use program (the dosing regimen of rADAMTS13, timing of dosing, its efficacy and safety, etc.) should be provided using information materials for healthcare professionals. Post-marketing information on the safety of rADAMTS13 in pregnant women should be collected.

7.R.5 Indication and target population for rADAMTS13

PMDA's view:

Clinical studies in patients with congenital TTP suggested the efficacy of routine prophylaxis or on-demand treatment with rADAMTS13 to prevent or treat acute TTP episodes, respectively, and showed its acceptable safety [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. Thus, the appropriate indication for rADAMTS13 should be "congenital thrombotic thrombocytopenic purpura."

Patients with congenital TTP have persistent severe deficiency of ADAMTS13 activity, but do not necessarily present with symptoms such as thrombocytopenia, and some patients can be followed untreated. Some patients require regular prophylactic infusions to replace the missing ADAMTS13, and others require on-demand infusions for acute exacerbation of TTP, etc. (Clinical guide for thrombotic thrombocytopenic purpura 2023, J *Thromb Haemost*. 2020;18:2496-502). Given these points, the package insert should advise that eligible patients must be selected by physicians with adequate knowledge of and experience in the treatment of hematologic disorder, according to individual patients' conditions, etc.

7.R.6 Dosage and administration

7.R.6.1 Prophylactic dosing regimen

The applicant's explanation about the prophylactic dosing regimen of rADAMTS13:

Patients in the prophylactic cohort of Study 281102 received rADAMTS13 40 IU/kg (± 4 IU/kg) Q2W or QW. Prophylaxis with rADAMTS13 demonstrated better clinical benefit than prophylaxis with SoC and showed favorable safety profile. In clinical studies, rADAMTS13 500 IU or 1500 IU was to be reconstituted with 5 mL of water for injection and infused intravenously slowly at a rate of 2 to 4 mL/min.

In many patients, the dosing frequency of their prior standard therapy at enrollment was selected as the dosing frequency of rADAMTS13. In the mFAS (patients aged ≥12 years), the dosing frequency at study enrollment was Q2W in 78% (28 of 36) of patients and QW in 22% (8 of 36) of patients. The efficacy and safety results by the initial dosing frequency in Study 281102 are shown in Table 37 and Table 38, respectively. The dosing frequency was changed after the start of study drug administration in 1 patient each in the prophylactic cohort of Studies 281102 and TAK-755-3002. Although evaluation has limitations due to the limited number of patients who received rADAMTS13 QW, the incidence rates of TTP events and TTP manifestations were lower with rADAMTS13 than with SoC, regardless of the dosing frequency, and the favorable efficacy of rADAMTS13 is expected as compared with SoC. All patients receiving SoC or rADAMTS13 QW experienced adverse events, but no adverse events were considered related to rADAMTS13. There were no major differences in the safety profile between QW and Q2W. There were no major differences in patient characteristics between QW and Q2W, except that the most common standard therapy at enrollment was FFP in the Q2W subgroup (85.7%) and S/D-treated plasma in the QW subgroup (50.0%).

Table 37. Incidence rates of TTP events and TTP manifestations by dosing frequency in the prophylactic cohort of Study 281102 (mFAS, Patients aged ≥12 years)

	Q2W			QW		
	Periods 1 and 2 combined		Period 3	Periods 1 and 2 combined		Period 3
	SoC (N = 28)	rADAMTS13 (N = 28)	rADAMTS13 (N = 26)	SoC (N = 8)	rADAMTS13 (N = 8)	rADAMTS13 (N = 8)
Acute TTP events	0.06 ± 0.326 1 (1)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)	0 0 (0)
Subacute TTP events	0.27 ± 0.849 3 (4)	0 0 (0)	0.04 ± 0.223 1 (1)	0.22 ± 0.632 1 (1)	0 0 (0)	0.17 ± 0.470 1 (1)
Thrombocytopenia	4.50 ± 5.707 17 (66)	2.29 ± 4.889 7 (28)	1.85 ± 5.177 7 (14)	1.79 ± 5.055 1 (8)	0.50 ± 0.920 2 (2)	0.31 ± 0.573 2 (2)
Microangiopathic hemolytic anemia	1.23 ± 2.180 9 (18)	0.39 ± 1.023 4 (6)	0.55 ± 0.864 8 (8)	0.22 ± 0.632 1 (1)	0.26 ± 0.729 1 (1)	0.41 ± 0.784 2 (2)
Renal dysfunction	0.34 ± 1.268 2 (5)	0.48 ± 1.753 2 (7)	0.09 ± 0.438 1 (3)	0 0 (0)	0.24 ± 0.675 1 (1)	0 0 (0)
Neurological symptoms	0.14 ± 0.528 2 (2)	0 0 (0)	0.09 ± 0.447 1 (2)	5.53 ± 8.872 4 (24)	3.64 ± 6.348 3 (16)	3.58 ± 4.138 6 (15)
Abdominal pain	0.14 ± 0.506 2 (2)	0 0 (0)	0 0 (0)	1.13 ± 1.665 3 (5)	0.91 ± 1.681 2 (4)	0.94 ± 2.183 2 (4)
Other TTP manifestations[a]	0.95 ± 1.616 10 (14)	0.26 ± 0.816 3 (4)	0.18 ± 0.503 3 (3)	2.25 ± 3.128 4 (10)	1.15 ± 1.949 3 (5)	1.00 ± 2.817 1 (6)

Upper row, Mean annualized event rate ± SD (events/year); Lower row, Number of subjects with event (Number of events)
a: All symptoms considered related to congenital TTP other than thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological symptoms, and abdominal pain

Table 38. Incidence of adverse events by dosing frequency in the prophylactic cohort of Study 281102 (Safety analysis set, Patients aged ≥12 years)

	Q2W			QW		
	Periods 1 and 2		Period 3	Periods 1 and 2		Period 3
	SoC (N = 30)	rADAMTS13 (N = 30)	rADAMTS13 (N = 27)	SoC (N = 8)	rADAMTS13 (N = 8)	rADAMTS13 (N = 8)
All adverse events	86.7 (26)	70.0 (21)	63.0 (17)	100.0 (8)	100.0 (8)	100.0 (8)
Adverse events considered related to study drug	50.0 (15)	13.3 (4)	3.7 (1)	37.5 (3)	0 (0)	0 (0)
Serious adverse events	6.7 (2)	0 (0)	7.4 (2)	37.5 (3)	0 (0)	25.0 (2)
Severe adverse events	6.7 (2)	3.3 (1)	3.7 (1)	50.0 (4)	25.0 (2)	37.5 (3)
Adverse events leading to study drug discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to study drug interruption	20.0 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypersensitivity reaction-related adverse events	36.7 (11)	0 (0)	7.4 (2)	37.5 (3)	12.5 (1)	25.0 (2)

Incidence % (n)

Among the 2 patients who changed their dosing frequency after the start of study drug administration, 1 patient in Study 281102 changed their dosing frequency from Q2W to QW according to the study rules due to 3 separate occurrences of TTP-related signs or symptoms (migraine, headache, migraine with aura) in Period 3. The 1 rollover patient in Study TAK-755-3002 changed their dosing frequency from Q2W to QW due to at least 3 separate occurrences of TTP-related signs or symptoms (attention concentration difficulty, worsened headache, anxiety) in the past 6 months, approximately 11 months after entering Study TAK-755-3002. Approximately 3 months later, the dosing frequency returned to Q2W (unknown reason), but this change was documented as a serious protocol deviation, and the dosing frequency was changed again to QW.

PMDA asked the applicant to explain how to select the prophylactic dosing frequency of rADAMTS13 in clinical practice.

The applicant's explanation:
Japanese and foreign guidelines do not provide clear guidance about the frequency of prophylactic infusions of FFP, a current standard therapy (Clinical guide for thrombotic thrombocytopenic purpura 2023, *J Thromb Haemost*. 2020;18:2496-502). In medical practice, the frequency of prophylactic infusions of FFP is selected, taking account of the severity of congenital TTP, response to treatment, tolerability, patient's convenience, etc., and treatment frequency is generally increased or decreased according to patient symptoms and platelet counts (*Blood*. 2019;133:1644-51). Thus, the dosing frequency of rADAMTS13 will be selected by physicians, taking account of the frequency of prior treatment, in addition to patient symptoms and platelet counts.

PMDA's view:
Study 281102 suggested the efficacy of rADAMTS13 at the dosing regimen tested in the prophylactic cohort and showed its acceptable safety, and comparison of the efficacy and safety of rADAMTS13 with SoC suggested a similar trend between Q2W and QW. Given these findings etc., the prophylactic dosing regimen of rADAMTS13 40 IU/kg Q2W or QW according to the patient's condition such as the symptoms and platelet counts, as specified in Study 281102, is appropriate. Though the number of Japanese patients evaluated in Study 281102 was very limited, taking also into account that there were no clear concerns about differences in the PK and efficacy and safety of rADAMTS13 between Japanese and non-Japanese populations [see Sections "6.R.1 PK differences between Japanese and non-Japanese populations," "7.R.3 Efficacy," and "7.R.4 Safety"], selection of the dosing regimen tested in Study 281102 as the recommended dosing regimen for Japanese patients with congenital TTP is appropriate. Since it is difficult to provide uniform guidance about the prophylactic dosing frequency of rADAMTS13, as with prophylactic infusions of FFP, a current standard therapy, the dosing frequency should be selected by physicians according to the patient's condition such as the symptoms and platelet counts, and the package insert should advise that the prophylactic dosing frequency of rADAMTS13 should be determined based on the patient's condition, the frequency of prior treatment, etc.

7.R.6.2 On-demand dosing regimen

The applicant's explanation about the on-demand dosing regimen of rADAMTS13:
The on-demand dosing regimen of rADAMTS13 in Study 281102 was chosen based on the goal to increase ADAMTS13 activity towards the normal range as soon as possible and maintain ADAMTS13 activity within or near the normal range during the ongoing acute event until the symptoms have resolved [see Section "6.R.2 Rationale for the dosing regimen in a global phase III study"]. In clinical studies, rADAMTS13 500 IU or 1500 IU was to be reconstituted with 5 mL of water for injection and infused intravenously slowly at a rate of 2 to 4 mL/min. rADAMTS13 was administered at the specified dosing regimen in 2 patients in the rADAMTS13 group in the on-demand cohort of Study 281102. Treatment ended on the day of acute TTP event resolution in 1 patient, and the other patient received rADAMTS13 until 2 days after the suspected acute TTP event had resolved. One patient received rADAMTS13 using the dosing regimen for the on-demand cohort for an acute TTP event in Study TAK-755-3002. This patient received rADAMTS13 until 2 days after the acute TTP event had resolved. Although the number of patients evaluated in the on-demand cohort was limited, recurrence or exacerbation of the disease may be avoided by continuing treatment until 2 days after acute TTP event resolution.

PMDA's view:
Although the number of patients treated with rADAMTS13 in the on-demand cohort of Study 281102 was very limited, given the pathophysiology of congenital TTP and the rationale for the dosing regimen selected and taking into account that the study suggested the efficacy of rADAMTS13 at this dosing regimen and showed its acceptable safety [see Sections "7.R.3.2 Efficacy of on-demand treatment" and "7.R.4 Safety"], the dosing regimen used in Study 281102 can be chosen as the on-demand dosing regimen for acute exacerbation of TTP.

As to the timing of treatment cessation, only 1 patient in the on-demand cohort of Study 281102 received rADAMTS13 until 2 days after acute TTP event resolution as specified, and the appropriateness of this dosing recommendation is unknown. Thus, the duration of on-demand treatment should be determined by physicians, according to the patient's condition such as the symptoms and platelet counts, and the package insert should advise that rADAMTS13 should not be continued without careful consideration.

Based on the considerations in Sections "7.R.6.1 Prophylactic dosing regimen" and "7.R.6.2 On-demand dosing regimen," the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections of the package insert. A final conclusion will be made, taking account of comments from the Expert Discussion.

Dosage and Administration
The rADAMTS13 vial should be reconstituted with 5 mL of the diluent provided, and the reconstituted solution should be infused intravenously slowly at a rate of 2 to 4 mL/min.

For routine prophylaxis, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg every other week. The prophylactic dosing frequency may be adjusted to 40 IU/kg once weekly according to the patient's condition.

For on-demand treatment of an acute event, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg once daily from Day 3.

Precautions Concerning Dosage and Administration
- The prophylactic dosing frequency should be determined based on platelet counts, clinical response, the frequency of prior treatment, etc.
- For on-demand treatment of an acute event, the duration of treatment should be determined based on platelet counts, clinical response, etc., and rADAMTS13 should not be continued without careful consideration.

7.R.7 Post-marketing investigations
The applicant's explanation about post-marketing investigations:

Due to the limited number of Japanese patients included in clinical studies, etc., the applicant plans to conduct a specified use-results survey, covering all patients with congenital TTP treated with rADAMTS13 (an observation period of 18 months [until 4 weeks after the last dose of rADAMTS13 in the case of on-demand treatment only], a planned sample size of 40 patients as the safety analysis population), to evaluate the safety etc. of rADAMTS13, including the incidences of shock and anaphylaxis and immunogenicity, in clinical practice. The planned sample size was determined, based on the number of patients with congenital TTP in Japan (70 patients) (Clinical guide for thrombotic thrombocytopenic purpura 2023), the estimated proportion of patients receiving routine prophylaxis (*Br J Haematol*. 2021;194:444-52), etc.

PMDA's view:
Given that there is limited clinical experience with rADAMTS13 in Japanese patients with congenital thrombotic thrombocytopenic purpura in clinical studies, etc., post-marketing surveillance, covering all patients with congenital thrombotic thrombocytopenic purpura treated with rADAMTS13, should be conducted until data from a specified number of cases will be collected. There is no clinical experience with rADAMTS13 in pregnant women with congenital TTP in clinical studies. No Japanese patients have received on-demand treatment with rADAMTS13, and there is no clinical experience with rADAMTS13 in Japanese adolescents aged ≥12 years. Thus, it is necessary to collect information on the safety etc. of rADAMTS13 in these patient subgroups. In accordance with “Risk Management Plan Guidance” (PFSB/SD Notification No.0411-1 and PFSB/ELD Notification No.0411-2 dated April 11, 2012), the details of post-marketing surveillance, including identification of safety specification, the appropriateness of risk classification, and the appropriateness of pharmacovigilance activities and risk minimization activities, will be finalized, taking account of comments from the Expert Discussion.

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

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

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

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

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

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

On the basis of the data submitted, PMDA has concluded that rADAMTS13 has efficacy in patients with congenital TTP, and that rADAMTS13 has acceptable safety in view of its benefits. rADAMTS13 is a recombinant ADAMTS13, and offering rADAMTS13 as a new treatment option for patients with congenital TTP to clinical practice has its significance. PMDA also considers that the efficacy of rADAMTS13, dosage and administration, etc. need to be further discussed.

PMDA has concluded that rADAMTS13 may be approved if rADAMTS13 is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 6, 2024

Product Submitted for Approval

Brand Name	Adzynma Intravenous 1500
Non-proprietary Name	Apadamtase Alfa (Genetical Recombination)/Cinaxadamtase Alfa (Genetical Recombination)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	August 16, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

The expert advisors supported PMDA's conclusion on the efficacy of rADAMTS13 in Section "7.R.3 Efficacy" in the Review Report (1), including the following points.

- Since the incidence rates of acute TTP events, subacute TTP events, and isolated TTP manifestations were not generally higher with rADAMTS13 than with SoC in the prophylactic cohort of Study 281102, etc., the prophylactic efficacy of rADAMTS13 in the prevention of acute TTP episodes is expected.
- Although efficacy evaluation has limitations due to the limited number of patients evaluated in the on-demand cohort of Study 281102, given the mechanism of action of rADAMTS13, increased platelet count and decreased LDH observed in the clinical courses of individual patients, etc., the efficacy of rADAMTS13 administered as on-demand treatment of an acute event is expected.

1.2 Clinical positioning of rADAMTS13 and indication

PMDA's conclusion on the clinical positioning of rADAMTS13:

There are no drugs approved for the indication of congenital TTP in Japan, and offering rADAMTS13 as an alternative treatment option to current standard therapy, i.e., plasma-derived products, to medical practice has its high significance.

The expert advisors supported the above conclusion by PMDA.
The expert advisors supported PMDA's conclusion that the appropriate indication for rADAMTS13 is "congenital thrombotic thrombocytopenic purpura."

1.3 Dosage and administration

The expert advisors supported the following conclusions by PMDA on the dosing regimen of rADAMTS13.

- For routine prophylaxis or on-demand treatment of an acute event, the specification of dose and dosing frequency of rADAMTS13 specified in Study 281102 are justified.
- The package insert should advise that the prophylactic dosing frequency should be determined based on the patient's condition such as platelet counts and clinical response, and the frequency of prior treatment.
- The following precautionary statements should be included in the package insert: For on-demand treatment of an acute event, the duration of treatment should be determined by physicians, according to the patient's condition such as platelet counts and clinical response; and rADAMTS13 should not be continued without careful consideration. Then, information on the timing of treatment cessation specified in Study 281102 (until 2 days after acute TTP event resolution) should be provided.

In view of the discussion above, the expert advisors supported PMDA's conclusion that the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

Dosage and Administration

The rADAMTS13 vial should be reconstituted with 5 mL of the diluent provided, and the reconstituted solution should be infused intravenously slowly at a rate of 2 to 4 mL/min.

For routine prophylaxis, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg every other week. The prophylactic dosing frequency may be adjusted to 40 IU/kg once weekly according to the patient's condition.

For on-demand treatment of an acute event, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg once daily from Day 3.

Precautions Concerning Dosage and Administration

- The prophylactic dosing frequency should be determined based on platelet counts, clinical response, the frequency of prior treatment, etc.
- For on-demand treatment of an acute event, the duration of treatment should be determined based on platelet counts, clinical response, etc., and rADAMTS13 should not be continued without careful consideration.

1.4 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, etc., PMDA has concluded that the risk management plan (draft) for rADAMTS13 should include the safety specification presented in Table 39, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 40 and a specified use-results survey (all-case surveillance) presented in Table 41.

Table 39. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis	• Inhibitor development	None
Efficacy specification		
None		

Table 40. 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 • Specified use-results survey (all-case surveillance)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate information materials (a proper use guide) for healthcare professionals

Table 41. Outline of specified use-results survey (all-case surveillance) (draft)

Objective	To evaluate the safety and efficacy of rADAMTS13 in clinical practice.
Survey method	Central registry system (all-case surveillance)
Population	Patients with congenital TTP
Observation period	18 months
Planned sample size	40 patients (as the safety analysis population)
Main survey items	Patient characteristics (age of diagnosis, prior treatment, underlying disease/complications, medical history, etc.), the use of rADAMTS13 (prophylactic/on-demand, daily dose, dosing frequency, duration of treatment, the number of doses, TTP events for which rADAMTS13 was administered, etc.), concomitant medications, clinical laboratory tests, the incidence of adverse events, 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 inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. As the product is an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Congenital thrombotic thrombocytopenic purpura

Dosage and Administration

The product vial should be reconstituted with 5 mL of the diluent provided, and the reconstituted solution should be infused intravenously slowly at a rate of 2 to 4 mL/min.

For routine prophylaxis, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg every other week. The prophylactic dosing frequency may be adjusted to 40 IU/kg once weekly according to the patient's condition.

For on-demand treatment of an acute event, the usual dosage in adults and adolescents aged ≥12 years is 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg once daily from Day 3.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product, until data from a specified number of cases will be collected, in order to obtain information on the characteristics of patients treated with the product, collect data on the safety and efficacy of the product as soon as possible, and take necessary measures to ensure proper use of the product.

Appendix

List of Abbreviations

ADA	Anti-drug antibodies
ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under ADAMTS13 activity-time curve
$AUC_{0\text{-}24h}$	AUC from time zero to 24 hours
$AUC_{0\text{-}70h}$	AUC from time zero to 70 hours
$AUC_{0\text{-}72h}$	AUC from time zero to 72 hours
AUC_{last}	AUC from time zero to time of the last quantifiable concentration
AUC_{all}	AUC from time zero to the time of the last observation
$AUC_{0\text{-}\infty}$	AUC from time zero to infinity
BMI	Body mass index
BU	Bethesda unit
BVDV	Bovine viral diarrhea virus
C_{ave}	Average ADAMTS13 activity
$C_{ave, ss}$	Average ADAMTS13 activity at steady state
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Total body clearance
CL_{cr}	Creatinine clearance
C_{max}	Maximum ADAMTS13 activity
$C_{max, ss}$	Maximum ADAMTS13 activity at steady state
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
DNA	Deoxyribonucleic acid
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum response
EPC	End of production cells
ER	Exposure-response
FAS	Full analysis set
FFP	Fresh frozen plasma
HCP	Host cell protein
HLGT	High level group terms
HLT	High level terms
ICH Q5A (R1) guideline	“Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin” (Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau [PMSB/ELD], Ministry of Health and Welfare Notification No. 329, dated February 22, 2000)
ICH Q5B guideline	"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 guideline	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
ICH S6 (R1) guideline	"Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau [PFSB/ELD], Ministry of Health, Labour and Welfare Notification No. 0323-1, dated March 23, 2012)
IU	International units
LDH	Lactate dehydrogenase
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
[redacted]	[redacted]
MMV	Mouse minute virus
mRNA	Messenger ribonucleic acid
NZW	New Zealand White
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PRV	Pseudorabies virus
PT	Preferred terms
Q	Peripheral clearance
QSP	Quantitative systems pharmacology
QW	Once weekly
Q2W	Every two weeks
rADAMTS13	Recombinant a disintegrin and metalloproteinase with a thrombospondin type 1 motif, number 13 Apadamtase alfa (genetical recombination)/cinaxadamtase alfa (genetical recombination)
RCo	Ristocetin cofactor activity
Reo 3	Reovirus type 3
RH	Relative humidity
rhVWF	Recombinant human von Willebrand factor
RNA	Ribonucleic acid
[redacted]	[redacted]
SEC	Size exclusion liquid chromatography
SD	Sprague-Dawley
S/D	Solvent/Detergent
SMQ	Standardised MedDRA queries
SOC	System organ class
The product	Adzynma Intravenous 1500
TK	Toxicokinetics
t_{last}	Time of last observed quantifiable ADAMTS13 activity
t_{max}	Time to maximum ADAMTS13 activity
TTP	Thrombotic thrombocytopenic purpura
$t_{1/2}$	Elimination half-life
ULN	Upper Limit of normal
ULVWF	Ultra large von Willebrand factor
V_{ss}	Volume of distribution at steady state

V_c	Central volume of distribution
V_p	Peripheral volume of distribution
VWF	von Willebrand factor
WCB	Working cell bank
X-MuLV	Xenotropic murine leukemia virus