

Clinical Pharmacology BLA Review

Division of Clinical Evaluation General Medicine

Office of Clinical Evaluation

Office of Therapeutic Products

BLA	125795/0
Product	ADZYNMA (recombinant ADAMTS13, TAK-755) lyophilized powder for solution
Sponsor	Takeda Pharmaceuticals U.S.A., Inc.
Indication	Prophylactic or on-demand enzyme replacement therapy for patients with congenital thrombotic thrombocytopenic purpura (cTTP)
Date Received	March 17, 2023
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1 EXECUTIVE SUMMARY

Takeda Pharmaceuticals U.S.A., Inc. seeks approval of its BLA for ADZYNMA (recombinant ADAMTS13, TAK-755) for prophylactic or on-demand enzyme replacement therapy for patients with congenital thrombotic thrombocytopenic purpura (cTTP). ADZYNMA is recombinant “a disintegrin and metalloproteinase with thrombospondin motifs 13 (rADAMTS13)” developed as a targeted enzyme replacement therapy (ERT) to provide ADAMTS13. ADZYNMA is a sterile, nonpyrogenic lyophilized powder for reconstitution for intravenous (IV) injection. The proposed dose of ADZYNMA as prophylactic ERT is 40 IU/kg body weight once every other week. The proposed dose of ADZYNMA as on-demand ERT is 40 IU/kg body weight on Day 1, 20 IU/kg body weight on Day 2, and 15 IU/kg body weight on Day 3 and thereafter until two days after the acute event is resolved.

The clinical pharmacology evaluation of this biologics license application (BLA) is based on data from 3 clinical studies in subjects with cTTP, and results from supportive population pharmacokinetic (popPK), exposure-response analysis, and Quantitative System Pharmacology (QSP) model analysis. Following IV administration of ADZYNMA, both ADAMTS13 antigen and activity followed bi-exponential PK profiles. The PK characteristics of ADAMTS13 antigen and activity following ADZYNMA IV administration were similar. ADZYNMA PK was approximately dose proportional between 20 and 40 IU/kg and is time independent. ADZYNMA IV administration at 40 IU/kg resulted in approximately 4- to 5-fold higher ADAMTS13 activity exposures (C_{max} , AUC) and lower inter-subject variability when compared to plasma-based therapies. Mean time duration above 10% ADAMTS13 activity and mean average ADAMTS13 activity levels (C_{ave}) were both approximately 3-to 4-fold higher following ADZYNMA IV administration than plasma-based therapies. The weight-based dosing effectively compensates for the majority of observed drug exposure variations across different age groups. No additional intrinsic factors were identified as covariates impacting ADZYNMA PK. Exposure-response relationship analysis results indicated 1) a noteworthy therapeutic impact of ADZYNMA compared to the SoC, and 2) average levels of ADAMTS13 activity (C_{ave}) significantly decreases

the risk of thrombocytopenia and microangiopathic hemolytic anemia (MAHA) in a concentration-dependent manner across different age groups, including adults, adolescents, and pediatrics. Immunogenicity assessment showed that no subjects with cTTP developed neutralizing antibodies against ADAMTS13.

The proposed dosing regimen of ADZYNMA administered by intravenous (IV) injection has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable. From clinical pharmacology standpoint, the BLA is acceptable to support approval.

2 INTRODUCTION

cTTP is an ultra-rare, life-threatening thrombotic disorder of the microcirculation caused by a severe deficiency of the ADAMTS13 protein. The biological role of ADAMTS13 is to regulate the activity of von Willebrand factor (VWF) by cleaving large and ultra-large VWF multimers to small units. Severe deficiency of ADAMTS13 can lead 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. The formation of these platelet-rich microthrombi is evidenced by platelet consumption and thrombocytopenia, which is a hallmark of uncontrolled cTTP.

Current standard of care (SoC) centers around ADAMTS13 replacement through regular prophylactic or on-demand infusions of commercially available plasma-derived therapies, such as fresh frozen plasma (FFP). For treatment of acute TTP events, patients receive daily plasma infusions for 1-5 days or until the platelet count rises to above $100 \times 10^9/L$. cTTP patients eventually receive prophylactic treatment, most often two plasma infusions per month, but 1-4 monthly infusions may be given depending on clinical and practical considerations. Volume restrictions set limits for how much ADAMTS13 supplementation can be provided via plasma infusion. The standard plasma infusion volume is 10 mL/kg, which corresponds to 20-30% ADAMTS13 supplementation. Additionally, plasma infusions may take 2-3 hours, are most often given every other week, and must be done in a hospital setting.

ADZYNMA (recombinant ADAMTS13, TAK-755) is recombinant “a disintegrin and metalloproteinase with thrombospondin motifs 13 (rADAMTS13)” developed as a targeted enzyme replacement therapy (ERT) for prophylactic or on-demand ERT for patients with cTTP. The aim of ADZYNMA therapy is to provide consistently higher and more sustained ADAMTS13 exposures relative to current SoC, with a significant decrease in infusion volume and duration. This improvement in ADAMTS13 exposures is expected to reduce the occurrence of acute and subacute TTP ~~exposures~~ events, as well as TTP manifestations relative to current SoC, without treatment-limiting adverse events.

This clinical pharmacology section of this application includes 3 clinical studies in subjects with cTTP: one completed Phase 1 study (Study 281101) and 2 ongoing Phase 3 studies (pivotal Study 281102 and continuation Study TAK-755-3002 [hereafter Study 3002]) (Table 1). To support this application, the applicant also developed a population pharmacokinetic (PK) and exposure-response analyses, and a quantitative systems pharmacology (QSP) model to provide supportive evidence for efficacy.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The clinical pharmacology key findings are summarized as following:

General PK Profile: Following IV administration of ADZYNMA, both ADAMTS13 antigen and activity followed bi-exponential PK profiles. PK characteristics of ADAMTS13 antigen and activity following ADZYNMA IV administration were similar. C_{max} of ADAMTS13 antigen and activity was achieved immediately after the end of infusion. At the dose of 40 IU/kg, the mean values of C_{max} for ADAMTS13 antigen and activity were 0.84 $\mu\text{g/mL}$ and 1.15 IU/mL, respectively. Mean AUC_{all} were 38.97 $\mu\text{g} \times \text{h/mL}$ and 52.81 IU $\times \text{h/mL}$ for ADAMTS13 antigen and activity, respectively. Mean IR for ADAMTS13 antigen and activity was 0.03 ($\mu\text{g/mL}$)/($\mu\text{g/kg}$) and 0.03 (IU/mL)/(IU/kg), respectively. Mean clearance (CL) was 0.05 L/h for both ADAMTS13 antigen and activity.

ADZYNMA (TAK-755) manufactured from two sites (TAK-755-(b) (4) and TAK-755-(b) (4) (commercial)) were used in the clinical development. The PK of ADZYNMA manufactured from the two sites were comparable.

PK Comparison between ADZYNMA and SoC: ADZYNMA IV administration at 40 IU/kg resulted in approximately 4- to 5-fold higher ADAMTS13 activity exposures (C_{max} , AUC) and lower inter-subject variability when compared to plasma-based therapies. Mean time duration above 10% ADAMTS13 activity and mean average ADAMTS13 activity (C_{ave}) were both approximately 3- to 4-fold higher following ADZYNMA IV administration than plasma-based therapies.

Dose proportionality: Following single-dose IV administration of ADZYNMA at 5 IU/kg, 20 IU/kg, and 40 IU/kg to adults and adolescents, dose-related increases in individual ADAMTS13 activity were observed and reached a maximum at approximately 1 hour post-infusion or earlier. ADZYNMA PK was approximately dose proportional between 20 and 40 IU/kg.

PK Over Time: The PK profile of ADAMTS 13 activity following ADZYNMA administration is time independent.

Intrinsic Factors Impacting ADZYNMA PK Profiles (PK in Specific Populations): No intrinsic factors such as age, gender, race, baseline estimated glomerular filtration rate (eGFR), and baseline bilirubin were identified as covariates impacting ADZYNMA PK. Therefore, there is no dose adjustment in the cTTP patient population beyond body weight-based dosing. ADAMTS13 activity were generally similar across the age groups (<6, 6 to <12, 12 to <18, and ≥ 18 years). The results from popPK analysis also showed that age did not significantly impact the PK of ADAMTS13 activity and overall exposure-response (E-R) relationship. The weight-based dosing effectively compensates for the majority of observed drug exposure variations across different age groups.

Pharmacodynamics: VWF antigen and VWF:ristocetin cofactor activity (VWF:RCo) were used to assess VWF platelet binding activity. Following IV doses of ADZYNMA at the recommended dose, both VWF antigen and VWF:Rco transiently decreased for 1 to 2 days with a 15% to 25% change from baseline.

Exposure-Response Relationships: The relationships between ADAMTS13 activity and the likelihood of isolated TTP manifestations, including composite TTP manifestation endpoints, after administering treatment (ADZYNMA vs. SoC) were evaluated. The E-R analysis results showed a noteworthy therapeutic impact of ADZYNMA compared to the SoC. The E-R analysis results indicated that ADAMTS13 activity Cave significantly decreases the risk of thrombocytopenia and microangiopathic hemolytic anemia (MAHA) in a concentration-dependent manner across different age groups, including adults, adolescents, and pediatrics. In addition, the results from the QSP model also provided confirmative evidence to support the use of ADZYNMA in subjects with cTTP.

Immunogenicity:

No cTTP patients tested positive for neutralizing antibodies against ADAMTS13. Thirteen (one in Study 281102 and 12 in Study 3002) of 67 patients treated prophylactically with ADZYNMA with confirmed cTTP tested positive for low-titer binding antibodies against ADAMTS13 with no observable clinical impact on the safety or efficacy of ADZYNMA, and no increase in antibody titers over time. Because of the low occurrence of ADA, the effect of these antibodies on the PK, PD, safety, and/or efficacy of rADAMTS13 products is unknown.

There are no data on immunogenicity in previously untreated patients (subjects naïve to plasma-based products), therefore, the risk of immunogenicity for naïve subjects to this drug product is unknown.

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125795 and finds it acceptable pending the following revisions shown below.

Reviewer's edits are in red color.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

ADZYNMA is a 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. ~~ADZYNMA is a recombinant form of the endogenous ADAMTS13 with similar pharmacokinetic (PK) and pharmacodynamic (PD) properties. The use of ADZYNMA in patients with cTTP provides targeted ADAMTS13 supplementation and replenishment of plasma ADAMTS13 activity which is expected to reduce or eliminate the spontaneous formation of VWF platelet microthrombi that leads to platelet consumption and thrombocytopenia, which is a marker of disease activity in patients with cTTP.~~

12.2. Pharmacodynamics

VWF antigen and VWF:ristocetin cofactor activity (VWF:RCo) were used to assess VWF platelet binding activity. Following IV doses of ADZYNMA at the recommended dose, both VWF antigen and VWF:Rco transiently decreased for 1 to 2 days with a 15% to 25% change from baseline.

12.3. Pharmacokinetics

The PK profile of ADZYNMA was determined based on clinical trial ADAMTS13 activity data analyses.

Following single-dose IV administration of ADZYNMA at 5 IU/kg, 20 IU/kg, and 40 IU/kg to adults and adolescents, dose-related increases in individual ADAMTS13 activity were observed and reached a maximum at approximately 1 hour post-infusion or earlier. At clinical dose of 40 IU/kg the mean (SD) half-life and mean residence time (MRT) in adults and adolescents were 47.8 (13.7) hours and 63.8 (16.0) hours, respectively.

The PK parameters of ADAMTS13 activity following IV administration of ADZYNMA at 40 IU/kg in adults and adolescents are described in *Table 2*.

Reviewer's Comments to Applicant:

Please include information for half-life and AUC0-168h.

Table 2. Pharmacokinetic Parameters of ADAMTS13 Activity following IV Administration of ADZYNMA in cTTP Patients ≥12 Years Old

Parameter (unit)	Mean (SD) Min; Max (N=23)
C_{max} (IU/mL)	1.15 (0.25) 0.78; 1.56
IR [(IU/mL)/(IU/kg)]	0.03 (0.01) 0.02; 0.04
AUC_{all} (IU*h/mL)	52.8 (12.9) 34.0; 84.0
MRT_{0-inf}^a (h)	63.8 (16.0) 44.8; 113
C_{ave} (0-168 h) (IU/mL)	0.30 (0.07) 0.20; 0.46
Duration ADAMTS13 Activity above 10% (days)	5.8 (1.2) 4.5; 8.9

AUC = area under ADAMTS13 activity-time curve; C_{ave} (0-168 h) = average ADAMTS13 activity from 0 to 168 hours dosing interval; C_{max} = maximum ADAMTS13 activity; IR = incremental recovery; MRT = mean residence time.

Note: 1 IU/mL ADAMTS13 activity corresponds to 100% average normal activity.

^a N=22

ADZYNMA IV administration at 40 IU/kg resulted in approximately greater than 4- to 5-fold higher ADAMTS13 activity exposures (C_{max} , AUC, and duration above 10% ADAMTS13 activity) and lower inter-subject variability when compared to plasma-based therapies.

Based on Population PK analysis leveraging available data (N=65) from adults, adolescents and pediatric patients below 12 years of age, the mean (SD) steady state C_{max} , AUC_{all} , C_{ave} , and duration ADAMTS13 activity above 10% following IV administration of ADZYNMA every other week in cTTP patients below 12 years of age were 1.02 (0.19) IU/mL, 54.0 (12.2) IU*h/mL, 0.16 (0.04) IU/mL, and 6.8 (2.1) days, respectively.

ADAMTS13 antigen and activity PK characteristics (MRT, V_{ss} , and CL) were similar across age groups in patients with cTTP. Body weight-based ADZYNMA dosing provides similar ADAMTS13 activity PK parameters (C_{max} and C_{ave}) across the different age groups including pediatric patients <12 years of age.

Specific Populations

Besides body-weight dosing regimen, no dose adjustment is required since no intrinsic factors such as age, gender, race, baseline estimated glomerular filtration rate (eGFR), and baseline bilirubin were identified as covariates impacting ADAMTS13 PK.

Pediatric Patients

Population pharmacokinetics (PK) analysis leveraging available data from adults, adolescents and pediatric patients below 12 years of age (N=65), suggests comparable ADAMTS13 activity exposures between patients below 12 years of age and patients aged 12 years and above receiving the recommended ADZYNMA dosing regimen [see *Use in Specific Populations (8.4)*].

12.6. Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of ADZYNMA.

Six of 54 patients treated prophylactically with ADZYNMA with confirmed cTTP tested positive for low-titer binding antibodies against ADAMTS13 with no observable clinical impact on the safety or efficacy of ADZYNMA, and no increase in antibody titers over time. No cTTP patients tested positive for neutralizing antibodies against ADAMTS13.

Because of the low occurrence of ADA, the effect of these antibodies on the PK, PD, safety, and/or efficacy of rADAMTS13 products is unknown [see *Warnings and Precautions (5.2)*].

There is no data on immunogenicity in previously untreated patients (subjects naïve to plasma-based products), therefore, the risk of immunogenicity for naïve subjects to this drug product is unknown.

Reviewer's Comments to Applicant:

Please update the immunogenicity information based on 120-safety updates results.

5 RECOMMENDATIONS

The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to section 4 for detailed Labeling Recommendations.

6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.1 Overview of Clinical Pharmacology Evaluation

The clinical pharmacology section of this BLA includes 3 clinical studies in subjects with cTTP: one completed Phase 1 study (Study 281101) and 2 ongoing Phase 3 studies (pivotal Study 281102 and continuation Study TAK-755-3002 [hereafter Study 3002]) (Table 1).

Both ADAMTS13 activity and antigen levels were measured for PK analysis of ADZYNMA. ADAMTS13 activity levels were measured using FRETS-VWF73 assay. Lower limit of quantification (LLOQ) was (b) (4). ADAMTS13 antigen level were measured using a (b) (4) assay. The LLOQ of the assay was (b) (4).

All post-infusion PK measurements were adjusted for baseline when baseline measurements were above LLOQ except samples collected by sparse sampling.

For pharmacodynamic analysis,

- VWF:RCo activity was measured using (b) (4) in the presence of VWF and the antibiotic Ristocetin. The LLOQ of the assay was (b) (4).
- VWF:Ag concentration was measured by an ELISA-based assay; the LLOQ of the assay was (b) (4).
- VWF multimer qualitative evaluation was assessed using (b) (4) sodium dodecyl sulfate (SDS)-agarose gel electrophoresis. (b) (4) SDS-agarose gel electrophoresis was used for quantitative evaluation. These analysis employed western blot with luminescence video imaging.
- ADAMTS13-mediated VWF cleavage products were visualized by SDS-poly-acrylamide gel electrophoresis followed by western blot staining.

To support this application, the applicant conducted population pharmacokinetic (PK) and exposure-response (E-R) analyses to 1) characterize ADAMTS13 activity following IV administration of ADZYNMA or standard of care (SoC), and 2) evaluate the relationship between ADAMTS13 activity and the occurrence of TTP events by isolated manifestations and composite endpoints. The Applicant also developed a quantitative systems pharmacology (QSP) model to provide a dynamic quantitative framework describing the relationship between ADAMTS13 activity, VWF activity, and platelets in cTTP patients. The QSP model evaluated the treatment benefits of ADZYNMA in virtual cTTP patients, who are phenotype matched to the cTTP subjects in Phase 3 study (Study 281102), to supplement the effect size in the Phase 3 trial.

Table 1. Clinical studies conducted to characterize clinical pharmacology of ADZYNMA in cTTP subjects

Study (Status)	Study Design	IP	Dosing Regimen; Frequency	Included PK, PD Analytes, Sampling Type	Number of Subjects ^a
281101 (Completed)	Phase 1, prospective, uncontrolled, open-label, multicenter, dose-escalation study evaluating the safety, including immunogenicity, and PK in subjects (12-65 years) with hTTP	TAK-755 (b) (4)	Single Dose: 5 IU/kg (n=3), 20 IU/kg (n=2), 40 IU/kg (n=9)	PK ADAMTS13 activity, ADAMTS13 antigen (serial samples) PD Platelets, VWF Antigen, VWF: RCo activity, ADAMTS13-mediated VWF Cleavage Products, VWF multimer concentration and pattern (both serial and semi-intensive samples)	15
281102 (Ongoing)	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 on-demand treatment of subjects (0 to 70 years) with severe cTTP	TAK-755 (b) (4), TAK-755 ^{(b) (4)} , and SoC	Prophylaxis: 40 IU/kg, Q1W or Q2W On Demand: 40 IU/kg D1, 20 IU/kg D2, 15 IU/kg D3 until 2 days after event resolution	PK and PD (PK-I, PK-II, PK-III^b) ADAMTS13 activity, ADAMTS13 antigen (serial samples) VWF antigen, VWF: RCo activity, ADAMTS13-mediated VWF cleavage products, VWF multimer concentration and pattern PK (Prophylaxis Period) ADAMTS13 activity, ADAMTS13 antigen (sparse samples included pre-dose and one-hour post collection) PK (On-demand Cohort) ADAMTS13 activity, ADAMTS13 antigen (sparse samples)	47
3002 (Ongoing)	Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of the safety and efficacy of TAK-755 in the prophylactic and on-demand treatment of subjects (0 to 70 years) with severe cTTP	TAK-755 (b) (4)	Prophylaxis: 40 IU/kg, Q1W or Q2W On Demand: 40 IU/kg D1, 20 IU/kg D2, 15 IU/kg D3 until 2 days after event resolution	PK and PD (Prophylaxis Visits): ADAMTS13 activity, ADAMTS13 antigen (sparse samples) VWF antigen, VWF:RCo activity (sparse samples) PK (During acute, sub-acute events): ADAMTS13 activity, ADAMTS13 antigen (sparse samples)	36

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; Ag=antigen; CSR=clinical study report; cTTP=congenital thrombotic thrombocytopenic purpura; D=day; hTTP=hereditary thrombotic thrombocytopenic purpura; iCSR=interim clinical study report; (b) (4); PD=pharmacodynamics; PK=pharmacokinetics; Q1W=once every week; Q2W=every 2 weeks; (b) (4); TAK-755=recombinant ADAMTS13 (formerly known as BAX 930 and SHP655) or rADAMTS13; VWF=von Willebrand factor; VWF:RCo=von Willebrand factor: ristocetin cofactor

^a Number of subjects evaluable for PK.

^b Pharmacodynamics was not collected in PK-III period.

Source: Applicant. Module 2, Section 2.7.2. Summary of Clinical Pharmacology Studies.

6.2 General Pharmacology and Pharmacokinetics

6.2.1 General Pharmacokinetic Profile

Following IV administration of ADZYNMA, both ADAMTS13 antigen and activity followed bi-exponential PK profiles. C_{max} of ADAMTS13 antigen and activity was achieved immediately after the end of infusion. As shown in Table 2, at the dose of 40 IU/kg, the mean values of C_{max} for ADAMTS13 antigen and activity were 0.84 µg/mL and 1.15 IU/mL, respectively. Mean AUC_{all} were 38.97 µg x h/mL and 52.81 IU x h/mL for ADAMTS13 antigen and activity, respectively. Mean IR for ADAMTS13 antigen and activity was 0.03 (µg/mL)/(µg/kg) and 0.03 (IU/mL)/(IU/kg), respectively. Mean clearance (CL) was 0.05 L/h for both ADAMTS13 antigen and activity. Above observation showed that PK characteristics of ADAMTS13 antigen and activity following ADZYNMA IV administration were similar.

Table 2. Summary of PK Parameters (Adults and Adolescent) After ADZYNMA(TAK-755-^{(b) (4)}) Administration

Parameter (unit)	ADAMTS13 Activity Mean (SD) (N)	ADAMTS13 Antigen Mean (SD) (N)
C _{max} (IU/mL)/(µg/mL)	1.15 (0.25) (n=23)	0.84 (0.17) (n=24)
IR [(IU/mL)/(IU/kg)]/ [(µg/mL)/(µg/kg)]	0.03 (0.01) (n=23)	0.03 (0.01) (n=24)
AUC _{all} (IU x h/mL)/(µg x h/mL)	52.81 (12.86) (n=23)	38.97 (11.15) (n=24)
MRT _{0-inf} (h)	63.79 (15.97) (n=22)	66.88 (18.92) (n=23)
C _{ave} (0-168 h) (IU/mL)	0.30 (0.07) (n=23)	0.22 (0.06) (n=24)
Duration ADAMTS13 Activity above 10% (days)	5.84 (1.18) (n=23)	ND
CL (L/h)	0.05 (0.01) (n=22)	0.05 (0.01) (n=23)
V _{ss} (L)	3.30 (0.620) (n=22)	3.02 (0.63) (n=23)

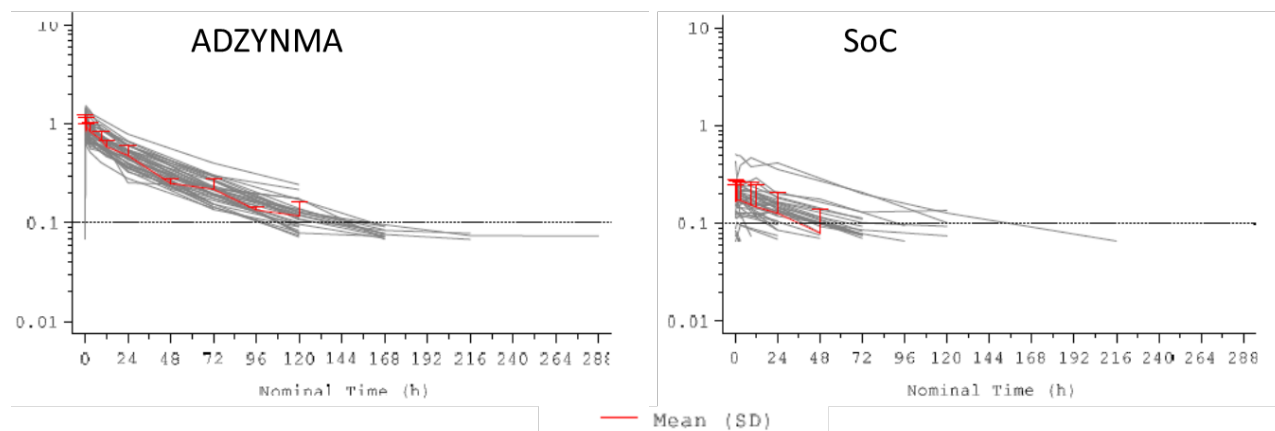
Source: The reviewer compiled from Applicant submitted CSR 281102 in Module 5.

6.2.2 Pharmacokinetics Comparison Between ADZYNMA and Standard of Care (SoC)

Current standard of care (SoC) therapy for cTTP is most often consisted of infusions of fresh frozen plasma (FFP). The aim of ADZYNMA therapy is to provide consistently higher and more sustained ADAMTS13 exposures relative to current SoC, with a significant decrease in infusion volume and duration.

In Study 281102, ADAMTS13 activity and antigen PK profiles were compared after administration of ADZYNMA (TAK-755-^{(b) (4)}, 40 IU/kg) and standard of care (SoC). Table 3 summarizes PK parameters of ADAMTS13 of ADZYNMA (TAK-755-^{(b) (4)}) and SoC. Similar to ADZYNMA, following IV administration of SoC, ADAMTS13 antigen and activity followed a bi-exponential PK profile. ADZYNMA IV administration at 40 IU/kg resulted in approximately greater than 4- to 5-fold higher ADAMTS13 activity exposures (C_{max} , AUC, and duration above 10% ADAMTS13 activity) and lower inter-subject variability when compared to plasma-based therapies (Figure 1).

Figure 1. ADAMTS13 Activity Mean (SD) and Individual PK-Time Profiles Following ADZYNMA (TAK-755-^{(b) (4)}) or SoC



Source: Applicant. Module 5, CSR 281102.

Table 3. ADAMTS13 PK Parameters (Adults and Adolescnets) After Administration of ADZYNMA (40 IU/kg) or SoC

a. ADAMTS13 Activity

Statistic	C _{max} (IU/mL)	t _{max} (h)	IR (IU/mL) / (IU/kg)	t _{1/2} (h)	AUC _{0-inf} (h x IU/ mL)	AUC _{all} (h x IU/ mL)	AUC ₍₀₋₁₆₈₎ (h x IU/ mL)	C _{ave} (0-168) (IU/mL)	Time above 10% activity (days)	MRT _(0-inf) (h)	CL (L/h)	V _{ss} (L)
TAK-755 ^{(b) (4)}												
N	34	34	34	34	32	34	27	27	34	32	32	32
Mean (SD)	1.01 (0.240)	0.33 (0.23, 1.10) ^a	0.025 (0.006)	47.12 (11.397)	50.01 (11.050)	44.40 (11.124)	44.39 (9.521)	0.26 (0.056)	5.2 (0.90)	64.40 (17.216)	0.0616 (0.0142)	3.844 (0.898)
Geo Mean (Geo CV%)	0.98 (23.6)	ND	0.024 (23.8)	45.98 (22.1)	48.82 (22.7)	42.98 (26.9)	43.42 (21.7)	0.26 (21.8)	5.1 (18.4)	62.62 (23.5)	0.0600 (24.7)	3.750 (22.5)
SoC												
N	36	36	26	23	2	32	23	22	36	2	2	2
Mean (SD)	0.19 (0.106)	3.44 (0.00, 23.50)	0.022 (0.024)	62.66 (28.281)	38.0, 43.3 ^b	10.6 (8.136)	11.41 (8.158)	0.07 (0.048)	1.7 (1.43)	72.5, 91.8 ^b	0.0392, 0.0887 ^b	2.85, 8.14 ^b
Geo Mean (Geo CV%)	0.19 (46.5)	ND	0.019 (53.6)	57.72 (42.2)	ND	7.572 (130.7)	9.24 (77.1)	0.06 (77.4)	1.6 (124.0)	ND	ND	ND

b. ADAMTS13 Antigen

Statistic	C _{max} (µg/mL)	t _{max} (h)	IR (µg /mL)/ (µg /kg)	t _{1/2} (h)	AUC _{0-inf} (h x IU/ mL)	AUC _{all} (h x IU/ mL)	AUC ₍₀₋₁₆₈₎ (h x IU/ mL)	C _{ave} (0-168) (IU/mL)	MRT _(0-inf) (h)	CL (L/h)	V _{ss} (L)
TAK-755 ^{(b) (4)}											
N	34	34	34	34	31	34	27	27	31	31	31
Mean (SD)	0.7213 (0.14852)	0.33 (0.23, 1.18) ^a	0.0303 (0.0065)	53.59 (13.355)	39.97 (10.086)	34.12 (9.647)	33.99 (7.851)	0.2010 (0.0462)	71.20 (16.540)	0.0455 (0.0118)	3.120 (0.657)
Geo Mean (Geo CV%)	0.707 (20.3)	ND	0.0297 (21.3)	52.01 (25.3)	38.79 (25.2)	32.83 (28.8)	33.11 (23.7)	0.196 (23.8)	69.33 (23.9)	0.0440 (27.1)	3.050 (22.3)
SoC											
N	36	36	26	17	2	32	25	24	2	1	1
Mean (SD)	0.1383 (0.074)	3.02 (0.00, 10.50) ^a	0.0197 (0.0064)	59.48 (23.049)	0.372, 26.9 ^b	7.739 (5.881)	7.764 (6.350)	0.0481 (0.0372)	10.7, 75.4 ^b	ND	ND
Geo Mean (Geo CV%)	0.1384 (47.1)	ND	0.0188 (32.1)	53.24 (61.8)	ND	5.440 (139.0)	5.196 (158.8)	0.0348 (128.3)	ND	ND	ND

Source: Applicant. Module 5, CSR 281102.

6.2.3 Comparison of ADZYNMA Pharmacokinetics of ADZYNMA from Two Manufacturing Sites (TAK-755-(b) (4) and TAK-755-(b) (4))

ADZYNMA (TAK-755) manufactured from two sites (TAK-755-(b) (4) and TAK-755-(b) (4)) were evaluated in the clinical development: TAK-755-(b) (4) was used in the Phase 1 dose-escalation study (Study # 281101) and Phase 3 study (Study 281102) Period I and Period II of prophylactic cohort. TAK-755-(b) (4), the commercial product, was used in the Phase 3 study (Study 281102) Periods I and III of prophylactic cohort. Prior to Study 281102 Period 1, the ADAMTS13 exposure after administration of TAK-755-(b) (4) and standard of care (SoC) were compared (PK-I). At the beginning of Period III of Study 281102, the PK profiles of TAK-755-(b) (4) and TAK-755-(b) (4) were compared with crossover PK assessment (PK-II).

Table 4 summarizes ADAMTS13 activity and antigen PK parameters after administration of TAK-755-(b) (4) or TAK-755-(b) (4). Similar PK characteristics were observed between TAK-755-(b) (4) and TAK-755-(b) (4): mean CL, Vss, and MRT PK parameters were also similar between TAK-755-(b) (4) and TAK-755-(b) (4): 0.04 L/h, 2.8 L, 70.5 h versus 0.05 L/h, 3.0 L, 66.9 h for ADAMTS13 antigen and 0.05 L/h, 3.4 L, 65.7 h versus 0.05 L/h, 3.3 L, 63.8 h for ADAMTS13 activity.

Additional PK comparability assessment was performed using bioequivalence statistical approach. As shown in Table 5, both ADAMTS13 activity and antigen PK parameters were comparable between TAK-755-(b) (4) and TAK-755-(b) (4). The geometric mean ratio and associated 90% CI for both AUC and C_{max} comparing TAK-755-(b) (4) and TAK-755-(b) (4) remained within the recommended 80% and 125% bioequivalence interval.

Table 4. Summary of PK Parameters (Adults and Adolescents) of ADAMTS13 After Administration of TAK-755-(b) (4) and TAK-755-(b) (4) (Study 281102 PK-II)

a. ADAMTS13 Activity

Statistic	C _{max} (IU/mL)	t _{max} (h)	IR (IU/mL)/ (IU/kg)	t _{1/2} (h)	AUC _{0-inf} (h x IU/ mL)	AUC _{all} (h x IU/ mL)	AUC ₍₀₋₁₆₈₎ (h x IU/ mL)	C _{ave(0-168)} (IU/mL)	Time above 10% activity (days)	MRT _(0-inf) (h)	CL (L/h)	V _{ss} (L)
TAK-755-(b) (4)												
N	27	27	27	27	26	27	27	27	27	26	26	26
Mean (SD)	1.16 (0.265)	0.35 (0.22, 2.78) ^a	0.03 (0.007)	52.19 (15.365)	58.57 (12.872)	53.48 (12.100)	51.87 (10.809)	0.31 (0.064)	6.14 (1.147)	65.71 (13.228)	0.05 (0.013)	3.42 (0.706)
Geo Mean (Geo CV%)	1.125 (23.7)	ND	0.03 (24.0)	50.27 (27.9)	57.33 (21.2)	52.26 (21.9)	50.85 (20.4)	0.30 (20.4)	6.05 (17.9)	64.47 (20.2)	0.05 (24.5)	3.34 (22.2)
TAK-755-(b) (4)												
N	23	23	23	23	22	23	23	23	23	22	22	22
Mean (SD)	1.15 (0.252)	0.33 (0.25, 1.08) ^a	0.03 (0.006)	47.80 (13.697)	57.57 (13.872)	52.81 (12.863)	51.26 (10.891)	0.30 (0.066)	5.84 (1.177)	63.79 (15.971)	0.05 (0.013)	3.30 (0.620)
Geo Mean (Geo CV%)	1.13 (23.4)	ND	0.03 (23.1)	46.20 (26.4)	56.04 (24.1)	51.41 (23.9)	50.18 (21.3)	0.30 (21.8)	5.74 (18.8)	62.17 (22.7)	0.05 (26.5)	3.24 (18.9)

b. ADAMTS13 Antigen

TAK-755 ^{(b) (4)}												
Statistic	C _{max} (µg/mL)	t _{max} (h)	IR (µg/mL)/ (µg/kg)	t _{1/2} (h)	AUC _{0-inf} (h x µg/ mL)	AUC _{all} (h x µg / mL)	AUC ₍₀₋₁₆₈₎ (h x µg / mL)	C _{ave(0-168)} (µg /mL)	Time above 10% activity (days)	MRT _(0-inf) (h)	CL (L/h)	V _{ss} (L)
N	27	27	27	27	25	27	27	27	0	25	25	25
Mean (SD)	0.81 (0.185)	0.33 (0.22, 2.63) ^a	0.03 (0.008)	53.16 (16.418)	44.38 (9.454)	38.96 (8.670)	37.75 (7.298)	0.22 (0.043)	ND	70.51 (20.004)	0.04 (0.0112)	2.80 (0.501)
Geo Mean (Geo CV%)	0.79 (22.6)	ND	0.03 (23.6)	51.18 (27.6)	43.44 (21.3)	38.05 (22.5)	37.06 (19.9)	0.22 (19.8)	ND	67.92 (28.6)	0.04 (28.2)	2.76 (18.2)
TAK-755 ^{(b) (4)}												
N	24	24	24	24	23	24	24	24	0	23	23	23
Mean (SD)	0.84 (0.167)	0.33 (0.28, 1.18) ^a	0.03 (0.007)	50.31 (16.134)	42.91 (12.476)	38.97 (11.148)	37.73 (9.266)	0.22 (0.055)	ND	66.88 (18.923)	0.05 (0.0132)	3.02 (0.634)
Geo Mean (Geo CV%)	0.83 (19.3)	ND	0.03 (19.5)	47.99 (32.1)	41.33 (28.1)	37.58 (27.5)	36.70 (24.0)	0.22 (24.3)	ND	64.41 (28.7)	0.05 (29.0)	2.97 (20.7)

Source: Applicant. Module 5, CSR 281102.

Table 5. Comparison of ADAMTS13 PK Parameters (Adults and Adolescents) After Administration of TAK-755-(b) (4) and TAK-755-(b) (4) (Study 281102 PK-II)

Parameter (Unit)	Treatment ^a	n	Geo LS Mean	95% CI of Geo LS Mean	TAK-755 ^{(b) (4)} vs TAK-755 ^{(b) (4)}	
					Ratio (%)	90% CI of Ratio (%)
ADAMTS13 Activity (IU/mL)						
C _{max} (IU/mL)	TAK-755 ^{(b) (4)}	23	1.161	1.045, 1.290	101.81	96.76, 107.13
	TAK-755 ^{(b) (4)}	23	1.141	1.027, 1.267		
AUC _(0-last) (h x IU/mL)	TAK-755 ^{(b) (4)}	23	47.53	39.89, 56.64	99.78	94.24, 105.64
	TAK-755 ^{(b) (4)}	23	47.64	39.98, 56.76		
AUC _(0-inf) (h x IU/mL)	TAK-755 ^{(b) (4)}	22	57.1	51.10, 63.80	100.24	94.13, 106.75
	TAK-755 ^{(b) (4)}	22	56.96	50.98, 63.64		
AUC _{all} (h x IU/mL)	TAK-755 ^{(b) (4)}	23	52.63	47.27, 58.59	100.96	96.10, 106.07
	TAK-755 ^{(b) (4)}	23	52.12	46.82, 58.03		
ADAMTS13 Antigen (µg/mL)						
C _{max} (µg/mL)	TAK-755 ^{(b) (4)}	24	0.8476	0.7726, 0.9299	106.43	100.79, 112.38
	TAK-755 ^{(b) (4)}	24	0.7964	0.7259, 0.8737		
AUC _(0-last) (h x µg/mL)	TAK-755 ^{(b) (4)}	24	33.88	28.44, 40.36	99.22	93.46, 105.33
	TAK-755 ^{(b) (4)}	24	34.15	28.67, 40.68		
AUC _(0-inf) (h x µg/mL)	TAK-755 ^{(b) (4)}	23	41.83	37.08, 47.18	98.32	92.63, 104.35
	TAK-755 ^{(b) (4)}	22	42.54	37.69, 48.01		
AUC _{all} (h x µg/mL)	TAK-755 ^{(b) (4)}	24	38.19	33.91, 43.01	101.11	95.92, 106.59
	TAK-755 ^{(b) (4)}	24	37.77	33.54, 42.53		

6.2.4 Dose Proportionality

Following a single dose of ADZYNMA, dose proportionality was evaluated for the 5, 20, and 40 IU/kg doses. The PK profiles were shown in Figure 2. For the 5 IU/kg dose, ADAMTS13 activity levels remained below limit of quantitation starting from Day 1. Table 6 summarizes the PK parameters of ADAMTS13 at the doses ranging from 5 to 40 IU/kg. ADZYNMA PK was approximately dose proportional between 20 and 40 IU/kg. This was corroborated by the final popPK model, please refer to pharmacometrics review for details.

Table 6. Summary of Key ADAMTS13 PK Parameters Resulting from Single IV administration of ADZYNMA 5, 20 and 40 IU/Kg in Adult cTTP Subjects

a. Activity

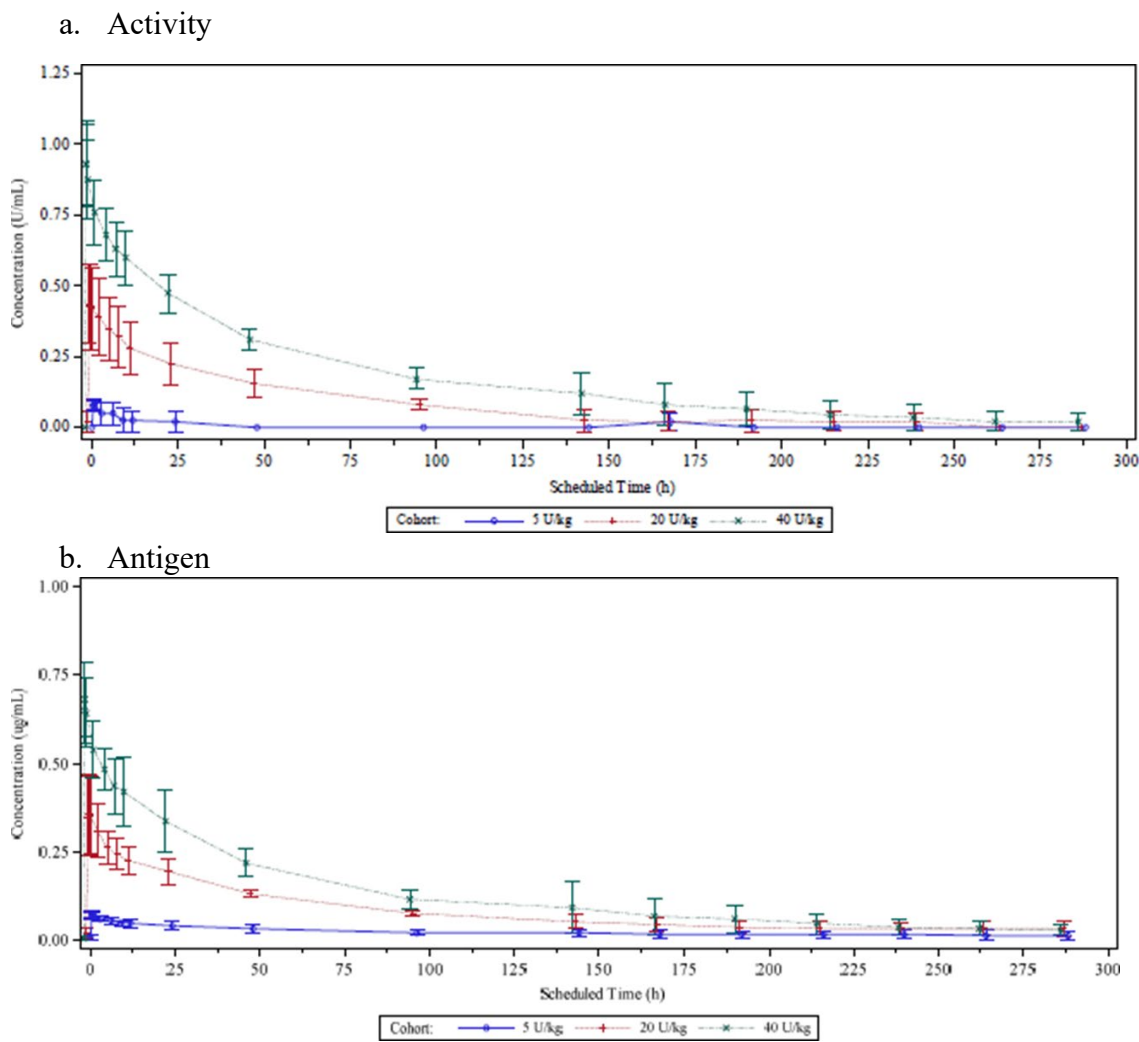
PK Parameters	Mean (SD)		
	5 U/kg (n=3)	20 U/kg (n=3)	40 U/kg (n=7)
IR (IU/mL/IU/kg)	0.02 (0.003)	0.02 (0.007)	0.02 (0.004)
C _{max} (IU/mL)	0.08 (0.02)	0.42 (0.15)	1.0 (0.14)
T _{max} (h) ^b	1.00 (0.52-1.00)	0.33 (0.25-0.53)	0.37 (0.22-0.58)
AUC _(0-inf) (IU x h/mL)	ND	19.5 (4.9)	54.5 (14.9)
AUC _(0-t) (IU x h/mL)	0.71 (0.86)	15.8 (4.9)	49.2 (14.1)
t _{1/2} (h)	ND	45.1 (21.2)	60.5 (13.5)
MRT _(0-inf) (h)	ND	62.1(27.6)	87.7 (26.3)
CL (mL/h)	ND	72.8 (24.5)	65.2 (24.2)
V _{ss} (mL)	ND	4240 (1230)	5300 (1030)

b. Antigen

PK Parameters	Mean (SD)		
	5 IU/kg (n=3)	20 IU/kg (n=3)	40 IU/kg (n=7)
IR (µg/mL/µg/kg)	0.02 (0.001)	0.03 (0.009)	0.02 (0.004)
C _{max} (µg/mL)	0.07 (0.002)	0.34 (0.126)	0.68 (0.103)
T _{max} (h) ^a	0.25 (0.25-0.52)	0.55 (0.53-0.97)	0.30 (0.22-1.12)
AUC _(0-inf) (µg x h/mL)	4.72 (1.02)	18.4 (1.73)	37.6 (13.5)
AUC _(0-t) (µg x h/mL)	4.05 (0.449)	17.3 (2.25)	35.3 (11.6)
t _{1/2} (h)	90.7 (32.9)	59.1 (20.1)	67.4 (13.5)
MRT _(0-inf) (h)	133.0 (58.37)	86.1 (37.00)	88.4 (21.59)
CL (mL/h)	50.1 (20.1)	53.0 (26.2)	64.5 (24.1)
V _{ss} (mL)	6050 (2170)	4160 (1300)	5510 (1680)

Source: Applicant. Module 5, CRS Study 281101.

Figure 2. Pharmacokinetic Profiles of ADZYNMA After Single Dose Administration in Adults

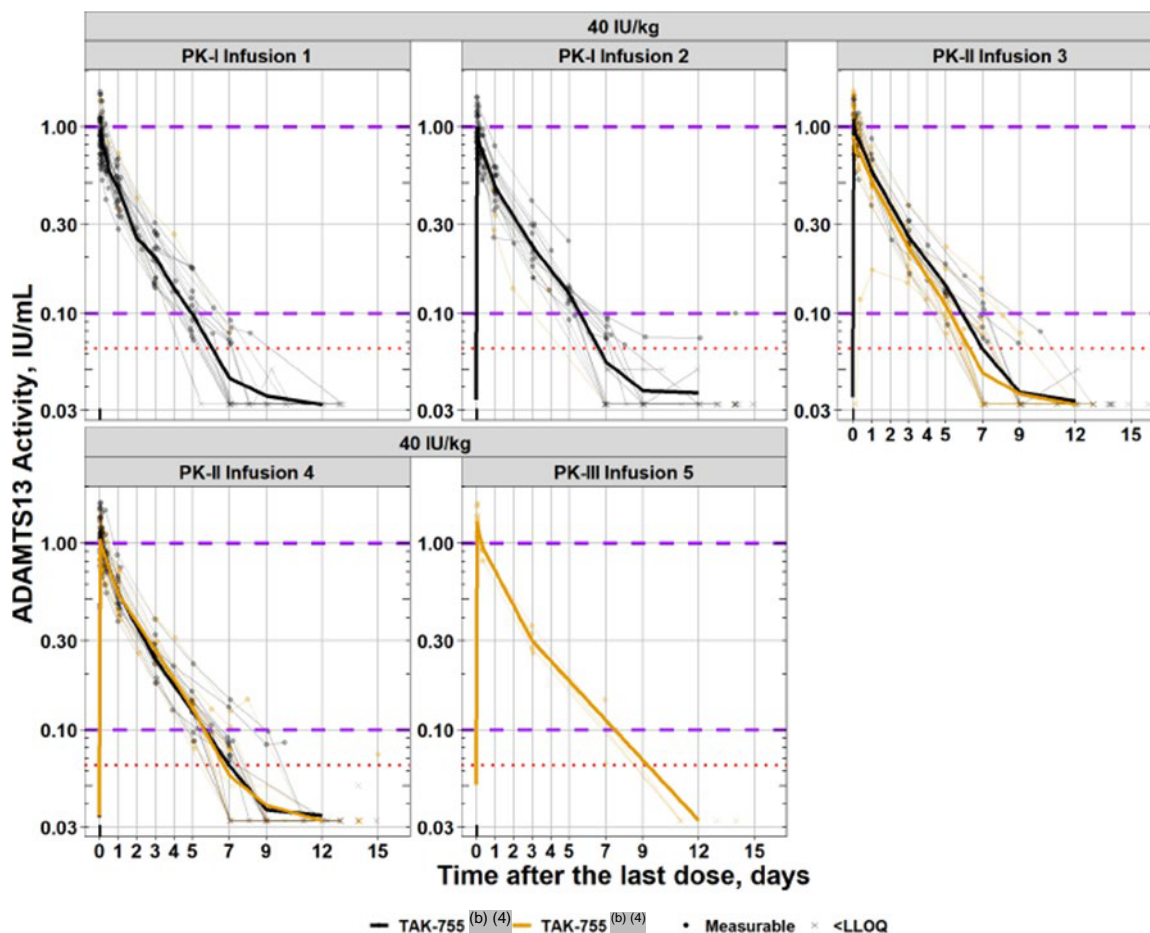


Source: Applicant. Module 5, CRS Study 281101.

6.2.5 Pharmacokinetics Over Time

Based on ADAMTS13 activity NCA results from Phase 3 Study 281102, neither TAK-755-(b) (4) nor TAK-755-(b) (4) exhibited time-dependent PK (Figure 3). The mean ADAMTS13 activity PK exposures (C_{max} and AUC) were similar between the PK-I and PK-II periods following TAK-755 (b) (4) administration. Based on limited ADAMTS13 activity NCA results from PK-III period of Phase 3 Study 281102, TAK-755 (b) (4) did not show evidence of time-dependent ADAMTS13 activity. Therefore, the PK of ADAMTS 13 activity following ADZYNMA administration is time independent. This observation was also supported by the PopPK analysis results: the clearance (CL) of ADAMTS13 activity was estimated to be linear.

Figure 3. Mean (Solid Line) and Individual (Grey lines) ADAMTS13 Activity-time Profiles Following Administration of ADZYNMA (TAK-755) 40 IU/kg (b) (4) by PK-I, PK-II, and PK-III Periods



Source: Applicant. Module 2, section 2.7.2. Summary of Clinical Pharmacology Studies.

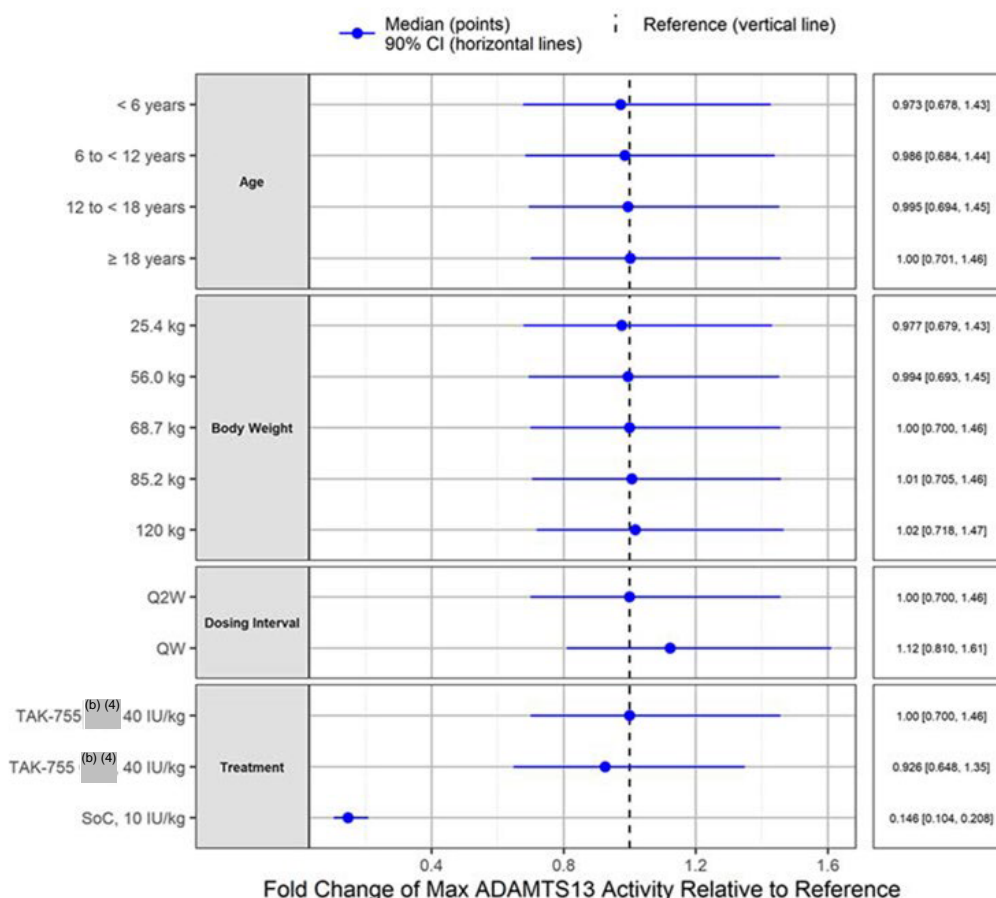
6.2.6 Pharmacokinetics Intrinsic and Extrinsic Factors and Pharmacokinetics in Specific Populations

Intrinsic and Extrinsic Covariates

To better characterize ADAMTS13 activity following IV administration of TAK-755 or SoC in cTTP subjects, the Applicant developed a population PK (PopPK) model using data from adults, adolescents and pediatric subjects below 12 years of age (N=65) in Studies 281101, 281102 and 3002. A two-compartment model with linear elimination and with fixed exponents for the effect of body weight on clearance and volume of distribution parameters was used to assess the time profiles of ADAMTS13 activity. Various intrinsic (such as body weight, age, race, sex, markers of renal/liver function, blood type, etc.) and extrinsic (such as dose, manufacturing site) covariates were assessed.

Based on the PopPK analysis, the influence of body weight on ADAMTS13 activity PK differences was offset when weight-based dosing was employed. Body weight did not exert any further impact on ADAMTS13 activity PK, e.g., maximum concentration (C_{max}) and average concentration (C_{ave}). No intrinsic factors such as age, gender, race, baseline estimated glomerular filtration rate (eGFR), and baseline bilirubin were identified as covariates impacting ADAMTS13 PK (Figure 4 & Figure 5). Therefore, no dose adjustment in the cTTP patient population beyond body weight-based dosing. Please refer to pharmacometrics consult review for details.

Figure 4. Effect of Key Covariates on Maximum ADAMTS13 Activity (C_{max})



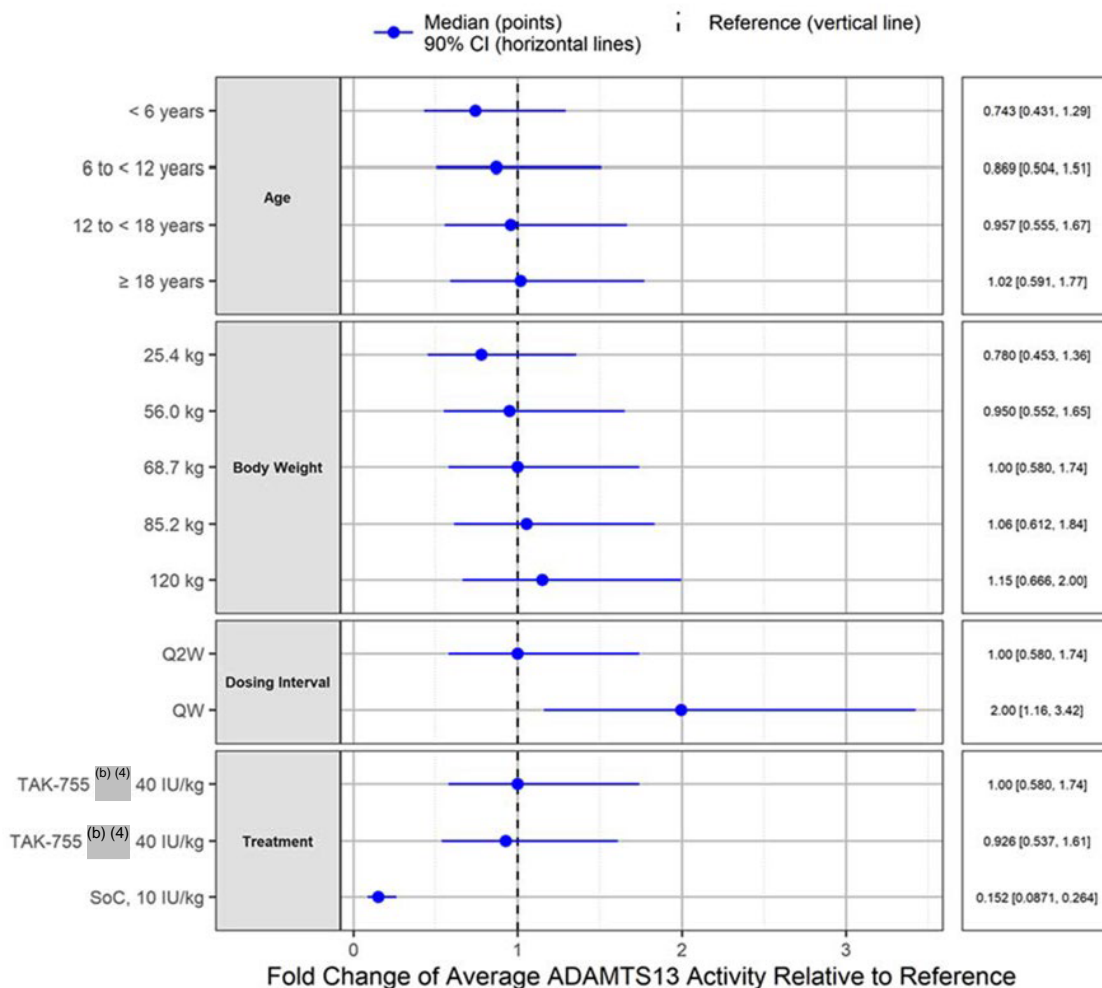
Source: Applicant. PopPK and Exposure-Response cTTP Report.

PK in Pediatric Subjects with cTTP

As for age, based on the NCA of ADAMTS13 activity in Study 281102, which included all pediatric patients (age <12 years) in this regulatory submission, the evaluable PK parameters for ADAMTS13 activity ((b) (4) ; PK-I and PK-II periods) were generally similar across the age groups (<6, 6 to <12, 12 to <18, and ≥18 years). The results from popPK analysis also showed that age did not significantly impact the PK of ADAMTS13 activity and overall ER relationship. The weight-based dosing effectively compensates for the majority of observed drug exposure

variations across different age groups. The age-related impact on PK is supported by the exploratory exposure-response (ER) analyses, wherein the effect of age on the ER relationship was found to be non-significant. Please refer to pharmacometrics consult review for detailed information.

Figure 5. Effect of Key Covariates on Average ADAMTS13 Activity (Cave)



Source: Applicant. PopPK and Exposure-Response cTTP Report.

6.3 Pharmacodynamics

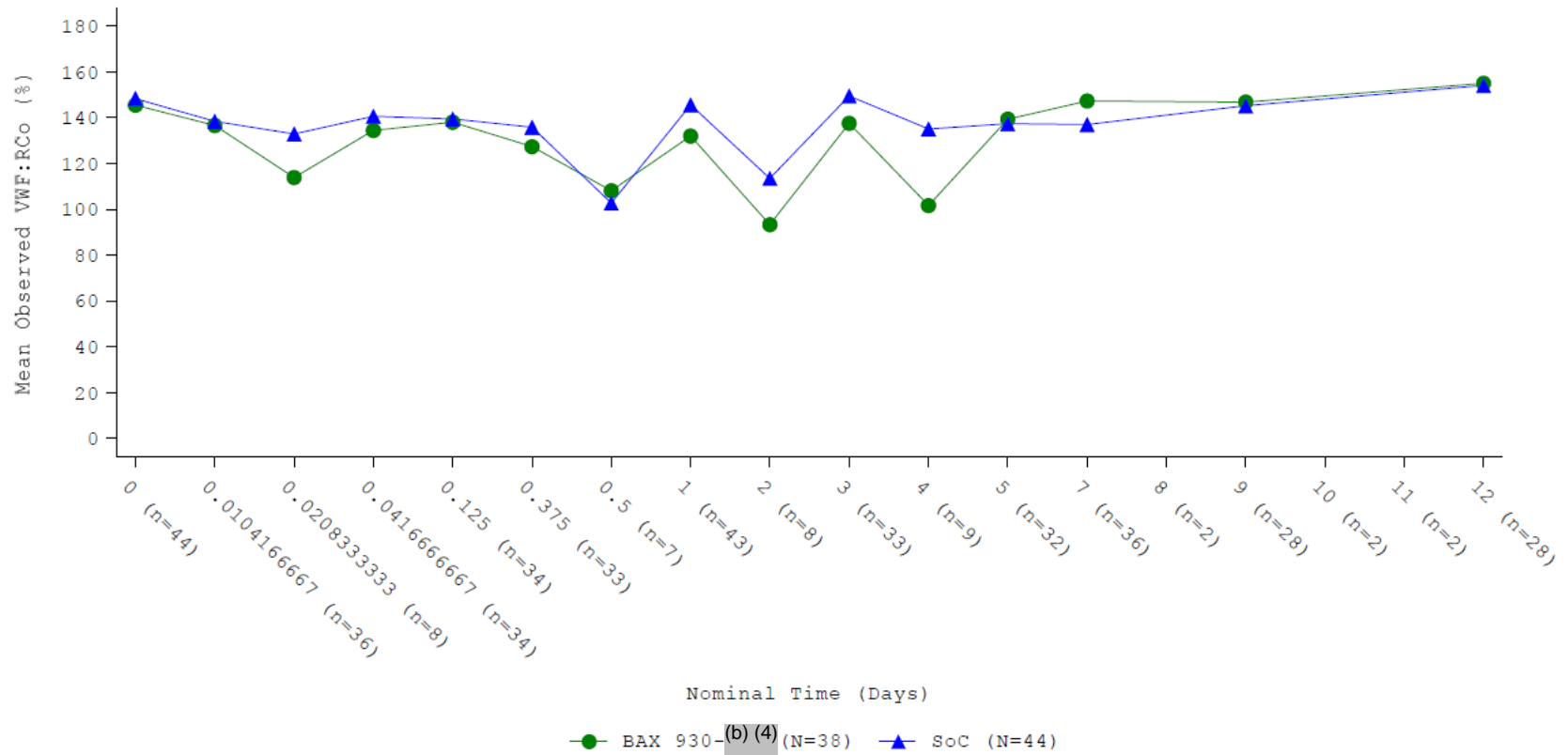
ADZYNMA is recombinant ADAMTS13 developed as a targeted ERT for prophylactic or on-demand enzyme replacement therapy for patients with cTTP. ADAMTS13 is a plasma zinc metalloprotease that regulates the activity of von Willebrand factor (VWF) by cleaving large and ultra-large VWF multimers to smaller units and thereby reducing the platelet binding properties of VWF and its propensity to form microthrombi. VWF: antigen (VWF:Ag), and VWF: ristocetin

cofactor activity (VWF:RCo) time series including baseline and following infusion of the SoC and TAK-755 treatment during the initial PK assessment in the Prophylactic Cohort was evaluated.

As depicted in Figure 6 and Figure 7, the mean VWF:RCo baseline activity in TAK-755 (PK-I and PK-II periods) and SoC treatment arms (PK-I period) were on average slightly elevated (approximately 140-150% of average normal activity). Following IV administration of TAK-755 (PK-I and PK-II periods) or SoC (PK-I period), a mean drop from baseline VWF: RCo of approximately 15% to 25% was on average observed for time points up to 1 to 2 days post-infusion. No obvious trend was observed between TAK-755 and SoC when looking at the overall time-series profiles. During PK-II, comparing TAK-755 (b) (4) and TAK-755 (b) (4), the latter resulted in a higher percentage of subjects with VWF cleavage products.

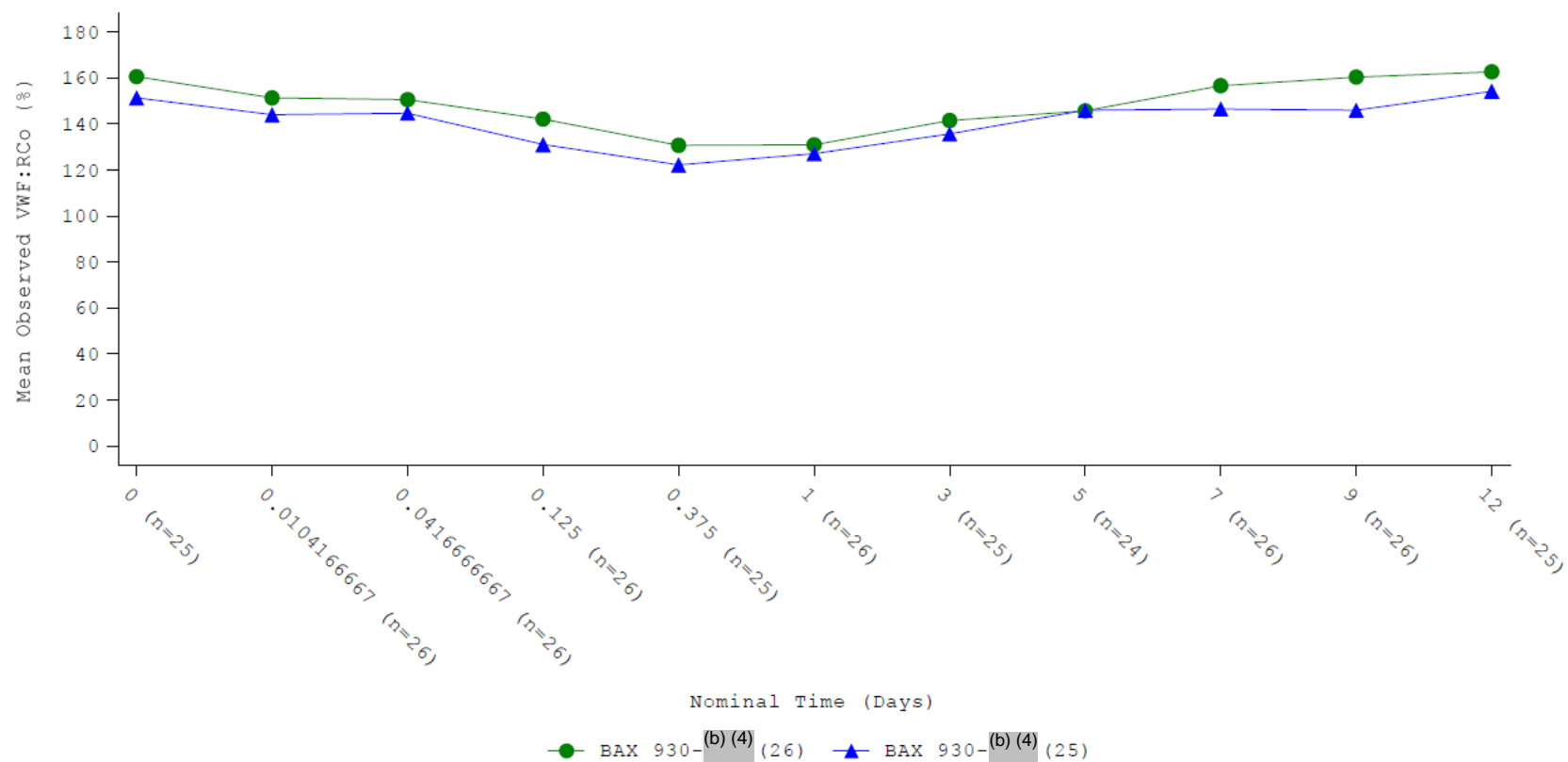
The high ratio of VWF antigen: ADAMTS13 activity is associated with risk of thrombosis. XX shows a paired nominal time point ratio of a) VWF antigen:ADAMTS13 activity and b) VWF activity:ADAMTS13 activity. Following IV infusion, these ratios fall before coming back to baselines. The reduction of the ratio was more evident for ADZYNMA compared to SoC. The results suggested that ADZYNMA may provide higher ADAMTS13 levels relative to VWF antigen and activity compared to SoC.

Figure 6. Mean Observed VWF:RCo (%) Activity-Time Profile Following TAK-755 (b) (4) and SoC for PK-I — PD Analysis Set



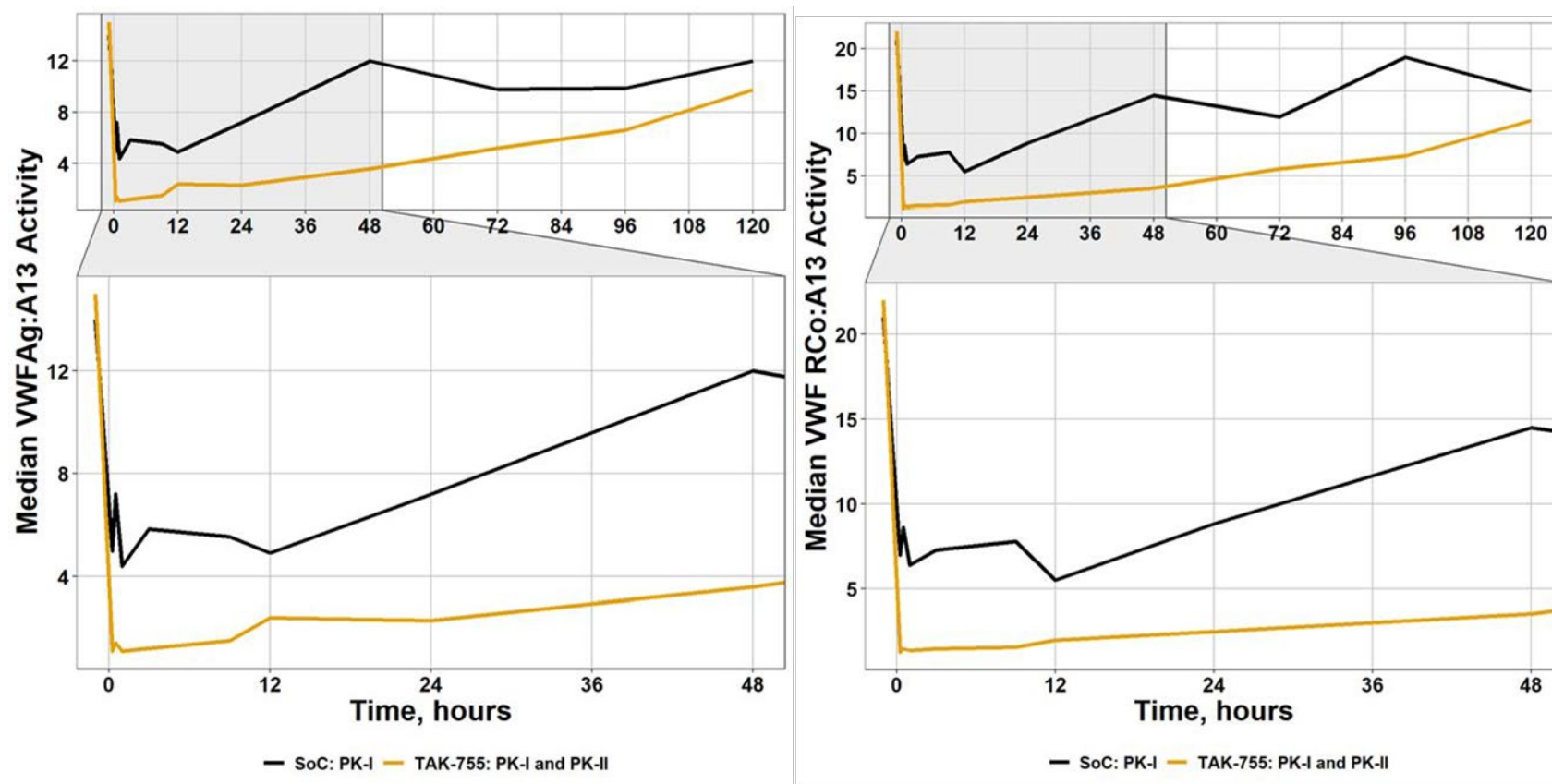
Source: Applicant. CSR 281102.

Figure 7. Mean Observed VWF:RCo (%) Activity-Time Profile Following TAK-755 (b) (4) and TAK-755 (b) (4) for PK-II — PD Analysis Set



Source: Applicant. Module 5, CSR 281102.

Figure 8. Median Time-Profiles of (a) VWF:Ag and ADAMTS13 Ratio (Left) and (b) VWF:RCo and ADAMTS13 Ratio (Right) Grouped by Treatment



Source: Applicant. Module 5, CSR 281102.

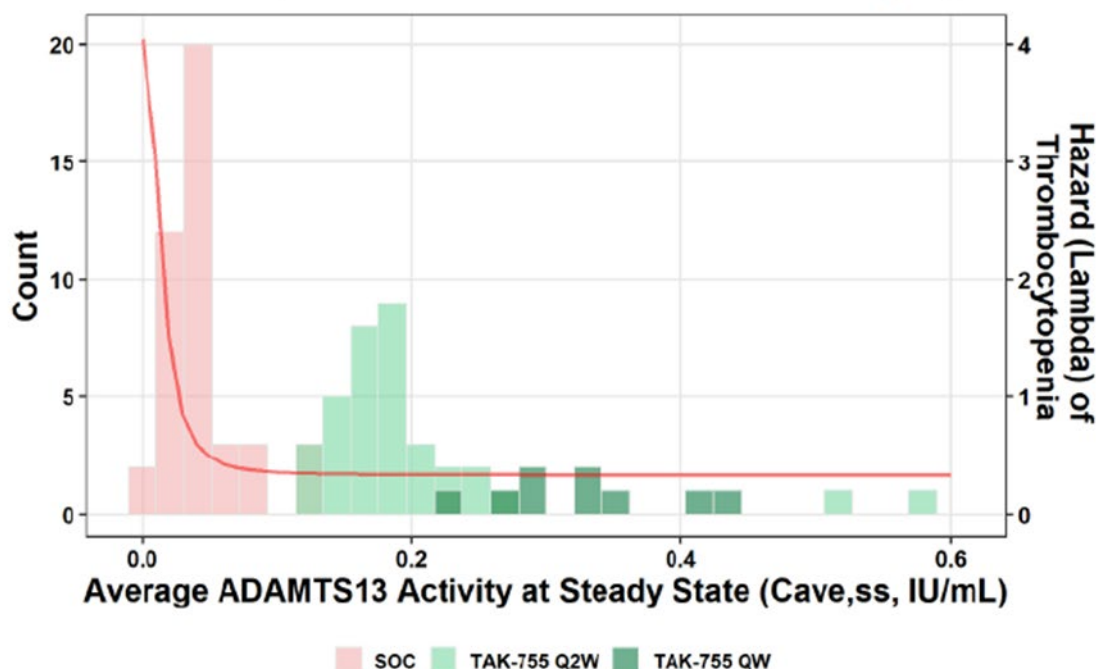
6.4 Exposure-Response Relationships

The Applicant developed population exposure-response (E-R) models to investigate the relationship between ADAMTS13 activity and the likelihood of isolated TTP manifestations, including composite TTP manifestation endpoints, after administering treatment (ADZYNMA vs. SoC). The primary ER analysis focused on modeling event count data. Additionally, other ER analyses were conducted using semi-parametric Cox-proportional-hazards modeling for recurring events and parametric repeated time-to-event (RTTE) models. Age's impact was assessed within these ER models to provide dosing recommendations for pediatric subjects (<12 years) with cTTP.

The E-R analysis demonstrated a significant treatment effect of TAK-755 compared to the standard of care (SoC). The relationship between the steady-state $C_{ave,ss}$ of ADAMTS13 activity and various endpoints, including thrombocytopenia events, MAHA events, and the composite TTP manifestations endpoint, was found to be steep and statistically significant. Specifically, for thrombocytopenia, the relationship showed an E_{max} corresponding to an 86.4% reduction in thrombocytopenia event counts, with an effective average ADAMTS13 activity (defined as EC_{ave50}) of 0.0296 IU/mL (or 3% activity). In addition, the effect of age (<12 and ≥ 12 years) on the drug-effect parameters of ADAMTS13 activity was not statistically significant, indicating a consistent ADAMTS13 activity-thrombocytopenia response relationship across adult, adolescent, and pediatric subjects (EC_{ave50} : 0.0149 IU/mL; E_{max} : 91.8% reduction in thrombocytopenia event counts).

Figure 9 illustrates the final relationship between the C_{ave} of ADAMTS13 activity and the count (left axis) or hazard (right axis) of thrombocytopenia. As the average ADAMTS13 activity increases, the hazard of thrombocytopenia (solid red line in the plot) decreases rapidly until an average ADAMTS13 activity of about 0.1 IU/mL (or 10% activity) is reached, after which the hazard remains relatively constant. Table 7 shows the probability of being thrombocytopenia-free (count=0) associated with steady-state ADAMTS13 C_{ave} activity (popPK model predicted) resulting from the administration of ADZYNMA and SoC. Similarly, a consistent and significant ER relationship was observed between average ADAMTS13 activity exposures and MAHA counts.

Figure 9. Average ADAMTS13 Activity at Steady State (Exposure)-Hazard of Thrombocytopenia (Response) Relationship Using Isolated Thrombocytopenia Event Counts (N=41; Adults, Adolescents, and Pediatric Subjects)



Note 1: Data from Period 1 and 2 based on MFAS, the prophylaxis cohort in study 281102 and patients <12 and ≥12 years of age.

Note 2: Model-predicted Hazard (Lambda) of Thrombocytopenia for mean $C_{ave,ss}$ ADAMTS13 Activity (IU/mL) of the SoC (10 IU/kg, 0.0447 IU/mL), TAK-755 Q2W (40 IU/kg, 0.202 IU/mL) and TAK-755 QW (40 IU/kg, 0.325 IU/mL) were 0.538, 0.336, and 0.333, respectively.

X-axis represent the distribution (histogram) of the average ADAMTS13 activity values at steady state; Left Y-axis represent the total number of subjects falling under each bin of steady state exposure (highlighted on X-axis) from period 1 and 2; Right Y-axis represents model predicted hazard (solid red line on the plot) of thrombocytopenia; The final Poisson model with random effect and sigmoidal E_{max} drug effect adequately described the observed thrombocytopenia counts; key drug effect parameters include: EC_{50} : 0.0149 IU/mL (or 1.5% activity); E_{max} : 91.8% reduction of thrombocytopenia counts
ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; $C_{ave,ss}$ =average concentration at steady state;
ER=exposure-response; MFAS=modified full analysis set; popPK=population pharmacokinetics; Q1W=once weekly;
Q2W=every 2 weeks; SoC=standard of care

Source: Applicant. PopPK and ER Report TGRD-PMX-TAK755-2375_PKER

The population E-R analysis results provided further support and validation to the findings from per-protocol statistical analyses, indicating a noteworthy therapeutic impact of ADZYNMA compared to the SoC. The results indicated that ADAMTS13 activity C_{ave} significantly decreases the risk of thrombocytopenia and MAHA in a concentration-dependent manner across different age groups, including adults, adolescents, and pediatrics. Please refer to Pharmacometrics population PK/PD consult review for detailed information.

Table 7. Count Exposure-response Model Predicted Probability of Thrombocytopenia-Free (Count=0) by Predicted Percentiles of ADAMTS13 $C_{ave,ss}$ Resulting From ADZYNMA (TAK-755) and SoC Administration (N=41)

Percentile of ADAMTS13 Activity $C_{ave,ss}$ exposures distribution	SoC (10 IU/kg)		TAK-755 Q2W (40 IU/kg)		TAK-755 Q1W (40 IU/kg)	
	ADAMTS13 $C_{ave,ss}$ (IU/mL)	Probability of Count 0 (%)	ADAMTS13 $C_{ave,ss}$ (IU/mL)	Probability of Count 0 (%)	ADAMTS13 $C_{ave,ss}$ (IU/mL)	Probability of Count 0 (%)
5%	0.0155	12.2	0.130	70.8	0.239	71.6
10%	0.0184	18.3	0.137	70.9	0.256	71.6
25%	0.0277	38.3	0.155	71.2	0.288	71.7
50% (Median)	0.0398	54.6	0.176	71.3	0.332	71.7
75%	0.0491	60.9	0.206	71.5	0.351	71.7
90%	0.0863	69.0	0.249	71.6	0.424	71.8
95%	0.121	70.6	0.396	71.7	0.427	71.8

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; $C_{ave,ss}$ =average concentration at steady state; ER=exposure-response; MFAS=modified full analysis set; popPK=population pharmacokinetics; Q1W=once weekly; Q2W=every 2 weeks; SoC=standard of care

Note: data from period 1 and 2 based on MFAS, the prophylaxis cohort in Study 281102 and subjects <12 and ≥12 years of age. First column represents the popPK model predicted steady-state ADAMTS13 activity C_{ave} exposure distributions (broken down by percentiles).

Source: Applicant. PopPK and ER Report TGRD-PMX-TAK755-2375_PKER

In addition to population PK and E-R analysis, the Applicant also developed Quantitative System Pharmacology (QSP) model to provide a dynamic quantitative understanding of ADAMTS13 activity relationship with VWF and platelets, to provide additional supportive evidence of the favorable risk benefit profile of ADZYNMA.

Based on pharmacometrics QSP consult review, the QSP model provides confirmative evidence to support the use/approval of ADZYNMA in patients with cTTP by integrating the current mechanistic understanding of the disease and pharmacology. Please see Pharmacometrics QSP consult review for details.

6.5 Immunogenicity

Anti-ADAMTS13 and anti-rADAMTS13 neutralizing antibodies were measured by the FRETs-VWF73 activity assay using a (b) (4) Bethesda method. No study subjects with cTTP developed neutralizing antibodies against ADAMTS13 during treatment of ADZYNMA in Studies 281101, 281102 and 3002. In Study 281102, one subject with iTTP had binding and neutralizing antibodies during treatment with TAK-755-(b) (4).

Anti-rADAMTS13/ADAMTS13 binding antibodies were monitored by ELISA assay. In

Studies 281101, 281102 and 3002, thirteen subjects with cTTP treated prophylactically with ADZYNMA tested positive for low-titer binding antibodies against ADAMTS13, and no increase in antibody titers over time. The effect of these antibodies on the PK, PD, safety, and/or efficacy of rADAMTS13 products is unknown. There are no data on immunogenicity in previously untreated patients (subjects naïve to plasma-based products), therefore, the risk of immunogenicity for naïve subjects to this drug product is unknown.

Two subjects had transient low titer anti-CHO antibodies.

6.6 Clinical Pharmacology Conclusions

Pharmacokinetics: Following IV administration of ADZYNMA, both ADAMTS13 antigen and activity followed bi-exponential PK profiles. PK characteristics of ADAMTS13 antigen and activity following ADZYNMA IV administration were similar. ADZYNMA PK was approximately dose proportional between 20 and 40 IU/kg. At the dose of 40 IU/kg, mean IR for ADAMTS13 antigen and activity was 0.03 (µg/mL)/(µg/kg) and 0.03 (IU/mL)/(IU/kg), respectively. Mean clearance (CL) was 0.05 L/h for both ADAMTS13 antigen and activity.

The PK profiles of ADZYNMA (TAK-755) manufactured from two sites (TAK-755-(b) (4) and TAK-755-(b) (4) (commercial)) were comparable. The weight-based dosing effectively compensates for the majority of observed drug exposure variations across different age groups.

No intrinsic factors such as age, gender, race, baseline estimated glomerular filtration rate (eGFR), and baseline bilirubin were identified as covariates impacting ADZYNMA PK.

Pharmacodynamics: VWF antigen and VWF:ristocetin cofactor activity (VWF:RCo) were used to assess VWF platelet binding activity. Following IV doses of ADZYNMA at the recommended dose, both VWF antigen and VWF:Rco transiently decreased for 1 to 2 days with a 15% to 25% change from baseline.

Exposure-Response Relationships: The E-R analysis results showed a noteworthy therapeutic impact of ADZYNMA compared to the SoC. The E-R analysis results indicated that ADAMTS13 activity Cave significantly decreases the risk of thrombocytopenia and microangiopathic hemolytic anemia (MAHA) in a concentration-dependent manner across different age groups, including adults, adolescents, and pediatrics. In addition, the results from the QSP model also provided confirmative evidence to support the use of ADZYNMA in subjects with cTTP.

Immunogenicity: No cTTP patients tested positive for neutralizing antibodies against ADAMTS13. Thirteen (one subject in Study 281102 and 12 subjects in Study 3002) of 67 patients treated prophylactically with ADZYNMA with confirmed cTTP tested positive for low-titer

binding antibodies against ADAMTS13 with no observable clinical impact on the safety or efficacy of ADZYNMA, and no increase in antibody titers over time. The effect of these antibodies on the PK, PD, safety, and/or efficacy of rADAMTS13 products is unknown. There are no data on immunogenicity in previously untreated patients (subjects naïve to plasma-based products), therefore, the risk of immunogenicity for naïve subjects to this drug product is unknown.

7 APPENDIX - INDIVIDUAL STUDY

7.1 Study #1 – Study 281101

Study Completion: February 22, 2016

Title: A Phase 1, Prospective, Uncontrolled, Open-label, Multi-center, Dose-escalation Study Evaluating the Safety and Pharmacokinetics in Hereditary Thrombotic Thrombocytopenic Purpura (hTTP)
Objectives: To evaluate safety, including immunogenicity and pharmacokinetics of BAX 930 (rADAMTS13) in hTTP. Primary Objective: To evaluate the safety of BAX 930 following single infusions at doses of 5, 20, and 40 U/kg body weight, including the occurrence of adverse events (AEs) (serious and non-serious) and formation of binding and inhibitory antibodies to BAX 930. Secondary Objectives: 1. To evaluate the PK of BAX-930 following single infusions at doses of 5, 20, and 40 U/kg body weight. 2. To evaluate the effect of BAX 930 on plasma von Willebrand factor (VWF) levels and multimeric patterns. Exploratory Objectives: To assess health-related quality of life (HRQoL) and previous treatment experiences of participating subjects.
Study Design This study was a Phase 1, prospective, uncontrolled, open-label, multicenter, dose-escalation study to evaluate the safety, including immunogenicity, and pharmacokinetics of BAX 930 (rADAMTS13) in a total of at least 14 evaluable subjects assigned to one of three dose cohorts (Planned: Dose Cohort 1 N=3; Dose Cohort 2 N=3; Dose Cohort 3 N=8) diagnosed with severe hTTP (plasma ADAMTS13 activity < 6%)..
Number of Subjects: Planned: 14 evaluable subjects with TTP Analyzed: 15 of 16 enrolled subjects who received the investigational product were included in the safety and pharmacokinetic analysis.
Diagnosis and Criteria for Inclusion: The main criteria for inclusion were subjects between 12 (Poland, and Germany: adolescent subjects were not to be enrolled) and 65 years of age, with documented diagnosis of severe hereditary ADAMTS13 deficiency, confirmed by genetic testing and ADAMTS13 activity < 6%, and not displaying any severe TTP symptoms at screening. Subjects ≥ 18 years of age were to have a Karnofsky score ≥ 60%, and < 18 years of age have a Lansky score ≥ 70%.
Study Treatments Investigational medicinal product(s): BAX 930 (rADAMTS13) Dose: 5 U/kg, 20 U/kg, and 40U/kg Formulation: injection, powder, lyophilized, for solution/suspension Route(s) of administration: intravenous (IV) Dose regimen: single dose

Pharmacokinetic Sampling Times

At pre-infusion (within 1 hour prior to the start of the infusion) and after the end of the infusion at 15 minutes (± 5 minutes), 30 minutes (± 5 minutes), 1 hour (± 5 minutes), 3 hours (± 10 minutes), 6 hours (± 10 minutes), 9 hours (± 15 minutes), 12 hours (± 2 hours), 24 hours (± 2 hours), 48 hours (± 2 hours), 96 hours (± 2 hours), 144 hours (± 4 hours), 168 hours (± 4 hours), 192 hours (± 4 hours), 216 hours (± 4 hours), 240 hours (± 4 hours), 264 hours (± 4 hours) and 288 hours (± 4 hours).

Pharmacokinetic Results:

Following single-dose administration of BAX 930 at 5 U/kg, 20 U/kg, and 40 U/kg to adults, dose-related increases in individual ADAMTS13:Ag and activity (as measured using FRETs-VWF73 and Technozym assays, which were found to be highly comparable) were observed and reached a maximum at approximately 1 hour or earlier. The profiles of ADAMTS13 fluorescence resonance energy transfer (FRETs-VWF73) and ADAMTS13 Technozym over time tracked well with ADAMTS13:Ag. The corroborated results show ADAMTS13:Ag and activity coverage, which was higher than baseline (predose) value for most data points during the 288-hour sample collection window.

The most robust PK data were derived from the 40 U/kg dose cohort, in which the greatest number of subjects (9 subjects, including 7 adults) were enrolled and values above the LLOQ were observed. The interpretation of the comparisons that include the lowest dose cohorts must be tempered by the low numbers of subjects.

Geometric mean Cl and V_{ss} of ADAMTS13 activity and ADAMTS13:Ag were comparable across dose cohorts. Geometric means $t_{1/2}$ ranged from 57.1 hours to 86.3 hours for ADAMTS13:Ag, 42.1 to 59.2 hours for ADAMTS13 FRETs-VWF73, and 59.6 hours to 88.6 hours for ADAMTS13 Technozym.

There was approximate dose proportionality with respect to ADAMTS13:Ag C_{max} (geometric means of 0.323 $\mu\text{g/mL}$ after 20 U/kg infusion and 0.672 $\mu\text{g/mL}$ after 40 U/kg infusion) and $AUC(0-\text{inf})$ (geometric means of 18.3 $\mu\text{g}\cdot\text{h/mL}$ after 20 U/kg infusion and 36.0 $\mu\text{g}\cdot\text{h/mL}$ after 40 U/kg infusion). Likewise, ADAMTS13 activity (FRETs-VWF73) C_{max} and total exposures increased approximately in proportion to the dose escalations. The geometric mean C_{max} was 0.398 U/mL after 20 U/kg infusion and 0.948 U/mL after 40 U/kg infusion; and geometric mean $AUC(0-\text{inf})$ was 19.1 U \cdot h/mL after 20 U/kg infusion and 53.1 U \cdot h/mL after 40 U/kg infusion. No apparent differences were observed for ADAMTS13 activity and ADAMTS13:Ag between the adolescents ($N=2$) and adults ($n=7$), where data were available.

However, the pediatric PK parameters could not be accurately estimated due to insufficient data from the sparse sampling scheme of the two adolescent subjects.

In addition to the pharmacokinetic results, evidence of pharmacodynamics activity was observed. With escalating BAX 930 doses, prolonged detectable ADAMTS13-mediated VWF cleavage products were present (all subjects up to 3 hours, 24 hours, and 48 hours postdose at 5 U/kg, 20 U/kg, and 40 U/kg, respectively). A trend for decreasing large multimers, a fraction of which also included ultra-large multimers, and increasing levels of the intermediate fraction was observed over the first 24 hours post infusion in individual profiles at BAX 930 doses of 20 U/kg or 40 U/kg. Furthermore, over the first 24 hours, the mean postdose VWF:RCo levels, were lower than mean baseline levels at most timepoints across the three dose cohorts. Decreases by almost 30% were observed in the first 9 hours. There was an increase in the platelet count in all dosing groups and a decrease of LDH in the first 96 hours.

Pharmacokinetic Conclusions:

- The most robust PK data are derived from the 40 U/kg dose cohort, in which there was the greatest number of subjects (9 subjects, including 7 adults) and values above the LLOQ. The interpretation of the comparisons that include the lowest dose cohorts must be tempered by the very low numbers of subjects.
- Following single-dose administration of BAX 930 at 5 U/kg, 20 U/kg, and 40 U/kg to adults, C_{max} and total exposures of ADAMTS13 activity and ADAMTS13:Ag appear to increase in a proportional manner to the dose escalation
- Notwithstanding limitations of the sparse sampling scheme, no apparent age-related differences were observed for ADAMTS13 activity and ADAMTS13:Ag between adolescents and adults, where data were available.
- The profiles for ADAMTS13 activities over time (as measured by FRETs-VWF73 and Technozym assays) tracked well with ADAMTS13:Ag.
- Apparent dose-related changes for increasing detectable ADAMTS13-mediated VWF cleavage products and decreasing VWF multimer sizes were observed with BAX 930 dose escalation.

- Pharmacodynamic effects were also observed with respect to platelet count and LDH in all dosing groups in the first 96 hours.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.2 Study #2 – Study 281102

Interim Analysis Data Cutoff Date: August 12, 2022

Title: 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 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP, Upshaw-Schulman Syndrome [USS], hereditary thrombotic thrombocytopenic purpura [hTTP]).

Objectives:

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.

Methodology:

This is 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 on-demand treatment of subjects with severe cTTP.

Number of Subjects:

Planned: ~ 57 subjects with severe cTTP: approximately 36 adult (≥ 18 years old) subjects and 12 adolescent (>12 to ≤ 17 years old) or pediatric (0 to <12 years old) subjects in the Prophylactic Cohort and approximately 6 adult subjects and 3 adolescent or pediatric subjects in the On-demand (OD) Cohort.

The interim analysis, with a data cutoff date of 12 Aug 2022, includes data from 32 (66.7%) evaluable (completed the study) subjects (29 adult and 3 adolescent subjects). Data from 48 subjects in the Prophylactic Cohort and 5 subjects the OD Cohort are presented.

Diagnosis and Criteria for Inclusion:

Subjects (aged 0 to 70 years) were to have a documented diagnosis of severe congenital TTP.

Study Treatments

Investigational product(s): recombinant ADAMTS13 (TAK-755, formerly BAX 930 and SHP 655)

Recombinant ADAMTS13 (rADAMTS13), as intravenous (IV) infusions. For the Prophylactic Cohort, dose administration of 40 IU/kg [± 4 IU/kg] was to be once every week (Q1W) or every two weeks (Q2W).

The location of the bulk drug substance (BDS) manufacturing of TAK-755 changed during this study and thus the investigational product (IP) is in some instances referred to with the manufacturing location, for example, TAK-755 ^{(b) (4)} manufactured in (b) (4), and TAK-755 ^{(b) (4)} manufactured in (b) (4).

Reference product(s):

The reference product was standard of care (SoC), as recommended by the investigator. Administration was to be IV infusions daily for the OD Cohort and either Q1W, Q2W, or Q3W for the Prophylactic Cohort.

Pharmacokinetic/Pharmacodynamic Sampling Times and Bioanalytical Methodology:

Blood samples will be drawn at the following standardized timepoints for adult and adolescent subjects (≥ 12 years of age): pre-infusion (within 60 min prior to the start of the infusion), and relative to the end of the infusion for all following timepoints, at 15 ± 5 min, 60 ± 5 min, $3 \text{ hr} \pm 0.5 \text{ hr}$, $9 \text{ hr} \pm 2 \text{ hr}$, $24 \text{ hr} \pm 2 \text{ hr}$, $72 \text{ hr} \pm 4 \text{ hr}$, $120 \text{ hr} \pm 12 \text{ hr}$, $168 \text{ hr} \pm 12 \text{ hr}$, $216 \text{ hr} \pm 24 \text{ hr}$ and $288 \text{ hr} \pm 24 \text{ hr}$.

PK Post-Infusion Laboratory Assessments for subjects undergoing Q1W dosing should not be performed at $168 \pm 12 \text{ hrs}$, $216 \pm 12 \text{ hrs}$ and $288 \pm 12 \text{ hrs}$ timepoints, after PK Infusion #1. However, PK assessments up to $168 \pm 12 \text{ hrs}$ timepoint should be performed after PK Infusion #2.

Timepoints for pediatric subjects (<12 years of age) include: pre-infusion (within 60 min prior to the start of the infusion) and, relative to the end of the infusion for all following timepoints, at 30 min±5 min, 12 hr±2 hr, 24 hr±2 hr, 48 hr±2 hr, 96 hr±2 hr, and 168 hr±4 hr. Timepoints may be adjusted to optimize the sampling scheme as pediatric data become available.

Timepoints for subjects who undergo PK-III include: pre-infusion (within 60 min prior to the start of the infusion) and, relative to the end of infusion for all following timepoints, at 15±5 min, 30±5 min, 60 min±5 min, 9 hr±2 hr, 72 hr±8 hr, 168 hr±12 hr, and 288 hr±24 hr.

Pharmacokinetic Bioanalytical Methodology:

- ADAMTS13 activity were to be measured by the FRETs-VWF73 assay. Results for samples with hemoglobin and bilirubin levels above assay acceptable limits were invalid and not reported. Lower limit of quantification (LLOQ) was (b) (4).
- ADAMTS13 antigen was to be measured using a (b) (4). The LLOQ of the assay was (b) (4).

Pharmacodynamic Bioanalytical Methodology:

- VWF:RCo activity was to be measured using (b) (4) in the presence of VWF and the antibiotic Ristocetin. The LLOQ of the assay was (b) (4).
- VWF:Ag concentration was to be measured by an ELISA-based assay; the LLOQ of the assay was (b) (4).
- VWF multimer qualitative evaluation was to be assessed using (b) (4) sodium dodecyl sulfate (SDS)-agarose gel electrophoresis. (b) (4) SDS-agarose gel electrophoresis was to be used for quantitative evaluation. These analyses employed Western blot with luminescence video imaging.
- ADAMTS13-mediated VWF cleavage products were to be visualized by SDS-poly-acrylamide gel electrophoresis followed by Western blot staining.

Pharmacokinetic & Pharmacodynamic Results:

- TAK-755 IV administration at 40 IU/kg resulted in approximately 5-fold higher ADAMTS13 exposures (C_{max} and AUC) and lower inter-individual variability when compared with SoC administration (plasma-based therapies).
- ADAMTS13 antigen and activity PK characteristics (bi-phasic profile, CL, VSS, and MRT) resulting from TAK-755 (b) (4) IV administration were similar.
- Mean time above ≥10% ADAMTS13 activity and Cave (0-168) were higher following TAK-755 versus SoC, suggesting that TAK-755 in comparison with SoC will provide consistently higher ADAMTS13 activity exposure.
- Geometric mean ratio and associated 90% CI for both AUC and C_{max} between TAK-755 (b) (4) and TAK-755 (b) (4) met the accepted 80% to 125% bioequivalence criteria. These favorable results support PK comparability between the 2 drug substance sources (b) (4).
- ADAMTS13 antigen and activity PK following TAK-755 (b) (4) administration was stationary (ie, did not change over time). Thus, PK characteristics of ADAMTS13 antigen and activity resulting from TAK-755 (b) (4) administration are not expected to change over the period of time.
- No subjects qualified for an impact assessment of immunogenicity on PK of ADAMTS13, as no subjects developed neutralizing antibodies.
- Body weight—based TAK-755 dosing provides generally similar ADAMTS13 activity PK exposures (C_{max}) across the different age groups including pediatrics cohorts (age≤12 years).
- Significant VWF:RCo modulation was not observed following TAK-755 and SoC treatment plausibly due to these VWF measurements taken during stable disease state.
- Following TAK-755 administration, prolonged detectable ADAMTS13 mediated cleavage products were present up to 72 hours post dose in >50% evaluable samples.

Conclusions:

In conclusion, TAK-755 treatment was associated with 5 times higher ADAMTS13 exposure levels, and demonstrated favorable efficacy and safety, when compared to SoC. These results support the clinical benefit of TAK-755 for both long term prophylaxis and treatment of acute TTP events in patients with cTTP.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.3 Study #3 – Study TAK-755-3002 (Study 3002)

Interim Analysis Data Cutoff Date: August 12, 2022

Title: A Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of the safety and efficacy of TAK-755 (rADAMTS13, also known as BAX 930/SHP655) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP; Upshaw-Schulman Syndrome, or hereditary thrombotic thrombocytopenic purpura)

Objectives:

The primary objective is to evaluate the long-term safety and tolerability of TAK-755 (a recombinant human disintegrin and metalloproteinase with thrombospondin motifs 13 [rADAMTS13]) in terms of related treatment-emergent adverse events (TEAEs) and related serious adverse events (SAEs) in both the prophylactic and the on-demand cohorts.

Methodology:

This Phase 3b study is an ongoing prospective, open-label, multicenter, single treatment arm continuation study. Enrolled subjects were to comprise both non-naïve (rollover) subjects who completed TAK-755 treatment in the parent Phase 3 Study 281102 and naïve (non-rollover) subjects who did not complete the pivotal Phase 3 study. Non-rollover subjects may have had no prior exposure to TAK-755, or they may have received TAK-755 as part of an Expanded Access Program, as part of the Phase 1 Study 281101, or as part of the Phase 3 Study 281102 if they withdrew due to an allergic reaction to standard-of-care therapy. Subjects not already enrolled in the study who experience an acute thrombotic thrombocytopenic purpura (TTP) event are eligible to enroll in the on-demand cohort.

Subjects in the prophylactic cohort were to receive regular long-term administration of 40 IU/kg TAK-755, once every 2 weeks (Q2W) or once every week (Q1W). Subjects were generally to start TAK-755 treatment at the same dosing frequency they were previously receiving prior to enrollment in the study.

Non-rollover subjects experiencing an acute TTP event, meeting all eligibility criteria, and consenting to treatment in the study, were to be enrolled in the on-demand cohort and treated with TAK-755 as follows:

- An initial dose of 40 IU/kg TAK-755 on Day 1.
- A subsequent dose of 20 IU/kg TAK-755 on Day 2.
- A daily dose of 15 IU/kg TAK-755 starting at Day 3 until 2 days after the acute TTP event is resolved.

Investigators may have used additional TAK-755 treatment if the clinical response with TAK-755 was not adequate after 1 week of treatment, in which case, subjects were to continue the dosing regimen recommended by the investigator during the acute TTP event until event resolution. Upon resolution of the acute TTP event, subjects could either enter the prophylactic cohort or complete the study and discontinue entirely from further participation.

Number of Subjects:

Planned: ~ 77;

Enrolled subjects were to comprise both rollover subjects (approximately 57) who completed TAK-755 treatment in the Phase 3 Study 281102 and non-rollover subjects (at least 20) who did not complete the Phase 3 study.

As of the date for this interim analysis (12 Aug 2022), 47 subjects were enrolled in the study; 36 subjects (29 rollovers and 7 non-rollovers), comprising 35 adults and 1 adolescent subject received TAK-755 prophylaxis. No pediatric subjects (<12 years) were dosed with TAK-755. All 36 subjects were analyzed for safety, efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and health-related quality of life (HRQoL) evaluations. No subjects were enrolled in the on-demand cohort. As of the interim analysis data cutoff, 35 subjects were ongoing in the study.

Diagnosis and Criteria for Inclusion:

Subjects (aged 0 to 70 years) with a documented diagnosis of cTTP with severe ADAMTS13 deficiency.

Study Treatments

Investigational product(s): recombinant ADAMTS13 (TAK-755, formerly BAX 930 and SHP 655)

Recombinant ADAMTS13 (rADAMTS13), as intravenous (IV) infusions. For the Prophylactic Cohort, dose administration of 40 IU/kg [\pm 4 IU/kg] was to be once every week (Q1W) or every two weeks (Q2W).

<p>Clinical Pharmacology-related Results:</p> <p>Pharmacokinetics: The ADAMTS13 activity PK parameters (Cmax, Tmax, and IR) resulting from TAK-755 administration, estimated from sparse sampling, were generally consistent with the parent Study 281102 interim results. Also, consistent with the parent study, all Ctrough values were below LLOQ across all evaluable subjects.</p> <p>Pharmacodynamics: No obvious trend in VWF:RCo modulation was observed from the PD data over the course of the study from sparse sampling.</p> <p>Immunogenicity: Anti-rADAMTS13 binding antibodies were detectable at low titer (1:20 or 1:40) in 5 rollover subjects providing an incidence rate of 13.9% for this study. Detection of these binding antibodies was not temporally associated with TTP events, AEs, or development of neutralizing antibodies. The titers remained low over time and did not increase. No neutralizing antibodies were detected in any subject.</p> <p>Conclusions: In conclusion, the results from this interim analysis are consistent with those reported in the parent Phase 3 Study 281102. These results support the therapeutic benefit of TAK-755 both for long term prophylaxis and in the treatment of acute and subacute TTP events in adult and adolescent patients with cTTP. Further, the results demonstrate a favorable safety and tolerability profile that is consistent with that of the Phase 3 study.</p>

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.