BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125795/0
CBER Received Date	March 17, 2023
PDUFA Goal Date	November 15, 2023
Division / Office	DCEH/Office of Therapeutic Products
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Megha Kaushal
Review Completion Date / Stamped Date	11/7/2023
Supervisory Concurrence	Prasad Mathew Nicole Verdun
Applicant	Takeda Pharmaceuticals
Established Name	rADAMTS13
(Proposed) Trade Name	ADZYNMA
Pharmacologic Class	Biologic-device combination product
Formulation(s), including Adjuvants, etc.	Recombinant ADAMTS13
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in a single-dose vial for intravenous use
Dosing Regimen	Prophylactic: 40 IU/kg once every other week On-demand: Day 1- 40 IU/kg; Day 2- 20 IU/kg; Day 3 – 15 IU/kg until 2 days after the acute event is resolved.
Indication(s) and Intended Population(s)	Prophylactic or on-demand enzyme replacement therapy in patients with congenital thrombocytopenic purpura (TTP)
Orphan Designated (Yes/No)	Yes

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GLOSSARY

ADAMTS13	a disintegrin and metalloproteinase with thrombospondin motifs 13
AE	adverse event
BLA	Biologics License Application
BLQ	below limit of quantification
CHO	Chinese Hamster Ovary
CMC	chemistry, manufacturing, and controls
FAS	full analysis set
FDA	Food and Drug Administration
FFP	fresh frozen plasma
IND	investigational new drug
IU	international units
IV	intravenous
LDH	lactate dehydrogenase
MAHA	microangiopathic hemolytic anemia
OD	on-demand
PA	Protocol Amendment
PK	pharmacokinetic
SAE	serious adverse event
SoC	standard of care
TEAE	treatment-emergent adverse event
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
VWF	von Willebrand factor

1. EXECUTIVE SUMMARY

Congenital thrombotic thrombocytopenic purpura (TTP) is an ultra-rare, life-threatening thrombotic disorder of the microcirculation caused by a severe deficiency of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13). Severe deficiency of ADAMTS13, generally considered to be <10 percent (<0.1 international units [IU]/mL) of mean normal activity, leads to accumulation of ultra-large von Willebrand factor (VWF) multimers with high platelet binding activity, which can result in spontaneous formation of widespread VWF-platelet-rich microthrombi and ischemic damage to multiple organs. Typical features of an acute TTP episode include thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and clinical symptoms resulting from a variable degree of ischemic organ damage, particularly affecting the brain, heart, and kidney. Current standard of care (SoC) therapy centers around ADAMTS13 replacement through acute or regular prophylactic infusions of commercially available, plasma-based therapies.

Recombinant ADAMTS13 (hereafter referred to as TAK-755) is a mixture of two protein species expressed in Chinese Hamster Ovary (CHO) cells. This original BLA submission seeks approval of TAK-755 for the prophylactic or on-demand (OD) enzyme replacement therapy in patients with congenital TTP. The primary basis to support licensure for the proposed indication for TAK-755 comes from an interim analysis of a single, adequate, randomized, well-controlled trial, Study TAK-755-281102.

Study TAK-755-281102 was a Phase 3, prospective, randomized, controlled, open-label, multicenter, 2-period crossover study with a single-arm continuation evaluating the safety and efficacy of TAK-755 in the prophylactic and OD treatment of subjects with severe congenital TTP. All subjects had been previously exposed to ADAMTS13 through plasma-based products. Subjects were in two cohorts: a prophylactic cohort and an OD cohort. Subjects enrolled in the prophylactic cohort were randomized to receive 6 months of treatment in Period 1 with either TAK-755 or SoC, followed by a further 6 months of treatment in Period 2 with the alternate treatment.

The primary efficacy endpoint was the incidence of acute TTP events in subjects with congenital TTP receiving TAK-755 or SoC prophylactically during the treatment periods. Secondary endpoints included the incidence of subacute events and isolated TTP manifestations (for TTP event definitions, refer to Section 6.1.8). The interim analysis included 37 randomized and dosed subjects. Zero acute TTP events occurred with TAK-755 prophylaxis. One event occurred during the SoC treatment.

Safety was based on the 48 unique subjects randomized in the prophylactic cohort and those in the OD cohort who were dosed. The most common adverse reactions for those who received TAK-755 included headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, vomiting. No deaths occurred. No neutralizing antibodies were detected. Anti-TAK-755-binding antibodies were detected in one subject at baseline but did not rise throughout the study duration. Two subjects had transient anti-CHO antibodies.

The Applicant has provided substantial evidence of effectiveness and safety based on a single well-controlled clinical investigation providing evidence of clinical benefit, supported by the pharmacokinetic (PK) studies and preclinical studies. The overall benefit-risk assessment is favorable, and the clinical review team recommends regular approval of TAK-755 for the prophylactic or OD enzyme replacement therapy in adult and pediatric patients with congenital TTP.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1: Demographics

Parameter	Safety Population N=48
Age (years)	-
Mean (SD)	30.6 (16.7)
Median	31
Min, max	3, 68
Sex [n (%)]	-
Male	19 (39.6)
Female	29 (60.4)
Ethnicity [n (%)]	-
Hispanic or Latino	1 (2.1)
Not Hispanic or Latino	39 (81.3)
Not reported	8 (16.7)
Race [n (%)]	-
Asian	6 (12.5)
Black	1 (2.1)
White	31 (64.6)
Multiple	1 (2.1)
Not reported	9 (18.8)

Source: Analysis by Clinical Reviewer
Abbreviations: N=number of subjects in the specified group or the total sample, n (%)=number of subjects with the specified characteristic, SD=standard deviation.

Reviewer Comment: *This demographic table is based on the 48 subjects (47 unique in the prophylactic cohort) that were randomized and dosed and one subject in the OD cohort.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Congenital TTP is an ultra-rare, life-threatening thrombotic disorder of the microcirculation caused by a severe deficiency of ADAMTS13. This protease specifically cleaves VWF multimers. Severe deficiency of ADAMTS13, generally considered to be <10 percent (<0.1 IU/mL) of mean normal activity, leads to accumulation of ultralarge VWF multimers with high platelet binding activity, which can result in spontaneous formation of widespread VWF-platelet-rich microthrombi and ischemic damage to multiple organs. The formation of these platelet-rich microthrombi leads to platelet consumption and thrombocytopenia, which is a hallmark of uncontrolled congenital TTP.

Congenital TTP exhibits an autosomal recessive mode of inheritance caused by homozygous or double heterozygous mutations in the ADAMTS13 gene on chromosome 9. The nature of these mutations is diverse and includes missense, nonsense, and splice site mutations, and less commonly deletions and insertions. The prevalence of congenital TTP is estimated to range from 0.4 to 4 per million, though a prevalence of up to 16.7 per million has been reported.

Congenital TTP is characterized by recurring acute episodes causing morbidity and premature mortality, as well as chronic subacute symptoms such as headache, abdominal pain, cognitive symptoms, and fatigue. Typical features of an acute TTP episode include thrombocytopenia, MAHA, and clinical symptoms resulting from a variable degree of ischemic organ damage, particularly affecting the brain, heart, and kidney.

Current SoC therapy centers around ADAMTS13 replacement through acute or regular prophylactic infusions of commercially available plasma-based therapies (including fresh frozen plasma [FFP], solvent/detergent-treated plasma, and factor VIII/VWF concentrates).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are no approved drugs or biologics for congenital TTP.

2.3 Safety and Efficacy of Pharmacologically Related Products

N/A

2.4 Previous Human Experience With the Product (Including Foreign Experience)

N/A; there is no previous human experience with this product.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

The FDA had the following meetings with the Applicant:

- June 2010: Pre-IND Meeting
- May 2012: Type B Pre-IND Meeting
- July 2018: Type C Chemistry, Manufacturing, and Controls (CMC) Meeting regarding variant product
- April 2019: Cell Line Discussion
- July 2021: Type C Clinical Meeting. The FDA did not agree to use the subacute manifestations as a key secondary endpoint as there is no consensus on the use of these definitions by the Applicant regarding acute and subacute manifestations in the medical community. In addition, the clinical manifestations are subjective and there is uncertainty in the time points for resolution.
- December 2021: Patient-reported outcome feedback given by clinical outcome assessment team (consult)
- April 2022: PK Responses
- Dec 2022: Pre-BLA Meeting. FDA agreed to use the Phase 3 data for the primary efficacy analysis. For pediatric data, we noted that durations of 6 months or less may not be adequate to allow for extrapolation to the adult data.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. The submission consisted of the five modules in the Common Technical Document structure. The modules were adequately organized and integrated to allow the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices and Submission Integrity

The Applicant noted that the study complied with good clinical practices. There were no clinical study conduct or data integrity issues that impacted the clinical review of this submission.

Bioresearch Monitoring inspections were issued for four clinical study sites that participated in the conduct of Study TAK-755-281102. The inspections did not reveal significant issues impacting the integrity of the data submitted in support of this application.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Study 281101, 281102
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 34
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

There were three investigators with financial disclosures. One investigator enrolled one subject. One investigator enrolled zero subjects. One investigator was the highest enrolling site (eight subjects). The Applicant states a sensitivity analysis of efficacy and safety results with and without Site 18 was conducted.

Reviewer Comment: *Bioresearch Monitoring inspected Site 18 and noted no significant issues.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

TAK-755 consists of a mixture of two protein species expressed in CHO cells. One protein species is representative of the native ADAMTS13 sequence. The second protein species differs from the native sequence by a single amino acid exchange at position 23 with Q (Glutamine) in the native protein (Apadamtase alfa) and R (Arginine) in the variant protein (Cinaxadamtase alfa).

4.2 Assay Validation

Please refer to the CMC memo for details regarding all assay validation for ADAMTS13 levels and immunogenicity.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical studies have been conducted to support the clinical trials and license application and included in vivo testing for efficacy, safety pharmacology, pharmacokinetics, and toxicity in rodent and nonrodent species, including nonhuman primates.

In vivo, the efficacy of TAK-755 as a prophylactic and a therapeutic was demonstrated in the recombinant VWF-induced congenital TTP model in ADAMTS13 knockout mice. In these studies, the range of doses of TAK-755 included the intended human dose in patients with congenital TTP (40 IU/kg) to 2 and 5 times the intended clinical dose and was found to be efficacious. The efficacy of TAK-755 was interval- and dose-dependent when administered before or after induction of TTP.

During the repeat-dose toxicity studies in rats and cynomolgus monkeys, VWF multimers were analyzed to demonstrate the ability of TAK-755 to cleave endogenous VWF. Overall, the results were indicative of in vivo cleavage of VWF in rats and cynomolgus monkeys, evidenced by the degradation of endogenous VWF multimers after dosing with TAK-755.

In TAK-755 repeat-dose studies, the dose regimens covered a variety of dosing regimens that will be used in the clinic for prophylactic treatment, including dosing every day, dosing every 3 days, and dosing once weekly. In general, systemic exposure (C_{max} and Area Under the Curve) increased with increasing doses; <2-fold accumulation from repeat dosing was observed; and no sex-related differences in systemic exposure to TAK-755 were noted. While binding and neutralizing antidrug antibodies were present in some rat studies, they did not result in a reduction in exposure. However, rabbits and monkeys did form binding and neutralizing antidrug antibodies that did impact exposure after repeat dosing.

Please refer to the Pharmacology/Toxicology memo for further details.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology memo for further details.

4.4.1 Mechanism of Action

TAK-755 is the recombinant form of the endogenous ADAMTS13. ADAMTS13 is a plasma zinc metalloprotease that regulates the activity of VWF by cleaving large and ultra-large VWF multimers to smaller units and thereby reducing the platelet binding properties of VWF and its propensity to form microthrombi.

4.4.2 Human Pharmacodynamics

Evidence of pharmacodynamic activity was observed with escalating doses; prolonged detectable, ADAMTS13-mediated, VWF cleavage products were present (all subjects up to 3 hours, 24 hours, and 48 hours post dose at 5 U/kg, 20 U/kg, and 40 U/kg,

respectively). A trend for decreasing large multimers, a fraction of which also included ultralarge multimers, and increasing levels of the intermediate fraction were observed over the first 24 hours post infusion in individual profiles at TAK-755 doses of 20 U/kg or 40 U/kg.

There was an increase in the platelet count in all dosing groups and a decrease of lactate dehydrogenase (LDH) in the first 96 hours.

4.4.3 Human Pharmacokinetics

Following single-dose administration of TAK-755 at 5 U/kg, 20 U/kg, and 40 U/kg to adults, C_{max} and total exposures of ADAMTS13 activity and ADAMTS13:Ag appeared to increase in a proportional manner to the dose escalation.

4.5 Statistical

Please refer to the Statical Review memo for further details. There was no formal statistical analysis provided for this study. All analyses were descriptive statistics.

4.6 Pharmacovigilance

Please refer to the Office of Biostatistics and Pharmacovigilance Review memo for further details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The clinical review focused on the interim data in the Phase 3 study that was submitted in Module 5 with review of the Phase 1/2 study as supportive evidence.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following materials from the submission were reviewed:

Module	Information
1.6	Meetings
1.14	Labeling
1.18	Proprietary names
5.2	List of Clinical Studies
5.3.5	Reports of efficacy and safety studies
5.3.5.1	Datasets and Case Report Forms

5.3 Table of Studies/Clinical Trials

Table 2: Studies/Clinical Trials Reviewed for This BLA

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	281101	Module 5.3.3.2	To evaluate the safety, including immunogenicity, and PK of TAK-755 in subjects diagnosed with congenital ADAMTS-13 deficiency (plasma ADAMTS-13 activity <6%) to establish the dosing of TAK-755 for the treatment of cTTP in the subsequent pivotal Phase 3 clinical study.	Phase 1 open-label, uncontrolled	Three Dose Cohorts: Dose Cohort 1: Single dose of TAK-755 at 5 U/kg BW. Dose Cohort 2: Single dose of TAK-755 at 20 U/kg BW. Dose Cohort 3: Single dose of TAK-755 at 40 U/kg BW All doses were administered intravenously.	16	Subjects with cTTP diagnosis	Single dose	Complete-Full CSR
Safety and Efficacy	281102	Module 5.3.5.1	To determine the incidence of acute TTP events in subjects with severe cTTP receiving either standard of care (SoC) or TAK-755 as a prophylactic treatment	Phase 3, prospective, randomized, controlled, open labelled, crossover	Prophylaxis Cohort: Randomized to receive 6 months of treatment in Period 1 with either TAK-755 (40 IU/kg) or SoC followed by a further 6 months of treatment in Period 2 with the alternate	Approximately 57 subjects (0-70 YOA) Interim Analysis: 48 in the prophylaxis cohort and 5 in the on-demand cohort	Subjects with cTTP diagnosis	Approximately 22 months in the prophylaxis cohort and approximately 1 month in the on-demand cohort. Subjects will	Ongoing-Interim CSR complete
					treatment. The treatment order was randomly assigned. Following the randomized crossover, all subjects were to enter the single arm Period 3, where they were to receive TAK-755 (40 IU/kg). On-Demand Cohort: Randomized to receive either SoC or 40 IU/kg TAK-755 (Day 1), 20 IU/kg TAK-755 (Day 2), and then 15 IU/kg TAK-755 daily until 2 days after the acute event has resolved. All doses are administered intravenously			cross-over from treatment with TAK-755 to SoC in 6-month periods.	

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	TAK-755-3002	Module 5.3.5.2	To evaluate the long-term safety and tolerability of TAK-755 (rADAMTS-13) in terms of related TEAEs and SAEs in both the prophylactic and the on-demand cohorts.	Phase 3b, prospective, open-label, continuation study	Prophylactic cohort: 40 IU/kg TAK-755 once Q1W or Q2W On-demand cohort: Randomized to receive 40 IU/kg TAK-755 (Day 1), 20 IU/kg TAK 755 (Day 2), and then 15 IU/kg TAK-755 daily until 2 days after the acute event has resolved. All doses are administered intravenously	Approximately 77 subjects Interim Analysis: 47 subjects enrolled	Subjects with cTTP diagnosis	A maximum of 3 years in the prophylaxis cohort and approximately 1 month in the on-demand cohort.	Ongoing-Interim CSR complete

Source: Module 5.2 Tabular List of All Clinical Studies
Abbreviations: ADAMTS-13=a disintegrin and metalloproteinase with thrombospondin motifs 13, BW=body weight, CSR=clinical study report, cTTP=congenital thrombotic thrombocytopenic purpura, PK=pharmacokinetic, Q1W=every week, Q2W=every two weeks, rADAMTS-13=recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13, SAE=serious adverse event, SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13, TEAE=treatment-emergent adverse events, TTP=thrombocytopenic purpura, YOA=years of age.

5.4 Consultations

The clinical outcome assessments team in CDER was consulted for the review of the patient-reported outcomes in this BLA.

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee was not convened for this product. The application did not raise significant safety or efficacy concerns that could not be addressed though information in the label; consultative expertise was not required, and no public health concerns arose upon the review of this file.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations sought for the review of this BLA.

5.5 Literature Reviewed (if applicable)

Tarasco, E, L Bütikofer, KD Friedman, JN George, I Hrachovinova, PN Knöbl, M Matsumoto, AS von Krogh, I Aebi-Huber, Z Cermakova, M Górska-Kosicka, KA Jalowiec, CR Largiadèr, Z Prohászka, G Sinkovits, J Windyga, B Lämmle, and JA Kremer Hovinga, 2021, Annual incidence and severity of acute episodes in hereditary thrombotic thrombocytopenic purpura, Blood, 137(25):3563-3575.

Scully, M, BJ Hunt, S Benjamin, R Liesner, P Rose, F Peyvandi, B Cheung, and SJ Machin, 2012, Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies, Br J Haematol, 158(3):323-335.

Stubbs, MJ, G Kendall, and M Scully, 2022, Recombinant ADAMTS13 in Severe Neonatal Thrombotic Thrombocytopenic Purpura, N Engl J Med, 387(25):2391-2392.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

This was a Phase 3, prospective, randomized, controlled, open-label, multicenter, 2-period crossover study with a single-arm continuation evaluating the safety and efficacy of TAK-755 in the prophylactic and OD treatment of subjects with severe congenital TTP (Upshaw-Schulman Syndrome, hereditary TTP).

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of the study was to determine the incidence of acute TTP events in subjects with severe congenital TTP receiving either SoC or TAK-755 as a prophylactic treatment.

Secondary objectives were:

- To evaluate the efficacy of TAK-755 in the treatment of acute TTP events as measured by the (1) number of acute TTP events responding to treatment, and (2) time to resolution in both the prophylactic and the OD cohorts
- To evaluate the incidence of isolated TTP manifestations including thrombocytopenia, MAHA, renal dysfunction, neurological signs and symptoms, and abdominal pain in the prophylactic cohort
- To evaluate the incidence of dose modification and supplemental dose for each treatment in the prophylactic cohort
- To evaluate the safety and tolerability of TAK-755 in terms of related adverse events (AEs) and serious adverse events (SAEs) in both the prophylactic and the OD cohorts
- To assess the immunogenicity of TAK-755 as measured by the incidence of binding and inhibitory antibodies to ADAMTS13 in both the prophylactic and the OD cohorts

Other objectives included assessing PK profile, health-related quality of life evaluations. Exploratory objectives included other PK assessments at the end of study ADAMTS13; level and time of occurrence of acute TTP events; and shifts in biomarkers of organ damage.

Reviewer Comment: *The primary objective and endpoint were evaluated in this review. Patient-report outcome measurements were determined to not be valid or reliable per the clinical outcome assessment review. Please see Section6.1.11.1. Incidence of all other TTP manifestations were descriptive.*

6.1.2 Design Overview

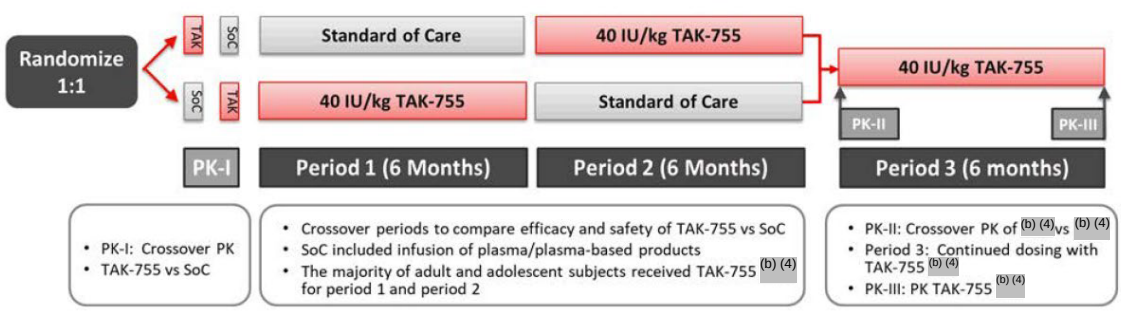
Study 281102 was a Phase 3, prospective, randomized, controlled, open-label, multicenter, 2-period crossover study with a single-arm continuation evaluating the safety and efficacy of TAK-755 in the prophylactic and OD treatment of subjects with severe congenital TTP.

All eligible subjects underwent a minimum washout period of between 5 and 7 days from their last prophylactic infusion, after which further screening procedures were conducted for the determination of eligibility. Subjects who met all eligibility criteria were

randomized equally to one of two prophylactic treatments: TAK-755 or SoC. Prior to beginning the prophylactic treatment in Period 1, subjects first underwent crossover PK assessments in PK-I.

Subjects enrolled in the prophylactic cohort were randomized to receive 6 months of treatment in Period 1 with either TAK-755 or SoC, followed by a further 6 months of treatment in Period 2 with the alternate treatment. The treatment order of either TAK-755 followed by SoC or SoC followed by TAK-755 was randomly assigned.

Figure 1: Prophylactic Cohort Crossover Design



Source: Module 5.3.5.1 Clinical Study Report p. 36/316
Abbreviations: IU=international units, (b) (4) PK=pharmacokinetic, (b) (4), SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13.

Reviewer Comment: *Drug substrate batches from* (b) (4) *and* (b) (4) *were comparable per the CMC review.*

Eligible subjects experiencing an acute TTP event could enter the study through the OD cohort, where they were randomized 1:1 to receive acute treatment with either their current SoC or TAK-755. The OD cohort was observed for approximately 1 month.

OD treatment with TAK-755 during acute TTP events was as follows:

- Subjects received an initial dose of 40 IU/kg [±4 IU/kg] TAK-755
- Subjects received a subsequent dose of 20 IU/kg [±2 IU/kg] TAK-755 on Day 2
- Subjects received an additional daily dose of 15 IU/kg [±1.5 IU/kg] TAK-755 until 2 days after the acute TTP event resolved

Acute TTP events were considered resolved when:

- Platelet count was ≥150,000/µL or platelet count was within 25 percent of baseline
- Elevation of LDH ≤1.5×of baseline or ≤1.5×upper limit of normal (ULN)

Upon resolution of the acute TTP event, subjects could elect to move to the prophylactic cohort, discontinue entirely, or, if eligible, re-enter the OD cohort in case of another acute TTP event.

6.1.3 Population

The subject had to meet ALL the following criteria to be eligible for the study:

- Subject or legally authorized representative provided signed informed consent (≥18 years of age) and/or assent form (signed by legal representative if subject was <18 years of age)
- Subject was 0 to 70 years of age, inclusive, at the time of screening. Subjects <18 years of age were to be enrolled only after at least 5 adults (≥18 years of age) each had at least 10 exposures with TAK-755 and were reviewed by the data monitoring committee
- Subject had a documented diagnosis of severe hereditary ADAMTS13 deficiency, defined as:
  - Confirmation by molecular genetic testing, documented in the subject history or at screening
  - ADAMTS13 activity <10 percent as measured by the (b) (4)-VWF73 assay, documented in subject history or at screening (subjects who were currently receiving SoC prophylactic therapy may have exceeded 10 percent ADAMTS13 activity at screening). Note: Subjects who were receiving prophylactic therapy were to be screened immediately prior to their usual prophylactic infusion
- Subject did not display any severe TTP signs (platelet count <100,000/μL and elevation of LDH >2×ULN) at screening (prophylactic cohort only)
- Subject was 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)
- Subjects ≥16 years of age had a Karnofsky score ≥70 percent and subjects <16 years of age had a Lansky score ≥80 percent
- Subject was hepatitis C virus-negative as confirmed by antibody or polymerase chain reaction testing OR hepatitis C virus-positive if their disease was chronic but stable
- If female of childbearing potential, subject presented with a negative blood or urine pregnancy test, confirmed no more than 7 days before the first administration, and agreed to employ adequate birth control measures for the duration of the study and to undergo quarterly pregnancy testing
- Sexually active males used an accepted and effective method of contraception during the treatment and until a minimum of 16 days after the last dose administered
- Subject was willing and able to comply with the requirements of the protocol

Subjects who met ANY of the following criteria were excluded from the study:

- Subject had been diagnosed with any other TTP-like disorder (MAHA), including acquired TTP
- Subject had a known hypersensitivity to hamster proteins
- Subject had experienced an acute TTP episode less than 30 days prior to screening (prophylactic cohort only)
- Subject had a medical history or presence of a functional ADAMTS13 inhibitor at screening
- Subject had a medical history of genetic or acquired immune deficiency that would interfere with the assessment of product immunogenicity, including

subjects who were human immunodeficiency virus-positive with an absolute cluster of differentiation 4 count <200/mm^3 or who were receiving chronic immunosuppressive drugs
- Subject had been diagnosed with severe cardiovascular disease (New York Heart Association Class 3 to 4)
- Subject had end-stage renal disease requiring chronic dialysis
- Subject had been diagnosed with hepatic dysfunction as evidenced by, but not limited to, any of the following:
  - Serum alanine aminotransferase ≥2×ULN
  - Severe hypoalbuminemia <24 g/L
  - Portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of esophageal varices)
- In the opinion of the investigator, the subject had another clinically significant concomitant disease that may pose additional risks for the subject
- Subject had been treated with an immunomodulatory drug, excluding topical treatment (e.g., ointments, nasal sprays), within 30 days prior to enrollment. Use of corticosteroids in conjunction with administration of FFP to prevent allergic reactions was permitted
- Subject had an acute illness (e.g., influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, bronchial asthma) at the time of screening (prophylactic cohort only)
- Subject was receiving or anticipated receiving another investigational drug and/or interventional drug within 30 days before enrollment
- Subject had a history of drug and/or alcohol abuse within the last 2 years
- Subject had a progressive fatal disease and/or life expectancy of less than 3 months
- Subject was identified by the investigator as being unable or unwilling to cooperate with study procedures
- Subject suffered from a mental condition rendering them unable to understand the nature, scope, and possible consequences of the study and/or evidence of an uncooperative attitude
- Subject was a family member or employee of the Sponsor or investigator
- If female, subject was pregnant or lactating at the time of enrollment
- Any contraindication to SoC medicinal product(s) as per local prescribing information

Reviewer Comment: *The eligibility criteria were reasonable.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Reconstituted intraperitoneal was administered by intravenous (IV) infusion at a slow infusion rate not to exceed 4.0 mL/minute. The doses administered were within the range of 15 to 40 IU/kg.

Subjects received IV infusions of TAK-755 for:

- Prophylactic treatment to prevent acute TTP events
- Treatment for acute TTP events
- Treatment for subacute TTP events
- PK assessments

The following medications were not permitted within 30 days before study entry or during the study:

- Immunomodulatory drugs
- Corticosteroids with an equivalent to hydrocortisone greater than 10 mg/day, excluding topical treatment (e.g., ointments, nasal spray) and except as part of an established premedication regimen during the SoC period of the study or in conjunction with administration of FFP to prevent allergic reactions
- Another intraperitoneal or interventional drug

6.1.5 Directions for Use

For the prophylactic cohort, the study drug was given as an IV infusion of 40 IU/kg every week or every 2 weeks.

For the OD cohort with an acute TTP event, the study drug was given as an IV infusion of 40 IU/kg on Day 1, 20 IU/kg on Day 2, and 15 IU/kg until 2 days after the acute TTP event was resolved.

Reviewer Comment: *The majority of the subjects in the prophylactic cohort were dosed every 2 weeks. Adjustments to dosing frequency were permitted.*

6.1.6 Sites and Centers

Subjects were enrolled in Austria (1), France (9), Germany (6), Italy (1), Japan (5), Poland (9), Spain (6), the United Kingdom (12), and the United States (15).

6.1.7 Surveillance/Monitoring

A data monitoring committee was involved to periodically review the safety data.

6.1.8 Endpoints and Criteria for Study Success

The incidence rate of acute TTP events among subjects receiving either TAK-755 or SoC prophylactically is the primary endpoint of this study.

Efficacy outcome measures were based on assessment of TTP events, defined in Table 3.

Table 3: TTP Event Definitions

	Acute TTP Event	Subacute TTP Event	Isolated TTP Manifestations
Criteria	Both of the following laboratory measures [a]	At least 2 of the following; at least 1 of which must include a laboratory measure [a]	Any of following
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	Drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/µL
Microangiopathic Hemolytic Anemia	Elevation of LDH >2× of baseline or >2×ULN	Elevation of LDH >1.5× of baseline or >1.5×ULN	Elevation of LDH >1.5× of baseline or >1.5×ULN
TTP-related Clinical Signs/Symptoms	Not required to meet criteria but to be recorded if observed	Organ-specific signs and symptoms, including but not limited to: Renal signs, as defined by increase of serum creatinine >1.5×baseline Neurological symptoms (eg, headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures) Fever (≥100.4°F/38°C) Fatigue/lethargy Abdominal pain	Organ-specific signs and symptoms, including but not limited to: Renal signs, as defined by increase of serum creatinine >1.5×baseline Neurological symptoms (eg, headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures) Fever (≥100.4°F/38°C) Fatigue/lethargy Abdominal pain

Source: BLA 125795/0 Module 5.3.5.1 Clinical Study Report Table 8, p. 63/316
a. In this instance, a laboratory measure refers to platelet counts or an LDH measurement.
Abbreviations: LDH=lactate dehydrogenase, TTP=thrombotic thrombocytopenia purpura, ULN=upper limit of normal.

Reviewer Comment: *In the July 2021 Type C Meeting, there was concern regarding the subacute events being included with the primary efficacy endpoint. FDA stated that since the TTP-related clinical signs/symptoms are subjective, we would not agree to include them as part of the primary endpoint. For example, a subject with a seizure has much more severe clinical symptoms than a subject with a headache yet they would be evaluated equally as a subacute event. It was agreed that only the acute TTP events could be used to evaluate the efficacy as the primary endpoint. No formal agreement was made on the subacute event category.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

An interim analysis was performed after 30 adult or adolescent subjects in the prophylactic treatment group completed the study.

The full analysis set (FAS) included all subjects with a confirmed congenital TTP diagnosis who received at least one dose of TAK-755 or SoC treatment after randomization. Subjects were included in the data group to which they were randomized.

Summary statistics related to acute TTP events were presented by period, by treatment, and in total for the following endpoints:

1. Number of subjects with acute TTP events
2. Total number of acute TTP events
3. Duration of the observation period for efficacy (*x* in years), to calculate the annualized acute TTP event rate
4. Annualized acute TTP event rate

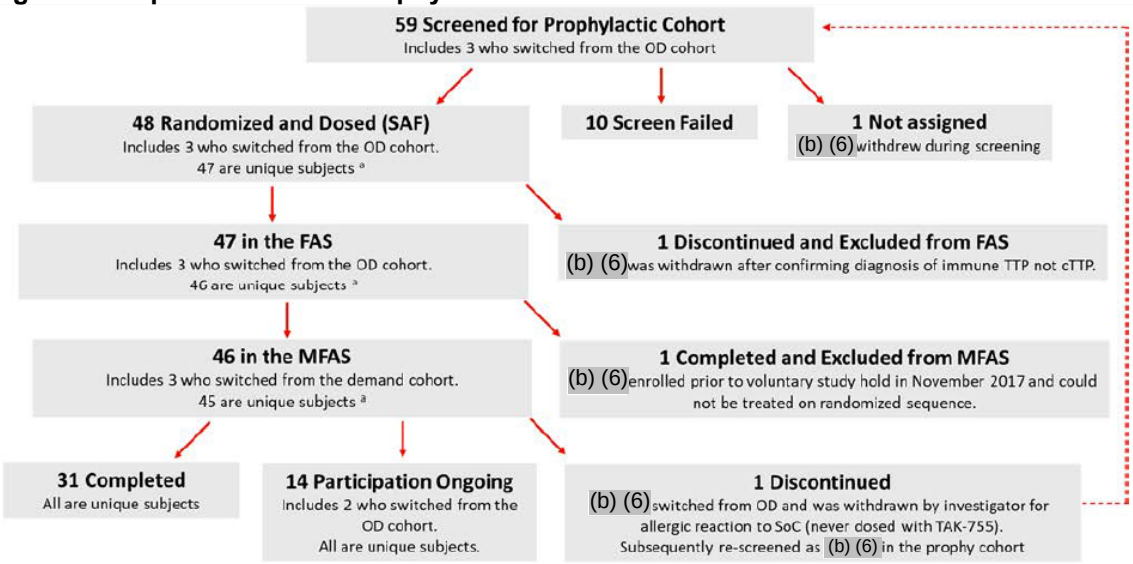
6.1.10 Study Population and Disposition

A total of 64 subjects (including adult, adolescent, and pediatric subjects) were enrolled (signed informed consent) in the prophylactic cohort or the OD cohort and screened. Ten subjects were screen failures.

One subject (Subject (b) (6)) completed treatment in the OD cohort and moved to the prophylactic cohort; this subject then discontinued the study from the prophylactic cohort due to the principal investigator's decision following an allergic reaction to the SoC treatment. Note: This subject is counted as discontinuing the study in both the OD and prophylactic cohorts. This same subject later reenrolled in the study in the prophylactic cohort, receiving different SoC (factor VIII instead of solvent/detergent-treated plasma), and was assigned a new subject number (Subject (b) (6)).

One additional subject was enrolled twice in the study, as allowed per protocol. Subject (b) (6) was enrolled in the OD cohort and completed the study with a completion visit. This subject then reenrolled in the OD cohort and received a new subject number (Subject (b) (6)); following completion of OD treatment, Subject (b) (6) moved to the prophylactic cohort and is still on-study.

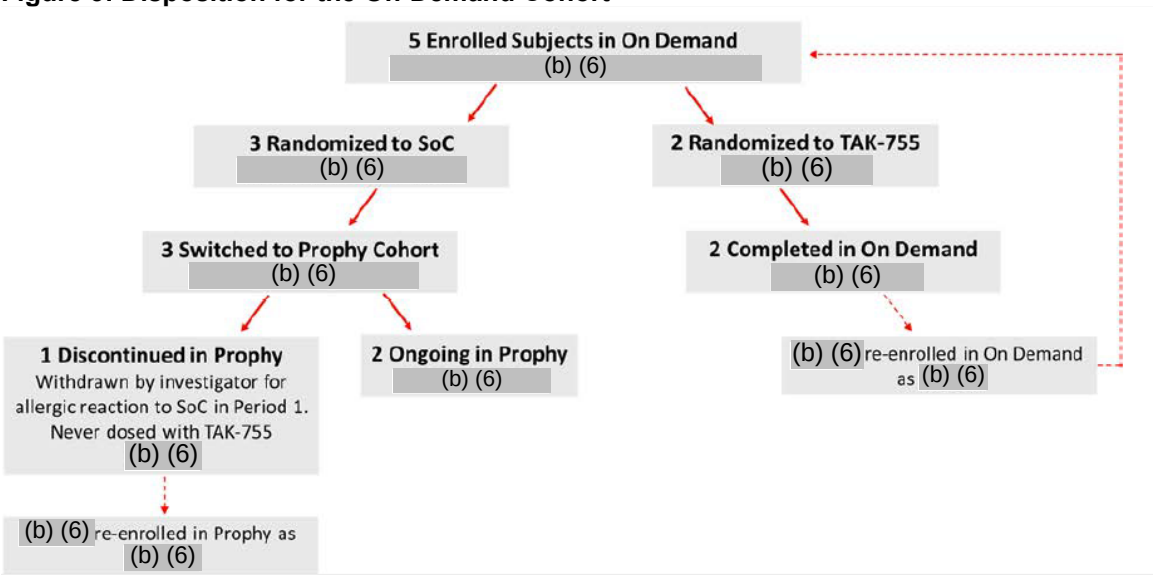
Figure 2: Disposition for the Prophylactic Cohort



Source: BLA 125795/0 Module 5.3.5.1 Clinical Study Report Figure 2, p. 116/316
Abbreviations: cTTP=congenital thrombotic thrombocytopenic purpura, FAS=full analysis set, MFAS=modified full analysis set, OD=on-demand, SAF=safety analysis set, SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13, TTP=thrombocytopenic purpura.

As of the interim analysis data cutoff date, a total of 46 unique subjects completed Period 1, and 42 unique subjects completed Period 2. Three unique subjects (281102-(b) (6), 281102-(b) (6), 281102-(b) (6)) were initially randomized and enrolled into the OD cohort and later moved to the prophylactic cohort after completion of OD cohort treatment. One unique subject (281102-(b) (6)) was rerandomized and enrolled under Subject ID (b) (6) in the prophylactic cohort.

Figure 3: Disposition for the On-Demand Cohort



Source: BLA 125795/0 Module 5.3.5.1 Clinical Study Report Figure 3, p. 117/316
Abbreviations: SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13.

Reviewer Comment: *The OD cohort will not be used for the primary efficacy analysis as this was not defined in the primary efficacy endpoint.*

6.1.10.1 Populations Enrolled/Analyzed

The FAS included all subjects with a confirmed congenital TTP diagnosis who received at least one dose of TAK-755 or SoC treatment after randomization. Subjects were included in the data group to which they were randomized.

The modified FAS included all subjects who were included in the FAS with the following modifications:

- For subjects enrolled prior to the study hold in November 2017: If TAK-755 was the randomized treatment for Period 1 and subjects were instead treated on SoC because TAK-755 was not available, the subjects were excluded from modified FAS.
- For subjects enrolled prior to the study hold in November 2017: If SoC was the randomized treatment for Period 1 and subjects were treated on SoC beyond the 6-month period specified in the protocol because TAK-755 was not available, only the efficacy data for Period 1 collected prior to the Month 6 visit was used in the modified FAS-based efficacy analysis. The period over which the endpoint was evaluated was between the first dose date and the date of the Month 6 visit for Period 1. Data in Period 2 and beyond was also included in the modified FAS-based efficacy analyses.

6.1.10.1.1 Demographics

Overall, there were 48 unique subjects with a median age of 31 years. There were 12 subjects in the pediatric age range (4 less than 6 years of age; 4 subjects 6 to 12 years and 4 subjects 12 to 18 years).

There were 19 male and 29 female subjects in the prophylactic cohort. There were 22 females who were of childbearing potential. Most adult subjects were white and not Hispanic or Latino.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of subjects in both the prophylactic (47 subjects, 97.9 percent) and OD cohorts (4 subjects, 80.0 percent) had received a prior treatment for congenital TTP, which was primarily FFP (33 subjects [68.8 percent] and 2 subjects [40.0 percent], respectively). Mean (SD) reported ADAMTS13 activity levels prior to enrollment were 3.49 percent (2.76 percent) and 2.72 percent (2.207 percent) in the prophylactic and OD cohorts, respectively.

There were eight subjects in the prophylactic cohort who had a history of acute TTP events in the past 12 months. There was one subject in the OD cohort who had an acute TTP event in the past 12 months.

One site administered expired product to one subject. No safety concerns were reported. One subject was incorrectly diagnosed with congenital TTP and withdrawn when it was determined subject had immune TTP. One subject moved from the OD cohort to the prophylactic cohort with a confirmed acute event.

6.1.10.1.3 Subject Disposition

See above.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint evaluated the incidence of acute TTP events among subjects receiving either TAK-755 or SoC prophylactically during the corresponding treatment periods.

Table 4 summarizes the suspected and treated acute TTP events in the prophylactic and OD cohorts.

Table 4: Suspected and Treated Acute TTP Events, Prophylactic and On-Demand Cohorts

Subject ID	Cohort/ Period at Event	Treatment at Event	Start/End Date	Results at Event Start		Met Protocol Definition of Acute Event?	Results at Event End Date	
				Platelets (10^9/L)[b]	LDH (U/L)[b]		Platelets (10^9/L)[b]	LDH (U/L)[b]
(b) (6)	Prophylactic/ Period 1	SoC (FFP Q2W)	20Apr2020/ 05May2020	104 (56.5% decrease from baseline)	454 (2.41 × baseline)	YES	279 [c]	194 (1.03× baseline) [c]
	OD	TAK-755	24Jun2022/ 29Jun2022	84	236 (1.10×ULN)	NO	270 [c]	205 (0.96× ULN) [c]
	OD	TAK-755	11Aug2021/ 14Aug2021	24 [a]	598 (2.43×ULN) [a]	YES	155 [c]	278 (1.13× ULN) [c]
	OD	SoC (FFP)	05Nov2021/ 07Nov2021	23 [a]	685 (2.78×ULN) [a]	YES	62	320 (1.30× ULN)
		SoC (FFP)	13Dec2021/ 15Dec2021 [d]	23	652 (2.65×ULN)	NO	101	323 (1.31× ULN)
	OD	SoC (S/D treated plasma)	20Oct2017/ 25Oct2017	20	458 (2.04×ULN)	NO	276 [c]	263 (1.17× ULN) [c]
	OD	SoC (S/D treated plasma)	29Nov2021/ 03Dec2021	65	211 (1.06×ULN)	NO	150 [e]	187 (0.94× ULN)

Source: BLA 125795/0 Module 5.3.5.1 Clinical Study Report Table 22, p. 147/316
a. Events confirmed by the central lab to meet protocol acute TTP event criteria.
b. Local lab results are presented. Additional lab results are provided in the subject narratives (section 14.3.3).
c. The lab results at the event end date met protocol definition of resolved event: (a) platelet count was >150,000/μL or platelet count was within 25 percent of baseline, whichever occurred first, and (b) elevation of LDH <1.5×baseline or <1.5×ULN.
d. Second acute event occurred during OD cohort and was not included in time to resolution endpoint analysis.
e. Subject (b) (6) did not meet protocol-defined criteria of resolved event because the platelet result was not confirmed by central lab (137×109/L).
Abbreviations: FFP=fresh frozen plasma, LDH=lactate dehydrogenase, OD=on-demand, Q2W=every two weeks, S/D=solvent/detergent, SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13, TTP=thrombotic thrombocytopenic purpura, ULN=upper limit of normal.

Prophylactic Cohort

An acute TTP event responding to TAK-755 is defined as a resolved event not requiring the use of another ADAMTS13-containing agent for its resolution. Acute TTP events were considered resolved when: (a) platelet count was ≥150,000/μL or platelet count was within 25 percent of baseline, whichever occurred first, and (b) elevation of LDH ≤1.5×baseline or ≤1.5×ULN. The time to resolution analysis is based on the investigator reporting a specific date of event resolution.

One acute TTP event occurred in one subject (Subject (b) (6)) while receiving SoC prophylactically during treatment Period 1 with a protocol-defined drop in platelet count, which was a >50 percent drop from baseline, and an LDH that was elevated >2-fold from baseline.

The acute TTP event in the prophylactic cohort duration was 15 days and met the definitions above for resolution.

Reviewer Comment: *Subject (b) (6)'s acute event was likely due to the viral infection based on the subject narrative.*

Subject (b) (6) *'s acute event was noted as resolved on Day 15 but they had no visits from Day 3 to Day 15, so it is unclear on which day this subject met the protocol definitions of resolution. The subject's observation period in this trial was less than a year.*

The subject's baseline ADAMTS13 level was below the limit of quantification (BLQ) on study Day 1, and the preinfusion ADAMTS13 level was not collected and noted as a major protocol deviation. Prior to the supplemental dose of SoC, the blood sample for testing was hemolyzed and no ADAMTS13 level was captured. This subject was infused with 10 mL/kg of FFP.

No acute TTP events occurred in 37 adult or adolescent subjects while receiving TAK-755 prophylaxis during the crossover treatment period and throughout the duration of the study, including in 35 subjects in Period 3 at the time of interim analysis data cutoff.

Due to the minimal events captured, only descriptive statistics on acute event rates are reported. The mean annualized acute TTP event rate was 0.05 among adult and adolescent subjects while receiving SoC, and 0 among subjects while receiving TAK-755 prophylaxis during the crossover periods and Period 3.

The longest duration of TAK-755 exposure was 22.6 months.

Reviewer Comment: *It is difficult to make a meaningful conclusion based on the one event that occurred in the SoC arm. However, based on the sparse ADAMTS13 levels collected and the PK data captured, there is a rise in ADAMTS13 level post administration of drug product, as expected, with subsequent resolution in both thrombocytopenia and increased LDH levels.*

On-Demand Cohort

A total of five subjects were enrolled in the OD cohort. Two of those subjects were randomized to receive TAK-755 treatment. During the OD period, there were six acute TTP events that occurred in five subjects. Two of those events occurred while subjects were treated with TAK-755. The remaining four events occurred while subjects were treated with SoC. One subject with an acute TTP event was treated with TAK-755 in the OD cohort; this was confirmed to meet the protocol definition of an acute event.

A description of the events for each subject is provided:

Subject (b) (6)

This subject's baseline ADAMTS13 level was 0.075 IU/mL. The subject received 40 IU/kg of the TAK-755, and the postinfusion ADAMTS13 level was 1.41 IU/mL. The following day, 20 IU/kg was administered. The preinfusion ADAMTS13 was 0.82 IU/mL with an increase in platelet count from 84 to 110×10^9/L and LDH decrease from 236 U/L to 214 U/L. Postinfusion ADAMTS13 was 1.42 IU/mL. For the next 4 days, the subject received 15 IU/kg of TAK-755 with increase in postinfusion ADAMTS13 level and platelet count of 270 K and LDH of 205.

Subject (b) (6)

This subject's baseline ADAMTS13 level was BLQ. The subject received 40 IU/kg of the TAK-755, and the postinfusion ADAMTS13 level was 0.87 IU/mL. The following day,

20 IU/kg was administered. The preinfusion ADAMTS13 was 0.51 IU/mL with an increase in platelet count from 24 to 47×109/L and LDH decrease from 598 U/L to 379 U/L.

Postinfusion ADAMTS13 was 0.83 IU/mL. For the next 2 days, the subject received 15 IU/kg of TAK-755 with an increase in postinfusion ADAMTS13 level and platelet count of 155 K and LDH of 278.

Subject (b) (6)

This subject's baseline ADAMTS13 level was BLQ. The subject received 1320 mL FFP, and the postinfusion ADAMTS13 level was 0.24 IU/mL. The following day, 990 mL of FFP was administered. The preinfusion ADAMTS13 was 0.26 IU/mL with a minimal increase in platelet count from 23 to 29×109/L and LDH decrease from 685 U/L to 463 U/L. Postinfusion ADAMTS13 was 0.48 IU/mL. The subject received another 990 mL of FFP with an increase in postinfusion ADAMTS13 level and platelet count of 102 K and LDH of 288.

ADAMTS13 level was performed 24 days post the last FFP infusion, which showed ADAMTS13 level at BLQ. Another event occurred 12 days later. ADAMTS13 levels were not captured during that event. However, the platelet count and LDH recovered on the event end date (at Day 2).

Subject (b) (6)

This subject's baseline ADAMTS13 level was 0.12 IU/mL. This Subject received 800 mL of plasma, and the postinfusion ADAMTS13 level was 0.22 IU/mL. The following day, 800 mL of plasma was administered. The preinfusion ADAMTS13 was 0.27 IU/mL with a minimal increase in platelet count from 20 to 35×10^9/L and LDH decrease from 458 U/L to 32 3U/L. Postinfusion ADAMTS13 was 0.39 IU/mL. The subject received another 800 mL of plasma with an increase in postinfusion ADAMTS13 level and platelet count of 120 K and LDH of 318. Three days postinfusion and the end of the event, the platelet count was 276 K and LDH was 263.

Subject (b) (6)

This subject's baseline ADAMTS13 level was BLQ. Subject received 400 mL of plasma, and the postinfusion ADAMTS13 level was 0.08 IU/mL. The following day, 420 mL of plasma was administered. The preinfusion ADAMTS13 was 0.12 IU/mL with a minimal increase in platelet count from 65 to 80×10^9/L and LDH decrease from 211 U/L to 201 U/L. Postinfusion ADAMTS13 was 0.27 IU/mL. The subject received another 400 mL of plasma for 2 more days with an increase in postinfusion ADAMTS13 level. The platelet count and LDH were not captured on the event end date.

Reviewer Comment: *Of the six acute TTP events in the OD cohort, four events were captured as not meeting the protocol definition of the event but were still treated.*

Based on Table 4, it is unclear why Subject (b) (6) *and the second event for Subject* (b) (6) *did not meet the protocol definition of an acute event, as the platelet count is below 50 K and the LDH rose to above 2×ULN. These should be re-adjudicated to meet the definition of an acute event.*

There was one event treated with TAK-755. This subject who was receiving treatment with TAK-755 responded to treatment with TAK-755 during the acute TTP event and the day to resolution was 3 days, which was similar to the other 4 events treated with SoC.

ADAMTS13 Levels

Of note, postinfusion ADAMTS13 levels were collected minutes post infusion during scheduled prophylactic infusion visits in the prophylactic study periods (Periods 1, 2, and 3) for subjects who consented to Protocol Amendment (PA) 9 (dated March 6, 2020) or later. Note that postinfusion samples were not taken more frequently than every 2 weeks for subjects with weekly dosing. Subjects consenting under versions of the protocol prior to PA 9 were required to have postinfusion ADAMTS13 levels collected every 12 weeks but not at every scheduled prophylactic infusion visit.

A total of 24 subjects consented prior to PA 9 to at least a portion of 1 of the prophylactic study periods. Of those, 14 subjects consented to PA 9 during Period 1, 8 during Period 2, and 2 during Period 3. All subjects had at least one postinfusion sample except for two subjects (Subjects (b) (6) and (b) (6)).

Reviewer Comment: *Although the PK data shows increase in ADAMTS13 levels post infusion, it appears this data is missing from many of the subjects who received the study drug while on the randomized portion of the trial. This lack of robust data was discussed with the Applicant numerous times pre-BLA and during the review cycle.*

6.1.11.2 Analyses of Secondary Endpoint(s)

Subacute Events

There were five subacute events in four subjects which occurred in the SoC cohort. There were two subacute events in two subjects during Period 3 while receiving TAK-755.

For the subacute events that occurred during Period 1/Period 2 with SoC, there were three events that received a supplemental dose of SoC. One subject received a supplemental dose of SoC and then switched to receive TAK-755 to treat the subacute TTP event. One subject had four supplemental doses during Period 3 to treat a subacute event.

From the two subjects who had a subacute event during Period 3 (receiving TAK-755), only one subject had a supplemental dose. This subject scheduled to receive TAK-755 was delayed and a subacute TTP event occurred and received SoC (due to admission at a nonstudy site). Upon transferring to a clinical site, the subject received TAK-755.

Isolated TTP Events

The incidence of isolated TTP manifestations was captured for the two groups (SoC versus TAK-755) based on the manifestation.

Refer to Table 3 TTP Event Definitions for definitions of isolated TTP manifestations.

There were 19 subjects of 38 subjects who experienced 75 thrombocytopenia manifestations while receiving SoC, and 9 subjects of 37 subjects with a total of 30 thrombocytopenia manifestations while receiving TAK-755.

There were 11 of 38 subjects who experienced 20 events of MAHA while receiving SoC, and 5 of 37 subjects with a total of 7 MAHA events while receiving TAK-755.

There were 7 of 38 subjects who experienced 29 neurological events while receiving SoC, and 4 of 37 subjects with a total of 18 neurological events while receiving TAK-755. The most common neurological events were headache or migraine. Others also reported lethargy or dizziness. There were no reports of seizure.

There were 2 of 38 subjects who experienced 5 renal dysfunction manifestations events while receiving SoC, and 3 of 37 subjects with a total of 8 renal dysfunction manifestations events while receiving TAK-755.

There were 5 of 38 subjects who experienced 7 manifestations while receiving SoC, and 2 of 37 subjects with a total of 4 abdominal pain manifestations while receiving TAK-755.

There were 14 of 38 subjects who experienced 24 other TTP manifestations while receiving SoC, and 6 of 37 subjects with a total of 9 other TTP manifestations while receiving TAK-755.

There were lower annualized event rates of TTP manifestations in the TAK-755 treatment arm compared to the SoC in Period 1 and 2, with the exception of renal dysfunction.

Table 5: Annualized Event Rates of TTP Manifestations, TAK-755 Treatment Arm Versus SoC (Age ≥12 Years)

Event	SoC	TAK-755	
	Period 1 and 2 (N=38)	Period 1 and 2 (N=37)	Period 3 (N=35)
Thrombocytopenia events			
Number of subjects with event (number of events)	19 (75)	9 (30)	9 (16)
Mean annualized event rate (SD)	4.10 (5.806)	1.84 (4.329)	1.44 (4.501)
Microangiopathic hemolytic anemia events			
Number of subjects with event (number of events)	11 (20)	5 (7)	11 (11)
Mean annualized event rate (SD)	1.36 (3.019)	0.35 (0.946)	0.53 (0.829)
Renal dysfunction events			
Number of subjects with event (number of events)	2 (5)	3 (8)	1 (3)
Mean annualized event rate (SD)	0.25 (1.094)	0.41 (1.551)	0.06 (0.378)
Neurological symptoms events			
Number of subjects with event (number of events)	7 (29)	4 (18)	8 (23)
Mean annualized event rate (SD)	1.35 (4.483)	0.88 (3.214)	1.06 (2.587)
Abdominal Pain events			
Number of subjects with event (number of events)	5 (7)	2 (4)	2 (4)
Mean annualized event rate (SD)	0.34 (0.940)	0.20 (0.832)	0.22 (1.069)
Other TTP manifestations [a]			
Number of subjects with event (number of events)	14 (24)	6 (9)	4 (9)
Mean annualized event rate (SD)	1.17 (2.030)	0.45 (1.175)	0.36 (1.395)

Source: BLA 125795/0 Module 5.3.5.1 Clinical Study Report Table 25, p. 157/316
Abbreviations: N=number of subjects in the specified group or the total sample, SD=standard deviation, SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13 TTP=thrombocytopenic purpura.

a- See Reviewer Comment below

Reviewer Comment: *TTP manifestations included a decrease in platelet count that did not meet the protocol-specified definition of "thrombocytopenia manifestation" and did not meet the definition of an acute or subacute event. "Other" TTP manifestations terms included hematoma, fatigue, nausea, epistaxis, and pyrexia.*

For all these TTP manifestations, the observed rates wer low and based on sparse events reported during the trial. There is no certainty that any of these events could be attributed to an upcoming acute TTP event or subacute event given the nonspecific nature of when collected, and there were marginal differences compared to baseline labs. For the other clinical manifestations, these endpoints do not appear to be clinically relevant, and therefore it is difficult to compare the rate in the TTP arm versus the SoC arm and make a meaningful conclusion. The clinical significance of the observed difference is unknown.

For the increased rate of renal dysfunction, these events were marginal increases above the threshold of 1.5×baseline serum creatinine, and most of the values were still below the upper limits of normal. There were no trends with a consistent increase in serum creatinine.

Of all the TTP manifestations collected, it was decided that the label would include only the TTP manifestations of thrombocytopenia and MAHA (LDH levels), as those may be relevant to the treating physician (platelet level and LDH levels). In the study, these events did not trigger administration of TAK-755.

6.1.11.4 Dropouts and/or Discontinuations

See Section 6.1.10 Disposition.

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory endpoints were not analyzed as part of this review, as the endpoint of composite TTP manifestations was limited to the first 6 months of treatment periods.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety measures for the study included:

1. Incidence of product-related and unrelated AEs and SAEs during each treatment period
2. Incidence of binding and inhibitory antibodies to ADAMTS13
3. Clinically relevant changes in vital signs, clinical chemistry, and hematology
4. Estimated total quantity of ADAMTS13 administered during the treatment of acute TTP events

Duration of Exposure

There were 49 subjects exposed to the study drug for up to 22.6 months with a mean exposure of 11.5 months. Duration of exposure varied by age group. Subjects less than 6 years of age had the lowest exposure with a mean of 1 month, followed by subjects 6 to 12 years of age with a mean exposure of 3.9 months.

In the prophylactic cohort, 47 subjects received a mean of 30 infusions of the study drug.

6.1.12.2 Overview of Adverse Events

In the treatment Periods 1 and 2, 33 out of 45 subjects (73.3 percent) experienced 229 TEAEs while receiving TAK-755, and 37 out of 44 subjects (84.1 percent) experienced 278 TEAEs while receiving SoC.

Table 6 is based on the Adverse Event Analysis Data Sets submitted to the BLA.

Table 6: Adverse Events by System Organ Class During Prophylaxis

System Organ Class	SoC Period 1 and 2 (N=44)	TAK-755 Period 1 and 2 (N=45)	TAK-755 Period 3 (N=36)
Any AE	37 (84.1)	33 (73.3)	26 (72.2)
Blood and lymphatic system disorders	6 (13.6)	4 (8.9)	4 (11.1)
Cardiac disorders	3 (6.8)	1 (2.2)	0 (0)
Congenital, familial, and genetic disorders	0 (0)	0 (0)	1 (2.8)
Ear and labyrinth disorders	0 (0)	2 (4.4)	1 (2.8)
Endocrine disorders	1 (2.3)	0 (0)	0 (0)
Eye disorders	3 (6.8)	3 (6.7)	1 (2.8)
Gastrointestinal disorders	11 (25)	12 (26.7)	12 (33.3)
General disorders and administration site conditions	14 (31.8)	7 (15.6)	7 (19.4)
Immune system disorders	6 (13.6)	3 (6.7)	1 (2.8)
Infections and infestations	15 (34.1)	19 (42.2)	16 (44.4)
Injury, poisoning, and procedural complications	7 (15.9)	3 (6.7)	2 (5.6)
Investigations	7 (15.9)	4 (8.9)	1 (2.8)
Metabolism and nutrition disorders	5 (11.4)	5 (11.1)	2 (5.6)
Musculoskeletal and connective tissue disorders	10 (22.7)	5 (11.1)	1 (2.8)
Nervous system disorders	13 (29.5)	14 (31.1)	12 (33.3)
Psychiatric disorders	3 (6.8)	3 (6.7)	0 (0)
Renal and urinary disorders	2 (4.5)	1 (2.2)	0 (0)
Reproductive system and breast disorders	2 (4.5)	3 (6.7)	3 (8.3)
Respiratory, thoracic, and mediastinal disorders	9 (20.5)	8 (17.8)	7 (19.4)
Skin and subcutaneous tissue disorders	12 (27.3)	5 (11.1)	6 (16.7)
Vascular disorders	4 (9.1)	6 (13.3)	2 (5.6)

Source: FDA Analysis based on Adverse Event Analysis dataset
Abbreviations: AE=adverse event, N, number of subjects in the specified group or the total sample, SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13.

Reviewer Comment: *There were an additional two subjects for TAK-755 included in the label, as these subjects had transitioned to the prophylactic cohort from the OD group.*

The OD cohort of five subjects had similar AEs, and all AEs were in subjects who received SoC. No AE was reported in the OD TAK-755 group.

Based on the FDA analysis with preferred terms during Period and Period 2 and the OD period, and for those events over 5%- the most common adverse reactions included headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, vomiting.

Reviewer Comment: *The selection of ARs for the label in Table 2 is based on the listing of treatment-emergent AE-s occurring more than 5% in the Study 281102 controlled comparison Period 1 and Period 2 and OD period. The rate of identified adverse reactions was derived from all reported adverse events of the selected ARs in Study 281102 overall period (N=48; 47 unique subjects from the prophy group and 1 unique*

subject from on demand group). As a result, all ARs reported over 5% were included in the PI.

6.1.12.3 Deaths

There were no deaths during the trial.

6.1.12.4 Nonfatal Serious Adverse Events

There were seven subjects in the SoC group who had an SAE. These SAEs included thrombocytopenia, abdominal pain, pyrexia, and headache. There was one subject who had an SAE while receiving TAK-755.

6.1.12.5 Adverse Events of Special Interest

All hypersensitivity reactions occurred in the SoC cohort.

All subjects were tested for total binding antibodies to ADAMTS13. If the total binding (total Ig) antibodies to ADAMTS13 were positive, the presence and levels of neutralizing (activity inhibition) antibodies to both plasma-derived ADAMTS13 and TAK-755 were tested.

Anti-TAK-755-binding antibodies were detected in two subjects in the prophylactic cohort. One subject had low titer positive results at baseline, but no increase in titer was observed during the study. The second subject was positive for anti-TAK-755-binding and neutralizing antibodies on study Day 309. This subject discontinued, as it was determined this subject had acquired/immune TTP.

Two additional subjects had transient, low titer anti-CHO antibodies at a single time point with subsequent negative anti-CHO antibody results.

Reviewer Comment: *It is unclear why a subject would have antidrug antibodies prior to treatment. It is reassuring that these antibodies were noted to be transient and did not have a clinical effect.*

There was no clinical sequalae identified with the subjects who had low titer anti-CHO antibodies. These antibodies were also noted to be transient.

Of note, there were no subjects on this trial that were naïve to plasma products or were previously untreated patients. Therefore, there is no data on immunogenicity for this patient population. It is unknown whether neutralizing antibodies will develop in naïve subjects. The ongoing trial has inclusion of subjects who are minimally treated or previously untreated where immunogenicity data should be captured.

6.1.12.6 Clinical Test Results

There were no clinically meaningful trends over time in laboratory parameters (other than congenital TTP-related laboratory assessments) and no clinically significant abnormalities in clinical laboratory parameters considered related to TAK-755. There were no clear differences between the prophylactic TAK-755 and SoC groups in crossover Periods 1 and 2 in shift patterns for any parameter, nor any obvious trends in shifts with extended duration of prophylactic TAK-755 treatment in Period 3.

6.1.12.7 Dropouts and/or Discontinuations

There were no AEs that led to discontinuation from the study.

6.1.13 Study Summary and Conclusions

The results from the interim analysis demonstrated a clinically meaningful benefit in reduction of acute TTP events and demonstrated efficacy with OD treatment of acute TTP events in children and adults with congenital TTP. This product provides an alternative option for subjects with reduced volume and reduced time in dosing.

The most commonly reported adverse reactions included diarrhea, migraine, upper respiratory tract infection, dizziness, and nausea. There were transient neutralizing and non-neutralizing antibodies reported without clinical sequelae. There were no hypersensitivity reactions in the TAK-755 cohort.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

Efficacy evaluation was primarily based on the Study 281102. Therefore, an integrated summary of efficacy was not conducted.

7.1.2 Demographics and Baseline Characteristics

See Section 1.1.

7.1.3 Subject Disposition

See Section 6.1.10.

7.1.4 Analysis of Primary Endpoint(s)

As above.

7.1.5 Analysis of Secondary Endpoint(s)

As above.

8. INTEGRATED OVERVIEW OF SAFETY

Safety evaluation was primarily based on the Study 281102. Therefore, an integrated summary of efficacy was not conducted. Additional safety data was reviewed from the ongoing Study 3002, which was consistent with Study 281102. This data was not included in the label at this time. Updated safety will be included after completion of both trials and review of the safety data.

8.4 Safety Results

8.4.1 Deaths

There were no deaths during this study.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable; each subject received the same dose of TAK-755.

8.5.8 Immunogenicity (Safety)

Please see Section 6.1.12.5, which discusses immunogenicity.

In the ongoing extension study, there were an additional 12 subjects that tested positive for low-titer binding antibodies to the drug product.

Reviewer Comment: *The clinical significance of non-neutralizing binding antibodies is unclear.*

Of note, plasma-product-naïve subjects were not included on this trial; therefore there is no immunogenicity data for these subjects. It is unknown if these subjects will develop neutralizing antibodies.

8.6 Safety Conclusions

No additional safety concerns arose from evaluation of the continuation safety and 120-day safety update report.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There were four congenital TTP subjects exposed to the study drug during pregnancy.

Two subjects in a long-term extension study were found to be pregnant early in the first trimester while receiving prophylaxis. Both subjects were discontinued from the study to comply with the protocol requirements.

The first subject had no further exposure and had a first trimester miscarriage approximately two months after study discontinuation. This was assessed as unrelated to the study drug.

The second subject resumed treatment under a compassionate use program and delivered a healthy full-term baby with no safety concerns reported by the investigator.

Two additional cTTP subjects were treated in a compassionate use program during pregnancy. The first subject, in the third trimester of her second pregnancy, experienced a stroke and thrombocytopenia that was refractory to daily plasmapheresis. At 33 weeks of gestation, treatment was started once weekly. ADAMTS13 activity levels normalized,

thrombocytopenia resolved, and a healthy baby was delivered at 37 weeks with no safety concerns reported by the treating physician.

The second subject had an exacerbation of her congenital TTP during her second trimester of pregnancy despite prior daily plasma exchange. Her pregnancy was considered to be at risk, with inadequate response to plasma-based therapies. The study drug was started once weekly and induced clinical remission. The baby was delivered by a cesarean section at week 29 and the treating physician reported no adverse events.

9.1.2 Use During Lactation

No data exist on the effects of TAK-755 on lactation in a controlled setting.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

This application is exempt from the Pediatric Research Equity Act because it is intended for a biologic product for which orphan designation has been granted. This product was evaluated in 12 pediatric subjects.

Reviewer Comment: Although there were only 12 pediatric subjects in this study, the etiology of congenital TTP and the treatment is the same for pediatric subjects. Based on the adult efficacy data in the clinical study and PK data, efficacy could be extrapolated to pediatrics.

10. CONCLUSIONS

The results from the interim analysis demonstrated a clinically meaningful benefit in reduction of acute TTP events and demonstrated efficacy with OD treatment of acute TTP events in children and adults with congenital TTP. This product provides an alternative option for subjects with reduced volume and reduced time in dosing.

The most commonly reported adverse reactions included diarrhea, migraine, upper respiratory tract infection, dizziness, and nausea.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table 7.

Table 7: Risk-Benefit Considerations and Recommendations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Congenital TTP is an ultra-rare, life-threatening thrombotic disorder of the microcirculation caused by a severe deficiency of ADAMTS13. This deficiency leads to accumulation of ultralarge von Willebrand factor (VWF) multimers with high platelet binding activity, which can result in spontaneous formation of widespread VWF-platelet-rich microthrombi and ischemic damage to multiple organs.	• Congenital TTP is a serious, life-threatening disease. • Congenital TTP can have a debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• Available treatment options require lifelong infusion and include SoC with FFP/Plasma. These products carry a potential risk of transmission of infection and can cause hypersensitivity. • Currently, there are no licensed products for congenital TTP.	• There is an unmet need for the lifelong requirement for plasma replacement infusions in patients with congenital TTP
Clinical Benefit	• The interim analysis of the clinical trial was submitted to evaluate the safety and effectiveness of rADAMTS13 in addition to the preclinical trials and PK investigation. • The efficacy was demonstrated for the treatment of congenital TTP. • TAK-755 was effective in increasing ADAMTS13 levels and increasing platelet levels and decreasing markers of macroangiopathic hemolytic anemia (LDH).	• The evidence for clinical benefit was demonstrated by increase in ADMATS13 levels in the PK data.
Risk	• The most common adverse reactions with TAK-755 were headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, vomiting. • In the clinical trial, no previously treated patient developed neutralizing antibodies. • No Grade 3 or higher hypersensitivity reactions were reported after treatment with TAK-755.	• TAK-755 has an acceptable safety profile, and the risks are addressed in the package insert.
Risk Management	• Risk management plans include adequate labeling in the warnings and precautions and common adverse events listed in the PI. • There is an unknown risk of immunogenicity in previously untreated patients.	• The package insert and routine pharmacovigilance activities are adequate to manage risk. • The unknown risk of immunogenicity in previously untreated patients will be further studied in the continuation study.

Abbreviations: ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13, FFP=fresh frozen plasma, LDH=lactate dehydrogenase, PI=package insert, PK=pharmacokinetic, rADAMTS13=recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13, SoC=standard of care, TAK-755=rADAMTS13, recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13, TEAE=treatment-emergent adverse events, TTP=thrombocytopenic purpura.

11.2 Risk-Benefit Summary and Assessment

The benefits of TAK-755 include:

- OD TAK-755 is effective for treatment of therapy in patients with congenital TTP
- TAK-755 demonstrated clinical benefit for prevention of acute TTP events

The risks of TAK-755 include:

- Potential hypersensitivity reactions
- Potential risk of immunogenicity

The results from the interim analysis demonstrated a clinically meaningful benefit in reduction of acute TTP events and demonstrated efficacy with OD treatment of acute TTP events in children and adults with congenital TTP. This product provides an alternative option for subjects with reduced volume and reduced time in dosing.

The most commonly reported adverse reactions included headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, vomiting.

The Applicant has provided substantial evidence of effectiveness and safety based on a single well-controlled clinical investigation providing evidence of clinical benefit, supported by the PK studies and preclinical studies. The overall benefit-risk profile favors approval of TAK-755 for use in adults and children with congenital TTP for prophylactic or OD enzyme replacement therapy.

11.3 Discussion of Regulatory Options

The available data supports regular approval for the indication of prophylactic or OD enzyme replacement therapy in adult and pediatric patients with congenital TTP.

11.4 Recommendations on Regulatory Actions

There are no approved products for congenital TTP and recombinant ADAMTS13 does not carry the safety concerns of plasma-based therapies, which is the current standard of care for congenital TTP. Hence, priority review was granted for this application.

The Applicant has met the statutory requirements for regulatory approval, and the review team recommends regular approval for prophylactic or OD enzyme replacement therapy in adult and pediatric patients with congenital TTP.

Based on the available data, the clinical efficacy and safety reviewer recommends regular approval of TAK-755.

11.5 Labeling Review and Recommendations

The revised package insert was reviewed, commented on, and revised by the appropriate discipline reviewers. FDA’s Advertising and Promotional Labeling Branch conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

The label has been modified to reflect the efficacy and safety data presented in this memo. The major changes to the draft label pertaining to efficacy and safety include:

1. Removal of majority of the secondary endpoint data in the label, as there were sparse and not meaningful conclusions
2. Removal of patient-reported outcome data since this is a single-arm trial
3. Update to the safety for the TAK-755-treated arm only (excluding SoC)

11.6 Recommendations on Post marketing Actions

No post marketing requirement or post marketing commitment studies are requested at this time. Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy, a post marketing commitment, or a required post marketing study that is specifically designed to evaluate safety as a primary endpoint.

For all other AEs, the Applicant will conduct routine pharmacovigilance.

There is an ongoing extension trial.

Reviewer Comment: *There was discussion with the Applicant regarding a post marketing commitment to investigate immunogenicity in previously untreated/naïve subjects. Through information requests and discussion at the Late-Cycle Meeting, the Applicant confirmed that the ongoing extension study will enroll naïve/minimally-treated subjects and will evaluate immunogenicity for those subjects.*