30 May 2024
EMA/352066/2024 Corr.1*
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adzynma

Common name: rADAMTS13

Procedure No. EMEA/H/C/006198/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

* Corrected on 4 November 2025 to update the 'International Non-proprietary Name' to 'common name' in the cover page of the EPAR

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List of abbreviations

ADAMTS13	a disintegrin and metalloproteinase with thrombospondin motifs 13
ADR(s)	adverse drug reaction(s)
AE	adverse event
AUC	area under the curve
AUC(0-inf)	area under the concentration-time curve from time zero to infinity
AUCall	area under the concentration-time curve from time zero to last sampling point
BDS	bulk drug substance
Cave(0-168h)	average concentration/activity for 0-168h interval
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
Cmax	maximum concentration or maximum activity
COVID-19	coronavirus disease 2019
Ctrough	trough concentration/activity
cTTP	congenital thrombotic thrombocytopenic purpura
EAER	exposure-adjusted event rate
EAS	efficacy analysis set
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5 Dimensions Questionnaire 3-Level
ER	exposure-response
ERT	enzyme replacement therapy
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FFP	fresh-frozen plasma
FVIII	factor VIII
GCP	Good clinical practice
HRQOL	health related quality of life
HR(s)	hazard ratio(s)

hTTP	hereditary thrombotic thrombocytopenic purpura (also known as cTTP)
IA	interim analysis
ICH	International Conference on Harmonisation
iCSR	interim clinical study report
IP	investigational product
IR	incremental recovery
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
iTTP	immune-mediated TTP
IV	intravenous
LDH	lactic dehydrogenase
MAHA	microangiopathic hemolytic anemia
MedDRA	Medical Dictionary for Regulatory Activities
MFAS	modified full analysis set
MRT	mean residence time
NCA	non-compartmental analysis
OD	on-demand
ORT	Orth, Austria
PD	pharmacodynamic(s)
PEQ	cTTP-Patient Experience Questionnaire
PK	pharmacokinetic(s)
popPK	population PK
PRO	patient-reported outcome
PT	preferred term
Q1W	once weekly
Q2W	once every 2 weeks
Q3W	once every 3 weeks
QSP	quantitative systems pharmacology
rADAMTS13	recombinant ADAMTS13
SAE	serious adverse event
SAF	safety analysis set
SD	standard deviation
S/DTP	solvent/detergent-treated plasma

SF-36v2	36-Item Short Form Health Survey Version 2.0
SIN	Singapore
SMQ	Standardized MedDRA Query
SOC	system organ class
SoC	standard of care
SY	Subject-years
t1/2	half-life
TAK-755	recombinant ADAMTS13
TEAE	treatment-emergent adverse event
TIA	transient ischaemic attack
Tmax	time to maximum concentration/activity
TSQM-9	9-item Treatment Satisfaction Questionnaire for Medication
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
US	United States
Vss	steady-state volume of distribution
VWF	von Willebrand factor
VWF:Ag	von Willebrand factor: antigen
VWF:RCo	von Willebrand factor: ristocetin cofactor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Manufacturing Austria AG submitted on 17 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Adzynma, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Adzynma was designated as an orphan medicinal product (EU/3/08/588) on 3 December 2008 in the following condition: treatment of thrombotic thrombocytopenic purpura (TTP).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Adzynma as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/adzynma.

The applicant applied for the following indication: Adzynma is indicated for enzyme replacement therapy (ERT) in patients with congenital thrombotic thrombocytopenic purpura (cTTP) due to ADAMTS13 deficiency.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0489/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0489/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Marketing authorisation under exceptional circumstances

Further to consultation with the applicant, the application was considered for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance rADAMTS13 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 September 2010	EMEA/H/SA/1646/1/2010/PA/III	
8 December 2016	EMEA/H/SAH/068/1/2016/PA/III	
26 July 2018	EMEA/H/SA/1646/2/2018/PA/III	
28 March 2019	EMEA/H/SA/1646/2/FU/1/2019/PA/III	
14 October 2021	EMA/SA/0000067032	
24 February 2022	EMA/SA/0000075394	
21 July 2022	EMA/SA/0000087869	

The Protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

- Potency assay, specifications for dimers and high molecular weight aggregates, determination of host cell protein content, drug substance characterisation, methods for biochemical characterisation of bulk drug substance and final drug product to demonstrate comparability of Phase 1 and Phase 3 clinical material;
  acceptability to change cell line as well as drug substance manufacturing facility during pivotal study, comparability exercise to support change of manufacturing facilities for commercial product, strategy for establishing release specifications and stability data;
  control strategy to monitor process and product composition regarding the ratio of the two molecular rADAMTS13 species included in the planned drug product;
  adequacy of proposed cell line characterization, release specification strategy for the drug substance, specifically with respect to monitoring of impurities, drug product stability strategy
- Appropriateness of animal model, safety pharmacology studies; need for genotoxicity, carcinogenicity and immunogenicity studies; chronic toxicity studies, reproductive and developmental toxicity studies, need for juvenile animal studies, general non-clinical strategy
- General clinical evidence generation strategy for hereditary and acquired TTP;
  Phase 1 study design: age groups, dose-escalation scheme, endpoints;

Phase 2/3 studies: age groups for inclusion, efficacy endpoints, dose regimen;
Phase 3 study: general design, efficacy endpoints, safety evaluation, sample size, study population, lead-in treatment, dosing regimen (prophylaxis and on-demand), definition of subacute TTP manifestations, prophylactic dose escalation, number of paediatric subjects to be included, on-demand treatment cohort, plans for continuation study;
hTTP specific PRO development and use of generic PRO instruments, PRO data statistical analysis plan continuation study;
staggered adult to paediatric introduction of new drug product during Phase 3 study;
PK comparability demonstration for drug substances of initial and commercial manufacturing processes as part of the Phase 3 study, PK comparability criteria;
amendments to the ongoing phase 3 study protocol: revision of secondary endpoint definitions regarding subacute disease manifestations, analysis plan;
plans to present compassionate use data for benefit/risk assessment;
Quantitative Systems Pharmacology (QSP) based modelling and simulation studies to provide supportive evidence: general considerations, external and internal validation, longitudinal exposure-response model, prediction of probabilities of clinically relevant effects;

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	17 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 August 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 January 2024
The following GCP inspection were requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:	
– A GCP inspection at 4 sites (sponsor and clinical investigator sites) in the United States, United Kingdom, and France was conducted between 25/09/2023 and 01/12/2023. The outcome of the inspection carried out was issued on	5 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint	26 February 2024

Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 March 2024
The CHMP Rapporteurs circulated an updated CHMP and PRAC Rapporteurs Joint Assessment Report on	14 March 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP Rapporteurs circulated an updated CHMP and PRAC Rapporteurs Joint Assessment Report	24 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation under exceptional circumstances to Adzynma on	30 May 2024
The CHMP adopted a report on similarity of Adzynma with Cablivi on	30 May 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	30 May 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Congenital thrombotic thrombocytopenic purpura (cTTP) is a serious disorder characterised by episodic microangiopathic haemolytic anaemia, thrombocytopenia that can result in organ damage and premature death. Untreated cTTP can be immediately or progressively fatal. Improved disease recognition and prompt treatment with plasma infusion and/or exchange therapy has reduced the mortality rate of TTP from 85–95% to 10–20% over the past 4 decades (Kremer Hovinga JA *et al,* Hereditary Thrombotic Thrombocytopenic Purpura. N Engl J Med 2019). Initial symptoms of cTTP may present immediately at birth, or later in life. Some patients remain asymptomatic for decades. Major morbidities and death at a young age are common.

The claimed indication for Adzynma is enzyme replacement therapy (ERT) in patients with congenital thrombotic thrombocytopenic purpura (cTTP) due to ADAMTS13 deficiency.

This indication encompasses prophylactic as well as on demand treatment of cTTP.

2.1.2. Epidemiology

Congenital thrombotic thrombocytopenic purpura is an ultra-rare, life-threatening, chronic, and debilitating blood clotting disorder with an estimated prevalence of 0.5 to 4 cases/million (Zhao T *et al,* BMC Genom Data 2021).

2.1.3. Biologic features, aetiology and pathogenesis

Congenital thrombotic thrombocytopenic purpura is caused by severe ADAMTS13 deficiency, generally considered to be <10% of mean normal activity, due to mutations in the ADAMTS13 gene. The autosomal recessive genetic deficiency of ADAMTS13 and clinical dysfunction of the VWF-ADAMTS13 axis is the underlying cause of cTTP. In patients with ADAMTS13 deficiency, reduced cleavage of VWF results in being prone to TTP, a thrombotic disorder of the microvasculature. ADAMTS13 regulates the size of von Willebrand factor (VWF) multimers by cleaving VWF at the Tyr1605-Met1606 bond in the A2 domain to form VWF fragments that, unlike the high molecular weight VWF multimers, do not promote thrombosis (Gao *et al.* 2008). VWF is a multimeric glycoprotein synthesised principally by vascular endothelial cells and megakaryocytes (Zheng 2015). It is essential for normal primary hemostasis and also serves as a carrier protein for coagulation factor VIII (FVIII), with which it circulates in blood as a noncovalently linked complex.

Conditions that are associated with increases in Von Willebrand Factor (VWF) activity, such as infections, trauma and pregnancy, are triggers for acute TTP events and consistent with the two peaks in initial presentation of cTTP: in newborns/childhood and during pregnancy. Symptoms may develop soon after birth, and childhood is a recognised vulnerable period for patients with cTTP. First presentation during pregnancy is also common, specifically during the second and third trimesters, where a remarkable increase in plasma VWF is thought to explain the increased risk for initial presentation, acute episodes, and intrauterine fetal growth restriction. Additional recognised risk factors for aggravation of cTTP and precipitation of an acute event are infections, trauma, and excessive alcohol intake.

2.1.4. Clinical presentation, diagnosis

The clinical presentation of cTTP lies on a spectrum of severity ranging from severe acute TTP episodes to chronic, recurring TTP manifestations which include thrombocytopenia, hemolytic activity, headache, abdominal pain, fatigue or lethargy, bruising, joint pain, muscular pain, forgetfulness, and confusion. While the disease presentation is multifactorial, the root cause of cTTP disease activity is driven by severe ADAMTS13 deficiency, defined as <10% ADAMTS13 activity.

To date, there is no formally adopted definition of an acute episode, though typical features include thrombocytopenia and MAHA which may be accompanied by clinical symptoms with a variable degree of ischemic organ dysfunction or damage, particularly effecting the brain, heart and kidney. When applying a broader clinical definition, the annual incidence of acute episodes was recently reported to be 0.36 (95% CI, 0.29-0.44) with regular plasma prophylaxis treatment and 0.41 (95% CI, 0.30-0.56) without regular plasma treatment in the international Hereditary TTP Registry. Without treatment of acute TTP episodes, mortality exceeds 90%.

Due to the persistent severe ADAMTS13 deficiency, patients with cTTP are at constant risk for developing signs and/or symptoms associated with increased TTP disease activity, especially in the presence of triggering factors such as infections. These "TTP manifestations" can be severe, and may exist as single manifestations (eg, only thrombocytopenia) or in combination (eg, thrombocytopenia in combination with headache). Existing understanding of cTTP pathophysiology suggests that TTP

manifestations are all due to spontaneous formation of VWF-platelet-rich microthrombi leading to varying degrees of organ ischemia, which in severe cases or over longer time, may lead to persistent organ damage associated with morbidity and premature mortality.

A significant proportion of patients with cTTP will experience major morbidities in multiple organs, such as strokes, kidney dysfunction leading to kidney failure, and cardiac injury. Patients with cTTP are always at risk of progressive organ dysfunction and severe exacerbations that could be life-threatening without appropriate treatment. Importantly, as many as 25% to 30% of cTTP patients have a history of stroke or TIA and often before the age of 40 years. The International hereditary TTP (hTTP) Registry reported that 12.5% of patients required hemodialysis or renal transplantation and 25% had chronic kidney disease. Compared with an age- and sex-matched US cohort, the probability of survival in patients with cTTP has been found to be lower at all ages, beginning at birth. Mortality among newborns with cTTP is reported to be 10%, with additional significant mortality before the age of 20 years.

2.1.5. Management

There are no medications approved for routine prophylactic treatment of cTTP.

Current SoC treatment centers around the principle of replacing the missing ADAMTS13 enzyme through on-demand or regular prophylactic infusions of available plasma-based therapies, mostly FFP or S/D plasma. The therapeutic rationale for ADAMTS13 replacement therapy is well understood in this genetic enzyme deficiency disorder and it has been demonstrated that plasma replacement therapy may reduce the frequency and severity of cTTP episodes and has been shown to resolve 96% of acute TTP events in patients with cTTP.

Kremer Hovinga *et al.,* also found that plasma exchange therapy increased ADAMTS13 activity, and decreased VWF antigen and factor VIII:C in a study of 21 patients with cTTP. Importantly, in the context of the treatment of cTTP, two plasma-derived concentrates containing factor VIII and VWF have been used: anti-haemophilic factor (Koate-DVI) and intermediate purity factor VIII (BPL 8Y). These products offset some of the risks but may require more frequent infusions.

Though shown to be effective for the treatment of cTTP, plasma-based therapies are reliant on donor plasma and have well-recognised drawbacks:

- Limited and inconsistent ADAMTS13 replacement results in up to ~25% of mean normal ADAMTS13 levels.
- Large volume of plasma therapies (often 10-15 ml/kg) are required to achieve the ADAMTS13 replacement needed to reasonably control symptoms in most patients with cTTP, which in turn requires burdensome inpatient hospital infusions taking 2 to 4 hours. Plasma therapies are also considered insufficient to prevent acute episodes and long term organ damage in clinical practice.
- There are well-recognised and frequent allergic and hypersensitivity reactions with plasma-based therapies, which are sometimes very severe and treatment-limiting despite premedication with glucocorticoids and antihistamines.
- To attenuate the allergic reactions, multiple prophylactic medications are commonly administered prior to plasma infusions, which have their own associated adverse effects and patient burdens.

There is therefore a clear unmet need for alternative options for the treatment of cTTP.

2.2. About the product

TAK-755 (previously known as "BAX 930" or "SHP655") is recombinant ADAMTS13. ADAMTS13 is a plasma zinc metalloprotease that binds and cleaves newly released ultra-large forms of von Willebrand factor (VWF) in the A2 domain between Tyr1605 and Met1606, usually anchored on the endothelial surface as strings/bundle.

This site-specific cleavage reduces the VWF size and its platelet-binding properties. Thus, the biological role of plasma ADAMTS13 is to regulate 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 induce formation of platelet rich microthrombi. As a recombinant equivalent to endogenous ADAMTS13, with similar potency, pharmacokinetic (PK) and pharmacodynamic (PD) properties, the use of TAK-755 in cTTP patients replenishes plasma ADAMTS13 activity, which is expected to reduce or eliminate the spontaneous formation of VWF-platelet microthrombi and thus, the occurrence of TTP events, as well as TTP manifestations.

TAK-755 is produced in a Chinese Hamster Ovary (CHO) mammalian expression system. TAK-755 is administered as an intravenous infusion. The intended clinical route of administration of TAK-755 is intravenous (IV). The recommended clinical dose for routine prophylaxis is administration of 40 IU/kg body weight of TAK-755 once every other week. The dosing frequency may be adjusted to 40 IU/kg once weekly based on prior dosing regimen or clinical response.

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation based on the unmet medical need and the rarity of the condition.

The applicant claimed that:

- The low prevalence of hereditary TTP, as well as
- the dearth of therapeutic options justify the request of a marketing authorization under exceptional circumstances, as intended in Article 14(8) of EC regulation 726/2004.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a lyophilized powder for reconstitution for intravenous injection containing 500 or 1500 international units (IU) of rADAMTS13 as active substance.

Other ingredients are: sodium chloride, calcium chloride dihydrate, L-Histidine, mannitol, sucrose and polysorbate 80 (E433).

The product is available in a vial (type I glass), with a butyl rubber stopper. Each dosage strength is supplied with 5 mL sterile Water for Injections (sWFI) in a vial (type I glass), with a butyl rubber stopper, as a solvent for reconstitution. In addition, each pack contains one reconstitution device (BAXJECT II Hi-Flow), one disposable syringe, one 25-gauge infusion set and two alcohol swabs.

2.4.2. Active substance

2.4.2.1. General Information

The active substance, rADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is a highly glycosylated protein containing four different types of glycosylation. Mature rADAMTS13 has a calculated polypeptide mass of 145 kDa and contains 77 cysteine residues of which 76 form disulfide bonds.

ADAMTS13 is a plasma metalloprotease which cleaves von Willebrand factor (VWF) multimers and downregulates its thrombogenic potential. A recombinant ADAMTS13 (rADAMTS13) protein was developed for use as treatment in thrombotic thrombocytopenic purpura (TTP) patients.

rADAMTS13 consists of a mixture of two protein species, expressed in Chinese Hamster Ovary (CHO) cells. They differ in a single amino acid exchange at position 97. The INN of the native rADAMTS13 is apadamtase alfa (Glutamin Q97) and the INN of the variant is cinaxadamtase alfa (Arginine R97). The applicant applied release testing and selected extended characterisation tests to compare pure Q97 native and pure R97 variant of rADAMTS13. The presented results show the similarity between Q97 and R97 rADAMTS13. It is agreed that the Q97 and R97 variant of rADAMTS13 have the same physicochemical, biophysical and biological properties. It can be expected that there likely is no negative impact on the functionality of the rADAMTS13 bivariant finished product due to the presence of both Q97 native and R97 variant rADAMTS13 in variable amounts. Also, the Applicant noted that an in-silico assessment of immunogenicity indicated no generation of novel immune-dominant MHC II T cell epitopes as result of the amino acid exchange Q97 to R97. The manufacturing process produces a mixture of two closely related species (product related substances). These two species share the same basic structural elements. No evidence of differences in terms of efficacy and safety has been provided. Thus, it is concluded that the two species are the same active substance.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturers and GMP

The active substance is manufactured and released at Takeda Manufacturing Singapore Pte Ltd, 2A Woodlands Industrial Park D Street 2, Singapore 737779. An appropriate GMP certificate from the Health Products Regulation Group (HSA) Singapore was provided. Also, this site is covered by a QP declaration. Appropriate GMP certificates for all other sites for storage of Master- and Working Cell Bank, release- and in-process-control testing were provided.

Description of Manufacturing Process and Process Controls

The manufacturing process uses a recombinant Chinese Hamster Ovary (CHO) cell line grown in suspension culture. The rADAMTS13 upstream cell culture process includes vial thaw, inoculum expansion, culture, and cell culture harvest. The rADAMTS13 downstream purification process includes virus inactivation, filtration and chromatography steps.

The batch/scale definition is considered acceptable.

Control of materials

The applicant listed all raw materials used for preparation of the fermentation media and buffers as well as chromatograph resins. No animal derived raw materials are used. In case non-compendial raw materials are used, appropriate specifications were established.

The applicant established a two-tiered cell bank and appropriately described the size of the cell banks and conditions for cryopreservation.

The Master Cell Bank (MCB) batch is derived from a pre-master cell bank of the rADAMTS13-expressing CHO cell clone X1. The source history of clone X1 was appropriately described. The Working Cell bank (WCB) is derived from one vial of the MCB. The culture conditions and preparation steps were the same as for the MCB. The production and qualification of future WCBs from the existing MCB is appropriately described and a suitable WCB specification is defined. The post-production cell bank (PPCB) is derived from a bioreactor aliquot of the phase 3 clinical production campaign representative of the commercial scale L from the last day of production. The PPCB cells accumulated multiple additional population doublings compared to the end of the chemostat and are therefore suitable to demonstrate stability beyond the in vitro cell age. Overall, the establishment of the two-tiered cell bank and the post-production cell bank is sufficiently described according to ICH Q5D.

It is important to note that, this cell line harbours two different sequence variants of rADAMTS13. This fact was discussed in several Scientific Advice procedures, and it was concluded that this cell line is exceptionally acceptable. It is noted that the Applicant failed in several attempts to create a monoclonal cell line suitable for commercial manufacturing only expressing apadamtase alfa. The characterisation panel of the MCB, WCB and PPCB is suitable to demonstrate the monoclonality of the cell line and the stable integration of the transgene beyond the planned in vitro cell age. Because the Applicant did not detect new sequence variants in the cell banks (MCB, WCB, EPC and PPCB) or during multiple campaigns of clinical manufacturing by applying sensitive next generation sequencing methods, it is agreed that a routinely performed nucleotide sequencing of the end of production cells (EPC) is not required. To conclude, based on the presented information and data, the cell banks comply with requirements especially according to ICH Q5B.

Control of critical steps and intermediates

The critical process parameters (CPPs) and (critical) in-process controls (IPCs) with their acceptable ranges are listed. The acceptable range for CPPs are proven acceptable ranges (PARs). The normal operating ranges are listed in the section 3.2.S.2.5 Process Validation. All IPC test methods were appropriately described.

No process intermediates were defined in the rADAMTS13 manufacturing process.

Process validation

Process validation- Upstream

The process performance qualification (PPQ) study for the upstream manufacturing process at the Singapore site includes one chemostat campaign. The PPQ result presentation was updated to show individual results rather than minimum, maximum, average and standard deviation.

The process parameters were maintained within their normal operating range. Process Parameter Data are provided for all individual steps. Some excursions of temperature and pH occurred during the cell propagation step and chemostat process. An appropriate deviation follow-up was performed, and it is agreed that these deviations do not have an impact on the PPQ conclusions. The monitored process parameters for the vial thaw and cell expansion steps, seed culture in bioreactors, cell propagation and chemostat production met all acceptance criteria. Also, the process attributes met the acceptance criteria. For the harvest and filtration the acceptance criteria were met. In addition, data for Process Attributes (IPCs) are provided. These are all within acceptable range or negative, as appropriate.

Overall, the variation for individual process attributes was low except for the glucose level in the bioreactor. However, the glucose levels were maintained well within the established normal operating

range. All deviations and non-conformances were appropriately investigated, and it is agreed that these do not impact the results of the PPQ.

Process validation- Downstream

The PPQ study for the downstream manufacturing process was performed with multiple batches. The PPQ result presentation was updated to show individual results rather than minimum, maximum, average and standard deviation.

The process parameters for every downstream manufacturing step were maintained within their acceptance criteria. Also, the process attributes as well as the release specification met the acceptance criteria for every batch. In general, the variance of the process attribute results for all process steps appeared low, except for assays that have a high variance themselves.

Several deviations and non-conformances occurred during the PPQ. The deviations and non-conformances were appropriately addressed and where necessary corrective and preventive actions were implemented. It is agreed that the deviations do not impact the conclusions from the PPQ study.

Data from two additional campaigns, has been provided that adequately support the inter- and intra-batch/run consistency demonstrated in the PPQ.

Impurities

Based on a risk assessment, the Applicant included a subset of product- and process related impurities into the PPQ-study. In addition, during process development representative scale-down models were used to study the removal of impurities.

The respective impurity clearance release limits were met. Of all impurities, only some will be tested in the active substance or finished product specification. This is acceptable, based on the shown clearance data as well as on several studies that confirmed robustness of the impurity removal.

Elemental impurities and extractable and leachables were evaluated by risk assessment. An appropriate summary of the risk assessment and results for elemental impurities and extractable and leachables was provided. The applicant´s conclusion that the risk of potential elemental impurities within the active substance is low is deemed acceptable. For extractables and leachables there is negligible safety concerns regarding sensitization potential, mutagenic potential or toxicity.

Hold Times

Hold times were first evaluated during the manufacturing process development and then confirmed in the PPQ. A cumulative hold time was assessed as part of the last PPQ batch and met the acceptance criteria. Also, all release acceptance criteria were met. In the end, the shortest hold time tested during PPQ was used to define the validated hold time. Overall, it is agreed that hold times were appropriately established.

Shipping Validation

The rADAMTS13 active substance will be shipped in an insulated shipping container (ISC) with multiple bottles per ISC. This ISC was already qualified for another protein active substance to be maintained at the same temperature. Overall, the shipping validation is deemed acceptable.

Manufacturing process development

The initial process development and manufacture of the active substance was performed at Takeda Orth. The process was scaled-up from lab scale bioreactors. The applicant performed multiple separate campaigns (fermentation runs) during development; each campaign yielded several active substance

batches (engineering batches included); multiple batches were produced from each of the processes developed: process 1.0, process 2.0, process 2.1 and process 3.0. The batches derived from process 3.1 (one fermentation run) are not included here but presented in Module S.4.4. The combined data have been used in the assessment of other sections but otherwise do not give rise to specific comments or concerns.

For process development elements of quality by design were used to identify critical quality attributes and critical process parameters. A risk-based control strategy focusing on potential risk for patients was developed that consist of process- and analytical control strategies.

Process characterisation studies were performed using qualified scale-down models. Univariate and multivariate experiments were performed. Process parameters with expected interactions were studied using design of experiment (DoE) studies.

Acceptance criteria for product quality attributes were defined based on the following considerations: (1) statistical analysis of limited manufacturing batches, (2) current product characterisation knowledge and manufacturing experience, and (3) internal platform knowledge relevant to production of highly glycosylated large complex proteins.

Results from process characterisation studies were used to define PARs and to assess parameter criticality. PARs were set based on the demonstration of acceptable process performance and product quality meeting defined acceptance criteria. Parameter criticality was evaluated based on the magnitude of change observed for each CQA across the characterised range, relative to its target control range or specification.

In a last step, after completion of the PPQ, the control strategy was further refined using a risk-based approach.

Overall, the approach to manufacturing process development and risk management is acceptable and follows principles as described in ICH Q8 and Q9.

Development History

The manufacturing process was scaled-up from bench scale to 1000 L bioreactor working volume. Material from the 1000 L manufacturing process (1.0) was used for non-clinical and phase 1 studies. The manufacturing process 2.0/2.1 and 3.0 was used to manufacture Phase 3 material. The manufacturing process 3.1 is the final commercial manufacturing process which was validated.

After detection of the single nucleotide polymorphism, which leads to the expression of the Q97 native protein and R97 rADAMTS13 variant the Applicant tried to establish a cell line only expressing the native Q97 protein. However, none of the Q97 protein expressing cell lines were suitable for development of a commercial process. The cell line stability, productivity and product quality did not meet the expectations. Also, these clones produced insufficient amounts for structural and functional analysis of the Q97 and R97 variant. Transposase facilitated expression in CHO-K1 SV cells also failed due to severe product truncation. In addition, the human cell line GEX was tested, but also yielded low expression levels. Furthermore, the individual forms were expressed in CHOZN (CHO-K1 GS -/-) cells. These cells were high producing but due to proteolytic activity in those cells a high amount of truncated rADAMTS13 was observed in the upstream and downstream process. After process modifications this issue was resolved and sufficient amounts of Q97 and R97 protein variant were manufactured for structural and functional characterization. Thus, it appears that that the Applicant indeed invested efforts to establish a clone that only expresses the native ADAMTS13 variant. Therefore, the decision to continue with the chosen production cell line is reasonable.

Overall, the development history of the manufacturing process was appropriately presented.

Impurity Clearance

Reproducible clearance of the process related impurities was demonstrated based on consistent removal during routine production and limited spiking studies. Because DNA and small molecule impurities are not release tested, the robustness of their removal under challenging conditions was further substantiated with data.

Control Strategy and Assignment of Quality Attributes

The quality by design approach of the Applicant starts with accumulation of product understanding using a quality target product profile (QTPP) followed by a critical quality attribute assessment. This risk assessment was performed on a list of potential critical quality attributes (CQAs). Potential CQAs were identified during rADAMTS13 development. The risk was assigned based on the impact of quality attribute on safety/immunogenicity (S/I), potency/efficacy (P/E), and pharmacokinetics (PK). The maximum expected variation or range of a given QA was considered based on development and characterisation data, non-clinical study data, primary literature and platform knowledge. The severity and uncertainty was assessed for each category. A list of CQAs is provided.

Based on data from pre-characterisation assessments, process parameters, raw materials, and material attributes with a potential to impact on CQAs and process performance indicators (PPIs) are defined. A process control strategy (PCS) assessment is performed to determine process capability risk score (PCRS) for each CQA. An analytical control strategy (ACS) is subsequently applied in accordance with the level of process capability risk in order to reduce residual risks in case where process capability cannot be further improves. Furthermore, regulatory requirements are established with the ACS.

Overall, the Applicant established a quality by design based development strategy that appears suitable to assign critical quality attributes and to establish a control strategy.

Comparability

Comparability studies were performed between material from three batches each of process 1.0 and 2.0, as well as process 2.0 and 3.0. Finally, four batches of process 3.0 were compared to seven process performance qualification batches from process 3.1. The differences between the manufacturing processes were appropriately presented and the number of batches included into the comparability exercise appears sufficient. No comparability was performed between material derived from process 2.0 and 2.1 because the only difference was the introduction of a pre-filter for nanofiltration. This is acceptable.

During the procedure a major objection was raised as comparability between active substance processes 1.0, 2.0, 3.0, and 3.1 (PPQ process) was not considered adequately demonstrated. In response, the Applicant provided appropriate additional data to support the conclusions on comparability of the manufacturing processes and the major objection was considered resolved.

2.4.2.3. Characterisation

For characterization of rADAMTS13 overall five clinical phase 3 lots (process 3.0) and seven process performance qualification batches (process 3.1) were used. A sufficient set of analytical methods focusing on the elucidation of the primary structure, posttranslational modifications, three dimensional structures and biological activity was applied.

In addition, purified plasma-derived ADAMTS13 was compared to rADAMTS13 from non-clinical and clinical manufacturing using assays to measure potency, molecular mass, homogeneity and integrity. Overall, it is agreed that the results are comparable.

Furthermore, the Applicant applied release testing and selected extended characterisation tests to compare pure Q97 native and pure R97 variant of rADAMTS13. Overall, the presented results show similarity between Q97 and R97 rADAMTS13. It is agreed that the Q97 and R97 variant of rADAMTS13 have the same physicochemical, biophysical and biological properties. It can be expected that there likely is no negative impact on the functionality of the rADAMTS13 bivariant finished product due to the presence of both Q97 native and R97 variant rADAMTS13 in variable amounts. Also, the Applicant noted that an in-silico assessment of immunogenicity indicated no generation of novel immune-dominant cell epitopes as result of the amino acid exchange Q97 to R97.

The applicant appropriately categorised process- and product-related impurities. During process development, impurity clearance was studied using scale-down models. The validation of impurity clearance for the downstream process was also performed during process performance qualification. It was also shown that the CHO protein pattern does not significantly change over the manufacturing campaign, indicating a stable bioreactor/chemostat process. Removal of impurities is further substantiated by investigating the effect of deliberate variations in process parameters.

The determinants of enzymatic activity/potency were not considered sufficiently characterised and a major objection was raised, requesting the Applicant to address (1) the true variability in the specific activity of the enzyme, and (2) the link between CQAs and biological (enzymatic) activity. With regard to point 1, the Applicant provided additional explanations and eventually tightened the specific activity acceptance range for active substance and finished product. Data indicate that variations in activity are not assay dependent which suggests that there is a true difference in enzymatic (specific) activity between batches. It is acknowledged that investigating this issue may be challenging at this stage. Nevertheless, the Applicant is recommended to further investigate which CQAs (i.e. physico-chemical parameters of the protein) impact biological (enzymatic) specific activity. **(Recommendation 1)**

2.4.2.4. Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specification includes tests for general properties, content, potency, identity, purity/impurities, microbiological quality and other characteristics.

The active substance release and stability specifications are justified based on analytical data from multiple batches. These include phase clinical study batches manufactured in Orth and Singapore, and process validation batches manufactured in Singapore. The specification range for specific rADAMTS13 activity includes data from additional batches from three post-PPQ campaigns. Commercial specification limits were calculated by statistical analysis of available batch data reflecting process and analytical variability. The release- and stability specifications are the same, which is acceptable because so far long-term storage did not show an impact on quality attributes. The justification of specification can be regarded clinically justified and is acceptable.

Analytical Procedures and Validation

Overall, the analytical procedures are adequately described. Validation of all non-compendial analytical procedures is provided.

For the rADAMTS13 activity assay all parameters required for a quantitative potency assay according to ICHQ2(R1) were appropriately evaluated and met the acceptance criteria. For accuracy testing 6 different dilutions of the internal reference standard covering a wide concentration range were tested three times. In addition, finished product samples were diluted and spiked with the reference standard and 5 concentrations were tested, covering the full measurement range. The quantification limit (LOQ) was established by 10 independent tests. All other parameters (precision, repeatability, specificity, linearity, range) were appropriately validated as well. Robustness was appropriately shown by

freeze/thaw and bench-top stability tests. Test unit incubation temperature was also appropriately established. Overall, the rADAMTS13 activity assay is regarded validated for release testing of rADAMTS13 active substance and finished product.

Batch Analyses

Release data of clinical phase 3 batch used to support the active substance shelf-life as well as multiple process performance qualification batches manufactured were provided. Data from earlier campaigns are provided in S.2.6. Overall, the presented data confirm the consistency of the manufacturing process.

Reference Standards

The current lyophilized reference standard is used for determination of rADAMTS13 activity and antigen. It was manufactured from two active substance batches. Retest data is based on evaluation under accelerated degradation conditions and appropriate results have been provided.

The in-house reference standard was calibrated against the WHO 1st international standard ADAMTS13 Plasma using the rADAMTS13 activity assay (FRETS-VWF73). Based on the presented information, the calibration of the current reference standard was appropriately performed.

A shift assessment was performed between the current reference standard and the previously used reference standard for determination of rADAMTS13 activity. A shift was observed. The applicant implies that this shift is the consequence of the very first implementation of an international reference standard and with this the change from units to international units, which is reasonable. Furthermore, from a clinical perspective the change was regarded non-critical. Comparable PK results were obtained from clinical phase I and phase III studies. Overall, the observed shift was appropriately justified not to be relevant.

For the rADAMTS13 antigen assay the value of the in-house reference standard was assigned using the total protein (UV) assay. A shift assessment was performed between the current reference standard and the previously used reference standard. This data indicates that the shift can be regarded not significant. Overall, based on the presented data, the calibration of the in-house reference standard as well as the bridging to the previous reference standard is regarded acceptable.

The applicant provided a description of the implementation and stability testing of future reference standards for the rADAMTS13 activity and antigen assays, which is acceptable.

Container Closure

The active substance container closure is a sterile USP Class VI polyethylene terephthalate glycol co-polyester (PETG) bottle with a high-density polyethylene (HDPE) screw cap. An appropriate in-house specification was established. Bottles and caps are received pre-sterilized by gamma radiation with a Certificate of Analysis issued from the vendor. The material was tested by the vendor by implantation tests (USP <88>, ISO 10993-6), in-vitro cytotoxicity tests (ISO 10993-5), genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3) as well as bacterial endotoxin test (USP <85>). According to the vendor all the tests met the requirements. A representative certificate of analysis from the vendor was provided. Furthermore, a toxicological assessment confirmed that extractables are qualified with minimal toxicological concern related to exposure to any of the potential extractables observed. Thus, it is agreed that the material of the active substance container closure meets required quality standards.

2.4.2.5. Stability

An ICH compliant stability study has been initiated. The protocol is provided and considered acceptable. Samples have been stored in PETG bottles; these are of the same material of construction as that used for storage of bulk active substance. The ongoing stability studies for the primary stability batches will be completed according to the protocols provided.

A shelf-life period is proposed for active substance stored at the applicable long-term storage temperature. This proposal is based on real time stability data for one clinical batch and for three PPQ batches. The combination of data from clinical manufacturing process and the intended commercial (PPQ) process is appropriate due to the presented comparability results. Except for a slight downward trend for rADAMTS13 Antigen, no significant trends were detected. Overall, the provided stability data so far indicate a stable product at the intended storage temperature.

Temperature cycling studies which simulate possible worst-case temperature excursions during manufacturing, sample handling and shipping have been initiated and data is available for cycling scenario A, B and C for one PPQ batch. The complete data set is available for cycling scenario A, B and C for one clinical batch. All active substance quality attributes were within the acceptance criteria and compared to untreated active substance there is no apparent change. The applicant concludes that the studies support that temperature excursions as tested in this study are acceptable during handling, shipping, and storage of the active substance. Based on the results provided, this appears reasonable. The stability will be further verified until the end of the study.

Forced degradation studies showed that appearance, rADAMTS13 activity by FRETS assay, dimers and aggregates are stability indicating parameters when exposed to the stress conditions.

The frequency of testing at the long-term storage condition in the post-approval stability protocol is in principle not according to the ICHQ1A(R2) recommended interval of every 3 months over the first year. However, the proposed frequency can be accepted based on the shown stability of the primary stability batches in excess of 24 months. Overall, the post-approval stability protocol is acceptable.

2.4.3. Finished Medicinal Product rADAMTS13

2.4.3.1. Description of the product and Pharmaceutical Development

The finished product is formulated as a sterile, non-pyrogenic lyophilized powder for reconstitution for intravenous injection. It is provided at a nominal dosage strength of 500 and 1500 international units (IU) per vial determined by means of the rADAMTS13 Activity assay (FRETS-VWF73). The finished product is filled in a clear colourless neutral Type I glass vial (USP, Ph. Eur, JP) with a nominal capacity of 10 mL. The vial is closed with a butyl rubber stopper with an inert coating (USP, Ph. Eur, JP), and sealed with an aluminum overseal and tamper proof snap off plastic cap.

Each dosage strength is supplied with a nominal volume of 5 mL sterile Water for Injection (sWFI) as a solvent for reconstitution. The reconstituted solution has a nominal activity of 100 IU/mL and 300 IU/mL, respectively.

Initially the Applicant proposed to label the finished product with the actual activity measured for each specific batch. This was not considered acceptable as the labelled content should be the same over all batches. Batch-specific labelling of a potency is unprecedented for recombinant proteins and is not accepted. A major objection was raised in this regard. In response, the Applicant accepted the use of nominal potency rather than actual potency and this was implemented in the product information. Consequently the major objection was considered resolved.

BAXJECT II Hi-Flow Needleless Transfer Device (BAXJECT II HF) will be supplied with rADAMTS13 finished product as a reconstitution device. Omnifix Syringe and Surflo Winged Infusion Set will also be supplied with as administration devices. Webcol alcohol swabs will be supplied to prepare the skin and vials prior to injection.

Formulation development

Influence of the different excipients were investigated. Histidine is added as a buffering agent. Sucrose is added for stabilization and mannitol is added as a bulking agent. During formulation development it was found that polysorbate 80 could stabilize rADAMTS13 activity and antigen content and the addition of Ca2+ could stabilize rADAMTS13 activity and decrease aggregates and dimers, respectively. Sodium chloride is a tonicity modifier and showed stabilizing effects during lyophilization. All excipients are of compendial grade. The formulation of rADAMTS13 finished product has remained the same throughout the pharmaceutical development. No solvents are used in the formulation of the finished product.

An overage is implemented to compensate for potential rADAMTS13 activity loss during manufacturing and ensure the product activity specification can be met. Filling is performed with a weight dosing system, which includes an overfill.

Manufacturing process development

Initial process development and manufacture of the finished product was performed at Takeda where the process was scaled-up from laboratory scale to 10 kg scale. When transferring the process for phase 3 clinical the manufacturing was performed at 15 kg to 20 kg (process C). This scale was increased to 15 kg to 50 kg before the process performance qualification was started.

During development from non-clinical to phase 1 and phase 3, the manufacturing process was adapted to the new lot sizes, potencies, facilities, and equipment.

Phase 3 consists of four process development steps A-D. Process A-C were used for the clinical batches and process D is the commercial manufacturing process for the finished product. The PPQ batches are manufactured by process D. The applicant details the development of the formulation process. There are differences between earlier process A and B and later processes in the way excipients are added. Initially two types of buffer had been used to reach target concentrations in the finished product while in later development phases and in the commercial process only one buffer is added which has a batch specific quantitative composition to enable the targeted finished product concentrations of active substance and excipients.

During the procedure a major objection was raised as comparability between finished product clinical development lots and commercial lots was not considered adequately demonstrated. In response, the Applicant provided appropriate additional data to support the conclusions on comparability of the manufacturing processes. In conclusion, comparability studies were performed and batches from the different processes were compared side by side based on routine in-process data, release testing, characterisation testing, and short-term stressed stability data. Detailed batch data results and comparative figures of extended characterisation of finished product lots manufactured from the different processes have been submitted as separate reports in Module 1.10 and is considered sufficient. The submitted data is considered sufficient to show comparability between the commercial and clinical lots and the major objection was considered resolved.

A risk-based approach as described in ICH Q9 Quality Risk Management was employed to guide the selection of process parameters to be investigated during process characterisation studies. Process parameters within each unit operation were assessed for their potential impact on both process performance and product quality, based on knowledge obtained during product development as well as general process understanding and experience. Results from process characterisation studies were

used to define proven acceptable ranges (PARs) and to finalise parameter criticality. PARs were set based on the demonstration of acceptable process performance and product quality meeting defined acceptance criteria. Parameter criticality was evaluated based on the magnitude of change observed for each CQA across the characterised range, relative to its target control range or specification.

The control strategy for the critical quality attributes is summarised and sufficiently described.

Some of the studied ranges are narrower than the proven acceptable ranges (PAR). The applicant justifies in 3.2.P.2.3 that the apparently wider PARs are based on the actual studied range which in some cases is wider than the intended studied range. This is acceptable.

Both liquid and lyophilized formulations were assessed in the development of the formulation matrix. The robustness of the final formulations was tested. Furthermore, the impact of the temperature for the final formulation was tested for 6 months at multiple temperatures. Storage at accelerated temperatures led to decrease in rADAMTS13 activity and specific activity and increase of dimers and aggregates.

Different formulation studies were confirmed with the PPQ batches like Mixing speed and mixing times for finished product preparation, maximum bulk active substance thawing time, minimum and maximum lot size at scale.

Sterilizing filtration and sterile filling process steps were established by experimental studies. In process controls (IPCs) for the sterilising filtration step and sterile filling step were defined to assure finished product quality.

To define the finished product temperatures for the lyophilization process, thermal analysis of the final formulation was performed. For phase 3, the production was transferred to a different manufacturing line. The lyophilization program had to be adapted due to the lyophilization equipment at the phase 3 production site. Toward the end of phase 3 (Process D), the maximum lot size was increased with no change in the lyophilization program required. This has been demonstrated with engineering test runs at the lower process limits and the subsequent engineering run in the second lyophilizer.

2.4.3.2. Manufacture of the product and process controls

The finished product manufacturing site is Takeda. Release and stability testing is carried out at a contract testing facility. Valid GMP certificates have been provided for the manufacturing and testing sites.

The finished product manufacturing process consists of thawing and formulation of the active substance, to reach target excipient and protein concentrations, followed by sterilizing filtration, sterile filling, lyophilization and crimping. After visual inspection, the vials are labelled and packaged and stored at a defined temperature range. An illustrative flow diagram of the finished product manufacturing process is provided below.

A product and process control strategy in accordance with ICH Q8, Q9 and Q10 guidance has been established for the manufacture and testing of the finished product. The criticality of each process parameter and selection of IPCs to assure process control were determined using a risk-based approach. The ranges of the critical and non-critical process parameters described in this section are the proven acceptable ranges (PARs).

During the procedure a major objection was raised requesting the Applicant to clarify and unambiguously describe the formulation step and also to implement tighter controls of potency after mixing to ensure the target potency is achieved. In response the Applicant provided further details and the formulation step is now adequately described. The active substance content is controlled by

weighing the active substance bottles before and after transferring the content to the formulation vessel. The applicant concluded that it was not feasible within the timelines of the MAA procedure to introduce changes or additional controls in the finished product manufacturing process. Instead, the applicant agreed to tighten the finished product release and shelf life specification for rADAMTS13 activity. This was considered acceptable and the major objection was resolved.

Process validation

An integrated, risk-based approach was applied for process validation. The process was developed at small-scale and scaled-up to commercial scale. Characterisation studies were performed at small scale or at full scale with buffer or product runs which supported the criticality assessment of critical process parameters (CPPs) and establishment of proven acceptable ranges (PAR) and normal operating ranges (NOR).

A bracketing approach was used to validate both the 500 IU/vial and 1500 IU/vial dosage strengths which is considered acceptable. For each dosage strength, one minimum and one maximum lot size was manufactured during formulation, yielding four PPQ lots. Two of these lots were split into two sub-lots after filling in the lyophilization unit. Overall, six full-scale batches of finished product were produced at the commercial manufacturer in accordance with a pre-approved process performance qualification (PPQ) protocol. Release results are available for five lots as one lot contained only 180 product vials for the lyophilization homogeneity study. The applicant justified that this lot was neither intended for release testing nor batch release.

Mixing validation was performed and showed that the manufacturing process of rADAMTS13 is capable to consistently produce homogenous solutions and to provide a finished product which meets predetermined quality attributes.

Sterilizing filtration validation was performed. Filter integrity testing was performed before using the filter. The sterilizing filtration process time is a critical process parameter with respect to microbial contaminants and bacterial endotoxins. In the sterilizing filter validation conducted prior to the PPQ, worst-case conditions were demonstrated. In the final container, the routine sterility testing as well as additional sterility and endotoxin testing complied.

The in-process hold time limit after the lyophilization step has been set based on commercial scale validation runs.

Overall, the sterilizing filtration was successfully executed according to the manufacturing batch records and protocol.

A homogeneity study was conducted for the filling process in the worst-case lot. The vials were tested for protein concentration by the validated Total Protein (UV) test method. Protein concentration was selected for evaluation because it represents the distribution of the active ingredient and should remain homogenous throughout the filling duration. The samples showed a slight increase in mean results between the sampling levels. The applicant´s explanations on this increase is comprehensible and can be accepted.

The lyophilization program consists of three major process steps: freezing, primary drying, and secondary drying. Parameters such as temperature, pressure and duration of each step were defined in the lyophilization program and were controlled automatically. After completion of the secondary drying step, the partially stoppered vials were fully stoppered by hydraulically lowering the lyo-shelves onto each other under final vacuum.

From the two lyophilizers, which will be used in the manufacturing process samples from 30 different pre-defined positions were tested for rADAMTS13 activity, residual moisture, appearance (lyophilized

cake and reconstituted solution), and reconstitution time. Acceptable results were achieved with both lyophilizers for all parameters. Homogeneity was demonstrated with this study.

Based on the data provided the finished product manufacturing process appears robust and provides a product that meets quality and stability attributes.

2.4.3.3. Product specification, analytical procedures, batch analysis

The release and stability specification has been established to ensure the identity, strength, purity, quality, and safety of the finished product.

The justification of the finished product specifications is in accordance with applicable pharmacopoeia requirements (USP, Ph. Eur) and ICH Guideline Q6B. The selected acceptance criteria reflect product quality requirements in terms of safety and efficacy and are based on the current knowledge of the manufacturing process and the inherent statistical variability of the analytical methods.

It is noted that the potency value is the parameter used for formulation of the finished product and that total protein content is routinely measured but not specified. The rADAMTS13 content is routinely measured by ELISA and specified. In the justification of specifications the assays including specific rADAMTS13 activity, rADAMTS13 antigen ELISA, and rADAMTS13 FRETS activity (FRETS-VWF73) were discussed more in detail with multiple rADAMTS13 finished product lots from process C (latest clinical phase 3 process) and D (process performance qualification process) because a shift occurred. For justification of the specification limits of (specific) rADAMTS13 activity, ELISA, and rADAMTS13 FRETS activity the Applicant considers that both pre- and post-shift data are important for the limit calculations and proposes to retain them. The specifications are therefore based on the pooled data. Importantly, the pre-shift batches (active substance and finished product) had been released and used for clinical phase 3 and met all clinical specifications and no impact on the product quality is expected. However, due to the inclusion of these batches the total variability in the finished product activity, specific activity and antigen results increases significantly, which is not entirely representative of the commercial process. The applicant has therefore included data of additional finished product batches, manufactured from two active substance campaigns post PPQ to support the calculation of finished product release acceptance ranges for rADAMTS13 activity and rADAMTS13 antigen ELISA. This is considered acceptable.

For testing of Dimers/Aggregates a suitable chromatography method was established. The method chosen is known for being prone to underestimate the presence of larger aggregates. Furthermore, no analytical method is in place for detection of fragments and other possible degradation products. However, the applicant justified that testing for aggregates in the finished product by chromatography is sufficient because of testing the LMWS in the active substance and furthermore, active substance data showed comparable results generated with an orthogonal method such as analytical ultracentrifugation. These justifications are considered acceptable.

The applicant is recommended to provide an update on the subsequent steps regarding the improvement of method variability and re-evaluation of the specification limits for percentage dimers in the finished product (**Recommendation 2**).

An inductively coupled plasma mass spectrometry (ICP-MS) limit test method was developed to measure the content of elemental impurities in rADAMTS13 finished product. The concentrations of all elemental impurities in scope of ICH Q3D in three rADAMTS13 finished product batches were below the control threshold of 30% of permitted daily exposure, which was calculated based on the maximum daily dose administered to patients. Based on these results it is not necessary to include any elemental

impurity controls for finished product release. The information on the control of elemental impurities is satisfactory.

A risk evaluation has been performed and submitted on all materials used during finished product manufacturing (active substance, finished product formulation, equipment and cleaning, primary packaging) for potential sources of nitrosating agents, amines, and N-nitrosamines. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures

State-of-the-art orthogonal analytical methods are used for testing the different release attributes. For all test method descriptions and for the non-compendial assays validation reports were provided.

The non-compendial assays for testing of rADAMTS13 FRETS Activity (FRETS-VWF73), specific rADAMTS13 activity and rADAMTS13 antigen ELISA have been validated and information is submitted in the active substance part.

Non-compendial methods for polysorbate 80, histidine, sodium, calcium, sucrose, and mannitol were fully validated according to guideline ICH Q2 (R1). Relevant validation parameters for each test method were taken into consideration. These test methods appear appropriately validated and can be accepted.

With respect to the compendial testing for general properties and microbial quality related aspects no issues were identified.

Changes in the analytical methods during the development of rADAMTS13 finished product are sufficiently described.

Reference standards

The same in-house reference standard is used for active substance and finished product testing. Reference is made to the active substance section.

Batch analysis

Batch analysis data from clinical phase 3 /process performance qualification (PPQ) batches with 500IU/vial and three clinical phase 3 /process performance qualification (PPQ) batches with 1500IU/vial were submitted. All parameters tested were within the defined specifications. The data submitted demonstrate consistency and conformity in the manufacturing process.

Container closure

The primary container closure consists of a 10 mL colorless Type I glass vial with a 20 mm butyl rubber stopper with lamination on the plug and top and coating on the sealing surfaces and an aluminum crimp seal. The primary packaging components are purchased from qualified manufacturers and suppliers and meet the requirements of the current European Pharmacopoeia (Ph. Eur.).

The finished product is lyophilized and will be reconstituted with sterile water for injection (sWFI) diluent using the BAXJECT II Hi-Flow Needleless Transfer Device (also referred to as BAXJECT II Hi-Flow) and administered using an Omnifix syringe and Surflo winged infusion set. All the devices are commercially available. The components are CE certified.

The applicant provided information on human factor studies and post-market surveillance for medical devices co-packed with Adzynma. The human factor studies referring to the Baxject II Hi-Flow device were conducted in 2008/2009 and will thus not have involved the current finished product. However,

as the product is to be administrated under supervision of a health care professional the omission of a target patient specific human factor study is considered acceptable.

2.4.3.4. Stability of the product

The proposed shelf life of rADAMTS13 finished product is 36 months stored at +5±3°C, including 6 months at +30±2°C/ 65±5% RH. After storage at +30±2°C/ 65±5% RH, the product must not be returned to the refrigerator to extend the storage duration.

The long-term and accelerated stability studies are performed with multiple PPQ and clinical stability lots covering both strengths (500 IU/vial and 1500 IU/vial).

The stability studies are conducted according to current ICH guidelines.

Long term stability data at +5±3°C and +30±2°C/ 65±5% RH are available for all clinical batches and PPQ batches.

Parameters tested at long-term storage conditions which were amenable for statistical analysis (i.e. quantitative parameters that exhibited variability in test results and/or trends over time) were evaluated statistically at real time storage in accordance with ICH Q1E.

So far all tested parameters in the long term stability studies are within the acceptance limits but showing trends for some parameters/batches. The applicant expects that the finished product will remain within the specifications for the entire shelf life despite the trends observed.

Data from an accelerated stability study at +40±2°C/ 75±5% RH for 6 months has been provided for all tested clinical and PPQ batches. The results for aggregates remained below the LOQ of the analytical method at long-term storage condition. Every other tested parameter meets the specification limits.

Stability of the reconstituted finished product was evaluated at room temperature (+25°C). All results met specifications and did not show any change that could lead to out of specification results during the observational period, demonstrating that the finished product is stable for a minimum of 6 hours at room temperature (+25°C) after reconstitution. This is appropriately reflected in the SmPC.

Additionally, the stability of the reconstituted product will be tested after 24 and 36 months storage at +5±3°C and +30±2°C/ 65±5% RH. The stability of the reconstituted product will be also tested after 36 months at the combined storage condition of +5±3ºC for 30 months followed by storage for 6 months at +30±2°C/ 65±5% RH by incubating the reconstituted product at room temperature (+25°C) for up to 6 hours.

The impact of temperature cycling on the long-term stability of rADAMTS13 finished product was evaluated.

A photostability study was conducted and data showed that rADAMTS13 finished product is sensitive to light exposure. This is reflected in the SmPC which states that the product should be stored in the original package in order to protect from light.

Forced degradation studies were carried out in order to verify that the test methods used in the rADAMTS13 stability program are stability-indicating as well as to identify the potential physical, chemical and functional degradation pathways of the finished product. Reconstituted finished product samples were exposed to thermal stress, acid, base, oxidizing agent and freeze-thaw cycles to create different forms of degradation. Lyophilized samples were exposed to light and freeze-thaw cycles. The stressed samples were assessed for appearance, potency, purity (measurement of dimers and aggregates), protein content and identity. Additionally, pH, osmolality and methionine oxidation were

measured. Sufficient information about the potential physical, chemical and functional degradation pathways of the finished product has been submitted.

In conclusion, based on the data provided, the proposed finished product shelf life of 36 months at +5±3°C including 6 months at +30±2°C/ 65±5% RH is considered acceptable.

2.4.3.5. Adventitious agents

The overall viral safety of rADAMTS13 is considered satisfactory:

- A comprehensive strategy including source and raw material testing, in-process testing, viral clearance process validation, and facility and procedural controls, is applied to ensure that rADAMTS13 active substance and the resulting finished product are free of endogenous and adventitious agents. Virus removal and inactivation steps are included in the manufacturing process of rADAMTS13 and contribute to the virus safety profile of the product. Sterile filtration at the end of the manufacturing process is implemented as well. The applicant provided a summary of the performed Adventitious Agents Safety Evaluation steps.
- The strategy includes facility controls to minimizing contamination with adventitious bacteria, fungi, or mycoplasma.
- During the production process, no product of biological origin is used.
- Global reduction factors reported were satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for non-enveloped viruses.
- Cell banks were extensively controlled. No viral particles other than retroviral-like particles normally seen in these cell types were observed.
- The starting materials from animal origin are mainly used indirectly or before the establishment of the cell banks.

Information on virus reduction kinetics from the different viruses and the different virus clearance steps have been provided. A sufficiently detailed summary of the virus elimination studies was included in the dossier.

TSE

At the stage of cell-line development foetal bovine serum (FBS) was used. The applicant justified that materials have been assessed with regards to TSE/BSE risk. The used FBS was sourced from healthy animals and was tested for the presence of relevant bovine viruses. The country of origin was the USA, which at the time of sourcing was free of Bovine Spongiform Encephalitis (BSE), which rendered the risk with regards to TSE minimal. This justification is endorsed.

The foetal bovine serum used in the cell line development is tested according to the relevant Ph. Eur. monograph and is in compliant with EMA Note for Guidance EMA/410/01 rev.3.

2.4.4. Finished Medicinal Product sterile Water for Injections

Each vial of finished product rADAMTS13 is reconstituted with the diluent, sterile Water for Injections (sWFI). The 5 mL (nominal) sWFI is presented in a single-use 6 R Type I glass vial.

The name, address and responsibility of each manufacturing site for sWFI including packaging and labelling have been listed. The respective authorisations have been provided. sWFI is produced by Hameln, Germany.

sWFI is prepared from Water for Injection (WFI) in bulk. WFI complies with corresponding current Ph. Eur. Monograph. In-process controls are in place. Flow diagram for the manufacturing process was submitted.

Process validation is described in detail, acceptable results were submitted. Process validation was performed prospectively with three sWFI validation batches. All results were within the acceptance limits.

Depyrogenation validation studies for vials as well as validation of stopper sterilization are clearly presented in the dossier. Requalification runs with the stoppers are done on a routine basis.

Terminal sterilization of sWFI produced with chlorobutyl rubber stoppers and the alternate bromobutyl rubber stoppers are performed with autoclaves. Terminal sterilization process of the filled, sealed, and capped glass vials of sWFI was successfully performed. All physical results conformed to the acceptance criteria. The temperature during the dwell period for all runs was not less than 121.5°C.

The acceptance criteria for both autoclave validations were fulfilled. The requirements according to EMA/CHMP/CVMP/QWP/850374/2015 with regard to sterilisation method, cycle and validation are considered sufficiently covered. Stopper sterilisation is performed at Hameln site, as specified in the dossier. Terminal sterilisation method including acceptance criteria as well as detailed description of terminal sterilization qualification and re-qualification is provided in the dossier. Worst case minimum and maximum load were investigated.

Hameln GmbH is the site of sterilization. This was confirmed by the Applicant, and it is in compliance with EMA/CHMP/CVMP/QWP/850374/2015.

Specifications in accordance with Ph. Eur./JP/USP are provided.

Batch analysis data of three consecutive lots are provided for products closed with chlorobutyl-stoppers and such closed with Bromobutyl-stoppers. Results are consistent and well within specifications.

The container closure system is described to a sufficient extent, drawings and detailed specifications are provided within the dossier.

Stability studies for sWFI were performed with both kind of stoppers. A shelf life for sWFI packaged with the finished product is proposed as 60 months when stored at no more than 30°C. The updated long term stability data at 30°C of sWFI performed with bromobutyl rubber stopper is provided and data are acceptable. A shelf life of 60 months stored at no more than 30°C is acceptable.

2.4.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

An extensive Module 3 was provided by the Applicant. Appropriate proof of GMP compliance of the manufacturing site in Singapore was provided. Overall, five Major Objections have been raised all of which have been adequately resolved.

Active Substance

The active substance manufacturing process and control strategy was described in detail. Process parameters (PPs and CPPs) and process attributes (PA) and their respective acceptance criteria are appropriately presented for every manufacturing process step. Process attributes are divided into process performance indicators (PPI) and in-process controls (IPC). The respective normal operating ranges and proven acceptable ranges (PAR) of the process parameters were indicated in different sections of the dossier. Information on raw and starting materials including information on quality and control of these materials is provided.

The active substance process provides two dedicated virus reduction steps (solvent/detergent treatment and nanofiltration) in combination with affinity and chromatography steps. Overall, an effective and robust clearance capacity for enveloped and non-enveloped adventitious viruses was confirmed. The risk of potential contamination and transmission of bacterial, viral, or TSE agents appears acceptably low.

The active substance, rADAMTS13, consists of a mixture of two protein species, expressed in Chinese Hamster Ovary (CHO) cells. They differ in a single amino acid exchange at position 97. The INN of the native rADAMTS13 is apadamtase alfa (Glutamin Q97) and the INN of the variant is cinaxadamtase alfa (Arginine R97). The applicant applied release testing and selected extended characterization tests to compare pure Q97 native and pure R97 variant of rADAMTS13. The presented results show the similarity between Q97 and R97 rADAMTS13. It is agreed that the Q97 and R97 variant of rADAMTS13 have the same physicochemical, biophysical and biological properties. It can be expected that there likely is no negative impact on the functionality of the rADAMTS13 bivariant finished product due to the presence of both Q97 native and R97 variant rADAMTS13 in variable amounts. Also, the Applicant noted that an in-silico assessment of immunogenicity indicated no generation of novel immune-dominant MHC II T cell epitopes as result of the amino acid exchange Q97 to R97. The manufacturing process produces a mixture of two closely related species (product related substances). These two species share the same basic structural element. No evidence of differences in terms of efficacy and safety has been provided. Thus, it is concluded that the two species are the same active substance.

It is noted that during manufacturing, for the R97 variant, first a marked drop is observed, then after several days of fermentation the level of this variant rises again. The applicant has described efforts made and limitations of the root cause investigations into the factors determining the amount of R97 versus Q97. These efforts and limitations are acknowledged.

Process validation of the upstream (chemostat process) and downstream active substance manufacturing process was performed including the validation of impurity clearance, hold times, resin and membrane lifetime and shipping. Additional data from three post PPQ campaigns adequately support the claim that the process is in a validated state.

The process development was performed at 1000 L and at 2500 L scale and is also based on qualified scale-down models. Univariate and multivariate experiments were performed. Process parameters with expected interactions were studied using design of experiment (DoE) studies. During the procedure a major objection was raised as comparability between active substance processes 1.0, 2.0, 3.0, and 3.1 (PPQ process) was not considered adequately demonstrated. In response, the Applicant provided appropriate additional data to support the conclusions on comparability of the manufacturing processes and the major objection was considered resolved.

The active substance was characterised with an extensive set of analytical methods. Structural and functional characterisation was also performed on the pure Q97 and R97 rADAMTS13 variants and showed that the variants are similar. In addition, it was shown that recombinant ADAMTS13 and plasma-derived ADAMTS13 are comparable with regard to potency, molecular mass, homogeneity and integrity.

The determinants of enzymatic activity/potency were not considered sufficiently characterised and a major objection was raised, requesting the Applicant to address (1) the true variability in the specific activity of the enzyme, and (2) the link between CQAs and biological (enzymatic) activity. With regard to point 1, the Applicant provided additional explanations and eventually tightened the specific activity acceptance range for active substance and finished product. Data indicate that variations in activity are not assay dependent which suggests that there is a true difference in enzymatic (specific) activity between batches. It is acknowledged that investigating this issue may be challenging at this stage.

Nevertheless, the Applicant is recommended to further investigate which CQAs (i.e. physico-chemical parameters of the protein) impact biological (enzymatic) specific activity (Recommendation 1).

The active substance specifications are sufficiently justified.

Analytical methods and method validations are adequately described. The well-established two-tiered reference standard system uses the international reference standard for ADAMTS13.

The shelf-life claim of 36 months is supported by real-time stability data.

Finished Product

The finished product consists of the lyophilisate (500 or 1500 IU rADAMTS13) in a vial, the solvent (5 ml sWfI) in a vial, the BaxJect II needleless transfer device, and one package insert (PI). Separate modules have been presented for the rADAMTS13 finished product and the solvent whereas the transfer device has been addressed in the Regional Information section.

Initially the Applicant proposed to label the finished product with the actual activity measured for each specific batch. This was not considered acceptable as the labelled content should be the same over all batches. Batch-specific labelling of a potency is unprecedented for recombinant proteins and is not accepted. A major objection was raised in this regard. In response, the Applicant accepted the use of nominal potency rather than actual potency and this was implemented in the product information. Consequently the major objection was considered resolved.

Pharmaceutical development was performed very detailed.

Finished product for non-clinical and phase 1 clinical studies was manufactured at Takeda. For phase 3 clinical the finished product manufacturing process was transferred to another Takeda manufacturing site. The formulation did not change between non-clinical, clinical phase 1 and clinical phase 3. During clinical phase 3 development, 500 IU/vial potency was implemented in addition to the original potency of 1500 IU/vial. Clinical Phase 3 includes development steps A – D (process D is conform to the commercial process). These process steps included process modifications, lot size increase and equipment adaptations.

During the procedure a major objection was raised as comparability between finished product clinical development lots and commercial lots was not considered adequately demonstrated. In response, the Applicant provided appropriate additional data to support the conclusions on comparability of the manufacturing processes. The submitted data is considered sufficient to show comparability between the commercial and clinical lots and the major objection was considered resolved.

Comparability studies between the different process development steps are performed and characterisation testing was performed with lots of the different process development steps and with the two potencies (1500IU/vial and 500IU/vial) to detect potential differences in the product quality attributes. The comparability assessment included lot release data, and results from extended characterization, stability and forced degradation studies using a broad range of physiochemical, biophysical, and biological assays.

The manufacturing of the finished product (thawing and formulation of the active substance, sterilising filtration, sterile filling, lyophilization and crimping, visual inspection, labelling and packaging) has been sufficiently presented. Of note a quality by design (ICHQ9) risk based approach was utilised to evaluate process parameters for their potential impact on both process performance and product quality, based on knowledge obtained during product development as well as general process understanding and experience.

Compendial excipients are used in the final formulation. For the formulation buffer, a 2.5% polysorbate 80 (w/w) and a 100 mM calcium chloride stock solution are prepared. During the procedure a major

objection was raised requesting the Applicant to clarify and unambiguously describe the formulation step and also to implement tighter controls of potency after mixing to ensure the target potency is achieved. In response the Applicant provided further details and the formulation step is now adequately described. The active substance content is controlled by weighing the active substance bottles before and after transferring the content to the formulation vessel. The applicant concluded that it was not feasible within the timelines of the MAA procedure to introduce changes or additional controls in the finished product manufacturing process. Instead, the applicant agreed to tighten the finished product release and shelf life specification for rADAMTS13 activity. This was considered acceptable and the major objection was resolved.

A sound panel of state-of-the-art methods is in use for release control of the finished product. The description of the used container closure system is widely acceptable. Based on the data provided, the proposed finished product shelf life of 36 months at +5±3°C including 6 months at +30±2°C/ 65±5% RH is considered acceptable.

The adventitious agent's safety evaluation has been largely sufficient discussed. The information provided for sWfI and transfer device is widely sufficient.

The risk of Nitrosamines contamination was determined to be negligible.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain further improvement of the control of dimers in the finished product, and to further investigation of CQAs with impact on biological activity. These points are put forward and agreed as recommendations for future quality development.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.7. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to further investigate which CQAs (i.e. physico-chemical parameters of the protein) impact biological (enzymatic) specific activity.
2. The applicant is recommended to provide an update on the subsequent steps regarding the improvement of method variability and re-evaluation of the specification limits for percentage dimers in the finished product.

2.5. Non-clinical aspects

2.5.1. Introduction

rADAMTS13 is developed as an enzyme replacement therapy (ERT) for patients with congenital thrombotic thrombocytopenic purpura (congenital TTP [cTTP]) (congenital deficiency of ADAMTS13).

A comprehensive set of TAK-755 nonclinical studies has been conducted to support the clinical trials and license application, and included *in vivo* testing for efficacy, safety pharmacology, pharmacokinetics (PK), and toxicity in rodent and nonrodent species, including nonhuman primates.

2.5.2. Pharmacology

rADAMTS13 recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13 was developed as an enzyme replacement therapy (ERT) for patients with congenital thrombotic thrombocytopenic purpura (congenital TTP [cTTP]). ADAMTS13 regulates the size of von Willebrand factor (VWF) multimers by cleaving VWF to form VWF fragments that unlike the high molecular weight VWF multimers, do not promote thrombosis (Gao *et al.* 2008). VWF, a multimeric glycoprotein that is essential for normal primary hemostasis and also serves as a carrier protein for coagulation factor VIII (FVIII), with which it circulates in blood as a noncovalently linked complex.

The autosomal recessive genetic deficiency of ADAMTS13 and clinical dysfunction of the VWF-ADAMTS13 axis is the underlying cause of cTTP. In patients with ADAMTS13 deficiency, reduced cleavage of VWF results in being prone to TTP, a thrombotic disorder of the microvasculature.

2.5.2.1. Primary pharmacodynamic studies

in vitro

To evaluate the physiological efficacy of human recombinant ADAMTS13 (rADAMTS13) in animal studies, the Applicant assessed whether the von Willebrand factor (VWF) of different animal species was recognised and cleaved by human rADAMTS13 *in vitro*. rADAMTS13-mediated proteolysis of VWF was investigated from ADAMTS13 KO mouse, Sprague Dawley rat, Dunkin Hartley guinea pig, minipig, and *Cynomolgus* monkey under moderate denaturing assay conditions in a broad-based *in vitro* study in order to find the relevant animal species for further *in vivo* studies. In addition, the specificity of VWF cleavage has been analysed by blocking ADAMTS13 activity through addition of neutralising anti-ADAMTS13 antibodies and with EDTA as metal ion chelating agent.

Various control and blocking experiments were performed to demonstrate that the VWF degradation observed was specifically accomplished by the action of the human rADAMTS13 added and not by endogenous VWF-cleaving proteases in the individual animal plasma samples.

The *in vitro* investigations demonstrated functional activity of rADAMTS13 in various animal species to confirm the relevance of different species for further *in vivo* non-clinical studies.

in vivo

In vivo primary pharmacodynamics studies were performed to evaluate the efficacy of both prophylactic and therapeutic administration of TAK-755 in ADAMTS13 KO mice. In these studies, the range of doses of TAK-755 included the intended human dose in patients with cTTP (40 IU/kg) to 2 and 5 times the intended clinical dose. Efficacy of TAK-755 was defined as the degree of prevention of decrease in platelet count and prevention of increase in lactate dehydrogenase (LDH), both parameters being markers of TTP. The in-life phase comprised different control parameters, like mortality, clinical findings, body weight, hematology, occurrence of schistocytes, clinical chemistry, macroscopic findings, as well as blood analysis. In addition, organ damage was assessed microscopically. Finally, necropsy was performed on the treated disease animal models.

The ADAMTS13 KO mouse was selected as a relevant disease animal model. The comparison between the untreated control group and the vehicle control group showed that it is an effective mouse model for TTP. Animals challenged with rVWF and treated with vehicle developed TTP-like symptoms (e.g. rapid onset of clinical symptoms, development of thrombocytopenia, decrease in body weight and hematocrit, as well as an increase in schistocyte counts and lactate dehydrogenase levels), which were absent in unchallenged animals, as previously described by Schiviz *et al*. (2012). As such, showing severe clinical symptoms and developing severe thrombocytopenia and thromboembolic changes in several organs, these mice closely mimic clinical symptoms in TTP patients.

In a primary pharmacodynamic study (Study Number: WH0211), the Applicant evaluated the efficacy of prophylactically administered BAX 930 in the thrombotic thrombocytopenic purpura (TTP) model in ADAMTS13 KO mice. TTP-like symptoms were induced in ADAMTS13 KO mice by injecting a high dose of a recombinant human von Willebrand factor (rVWF) preparation which contained ultra-large VWF multimers.

Groups of animals were prophylactically treated with 200 FRETS-U/kg BAX 930 at different time points ranging from 5 minutes to 120 hours before triggering TTP by administration of 2000 RCo/U of rVWF. Animals treated with buffer and challenged with a high dose of rVWF served as negative controls. Unchallenged animals served as background controls. Efficacy of the test item was defined as the degree of prevention of platelet drop and prevention of increase in LDH, being hallmarks of TTP. Organ damage was also assessed and histologically scored. Morbidity in negative controls treated with buffer prior to challenge with rVWF was 100%.

As for the TTP-related microscopic findings, these consisted as expected of myocardial necrosis, hemorrhage, and inflammation as well as acute tubular necrosis and increased severity of tubular casts, recorded for both, the heart and kidney. Buffer-treated animals had the most severe TTP-related findings. The prolongation of the treatment interval (120h) caused an increase in the severity grade of all those findings, though the severity grade of acute myocardial necrosis and hemorrhage was still lower in this treatment group (120h), than in the buffer-treated animals.

TTP-related macroscopic findings were only recorded in buffer-treated animals. Animals prophylactically treated with BAX 930 either had no TTP-related lesions (5min / 3h) or significantly reduced severity grades.

It can as such be concluded that a treatment interval-dependent prophylactic effect of BAX 930 was shown in the rVWF-induced TTP model. TTP-related renal lesions were absent in all groups treated with BAX 930. Groups treated 3 hours or less prior to TTP induction were entirely protected from TTP-related lesions including myocardial lesions. Prophylactic administration of TAK-755 prevented the onset of VWF-mediated microvascular thrombosis, and therapeutic administration of TAK-755 acutely resolved pre-existing or growing thrombi in the brain after rVWF challenge.

Treatment with 1-200 FRETS-U/kg BAX 930 led to a dose-dependent normalisation of mean hematocrit and hemoglobin levels compared to those of untreated mice and prevented elevation of serum LDH levels ($p < 0.0001$). However, animals receiving the low dose of 1 FRETS-U/kg BAX 930 still showed severe thrombocytopenia. Clinically relevant protection was shown for doses starting with 40 FRETS-U/kg of BAX 930 and above.

The therapeutic effect of rADAMTS13 (BAX930) was assessed in several nonclinical studies. BAX930 was administered intravenously at five different dose levels to ADAMTS13 KO mice, the murine model of TTP. To induce TTP ADAMTS13 deficient mice were challenged with 2000 U/kg rVWF. Challenged and vehicle treated or reference item treated animals served as controls. As a control for the development of the TTP model, unchallenged and untreated animals were included in the study.

With administration of increasing dose levels of BAX930 (5 to 200 U/kg) the incidence and severity of TTP findings decreased. Animals treated with BAX930 at the highest dose (200 U/kg) showed only minor clinical findings, almost no schistocytosis, no macroscopic findings, no thrombocytopenia and compared with untreated control normal levels of LDH and hematocrit. For the increased platelet counts a statistically significant linear dose-response relationship was evaluated. Doses of 40, 80, and 200 U/kg BAX930 showed statistically significantly higher platelet counts than the control Buffer. Treatment with 200 U/kg BAX930 demonstrated to be the most therapeutically effective dose in the applied murine TTP model.

In another study, ADAMTS13 KO mice received an intravenous injection of a high dose of rVWF. 15, 30 or 180 minutes later, animals were treated with one dose of BAX 930 or buffer for BAX 930 (15 minutes study arm only). Background control groups were left untreated. A study on dose dependency in the TTP model of therapeutic efficacy was also employed, as well as a study to evaluate the therapeutic efficacy of different doses in the rVWF-induced TTP model in ADAMTS13 KO mice.

In conclusion, both prophylactic and therapeutic treatments with TAK-755 were shown to be efficacious in the rVWF-induced TTP model in ADAMTS13 KO mice. The efficacy of TAK-755 was interval- and dose-dependent when administered before or after induction of TTP. Treatment with TAK-755 showed similar or slightly improved efficacy compared to treatment with the current standard of care, Octaplas (fresh frozen human plasma).

The study conducted by Adili and Holinstat (2019) examined the prophylactic and therapeutic efficacy of TAK-755 treatment on the formation and resolution of pial microvascular thrombosis in the ADAMTS13 deficient mouse model. This study showed that prophylactic administration of TAK-755 prevented onset of the VWF-mediated pial microvascular thrombosis, and therapeutic administration of TAK-755 acutely resolved pre-existing or growing pial microvascular thrombi in the brain of ADAMTS13-deficient mice after rVWF challenge. This indicates that TAK-755 could be a potential therapy for microvascular thrombosis in cTTP patients. Although pial and cerebral microvessels share several morphophysiological properties, there are notable distinctions. Pial microvessels lack astrocyte ensheathment and the characteristic blood-brain barrier properties found in cerebral microvessels. However, this observation made in pial microvessels may not fully reflect cerebral microvascular thrombosis. No non-clinical biodistribution studies have been submitted.

2.5.2.2. Secondary pharmacodynamic studies

A publication was provided by Rossato (2022), pointing out, that high-dose TAK-755 administration (3111 U/kg) did not increase the bleeding tendency in a rat tail-tip bleeding model, either TAK-755 alone or in combination with 30mg/kg anticoagulant enoxaparin or 30mg/kg acetylsalicylic acid (ASA).

However, this tail tip bleeding study presented in the secondary pharmacology section currently specifically addresses the potential risks associated with exaggerated pharmacology and temporary bleeding risks related to TAK-755, which is not considered secondary pharmacology. The applicant indicates that ADAMTS13 primarily targets unfolded VWF and that no other substrates of ADAMTS13 have been identified from the overview of existing literature. They also note that ADAMTS13 is present in low levels in the plasma and has a high affinity for unfolded VWF. The applicant discusses the complex interaction between ADAMTS13 and VWF, emphasising specificity and lack of off-target effects. Literature references provided by the applicant also suggest that, in contrast to other proteases, ADAMTS13 is not released or specifically activated upon demand, but is in plasma present in its active form, which requires the enzyme to be highly specific to its substrate in order to prevent undesired non-specific proteolytic effects. Moreover, clinical studies show that TAK-755 administration at 40 IU/kg effectively restored ADAMTS13 activity to physiological levels with acceptable safety

margins, suggesting no unintended consequences. Nonclinical studies with supra-pharmacologic doses of TAK-755 did not result in acute or sub-acute effects other than cleavage of VWF. Adverse effects seen in toxicological studies with monkeys and rabbits were caused primarily by cross-reactivity of the neutralising ADA's to rhADAMTS13 with the animal endogenous ADAMTS13, causing ADAMTS13 shortage, precluding VWF multimer cleavage and leading to TTP-like effects. Considering the above, a secondary pharmacology study was not conducted as the intended use and lack of reported enzymatic activity outside of VWF cleavage.

2.5.2.3. Safety pharmacology programme

According to the ICH S7A guidance, "for biotechnology-derived products that have highly specific targets, it may be sufficient to evaluate safety pharmacology endpoints as a part of toxicology studies and safety pharmacology studies can be reduced or eliminated for these products." TAK-755 is such a biotechnology-derived recombinant human ADAMTS13, therefore the mechanism of action is well known. The observation of general conditions (i.e., behavior, appearance, body weight) in single- or repeat-dose toxicity studies and histopathology in the repeat-dose toxicity studies in rats and monkeys was considered. No undesirable pharmacodynamic properties that may affect CNS were expected by the rADAMTS13 product.

No specific or separate safety pharmacology studies were performed for the CNS, nor for the cardiovascular and respiratory system. All relevant safety pharmacology endpoints were included in the nonclinical RDTS developmental package.

CNS safety pharmacology endpoints were implemented in three GLP-compliant repeat-dose toxicity studies in rats (Study number 504247) and *Cynomolgus* monkeys (study numbers 8234215 and 8243420), and CV & respiratory parameters were evaluated in the RDTS in *Cynomolgus* monkeys (study number 8243420). Animals were observed daily for behaviour, appearance, vital functions, and any evidence of ill-health. No clinical signs in any animal that could be attributed to TAK-755 administration were observed in either study.

Importantly, there were no TAK-755-related findings related to CNS and no microscopic findings in the brain. The NOAEL in the pivotal rat and *Cynomolgus* monkey studies were 1820 IU/kg and 400 U/kg, respectively.

Due to the provided study results, TAK-755 can be considered not to affect the CNS systems, the CV or the respiratory system. However, it should be noted that even though no safety concerns arose from the study, an unusually large number of deviations to the study protocol was noted with regards to the cardiovascular investigations (measured electrocardiography). Many "inadvertent" events that occurred accidentally or study points that were unintentionally just not carried out were registered in the course of the study (8243420). These events were properly documented and no GLP compliance concerns were raised in this pivotal pharmacological safety study (which was implemented into the toxicological study).

2.5.2.4. Pharmacodynamic drug interactions

TAK-755 is a therapeutic recombinant protein intended as an ERT for ADAMTS13 deficiencies in cTTP. An interactive study between TAK-755 and acetylsalicylic acid or enoxaparin was conducted in a rat tail-tip bleeding model, not significantly increasing bleeding tendency.

2.5.3. Pharmacokinetics

The applicant submitted an extensive panel of analytical method validations and four absorption studies. Additionally, toxicokinetic investigations (plasma TAK-755 and plasma TAK-755 activity as well as anti-TAK-755 binding and neutralising antibodies) were included in the conducted toxicology studies.

The applicant submitted 12 validation reports on the analytical methods used in the submitted non-clinical pharmacokinetics and toxicokinetics investigations. Specifically, analytical methods for measuring PK in ADAMTS13 KO mice, Sprague Dawley rats, and *Cynomolgus* monkeys were developed. The scope of the submitted validation studies is adequate to demonstrate that these assays are capable of reliably detecting TAK-755 protein levels, TAK-755 activity and TAK-755 ADAs in animal plasma.

TAK-755 activity was determined in a fluorescence resonance energy transfer substrate activity assay (FRETS-VWF73 ADAMTS13 activity assay), which is based on the enzymatic activity of ADAMTS13 to cleave fluorogenic large VWF multimers. The protein TAK-755 was measured in an ELISA. Finally, binding ADAs in Sprague Dawley rats and *Cynomolgus* monkeys were also detected by a validated ELISA, whereas neutralising ADA in Sprague Dawley rats, NZW rabbits, and *Cynomolgus* monkeys were detected in a Bethesda-like assay. In addition, also an anti-CHO host cell protein ELISA was validated to determine the potential immunogenicity of CHO host cell proteins in *Cynomolgus* monkey. Importantly, no validation studies for NZW rabbits were submitted. However, the evaluation of some qualification/validation endpoints for toxicokinetics, binding and neutralising ADAs as well as ADMATS13 activity can be found in the annexes of the repeated dose toxicity Study AU0112W01 (Annex 5, 6 and 7). Furthermore, the NZW rabbit was considered not to be a suitable non-clinical species because of cross-reaction of TAK-755 neutralising ADAs with the endogenous ADAMTS13 and the subsequent development of a TTP disease phenotype in the otherwise healthy animals. Additionally, no method validation for either FRETS or ELISA based methods was provided for minipig pharmacokinetics studies. Based on the supportive use of the minipig study, and the fact that minipigs were not used in toxicology testing, there was no need for the Applicant to provide the method validation for this species.

The applicant submitted four absorption studies. Specifically, a pharmacokinetics study in ADAMTS13 KO mice (Study PV2521007, n=10 per group and sex and sampling time, 40, 80 and 200 U/kg administered), a pharmacokinetics study in rats (Study PV2531005, n=1 per sex and sampling time, 80, 200, and 400 U/kg administered), and two pharmacokinetics studies in Göttingen minipigs (Study WH0811 and WH0411, n=3-5 male pigs per dose group, i.v. or s.c. administration, 200 or 1000 U/kg administered). Of note, PK data for *Cynomolgus* monkeys were evaluated in studies that were submitted in the toxicology Module of the dossier (e.g. Study 8234215).

In ADAMTS13 KO mice, exposures (Cmax and AUC) increased dose proportionally in terms of measured protein content and activity. Terminal plasma half-life ranged between 10.0 and 17.3 hours for TAK-755 activity and from 15.4 to 20.2 hours for TAK-755 protein. Tmax was already achieved 5 minutes post-dose. The volume of distribution of ADAMTS activity and protein varied between 113 and 178 mL/kg for all 3 doses. These values demonstrates that TAK-755 apparently also partitions into compartments outside blood (according to the Applicant, mice have a plasma volume of 48.8 mL/kg body weight). Similar clearance values were measured in all dose groups (ranging between 7.0 and 8.3 mL/h/kg in terms of TAK-755 activity and protein content, respectively). Importantly, *in vivo* recoveries of TAK-755 for both TAK-755 activity and TAK-755 antigen were approximately 50 to 60 %.

In rats, exposure (Cmax and AUC) to TAK-755 protein and activity proportionally increased with increasing dose. Regarding TAK-755 protein, terminal half-life ranged from 23.5 to 24.0 hours,

whereas in terms of activity it ranged from 16.7 to 25.6 hours post-dose. Similarly as in ADAMTS13 KO mice, also in rats Tmax was already achieved 5 minutes post-dose. The volumes of distribution were lower in the rat compared to the ADAMTS13 KO mouse, whereby they ranged between 59.6 and 72.6 mL/kg for TAK-755 activity and 86.4 and 95.0 mL/kg for TAK-755 protein. Similarly as in the prior mouse study, this demonstrates that the administered TAK-755 also partitions to compartments outside blood (according to the Applicant, the rat has a total plasma volume of 31.3 mL/kg body weight). The clearance of TAK-755 activity ranged between 3.1 and 3.2 mL/h/kg, whereas it ranged between 2.0 and 2.9 mL/h/kg in terms of TAK-755 protein content. In the rat, *in vivo* recovery ranged from 60% to 66% for TAK-755 activity, and 49% to 57% for TAK-755 protein levels.

In Göttingen Minipigs, no ADAs were detected in any of the collected plasma specimens. Furthermore, the VWF multimer pattern analysis demonstrated only very limited cleavage of endogenous VWF by TAK-755 (as demonstrated by agarose gel electrophoresis followed by in-gel immunodetection with a polyclonal anti-human VWF antibody), specifically only in animals that received s.c. injections. Tmax in Göttingen Minipigs was 5 minutes post-dose in i.v. groups, but up to 30 hours post-dose in s.c. groups. Exposures (expressed in $AUC_{0\text{-tlast}}$) were 68.25 U/mL/*h (activity) and 39.81 µg/mL*h (protein) after i.v. administration, and 47.16 U/mL/*h (activity) and 26.23 µg/mL*h (protein) after s.c. ministration. The *in vivo* recovery after i.v. administration was 61.0% (activity) and 45.6% (protein), and 13% (activity) and 9.6% (protein) after s.c. administration. Terminal plasma half-life was 46.96 hours (activity) and 48.83 hours (protein) after i.v. administration, and 56.76 hours (activity) and 41.25 hours (protein) after s.c. administration. Finally, bioavailability after s.c. administration was calculated at 65.9% (protein) and 69.1% (activity) relative to the bioavailabilities after i.v. administration.

Apart from a placental transfer feasibility study in rats (Study 495388, submitted in the toxicology part of the dossier), no dedicated distribution studies were submitted. Importantly, volumes of distribution of TAK-755 levels and activities determined in rats and mice demonstrate that TAK-755 also distributes to compartments outside the blood circulation. However, it is agreed that no further distribution studies (e.g. organ distribution radiolabelling studies) are warranted, as TAK-755 will presumably not be liable for accumulation in tissues.

No metabolism studies were submitted. TAK-755 is a recombinant protein that will be degraded through regular protein katabolism into its amino acids.

Also, no excretion studies were submitted. TAK-755 is a recombinant protein that will be degraded through regular protein katabolism into its amino acids. No excretion of the intact protein via the kidney or via bile is expected in renally and hepatically non-compromised patients.

Finally, no pharmacokinetic drug interaction studies were submitted. This is justified by the applicant as the proposed mode of action of TAK-755 is highly specific (cleavage of ultra-large VWF multimers), and as this mode of action is currently not targeted in any ways by other therapies.

2.5.4. Toxicology

The applicant submitted an extensive toxicology dossier consisting of 7 repeated dose toxicity studies, 3 reproductive and developmental toxicity studies, 2 local tolerance studies, and three other toxicity studies (risk assessments on the excipients and the Q97R mutant contained in the TAK-755 drug product). The scope of the submitted toxicology studies is considered sufficient for a recombinant protein product such as TAK-755.

2.5.4.1. Single dose toxicity

No single dose toxicity studies were submitted. However, single dose toxicity was examined in *Cynomolgus* monkeys in a dose-escalation study (Study 8234215).

2.5.4.2. Repeat dose toxicity

The applicant submitted seven repeated dose toxicity studies. Specifically, four GLP-compliant repeated dose toxicity studies were conducted with rats (Study 527739, Study PV2511001, Study 504247 and Study 523430), a non-GLP compliant study was conducted with NZW rabbits (Study AU0112W01), and two GLP-compliant studies were conducted with *Cynomolgus* monkeys (Study 8234215 and Study 8243420). Apart from the regular panel of toxicologic and toxicokinetic investigations, also the formation of anti-TAK-755 antibodies (binding and neutralising) was examined in the submitted studies. In some of the studies, also cleavage of large molecular weight VWF multimers by TAK-755 was investigated. The studies in rats were conducted along the guidance provided in the ICH M3(R2) document (longest duration of repeated dose toxicity study in rats was six months). Importantly, no non-rodent repeated dose toxicity study with a duration of ≥ 6 months was submitted, which formally violates the guidance in ICH M3(R2). However, the Applicant sufficiently well demonstrated in shorter-term GLP-compliant (*Cynomolgus* monkeys) and non-GLP-compliant (NZW rabbits) non-rodent studies that rabbits and monkeys are not suited for longer-term repeated dose toxicity studies (vide infra). This was also agreed upon in a prior EMA scientific advice procedure (Procedure No.: EMEA/H/SAH/068/1/2016/PA/III).

Repeated dose toxicity in rats was studied in the early GLP-compliant Study 527739, in which TAK-755 was intravenously administered to Sprague-Dawley rats (n=10 per sex and dose in the main toxicity groups, n=5 per sex and dose in recovery groups and n=3 per sex and dose in toxicokinetic satellite groups) for 5 consecutive days at 0, 80, 200 and 400 U/kg body weight. Reversibility of effects was studied after a 2-week recovery period. In the GLP-compliant Study PV2511001, 0, 80, 400 and 800 U/kg body weight of TAK-755 were administered every third day for 28 consecutive days to Crl:CD rats (n=10 per sex and dosing regimen in the main toxicity groups, n=5 per sex and dose in recovery groups, n=3 (vehicle groups) or n=9 (TAK-755 groups) per sex and dose in toxicokinetics groups, and n=5 per sex and dose for the binding and neutralising ADA investigations). A 2-week recovery period was used in this study. In a similar GLP-compliant study (Study 504247), the toxicity of TAK-755 at 0, 800 and 1820 U/kg body weight during and after repeated daily intravenous administration was examined for 30 consecutive days in Sprague Dawley rats (n=10 per sex and dose in the main toxicity groups, n=5 per sex and dose in recovery groups and n=3 (vehicle groups) or n=6 (TAK-755 groups) per sex and dose in the toxicokinetics and binding and neutralising ADA groups). The recovery period lasted 2 weeks. Finally, in the pivotal GLP-compliant rat Study 523430, the Applicant investigated the toxicity of TAK-755 when intravenously administered every third day for a consecutive period of 6 months to Sprague Dawley rats at 0, 80, 200 and 400 U/kg body weight (n=15 per sex and dose in the main toxicity groups, n=5 per sex and dose in recovery groups, n=3 (vehicle groups) or n=6 (TAK-755 groups) per sex and dose in toxicokinetics groups, and n=5 per sex and dose in binding and neutralising ADA groups). A recovery period of 4 weeks was included in this study.

In these rat studies, no TAK-755 related adverse effects were noted in terms of clinical signs, body weights, body weight changes, food consumption, ophthalmology, clinical pathology parameters (haematology, coagulation, clinical chemistry, and urinalysis), gross necropsy, sperm motility and morphology, organ weights and histopathology. In terms of toxicokinetics (TAK-755 activity and/or antigen level), systemic exposure to TAK-755 in rats proved to be generally dose-proportional and did not display a notable sex difference. Systemic exposure to TAK-755 was higher at the end than at the beginning of the experiments, most likely because of the extended terminal half-lives of TAK-755 in

rats (> 20 hours). In general, in the collected rat plasma samples, binding and neutralising anti-TAK-755 antibodies were measured in a dose- and time-dependent fashion. Interestingly, none of the animals in the pivotal long-term Study 523430 had anti-TAK-755 antibodies with neutralising properties (contrarily to the preceding shorter-term rat repeated dose toxicity studies). Where included, the Applicant claimed that the VWF multimer analyses demonstrated that the administered TAK-755 cleaved very high molecular weight VWF multimers, thereby demonstrating pharmacologic efficacy in the rat. To conclude, TAK-755 was very well tolerated in rats, with the NOELs or NOAELs being the highest administered TAK-755 dose in all submitted studies.

Apart from rats, one non-GLP compliant feasibility study with NZW rabbits was submitted (Study AU0112W01). In this study, the toxicity profile, ADA formation potential and VWF multimer cleavage potential of TAK-755 were investigated after repeated intravenous administration (for a consecutive period of 2 weeks, administration every third day) in female NZW rabbits (n=4 per dosing regimen) at 0, 80, 400 and 800 U/kg.

No signs of clinical toxicity were recorded during the course of this experiment. However, TAK-755 administration led to decreased haematocrit, decreased haemoglobin, and decreased platelet counts in one animal at 800 U/kg (a similar decrease in platelet count was also observed for a second animal in the 800 U/kg group). This animal also had haemorrhages in the skin, skeletal muscle, axillary lymph nodes and thymus. Most animals in the 400 and 800 U/kg groups had myocyte degeneration/necrosis in the heart (higher severity at 800 U/kg), and also acute to sub-acute myocardial inflammation was observed. None of these findings were observed at 0 and 80 U/kg. Apart from these findings, administration of TAK-755 did not lead to adverse effects in terms of clinical signs, body weight, clinical pathology parameters, macroscopic pathology and organ weights. At the end of the experiment, all animals that had received TAK-755 had formed anti-TAK-755 binding antibodies, whereby titres in general increased with increasing TAK-755 doses. Even more important, all animals in the 800 U/kg group and 3 out of 4 animals in the 200 and 80 U/kg group had neutralising anti-TAK-755 antibodies at the end of the experiment. Because of neutralisation of the administered TAK-755, the toxicokinetics could only reliably be determined after the first administration. Interestingly, endogenous VWV multimers were obviously not degraded by TAK-755 at all applied dose levels (as determined in the conducted low- and high-resolution agarose gel electrophoresis investigation), questioning the pharmacological efficacy of TAK-755 in NZW rabbits.

Based on all these findings, the Applicant concluded that the NZW rabbit is susceptible to cross-reaction of neutralising anti-TAK-755 antibodies with the endogenous rabbit ADAMTS13, which ultimately leads to the generation of the TTP phenotype in the affected animals. The applicant therefore proposed that NZW rabbits are unsuitable for non-clinical safety assessments (such as rabbit EFD studies) of TAK-755 as a.) the TTP phenotype leads to a problematic safety profile, b.) the high incidence of neutralising ADAs leads to enhanced drug clearance in NZW rabbits, and c.) TAK-755 appears to be not pharmacologically active in NZW rabbits. Based on the submitted data it is agreed that NZW rabbits are not suited for toxicity studies with TAK-7555.

Finally, two GLP-compliant short-term repeated dose *Cynomolgus* monkey studies were submitted. In Study 8234215, the Applicant examined the pharmacokinetics and the toxicology (dose-finding and repeated dose administration) of TAK-755 after intravenous administration to *Cynomolgus* monkeys (with n=3 males and females and doses of up to 1790 U/kg in the escalating dose phase; and with n=3 males and females at doses of 0 or 800 U/kg in the repeated dose phase, whereby one male and female were used in the vehicle groups and two males and females were treated with TAK-755). TAK-755 was administered on Day 1 and 15 in the dose escalating fraction of this study, and once a week during a 4-week period in the repeated dose phase. In Study 8243420, TAK-755 was intravenously administered to *Cynomolgus* monkeys each day for a consecutive period of 4 weeks at 0, 80, 200 and

400 U/kg. Two animals per sex and group were kept for the recovery period, which lasted 2 weeks. In this study, also cardiovascular examinations were included.

No test-article related alterations were noted in the dose escalating part of Study 8234215. In both studies, no mortalities and clinical findings correlated with the administration of TAK-755. Furthermore, no direct test-article related effects on body weights, ophthalmoscopy, electrocardiography, blood pressure, respiratory rate, blood gas analysis, urine analysis, organ weights, gross pathology and histopathology were observed. Finally, also no adverse effects at the injection sites were recorded.

However, importantly, a variety of test-article related effects were identified in female *Cynomolgus* monkeys that correlated with the administration of higher TAK-755 doses. At the end of the repeated administration of 800 U/kg TAK-755 in Study 8234215 and 400 U/kg (and to some extent 200 U/kg) in Study 8243420, thrombopenia, haemolytic anaemia (decreases in red blood cell count, haemoglobin and haematocrit), increased reticulocytes, bilirubinaemia, generalised macroscopic skin haematoma or red foci in kidneys and the stomach, haemorrhage or congestion/haemorrhage in the heart, adrenals, stomach and skin, or proteinaceous casts in the kidneys were observed in female monkeys. No such alterations were observed in control group monkeys. Interestingly, also no similar changes were observed in male monkeys that had received TAK-755. These findings are similar with the observations in the NZW Study AU0112W01.

The applicant hypothesises that also in monkeys, neutralising anti-TAK-755 antibodies likely cross-reacted with the native endogenous ADAMTS13 enzyme and therefore led to the formation of the TTP phenotype in animals that had received consecutive administration of higher doses of TAK-755. This hypothesis is supported by the high incidences and titres of binding and especially neutralising anti-TAK-755 antibodies in the treated monkeys: For example, in Study 8243420, anti-TAK-755 binding antibodies were found in a time- and dose-dependent fashion (except for the control group animals), specifically in 4, 7 and 10 out of 10 animals in the 80, 200 and 400 U/kg groups, respectively. From these binding-ADA positive animals, 1, 6 and 8 animals proved also positive for neutralising anti-TAK-755 antibodies, respectively. Furthermore, the Applicant claims that the examined pattern of VWF cleavage in Study 8243420 supports the hypothesis that cross-reactive neutralising anti-TAK-755 antibodies lead to the generation of the TTP phenotype in affected female monkeys: At the end of dosing, the Applicant claims that no decrease of high molecular weight VWF multimers was measured, whereas at the beginning of dosing the VWF multimer molecular weight was claimed to be partially decreased (which would demonstrate pharmacologic activity of TAK-755 in monkeys). This would suggest that towards the end of the experiment, antibodies had neutralised the enzymatic activity of the administered TAK-755 and the endogenous ADAMTS13 enzyme.

Due to the generation of the TTP phenotype after repeated administration of TAK-755 to *Cynomolgus* monkeys, this species indeed appears not to be suited for longer term toxicity studies. Therefore, no longer-term repeated dose toxicity studies with *Cynomolgus* monkeys were conducted (usually required according to the ICH M3(R2) or ICH S6(R1) guidelines). This was also already communicated in the EMA scientific advice procedure EMEA/H/SAH/068/1/2016/PA/III).

Regarding toxicokinetics in *Cynomolgus* monkeys, exposure to TAK-755 activity and protein levels (in terms of Cmax and AUC) increased during the course of the experiment. Furthermore, dose-proportionality was approximately attained for the measured TAK-755 activity and antigen levels. Of note, no anti-CHO host cell protein antibodies were detected in the treated *Cynomolgus* monkeys in both studies.

Four concerns were originally identified on the cross-reactivity of anti-TAK-755 neutralising antibodies in NZW rabbits and *Cynomolgus* monkeys.

Importantly, according to the Applicant, rats and monkeys were considered to be pharmacologically active species based on the results of the VWF multimer size measurements by electrophoresis on high and low resolution agarose gels, conducted in the 4-week studies. However, as can be evidenced from Figure 1 (monkeys) and Figure 2 (rats) further below, visual inspection of the submitted data suggests that the apparent decrease in the intensity of the staining to which the Applicant refers, was marginal at best and can easily be interpreted as being due to normal inter-sample variability because of low method sensitivity. Furthermore, the effects were seen only in some animals and were inconsistent, and, surprisingly, some rat samples appeared to demonstrate an increase, rather than a decrease, of the staining intensity in the high MW region. Respectively, the observed results are not considered to be a sufficient proof of pharmacological activity of rADAMTS13 in rats and monkeys *in vivo*. However, the efficacy of rADAMTS13 in the KO mouse model and in the clinical settings has been observed.

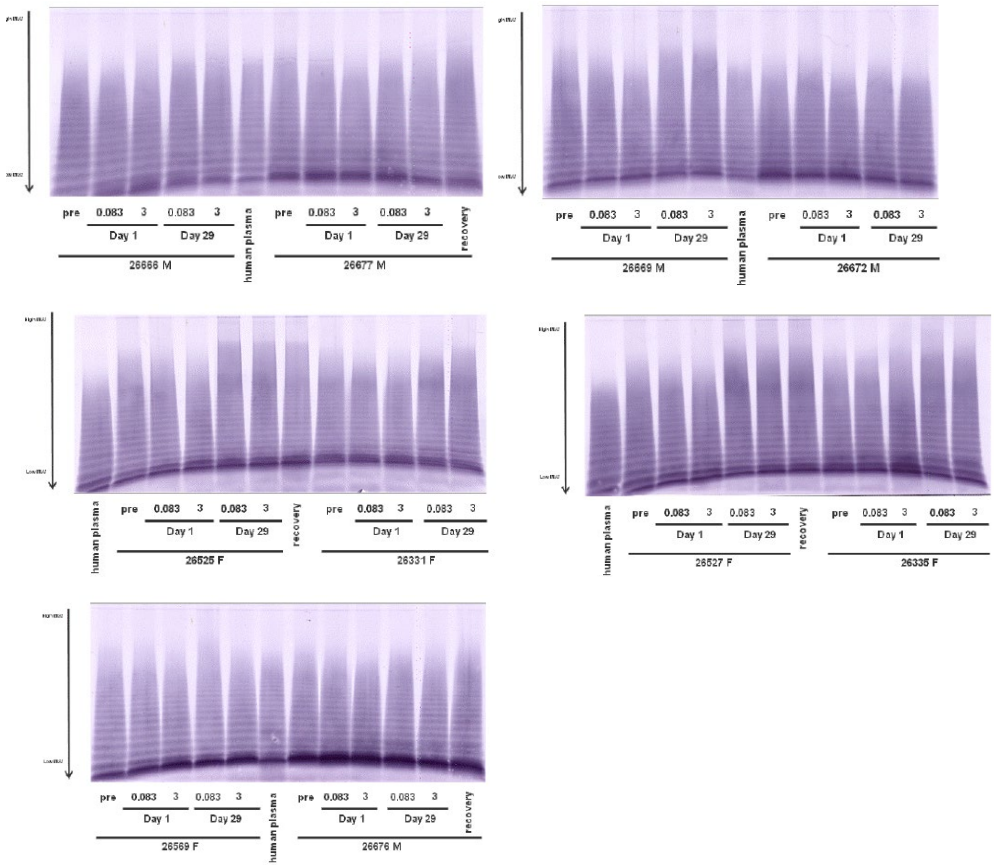


Figure 1 . Low resolution agarose gels of high-dose monkeys (400 FRETS-U/kg) in the 4-week pivotal study. According to the Applicant, lower intensity of the staining in the high MW region was observed in animals 26669M, 26525F, 26331F and 26527F.

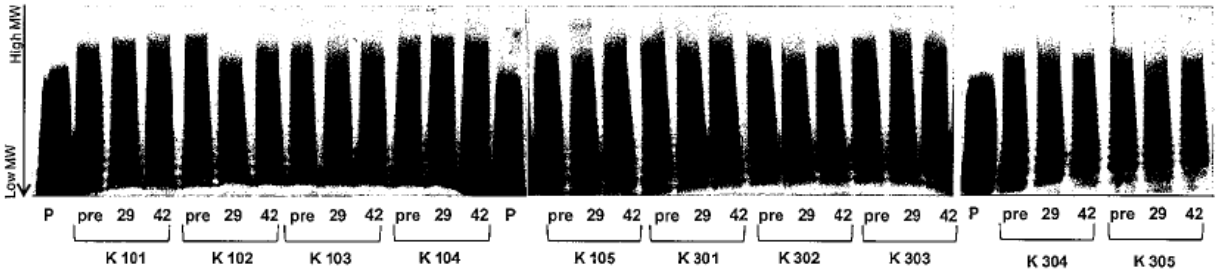


Figure 2 . Low resolution agarose gels of high-dose rats (800 FRETS-U/kg) in the 28-day rat study.

According to the Applicant, animals K102, K103, K105, K301 and K302 demonstrated a decrease in the intensity of the staining in high MW region on Day 29 of the treatment. However, it is noted that in some animals, e.g. K104 and K303, apparently an increase in staining was observed, demonstrating the unreliability of the gathered results.

Finally, the following table lists the exposure multiples at the claimed NOALEs (U/kg) in the conducted repeated dose toxicity studies (and reproductive toxicology studies) in comparison with exposures achieved in patients:

Table 1 : NOAEL and Margin of Safety Based on AUC and Cmax

							Prophylaxis Margin of Safety [a]		
Report	Species (Study Type)	Dose Regimen	NOAEL (U/kg)	C_{max} (U/mL)	AUC_{last} (h*U/mL)	t_{last} (h)	Dose Ratio (U/kg) [b]	C_{max} [c]	Q2W AUC [d]
Single Dose Escalation									
8234215	Monkey (Dose escalation)	QD	1790 [e]	33.0	654	60	45	29	50
Repeat-Dose Toxicology Studies									
527739	Rat (5 day)	QD	400	6.04/4.30 (M/F)	83/63 (M/F)	24	10	5.4/3.8 (M/F)	16/12 (M/F)
PV2511001	Rat (28 day)	Q3D	800	14.3	244	72	20	13	16
504247	Rat (30 day)	QD	1820 (IU/kg)	109	1150	24	46	97	222
523430	Rat (26 week)	Q3D	400	9.56	223	72	10	8.5	14
8243420	Monkey (1 month)	QW	400	8.70 [f]	182 [f]	70	10	7.8	12
Reproductive Toxicology Studies									
497081	Rat (female fertility and embryo-fetal development)	Q3D	400	4.41 [g]	97.6 [g]	54	10	3.9	8.4
496821	Rat (pre-and postnatal development)	Q3D	400	4.41 [h]	97.6 [h]	54 [h]	10	3.9	8.4

Source: Reports 8234215, 527739, 504247, PV2511001, 523430, 8243420, 497081, and 496821.

AUC: area under the concentration-time curve; AUC_{last}; AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration; C_{ave}: average concentration; $C_{ave,ss}$: average concentration during a dosing interval, at steady state; C_{max}: maximum observed concentration; $C_{max,ss}$: maximum observed concentration during a dosing interval, at steady state; cTTP: congenital thrombotic thrombocytopenic purpura; F: female(s); M: male(s); NOAEL: no observed-adverse-effect level; PK: pharmacokinetic(s); Q2W: once every 2 weeks; Q3D: once every third day; QD: once daily; QW: once weekly; t_{last}: time of last observed quantifiable concentration.

[a] The 40 IU/kg clinical prophylactic dose PK parameters used in margin calculations are from a final population PK analysis conducted leveraging one Phase 1 cTTP study and two ongoing Phase 3 cTP studies (Final popPK/PD report). At steady state, the modeled mean $C_{max,ss}$ value was 1.12 IU/mL (Q2W administration). The mean $C_{ave,ss}$ value was 0.216 IU/mL (Q2W administration). Preliminary parameters for on-demand treatment regimen are not available, but the AUC is anticipated to be approximately 2-fold higher than prophylaxis treatment.

[b] Margin of safety = Nonclinical dose (U/kg) of NOAEL/Clinical dose (40 IU/kg).

[c] Margin of safety = Nonclinical C_{max} of NOAEL/Clinical C_{max} (1.12 IU/mL).

[d] Margin of safety = Nonclinical AUC_{last} at NOAEL/(C_{ave} for 40 IU/kg for Q2W [0.216 IU/mL] regimen * t_{last} value for nonclinical study).

[e] 1790 U/kg was a well-tolerated dose.

[f] Values from the initial weekly dose were used; following the Week 4 dose there was a high incidence of neutralizing antibodies with lower exposure.

[g] Values are after repeated dosing near last dose day; either Day 31 or 34 of study.

[h] No toxicokinetic was conducted for Report 496821; values are from Report 497081.

Importantly, this compilation demonstrates that in the pivotal rat (repeated dose toxicity and reproductive toxicity) and rabbit studies (1 month monkey repeated dose toxicity studies), exposure multiples at the claimed NOAELS were only approximately 8 to 14-fold higher than exposures achieved in the clinical prophylaxis regimen (in terms of AUC_{last}). Of note, the Applicant considers the highest tested dose level in the 28-day monkey study (Study 8243420) as NOAEL; however, this notion is not supported, as the test-article related adverse effects noted in this study were already seen in both

mid- and high dose animals. Based on this, the NOAEL in Study 8243420 should be set at the lowest dose level of 80 FRETS-U/mL.

Cross-reaction of neutralising anti-TAK-755 antibodies with the endogenous ADAMTS13 monkey enzyme only led to the generation of the TTP phenotype in female monkeys, but not in male monkeys (both in Studies 8234215 and 8243420). Importantly, there was no relevant difference in the number of male and female animals with ADAs in the 4-week monkey study (Study 8243420, see Table 5 below).

Table 2 : ADA positive animals in Study 8243420

BAX930 4-Week Intravenous Administration Toxicity Study in the Cynomolgus Monkey, Including Cardiovascular Investigations, With a 2-Week Recovery Phase								
Daily Dose (U/kg)	**0 (Control)**		**80**		**200**		**400**	
Number of Animals (Main)	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Number of Animals (Recovery)	**M: 2**	**F: 2**	**M: 2**	**F: 2**	**M: 2**	**F: 2**	**M: 2**	**F: 2**
Immunology								
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Died or Euthanized Moribund	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Animals With Binding Antibodies (After 32 Days)	0/5	0/5	2/5	2/5	4/5	3/5	5/5	5/5
Animals With Neutralizing Antibodies (After 32 Days) [a]	0/5	0/5	1/5	0/5	3/5	3/5	4/5	4/5
Animals With Binding Antibodies (After Recovery)	0/2	0/2	0/2	1/2	2/2	1/2	2/2	2/2
Animals With Neutralizing Antibodies (After Recovery) [b]	0/2	0/2	0/2	0/2	1/2	1/2	2/2	2/2

2.5.4.3. Genotoxicity

No genotoxicity studies were submitted as TAK-755 is a recombinant protein that is not expected to react with the DNA.

2.5.4.4. Carcinogenicity

Similarly, no carcinogenicity studies were submitted as TAK-755 is an enzyme replacement therapy that replaces an endogenous human protein that is not suspected to be involved in tumorigenic signalling.

2.5.4.5. Reproductive and developmental toxicity

In terms of reproductive and developmental toxicity, two GLP-compliant studies were conducted in Sprague Dawley rats. In study 497081 a total of 80 female rats was injected with the test article every third day at dose levels of 0, 80, 200 or 400 U/kg (20 animals/group) from 2 weeks before mating to GD 16. In study 496821 a total of 96 female rats was injected as above (i.e., Q3D 0, 80, 200 or 400 U/kg; 24 animals/group) from GD 6 to weaning (or ~lactation day 21). Examinations included female fertility and embryo-foetal development (Study 497081), parturition, lactation, post-natal development and reproductive function of F1 offspring (Study 496821). No adverse effects of the test article were identified on any of these aspects and the NOAEL was defined as 400 U/kg.

A supplementary non-GLP study (495388) was conducted, evaluating the passage of the test article from the maternal to the foetal serum over the placenta. A single IV bolus of 3200 U/kg into pregnant Sprague Dawley rats on GD 21 demonstrated that foetal serum concentrations reach ~0.6% of maternal serum concentrations, 30 min post injection.

Taken together, the test article exerts no toxic effect on reproduction and development, within the scope of the conducted studies. Seminology and microscopic evaluation of reproductive organs of males in the 4-week and 26-week chronic rat toxicity studies did not reveal concerns for male fertility.

2.5.4.6. Local Tolerance

The local tolerance of TAK-755 was investigated in NZW rabbits in the GLP-compliant Studies PV2541101 and 20248970. Furthermore, clinical signs after intravenous TAK-755 injection were also examined in the conducted repeated-dose toxicity studies in *Cynomolgus* monkeys and rats.

In Study PV2541101, the Applicant examined the local tolerance of TAK-755 (311 U/mL) after intravenous, intraarterial and paravenous administration in NZW rabbits (n=2 males and females per group) compared to administration of vehicle control (separate animal groups) and saline (injected into the left ear of each animal). In total, 5 mL were administered i.v. and i.a., whereas 0.5 mL were administered paravenously. Similarly, in Study 20248970, 316 U (contained in a 1 mL injection) were administered to 8 NZW rabbits (approximately 2 inches on the right side of the spine). The same animals also received a control article s.c. injection (approximately 2 inches on the left side of the spine).

2.5.4.7. Other toxicity studies

No antigenicity study was submitted. However, antigenicity evaluations (i.e. humoral immune responses towards the recombinant protein) were incorporated in the submitted repeated dose toxicity studies. Specifically, the incidence of ADAs (binding and neutralising ADAs) was assessed in rats, NZW rabbits and *Cynomolgus* monkeys after repeated administration.

No stand-alone immunotoxicity studies were submitted. TAK-755 is a recombinant protein and will be used as enzyme-replacement therapy to substitute insufficient expression of an endogenous enzyme (ADAMTS13). Therefore, it is unlikely that TAK-755 would result in immunotoxicity. Furthermore, macroscopic and microscopic evaluations of primary and secondary immune organs was included in the submitted repeated dose toxicity studies, and TAK-755 did not elicit direct adverse effects in these off-target organs.

No dependence studies were submitted as TAK-755 is a recombinant protein that is not expected to lead to neurologic alterations that could end up in dependence, and as TAK-755 constitutes an enzyme replacement of an endogenous enzyme that is not involved in neurologic signalling.

Furthermore, no toxicity studies on metabolites were submitted as metabolites of TAK-755 will be its single amino acids that will get liberated through regular protein katabolism.

Two studies were submitted in Module 4.2.3.7.6 (impurities): In Study RA12RS08, the Applicant provided a risk assessment on the excipients contained in the TAK-755 product. These excipients are L-histidine, calcium chloride, sodium chloride, mannitol, sucrose and tween 80 (polysorbate 80). Furthermore, in Study RA12BM08RI, the Applicant provided a risk assessment on the excipient tween (polysorbate) 80.

The applicant's proposal that (apart from potential hypersensitivity to tween 80) no risks are expected from the excipients contained in the TAK-755 product is supported.

Finally, an *in silico* study (Study A10886M-SHP655) was submitted in Module 4.2.3.7.7 (other toxicity studies) in which the Applicant examined whether the Q97R mutant in TAK-755 poses an immunogenicity risk compared to the wild-type amino acid sequence of ADAMTS13. In this study, the Applicant concluded that no new MHC II T-cell epitopes are formed in TAK-755 due to the Q97R

mutation. The final prove of a lacking immunogenic potential of the Q97R mutant needs to be brought especially in clinical studies.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the guideline CHMP/SWP/4447/00 (1), rADAMTS13 as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment. Therefore, rADAMTS13 is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical package essentially followed the guidance provided in both applicable EMA Guideline ICH M3 and S6. The tail tip bleeding study presented in the secondary pharmacology section currently specifically addresses the potential risks associated with exaggerated pharmacology and temporary bleeding risks related to TAK-755, which is not considered as secondary pharmacology. The applicant indicates that ADAMTS13 primarily targets unfolded VWF and that no other substrates of ADAMTS13 have been identified from the overview of existing literature. They also note that ADAMTS13 is present in low levels in the plasma and has a high affinity for unfolded VWF. The applicant discusses the complex interaction between ADAMTS13 and VWF, emphasising specificity and lack of off-target effects. Literature references provided by the applicant also suggest that, in contrast to other proteases, ADAMTS13 is not released or specifically activated upon demand, but is in plasma present in its active form, which requires the enzyme to be highly specific to its substrate in order to prevent undesired non-specific proteolytic effects. Moreover, clinical studies show that TAK-755 administration at 40 IU/kg effectively restored ADAMTS13 activity to physiological levels with acceptable safety margins, suggesting no unintended consequences. Nonclinical studies with supra-pharmacologic doses of TAK-755 did not result in acute or sub-acute effects other than cleavage of VWF. Adverse effects seen in toxicological studies with monkeys and rabbits were caused primarily by cross-reactivity of the neutralising ADA's to rhADAMTS13 with the animal endogenous ADAMTS13, causing ADAMTS13 shortage, precluding VWF multimer cleavage and leading to TTP-like effects. Based on the above findings, the applicant argues that a secondary pharmacology study would add little value to overall risk assessment considering the intended use and lack of reported enzymatic activity outside of VWF cleavage. This is endorsed.

No non-clinical biodistribution studies have been submitted. Therefore, whether TAK-755 can enter blood brain barrier, treat neurological complications associated with microvascular thrombosis in the brain of patients with TTP is not clear.

Pharmacokinetics

No concerns were identified in the submitted non-clinical pharmacokinetics studies.

Toxicology

In monkeys and rabbits, TTP-like effects were seen in the mid- and high-dose treated animals which were ascribed by the Applicant to the cross-reactivity of the neutralising ADAs against the endogenous animal ADAMTS13. This was consistent with the detection of neutralising ADAs in the affected animals.

Upon CHMP request, the Applicant has provided additional data on primary sequence homology between the monkey, rat and rabbit ADAMTS13 and the VWF substrate to further support this hypothesis. Data from the National Center for Biotechnology Information alignment tool indicate that high confidence ADAMTS13 ortholog in monkey indeed shows a high degree of primary homology with

human ADAMTS13 (91.59%), while for rats, it is lower (66.81%). This supports an assumption that neutralising ADA's against rhADAMTS13 in monkeys would be capable of cross-reactivity with endogenous monkey ADAMTS13, precluding VWF multimers cleavage and leading to TTP-like symptoms. On the other hand, a much lower degree of sequence homology between rat and human ADAMTS13 is consistent with the absence of TTP-like symptoms in rats, as the interaction of rat ADA's against rhADAMTS13 with native rat ADAMTS13 would likely be much weaker or not occur at all.

A high confidence ortholog of human ADAMTS13 was not identified for rabbit; however, the Applicant has provided the reference to the paper of Muia *et al.* (2019) who have demonstrated that rabbit plasma ADAMTS13 was capable of cleaving human rVWF71 (71 aminoacid sequence) at the level of 290% of the human ADAMTS13, whereas for monkey (macaque) plasma it was 86% and for rat plasma 1.6%. This suggests that rabbit ADAMTS13 can very efficiently cleave human VWF. The applicant speculated that this indirectly points to the high degree of similarity between rabbit and human ADAMTS13, which in turn makes it plausible that neutralising ADA's against rhADAMTS13 in rabbits would also be reactive against the endogenous rabbit ADAMTS13, leading to TTP-like symptoms in this species.

In rabbits, administration of rADAMTS13 at 400 and 800 FRETS-IU/kg caused treatment-related adverse heart effects consisting of focally extensive histiocytic/heterophilic inflammation associated with minimal to mild myocardial degeneration. The applicant argued that these adverse heart changes were not observed in rats and monkeys, and that rabbits thus demonstrated a unique toxicity profile, consistent with the lack of pharmacological activity of rADAMTS13 in these species. However, adverse heart effects were also seen in monkeys. In particular, in the 4-week pivotal monkey study one mid-dose female showed slight multifocal myocardial degeneration of the myocardium of the left ventricle, whereas in one high-dose female from the recovery group degeneration of the myocardium, hemorrhage, extramedullary hematopoiesis, and hypertrophy of the media of small vessels in the myocardium were evidenced. Furthermore, in the exploratory monkey study hemorrhage in the heart was observed in 1/2 females of the repeated dose part of the study. As the effects were observed only in a few animals, their relationship with the treatment was not clear. Upon request the Applicant has provided additional arguments that the observed effects were secondary to the immunogenic response to a human protein in rabbits and monkeys and were not related to the direct pharmacological action of the substance. Indeed, it is known that low ADAMTS13 plasma activity leads to microthrombi formation and may result in progressive ischemic organ injury, including cardiac damage. Based on the provided data on sequence homology in different species, the ability of the rabbit and monkey neutralising ADA's to cross-react with endogenous ADAMTS13 in these species is indeed considered plausible. Furthermore, there appeared to be indeed a consistency between the neutralising ADA's presence and adverse cardiac changes in individual animals in both rabbit and monkey studies. Taken together, it is considered plausible that adverse cardiac findings were secondary to the immunological response of monkeys and rabbits to a human protein and are not caused by the direct pharmacological action of the substance. As immunogenicity in non-clinical species is not considered to be predictable of immunogenicity in humans, the observed effects are thus not considered relevant for the human risk assessment.

Cross-reaction of neutralising anti-TAK-755 antibodies with the endogenous ADAMTS13 monkey enzyme only led to the generation of the TTP phenotype in female monkeys, but not in male monkeys (both in Studies 8234215 and 8243420). Importantly, there was no relevant difference in the number of male and female animals with ADAs in the 4-week monkey study (Study 8243420); thus, the observed difference in the observed adverse effects cannot be explained by higher number of females vs males developing ADAs.

Consequently, it was not clear why only female monkeys were affected, but not male ones. Therefore, the Applicant was requested to discuss this sex-dependent susceptibility, and to also discuss whether

an increased susceptibility to cross reactions of neutralising antibodies with endogenous proteins could also apply to female patients receiving TAK-755 or in case of pregnancy to the foetus and/or newborn. The applicant responded to this request that in Study 8243420 the animals with the highest titers of neutralising ADAs were the two females (26521F and 26525F) that also developed the TTP-like phenotype. Additionally, the Applicant speculated that the male animal 26681M might have also developed the TTP-like phenotype had it been in the recovery cohort, as it also had high titers of neutralising ADAs. The applicant additionally speculated that the aspect that only female animals developed the TTP-like phenotype in the monkey studies could merely be a chance finding. Finally, and most importantly, the Applicant summarised that in the entire clinical development of ADAMTS13 no neutralising antibodies have yet been detected. This indeed suggests that the finding that exclusively female monkeys developed the TTP-like phenotype due to neutralising ADAs likely occurred by chance alone and therefore is not relevant for patients. Therefore, this concern was considered resolved.

Additionally, the Applicant was asked to broadly discuss the potential relevance of the identified cross-reactivity of anti-TAK-755 neutralising antibodies against endogenous ADAMTS13 and the associated pathologies in NZW rabbits (Study AU0112W01) and *Cynomolgus* monkeys (Studies 8234215 and 8243420) for patients. In response to this request the Applicant also communicated that in the clinical development of ADAMTS13 no neutralising ADAs have been identified so far. This supports the notion that cross-reaction of neutralising ADAs with other endogenous proteins is unlikely as ADAMTS13 appears to be of low potency to induce ADAs in patients.

Genotoxicity

No genotoxicity studies were submitted as TAK-755 is a recombinant protein that is not expected to react with DNA, which is considered acceptable in line International Council for Harmonization (ICH) S6 (R1).

Carcinogenicity

Similarly, no carcinogenicity studies were submitted as TAK-755 is an enzyme replacement therapy that replaces an endogenous human protein that is not suspected to be involved in tumorigenic signalling in line International Council for Harmonization (ICH) S6 (R1).

Reproductive and developmental toxicity

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see SmPC section 4.6 and 5.3). The use of Adzynma during pregnancy may only be considered after a thorough individual risk benefit analysis by the treating physician before and during treatment.

There is insufficient information on the excretion of rADAMTS13 in human or animal milk but it is unlikely that it is excreted in human milk due to its high molecular weight. The decision either to discontinue breast-feeding or discontinue Adzynma should take into account the importance of this medicinal product to the mother.
No human data are available on the effects of rADAMTS13 on male and female fertility. Animal data do not indicate direct or indirect harmful effects with respect to male or female fertility (see SmPC section 4.6 and 5.3).

Local tolerance

No specific safety concerns were identified.

Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, rADAMTS13 is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, single dose toxicity, toxicity to reproduction and development, local tolerance and immunogenicity. From a non-clinical perspective, the submitted data are considered appropriate to support marketing authorisation of Adzynma as an enzyme replacement for cTTP.

In addition, both prophylactic and therapeutic treatments with TAK-755 were shown to be efficacious in the rVWF-induced TTP model in a relevant ADAMTS13 KO mice and showed similar or slightly improved efficacy compared to treatment with the current standard of care (fresh frozen human plasma).

All relevant information has been included in the SmPC sections 4.6 and 5.3.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 3 Clinical Studies in the Dossier

Study / Analysis - Status	Study or Analysis Title	Data Presented
281101 Completed	A Phase 1, Prospective, Uncontrolled, Open-label, Multicenter, Dose-escalation Study Evaluating the Safety and Pharmacokinetics in Hereditary Thrombotic Thrombocytopenic Purpura (hTTP)	Completed results include safety, PD, and PK data for 15 subjects who received a single dose of TAK-755 at 5 IU/kg (n=3), 20 IU/kg (n=3), or 40 IU/kg (n=9).
281102 Ongoing	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])	Interim results consist of efficacy, safety, PK, PD, and HRQoL data in 48 subjects (47 unique subjects) in the prophylactic cohort and 5 subjects (4 unique subjects) in the on-demand cohort. As of the interim data cutoff, 32 subjects have completed the study in prophylactic cohort. The mean duration of TAK-755 exposure for all subjects is 11.5 (SD 6.31) months.
TAK-755-3002 Ongoing	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)	Interim results include safety, efficacy, PK, and PD data for 36 subjects who received prophylactic TAK-755 treatment, 29 of whom rolled over from Study 281102 and 7 subjects who were non-rollovers. At the time of the interim analysis, the 36 subjects have received prophylactic treatment with TAK-755 for a mean duration of 6.3 (SD 4.82) months.

2.6.2. Clinical pharmacology

The clinical pharmacology studies supporting this marketing application consist of 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]) in subjects with cTTP. The PK, PD, and PK/PD data are based on 15 cTTP subjects in Study 281101, 47 cTTP subjects in the pivotal Phase 3 study pharmacokinetic full analysis set (PKFAS; Study 281102), and 36 cTTP subjects (including 29 rollover and 7 non-rollover subjects from Study 281102) in the continuation Phase 3 study PKFAS (Study 3002). Summaries of the study design, dosing regimen, PK and PD analytes, and associated sample collection types are shown in Table 7.

The PK analyses in both studies included measurements of ADAMTS13 antigen and activity, and PD analyses included measurements of VWF antigen, von Willebrand factor: ristocetin cofactor (VWF:RCo) activity, VWF multimer patterns, and VWF cleavage products.

Table 7 Studies conducted to characterise the clinical pharmacology of TAK-755 in cTTT 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 See Section 2.1.1	TAK-755 ORT	**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 See Section 2.1.2	TAK-755 ORT, TAK-755 SIN, 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 See Section 2.1.3	TAK-755 SIN	**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; ORT=Orth, Austria; PD=pharmacodynamics; PK=pharmacokinetics; Q1W=once every week; Q2W=every 2 weeks; SIN=Singapore; 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.

Pharmacology Assays

ADAMTS13 activity in human plasma by FRETS-VWF73 assay

A synthetic fluorescence resonance energy transfer substrate consisting of 73 amino acids which is derived from the vWF A2 domain covering the cleavage site of ADAMTS13 (FRETS-VWF73). This peptide was modified with 2 fluorogenic residues (Donor and Acceptor/Quencher). Upon cleavage of FRETS-VWF73 by ADAMTS13 donor and acceptor/quencher residues are separated. Fluorescence can be emitted and, thereby, ADAMTS13 activity quantified. Fluorescence evolution was measured with λex=340 nm and λem=450 nm (Baxter/KREMS method) or λex=355 nm and λem=460 nm (LabCorp

SHA method) due to the filters of wavelength available for different instruments. Samples are measured against a reference standard of diluted pooled normal human plasma. This normal plasma pool had been calibrated against the World Health Organization (WHO) 1st International Standard (IS) for ADAMTS13. The resulting FRETS-VWF73 activity data are expressed in mIU/mL in the bioanalysis report. The assay cannot distinguish between rADAMTS13 and endogenous ADAMTS13 activity.

Haemoglobin and bilirubin resulting from haemolysis have fluorescent and absorbing properties and are well known to interfere with the FRETS-VWF73 activity assay. To evaluate potential interference, samples were spiked with various concentrations of hemoglobulin and bilirubin. Following the completion of the FRETS-VWF73 assay measurement, samples were measured at 405 nm/452 nm for haemoglobin and 452 nm/577 nm for bilirubin. Based on measured absorbance and results of ADAMTS13 FRETS-VWF73 activity, a threshold of optical density (OD) was determined for potential interference of haemoglobin and bilirubin.

Table 8: Method validation summary -ADAMTS13 activity quantification

Analyte	ADAMTS13 Activity	ADAMTS13 Activity	ADAMTS13 Activity	ADAMTS13 Activity
Test facility	Baxter	KREMS	LabCorp SHA	Baxter
Document ID	OR-13-00589-02-VB.01	S01-097-02-VR, S01-147-02-VR; FHSOP-31-0023-TI001-06-VR.01 (LLOQ), A3 to S01-097-02-VR (LTS)	8471-005	OR-13-00660-01-VB.02
Assay platform	FRETS-VWF73 Activity	FRETS-VWF73 Activity	FRETS-VWF73 Activity	Technozym ELISA
Matrix	Citrated plasma	Citrated plasma	Citrated plasma	Citrated plasma
MRD	1:10	1:10	1:10	1:30
Calibrator	NHP calibrated to WHO IRS for A13	NHP calibrated to WHO IRS for A13	NHP calibrated to WHO IRS for A13	Calibrator stock in Technozym ELISA kit
Calibration curve range (in well)	0.005 to 0.08 U/mL	5 to 80 mIU/mL	5 to 80 mIU/mL	0.065 to 3.487%
Validation samples	0.031 U/mL to 2 U/mL rA13 in hTTP plasma or buffer	60, 65, 100 to 1600 mIU/mL rA13 in hTTP plasma	targeted 65 to 2000 mIU/mL rA13 in HI-plasma or endogenous A13 in plasma	3.1 to 200% rA13in hTTP
Intra-assay accuracy (%bias)	cTTP plasma: 0.80% to 2.80%	rAS13: 2.0% to 24.4% A13: 2.1%	rA13: -15.8% to 18.9% A13: -17.5% to 16.7%	cTTP plasma: -5.26% to -4.04%
Intra-assay precision (%CV)	cTPP plasma: 1.54% to 2.33%	rA13: 0.4% to 6.8% pA13: 5.1%	rA13: 2.1% to 18.3% A13: 0.6% to 23.5%	cTPP plasma: 1.63% to 1.92%
Inter-assay accuracy (%bias)	cTTP plasma: -4.89% to 4.64%; FCP buffer: 0.81% to 14.98%	rA13: 3.8% to 22.4% pA13: 2.0%	Within ±20%, ±25% at LLOQ and ULOQ	cTTP plasma: -11.74% to 4.38%
Inter-assay precision (%CV)	cTPP plasma: 2.89% to 18.03%; FCP buffer: 2.14% to 10.84%	rA13: 3.4% to 12.0% pA13: 3.3%	rA13: 8.2% to 14.7% A13: 9.8% to 13.4%	cTPP plasma: 3.09% to 10.17%
LLOQ	0.05 U/mL	65 mIU/mL	65 mIU/mL	3.1%
Dilutional linearity	1:160 (1 U/mL)	1:640 (2000 mIU/mL)	1:160 (2000 mIU/mL)	105%
Selectivity/matrix interference	Selectivity: -17.87 to 26.67% Bias (2/12 >20%)	Selectivity: 0.1% to 18.2% Bias; Hb cutoff (1 mg/mL): >0.139; bilirubin (0.1 mg/mL) cutoff >0.138	Selectivity: all within ±25% at LLOQ and ULOQ. Hb cutoff (1 mg/mL): >0.202; bilirubin (0.1 mg/mL) cutoff >0.238	Selectivity: -14.45% to 9.80% Bias
Freeze/thaw stability	2	2	4 (-20°C), 5 (-70°C)	2
Ambient stability	60 minutes	1 hour	13 hours 51 minutes	60 minutes
4°C stability	ND	ND	49.5 hours	ND
-70°C stability	6 months	27 months	27 months (KREMS)	6 months
Studies supported	281101	281102, TAK-755-3002	TAK-755-3002 (China)	281101

A13=ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13); cTTP=congenital thrombotic thrombocytopenic purpura; CV=coefficient of variation; ELISA=enzyme-linked immunosorbent assay; FCP=final container product; FRETS-VWF73=fluorescence resonance energy transfer substrate composed of 73 amino acids from the A2 domain of von Willebrand factor; Hb=hemoglobin; HI=heat-inactivated; hTTP=hereditary thrombotic thrombocytopenic purpura; ID=identification; IRS=international reference standard; LLOQ=lower limit of quantification; MRD=minimum required dilution; ND=not determined; NHP=normal human plasma; pA13=plasma-derived ADAMTS13; rA13=recombinant ADAMTS13; SHA=Shanghai; ULOQ=upper limit of quantification; WHO=World Health Organization

vWF:Ristocetin Cofactor (VWF:RCo) Activity Assay (LabCorp Esoterix)

The platelet agglutination method for measurement of the ristocetin cofactor activity of vFW was implemented for pharmacodynamic assessment. The BC von Willebrand reagent (Siemens Healthcare Diagnostics) was used to measure native vWF:ristocetin cofactor activity in 3.2% citrated patient plasma: functional vWF from the sample causes agglutination of stabilised platelets in the presence of ristocetin. Agglutination reduces the turbidity of the reaction mixture and the change in OD is measured by the Behring Coagulation System analyser. The VWF:RCo activity of the sample is then calculated based on the high or low calibration curve prepared using standard human plasma with a known concentration of VWF:RCo activity that has been calibrated against the WHO 6th IS for VWF. The platelet agglutination method for VWF:RCo activity using a BCS analyser was validated for its accuracy and precision, dilutional linearity, carry-over, selectivity and stability.

VWF:Antigen Assay (LabCorp Esoterix)

The quantity of human VWF total antigen in 3,2% citrated human plasma is assessed in vitro using the Asserachrom vWF antigen (VWF:Ag) ELISA at LabCorp Esoterix. Diluted sample is added to a rabbit anti-human vWF antibody coated microtiter plate to which free vWF antigen present in the plasma will bind. Following incubation, unbound plasma protein is washed away and an HRP-conjugated rabbit anti-VWF antibody is added that will bind to the free antigenic determinants of the bound VWF. Following additional incubation and washing, TMB substrate is added and after stopping, the reaction absorbance is measured at 450 nm. The absorbance is directly proportional to the VWF, which can be quantified against a calibration curve. The assay was validated in citrated plasma from normal donors. Validation was carried out with the VWF WHO standard (07/316) spiked in VWF-depleted plasma as well as recombinant vWF spiked in vWF-depleted samples and normal human plasma, and plasma-derived vWF.

2.6.2.1. Pharmacokinetics

Study 281101 was a Phase 1, prospective, uncontrolled, open-label, multicenter, dose escalation study to evaluate safety including immunogenicity and ADAMTS13 PK following single dose administration of TAK-755. A total of at least 15 evaluable subjects with a documented diagnosis of severe cTTP were assigned to 1 of 3 dose cohorts: 5, 20, and 40 IU/kg.

ADAMTS13 activity in plasma was measured using FRETS-VWF73 and Technozym assays. The FRETS-VWF73 assay was also used to determine the actual BAX 930 dose potency of the investigational product lots. Hereafter, plasma ADAMTS13 FRETS-VWF73 results are accordingly presented as the primary analysis for ADAMTS13 activity.

The mean concentration-time profiles of plasma ADAMTS13 FRETS-VWF73 in adults are shown in In-Text Figure 5. Human ADAMTS13 activity PK characteristics following TAK-755 administration was similar to those previously reported following fresh-frozen plasma (FFP) administration, ie, bi-exponential profile.

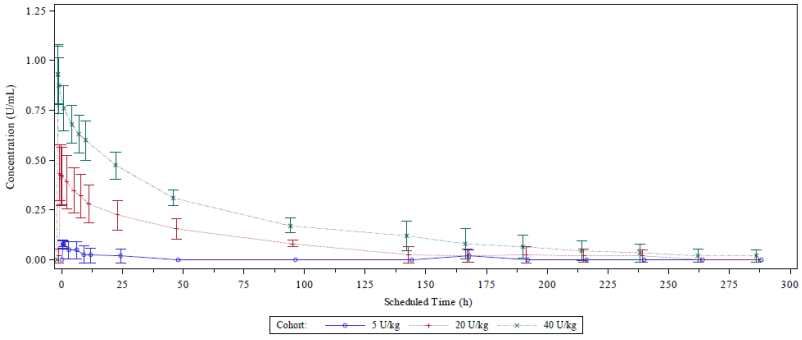


Figure 3 : Mean (standard deviation) plasma ADAMTS13 FRETS-VWF73 concentration-time profiles in adults

Key plasma ADAMTS13 FRETS-VWF73 PK parameters in adults are summarized in Table 9.

Table 9 : Summary of key plasma ADAMTS13 FRETS-VWF73 pharmacokinetic parameters in adults

Pharmacokinetic Parameters	Mean (Standard Deviation) [Geometric Mean]		
	5 U/kg (n = 3) [a]	**20 U/kg (n = 3)**	**40 U/kg (n = 7)**
IR (U/mL*kg/U)	0.0155 (0.00307) [0.0153]	0.0208 (0.00723) [0.0200]	0.0234 (0.00351) [0.0232]
C_{max} (U/mL)	0.080 (0.018) [0.079]	0.415 (0.149) [0.398]	0.957 (0.140) [0.948]
t_{max} (h) [b]	1.00 (0.52 – 1.00)	0.33 (0.25 – 0.53)	0.37 (0.22 – 0.58)
$AUC_{(0\text{-}inf)}$ (U*h/mL)	ND	19.5 (4.89) [19.1]	54.5 (14.9) [53.1]
$AUC_{(0\text{-}t)}$ (U*h/mL)	0.706 (0.858) [0.325]	15.8 (4.88) [15.3]	49.2 (14.1) [47.8]
$t_{1/2}$ (h)	ND	45.1 (21.2) [42.1]	60.5 (13.5) [59.2]
$MRT_{(0\text{-}inf)}$ (h)	ND	62.100 (27.641) [58.464]	87.656 (26.339) [84.178]
Cl (mL/h)	ND	72.8 (24.5) [70.2]	65.2 (24.2) [62.0]
V_{ss} (mL)	ND	4240 (1230) [4110]	5300 (1030) [5220]

$AUC_{(0\text{-}inf)}$ = Area under the plasma-time concentration curve from zero to infinity;
$AUC_{(0\text{-}t)}$ = Area under the plasma-time concentration curve from zero to the last measured timepoint;
Cl = Systemic clearance; C_{max} = Maximum concentration following infusion;
IR = Incremental recovery; max = Maximum; min = Minimum; MRT = Mean residence time;
ND = not determined; $t_{1/2}$ = Half-life; t_{max}: Minimum time to reach C_{max};
V_{ss} = Volume of distribution at steady state
[a] n = 1 for $AUC_{(0\text{-}inf)}$, $t_{1/2}$, $MRT_{(0\text{-}inf)}$, Cl, and V_{ss}.
[b] Median (min - max).

Study 281102 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 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with cTTP. 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) (please also refer the efficacy Section).

Two crossover PK evaluations (PK-I and PK-II) and an end-of-study ADAMTS13 PK evaluation (PK-III) may have been performed for up to 288 hours post-infusion in the Prophylactic Cohort.

ADAMTS13 activity PK parameters resulting from TAK-755 or SoC administration are presented in Table 10 (**PK-I**). Following IV administration of TAK-755 ORT, both ADAMTS13 antigen and activity followed bi-exponential PK profiles.

Table 10: ADAMTS13 activity PK parameters for PK-I in adults and adolescents – PK analysis set

Statistic	C_{max} (IU/mL)	t_{max} (h)	IR (IU/mL) / (IU/kg)	$t_{1/2}$ (h)	$AUC_{0\text{-}inf}$ (h*IU/ mL)	AUC_{all} (h*IU/ mL)	$AUC_{(0\text{-}168)}$ (h*IU/ mL)	$C_{ave\ (0\text{-}168)}$ (IU/mL)	Time above 10% activity (days)	$MRT_{(0\text{-}inf)}$ (h)	CL (L/h)	V_{ss} (L)
TAK-755 ORT												
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)[a]	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

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; $AUC_{0\text{-}168}$=area under the concentration-time curve from zero to time 168 h; AUC_{all}=area under the concentration-time curve from zero to last sampling time; $AUC_{0\text{-}inf}$=area under the concentration-time curve from zero to infinity; $C_{ave\ (0\text{-}168)}$=average concentration from time 0 to time 168 h; CL=clearance; CV=coefficient of variation, Geo=geometric; IR=incremental recovery; MRT=mean residence time; N=number of subjects included in the analysis; ND=not determined; NCA=non-compartmental analysis; PK=pharmacokinetic; SD=standard deviation; SoC=standard of care: $t_{1/2}$=half life; t_{max}=time at C_{max}; V_{SS}=volume of distribution at steady state.
There are 2 rescreened subjects which are allowed by protocol. Each rescreened subject was treated as 2 different subjects for analysis, and all data as collected were included.
For $AUC_{(0\text{-}168)}$, if concentration at the end of the interval is available but collection time was missing, AUC was calculated using the scheduled time. If concentration at the end of the interval is missing, $AUC_{(0\text{-}168)}$ was not calculated per pre-specified NCA plan.
Average concentration [$C_{ave\ (0\text{-}168h)}$] was calculated as $AUC_{(0\text{-}t)}$/t over 0-168 hours, using actual time for t.
[a] Median (min, max) is presented for T_{max}.
[b] Only min, max is presented.

Bioequivalence

The TAK-755 bulk drug substance (BDS) sources used in the conduct of Phase 3 pivotal study 281102 was manufactured at 2 different sites: Orth, Austria (ORT; referred to as TAK-755 ORT) and Singapore (SIN; referred to as TAK-755 SIN). Whitin the study, the objective of **PK-II** was to demonstrate that the ADAMTS13 activity (and ADAMTS13 antigen) exposures (AUC and maximum activity [Cmax]) were comparable between TAK-755 ORT and TAK-755 SIN. Both TAK-755 materials were administered 14 days apart in a cross-over design.

The geometric mean ratio and associated 90% confidence interval (CI) for both AUC and Cmax between TAK-755 ORT and TAK-755 SIN remained within the 80% and 125% bioequivalence range. This analysis supports the PK comparability of ADAMTS13 antigen and activity between TAK-755 ORT and TAK-755 SIN.

Table 4 : Statistical comparison of pharmacokinetic parameters (adults and adolescents) for PK-II- pharmacokinetic analysis set

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

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; $AUC_{(0\text{-}inf)}$=area under the plasma-time concentration curve from zero to infinity; $AUC_{(0\text{-}last)}$=area under the plasma-time concentration curve from zero to the last measured timepoint; CI=confidence interval, C_{max}=maximum concentration; Geo=geometric, LS=least squares

[a] TAK-755 ORT = rADAMTS13 manufactured in Orth, Austria; TAK-755 SIN = rADAMTS13 manufactured in Singapore.

Results are based on linear mixed model with sequence, period (from PK-II cross-over), and treatment as fixed effects, and subject nested within sequence as a random effect. The data were log-transformed prior to the analysis (Table 14.2.5.2.7).

Pharmacokinetic parameters are included in the statistical comparison as per predefined noncompartmental analysis criteria.

Subject passed screening and entered the study more than once and is included as 2 study subjects. All data for each subject ID are included in the analyses.

The objective for **PK-III** was to assess if any time-dependent PK changes occurred due to long-term exposure to TAK-755 SIN at the end of Period 3. PK sampling involved semi-intensive to sparse sampling of eligible subjects (N=5). ADAMTS13 activity (and ADAMTS13 antigen) -time profiles and associated PK parameters resulting from TAK-755 SIN IV administration are described in Table 12.

Table 5 : Summary of PK parameters (adults and adolescents) resulting from TAK-755 SIN administration (PK-III period) – PK analysis set

Statistic	C_{max} (µg/mL)	t_{max} (h)[b]	IR (IU/mL)/ (µg/kg)	$t_{1/2}$ (h)	$AUC_{0\text{-}inf}$ (h* µg / mL)	AUC_{all} (h* µg /mL)	Time above 10% activity (days)	$MRT_{(0\text{-}inf)}$ (h)	CL (L/h)	V_{ss} (L)
ADAMTS13 Antigen										
N	5	5	5	4	3	5		3	3	3
Mean (SD)	0.88 (0.21)	0.33 (0.27,0.35)	0.03 (0.01)	40.2 (2.9)	43.4 (3.1)	47.9 (20.8)	ND	48.7 (3.8)	0.05 (0.01)	2.5 (0.68)
Geo Mean (Geo CV%)	0.86 (23.8)	ND	0.03 (22.3)	40.1 (7.1)	43.3 (7.1)	44.3 (47.5)		48.6 (8.1)	0.05 (22.0)	2.5 (29.1)
ADAMTS13 Activity										
N	5	5	5	5	5	5	5	5	5	5
Mean (SD)	1.26 (0.26)	0.33 (0.27,1.07)	0.032(0.01)	33.9 (4.30)	58 (11.53)	62.7 (23.3)	6.2 (2.95)	41.1 (7.4)	0.05 (0.01)	2.2 (0.43)
Geo Mean (Geo CV%)	1.24 (20.2)	ND	0.031(19.6)	33.6 (12.5)	57.04 (20.9)	58.8 (43.3)	5.6 (60.7)	40.6 (17.8)	0.05 (23.7)	2.2 (20.9)

Geo CV=geometric coefficient of variation, SD=standard deviation, Geo=geometric; ND=not determined: this parameter is not applicable for this analyte.
Subject passed screening and entered the study more than once and is included as 2 study subjects. All data for each subject ID are included in the analyses.

Study 3002 is a Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of study 281102. As of the date for the 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. 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 cut-off, 35 subjects were ongoing in the study. A summary of the PK parameters (Cmax, Tmax, IR, and Ctrough) for ADAMTS13 activity from sparse PK sampling is provided in Table 13.

Table 6 : Summary of pharmacokinetic parameters for PK sparse sampling for adolescent and adult subjects in the prophylactic cohort (pharmacokinetic full analysis set)

Dosing Frequency: Every 2 Weeks

		Naïve			
Analyte	Statistics	C_{max} (IU/mL)	T_{max} (h)	IR (IU/mL)/(IU/kg)	C_{trough} (IU/mL)
ADAMTS13 Activity (IU/mL)	n	4	4	4	4
	Mean(SD)	1.345 (0.89484)	ND (ND)	0.03172 (0.020505)	0.000 (0.0000)
	CV%	66.5	ND	64.6	ND
	Median	1.491	0.29	0.03411	0.000
	Min, Max	0.300, 2.10	0.22, 1.07	0.00751, 0.0512	0.00, 0.00
	Geo. Mean	1.042	ND	0.02502	ND
	Geo. CV%	115.5	ND	109.0	ND

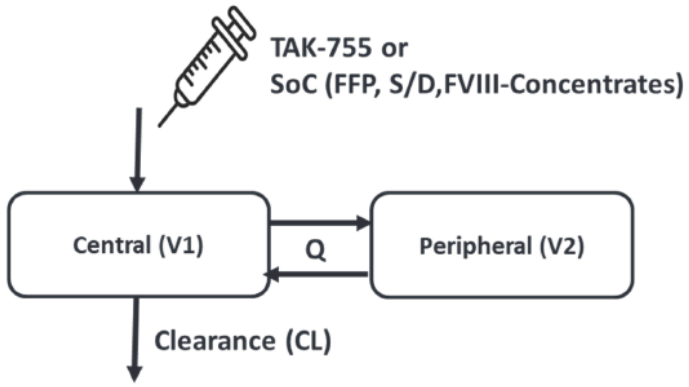
CV = coefficient of variation, SD = standard deviation, Geo = geometric; ND = not determined.
Adolescent subjects are those of age >= 12 years of age and < 18 years of age. Adult subjects are those of age >= 18 years of age.
Adult subjects (> = 18 years) are only available at IA data cut-off.
Source: Cross-reference: Listing 16.2.6.6

Integrated popPK

The popPK analysis of ADAMTS13 activity in the cTTP patient population was evaluated based on data from the completed Phase 1 study (281101) and 2 ongoing Phase 3 studies (281102 and 3002). This integrated popPK method supplements the observed longitudinal ADAMTS13 activity time profiles in Phase 3 studies leveraging actual dose, date and time of treatment administration where sparse or semi-intensive PK samples were collected. Final ADAMTS13 activity popPK model predicted longitudinal outputs (time profiles) were used to perform an ER analysis and QSP analysis.

The popPK analysis included a total of 65 unique subjects with a total of 2462 samples (distribution of rich, semi-intensive, and sparse samples) with measurable ADAMTS13 activity.

The PK of ADAMTS13 activity in cTTP subjects was described using a 2-compartment model with zero-order infusion, first order linear elimination from the central compartment. In all studies, the dose of TAK-755 and SoC treatment types was administered based on actual body weight. Therefore, the effect of body weight was incorporated a priori in the model using a power function centered to the median body weight (ie, 68.7 kg) in the final popPK dataset (fixed allometric exponents on CL and central volume of distribution (V1)). Absolute dosing amount (IU) of ADAMTS13 was used for popPK modeling. The effect of TAK-755 material type (ORT vs SIN), SoC and concentrations on the relative ADAMTS13 activity (Frel) were added to the population PK model.



CL=clearance; ER=exposure-response; FFP=fresh-frozen plasma; FVIII=Factor VIII; PK=pharmacokinetics; popPK=population pharmacokinetics; Q=inter-compartmental clearance; S/D=solvent/detergent products; V1=central volume of distribution; V2=peripheral volume of distribution

Figure 4 : Final population PK model characterising ADMATS13 activity in cTTP subjects

Table 7 : Population PK model of ADAMTS13 (run0314b) – parameter estimates

Parameters	Main Analysis				Bootstrap Analysis		
	Estimate	(RSE%)	BSV (RSE%)	Shrinkage	Median	90% CI	95% CI
CL (L/h)	**0.0398**	**10.7**	**36.3% (45.8)**	**14.3%**	0.0402	(0.0301, 0.0493)	(0.0288, 0.0506)
	× $(WT/68.7)^{0.75}$		NA (NA)	NA	NA	NA	NA
V1 (L)	**2.69**	**4.99**	**25.4% (20.9)**	**4.9%**	2.71	(2.42, 2.96)	(2.35, 3.00)
	× $(WT/68.7)^{1.0}$		NA (NA)	NA	NA	NA	NA
Q (L/h)	**0.0456**	**12.1**	**NA (NA)**	**NA**	0.0487	(0.0307, 0.205)	(0.0272, 0.487)
	× $(WT/68.7)^{0.75}$		NA (NA)	NA	NA	NA	NA
V2 (L)	**3.71**	**51.4**	**NA (NA)**	**NA**	3.43	(1.09, 16.6)	(1.04, 19.9)
	× $(WT/68.7)^{1.0}$		NA (NA)	NA	NA	NA	NA
Frel	**1, Fixed**	**NA**	**NA (NA)**	**NA**	NA	NA	NA
	× (1 - 0.0737) if TAK-755 ORT Material	32.3	NA (NA)	NA	-0.0720	(-0.112, -0.0200)	(-0.120, -0.00858)
	× (1 - 0.390) if SoC	6.14	NA (NA)	NA	-0.374	(-0.419, -0.301)	(-0.427, -0.270)
	× (1 - 0.933) if FVIII:VWF Concentrates	2.06	NA (NA)	NA	-0.915	(-0.982, -0.832)	(-0.986, -0.828)
Error Model	**Additive (IU/L): 79.9**	**16.4**	**NA (NA)**	**NA**	75.9	(43.7, 104.0)	(41.0, 108.0)
	Proportional (Fraction): 0.204	**14.7**	NA (NA)	NA	0.203	(0.134, 0.265)	(0.124, 0.275)

CL = clearance; V1 = central volume of distribution; V2 = peripheral volume of distribution, Q = peripheral clearance; BSV = between-subject variability; RSE = relative standard error; Frel = relative ADAMTS13 activity; SoC = standard of care (fresh frozen plasma, solvent/detergent or Other).

Note 1: The reference subject is a 68.7-kg patient who received TAK-755 as the SIN material. Parameter correlation and a detailed table of all parameter estimates are presented in Appendix 1 (Section 11.11 and 11.12)

Note 2: Of a total of 2000 bootstrap runs, a total of 1618 (80.9%) successfully converged ("Minimization Successful") and 1387 (69.4%) successfully converged with no final zero gradient ("Minimization successful and No Final Zero gradient"). Results for the 1387 runs are presented in the above table.

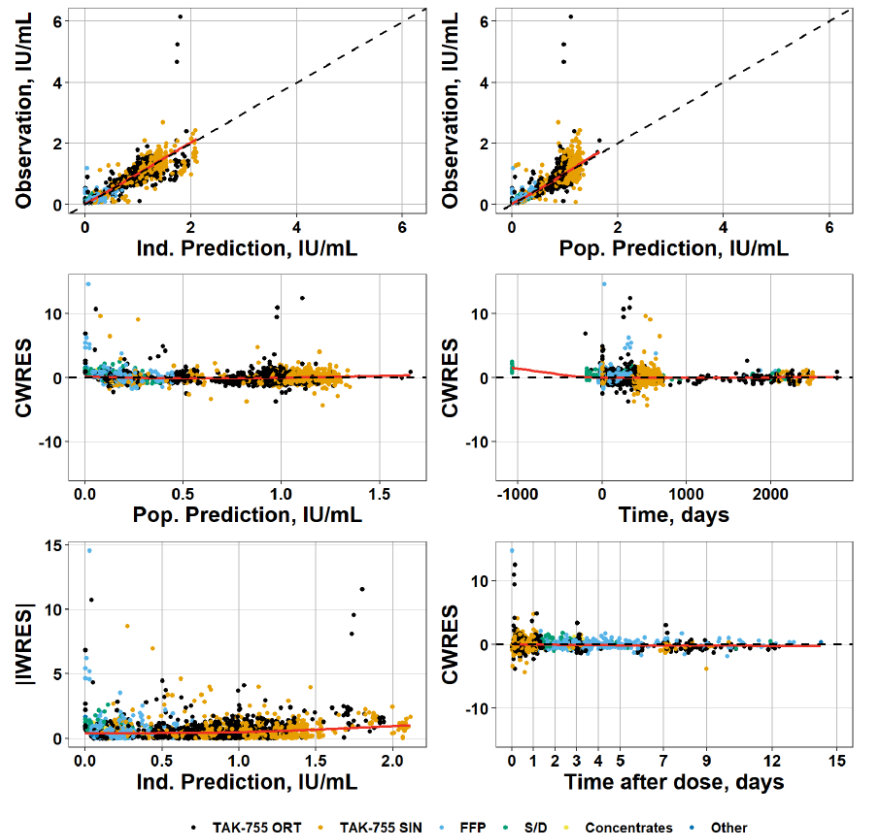
Note 3: The 90% CI corresponds to the 5% - 95% percentiles. The 95% CI corresponds to the 2.5% - 97.5% percentiles.

Note 4: BSV is presented as a % coefficient of variation (CV%) derived from the standard deviation of the random effect (η_i) as (100 x $(\exp(\omega^2)-1)^{0.5}$) .

Note 5: RSE was derived as the standard error (SE) / mean x 100.

Objective Function = 27068.413. The condition number (229) was low (typically interpreted as <1000) suggesting that parameters were adequately identified

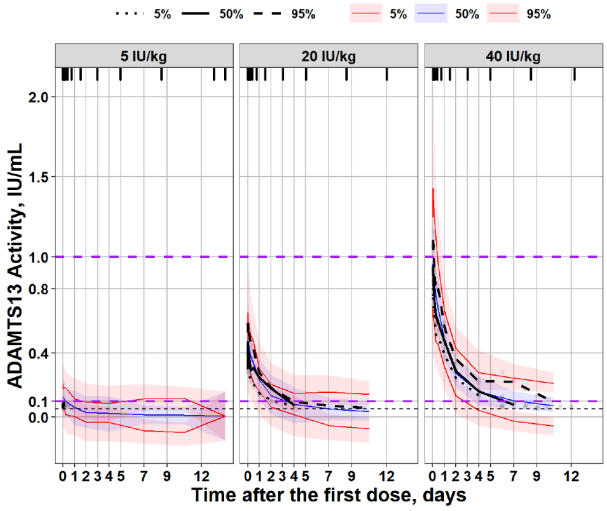
The **goodness-of-fit of ADAMTS13 activity** is presented in Figure 7.



Note: Time 0 was set as the first TAK-755 dose. Some patients received the solvent/detergent prior to the first TAK-755 dose and therefore may have negative time as presented in the middle right panel.

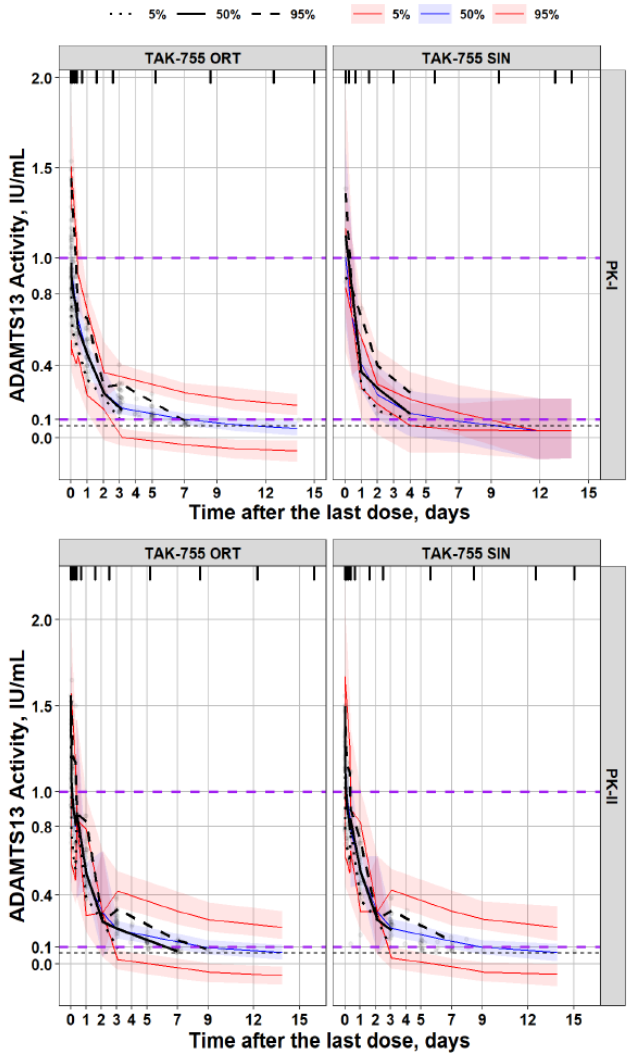
Figure 5 : population PK model of ADAMTS13 (run0314b) – overall goodness of fit

Results for the visual predictive check (VPC) for Study 281101 are presented in Figure 8. Results for the VPC of the ORT and SIN materials of TAK-755 for the PK I and II Visits in Study 281102 are presented in Figure 9.



Note: The purple dashed lines represent 10% (0.1 IU/mL) and 100% (1 IU/mL) ADAMTS13 activity, respectively. The dashed black lines represent the 5th and 95th percentiles of ADAMTS13 activity and the solid black line represents the median (50th percentile) of ADAMTS13 activity. The red solid lines are the model-predicted 5th and 95th percentiles and the shaded red area represent their respective 95% percentile interval (PI). The blue solid line is the model-predicted median (50th percentile) and the shaded blue area represents the 95% PI.

Figure 8: Visual predictive check of ADAMTS13 (run0314b) – study 281101



Note: The purple dashed lines represent 10% (0.1 IU/mL) and 100% (1 IU/mL) ADAMTS13 activity, respectively. The dashed black lines represent the 5th and 95th percentiles of ADAMTS13 activity and the solid black line represents the median (50th percentile) of ADAMTS13 activity. The red solid lines are the model-predicted 5th and 95th percentiles and the shaded red area represent their respective 95% percentile interval (PI). The blue solid line is the model-predicted median (50th percentile) and the shaded blue area represents the 95% PI.

Figure 9: visual predictive check of ADAMTS13 (run0314b) – study 281102 TAK-755 ORT and SIN material – PK infusion I and II

Absorption

TAK-755 is administrated via the IV route. Therefore, absorption from the infusion site is not applicable. Based on recombinant ADAMTS13 molecular weight (172 kDa) and absorption, distribution, metabolism, and excretion (ADME) properties, a dedicated ADME study has not been performed.

Distribution

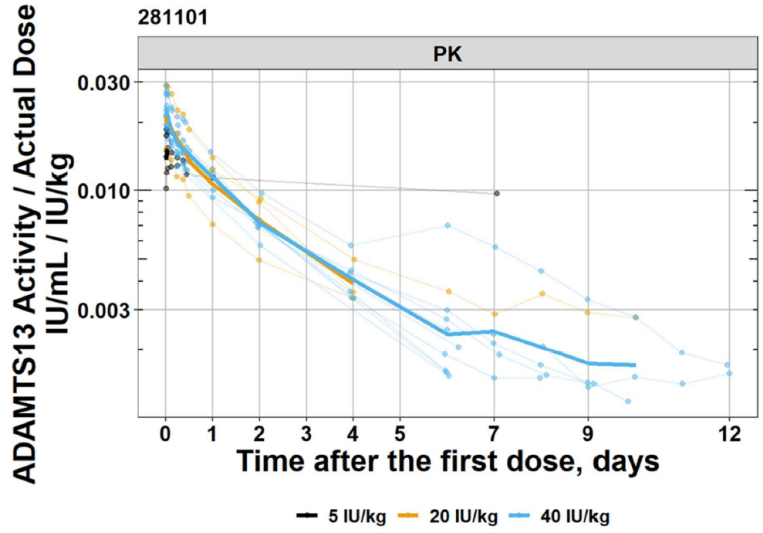
Based on an integrated popPK analysis, the total volume of distribution (V1+V2) of TAK-755 was 6.40 (2.69+3.71) L, which is consistent with the total blood volume in a 68.7 kg subject (ie, 0.075 L/kg) and suggests that ADAMTS13 does not distribute into tissues, according to the Applicant.

Elimination

Consistent with other exogenous protein therapeutics, TAK-755 is expected to be ultimately degraded into individual constituent amino acids, which are reincorporated into the normal protein pool.

Dose proportionality and time dependencies

TAK-755 PK is approximately dose proportional between 20 and 40 IU/kg. The mean dose-adjusted time profiles of ADAMTS13 activity for the 5, 20, and 40 IU/kg doses overlapped following IV administration, and those for the 20 and 40 IU/kg dose levels followed a time profile that decreased in a similar manner (Figure 10). It should be noted that for the 5 IU/kg dose (~8-fold lower dose than the clinical proposed dose of 40 IU/kg), ADAMTS13 activity levels remained below the limit of quantitation starting from Day 1. Thus, if only the 20 and 40 IU/kg dose levels are considered with complete eligible PK profiles, ADAMTS13 activity PK can be considered approximately dose proportional. This is corroborated by the final popPK model.



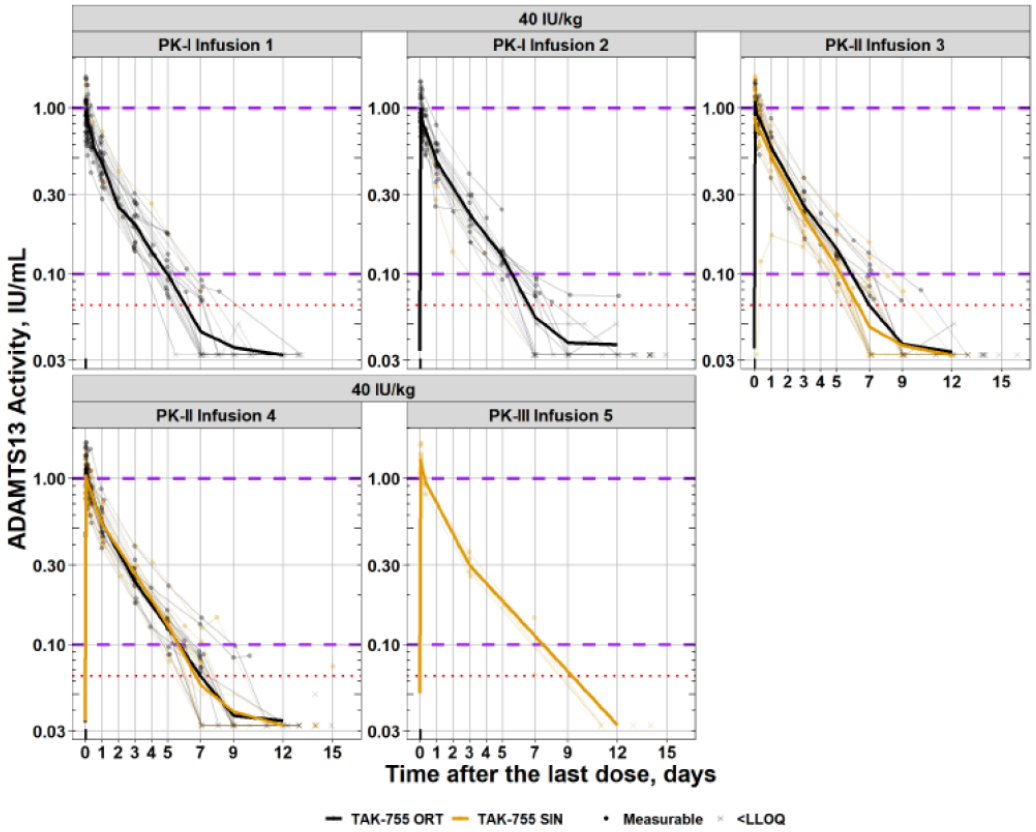
ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; PK=pharmacokinetics
Note: A minimum of 3 data points per nominal time point was required to derive a mean ADAMTS13 activity.
Source: PopPK and ER Report TGRD-PMX-TAK755-2375_PKER Figure 4

Figure 10: actual dose-normalised ADAMTS13 activity time series resulting from single doses of 5, 20, and 40 IU/kg administration (study 281101)

According to the Applicant, the PK of ADAMTS13 activity following TAK-755 administration is stationary (i.e., time independent) and does not change with repeated administration. Based on limited ADAMTS13 activity NCA results from PK-III period (semi-sparse collection) of Phase 3 Study 281102, TAK-755 SIN did not show evidence of time-dependent ADAMTS13 activity. In addition, the mean ADAMTS13 activity PK exposures(Cmax and AUC) were similar between the PK-I and PK-II periods following TAK-755 ORT administration, suggesting that neither TAK-755 ORT nor TAK-755 SIN exhibit time-dependent PK.

This observation is supported by the integrated popPK results. The CL of ADAMTS13 activity was estimated to be linear (PopPK and ER Report).

In summary, PK exposures of ADAMTS13 activity at steady state can be predicted from a single dose (linear PK over time).



ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; ER=exposure-response; LLOQ=lower limit of quantification; ORT=Orth, Austria; PK=pharmacokinetics; popPK=population pharmacokinetics; SIN=Singapore
Note: The purple dashed lines represent reference 10% (0.1 IU/mL) and 100% (1 IU/mL) ADAMTS13 activity, respectively; the dashed red line represents the LLOQ of assay (0.065 IU/mL). For this figure, ADAMTS13 activity below the LLOQ was set to half the LLOQ for the calculation of mean ADAMTS13 activity. A minimum of 3 datapoint per nominal time point was required to derive a mean ADAMTS13 activity. PK-III period consisted of only semi-intensive PK sampling per protocol schedule of activities.

Figure 6: Mean (solid line) and individual (grey lines) ADMATS 3 activity-time profiles following administration of TAK-755 IU/kg (ORT or SIN) by PK-I, PK-II, and PK-III periods

Individual post hoc PK parameters (CL, V1, Q, and V2) were derived with the final population PK model (run0314b, N=65) and simulations were performed to predict steady state ADAMTS13 activity time profiles for each treatment (TAK-755 vs. SoC), manufacturing site (ORT and SIN materials) and dosing interval (QW and Q2W). Descriptive statistics of ADAMTS13 exposure parameters and duration/percentage of days above 10% for the ORT and SIN materials of TAK-755 are presented in Table 15.

Table 8: Descriptive statistics of ADAMTS13 exposure parameters and duration/percentage of days above 10 % (run0314b) – ORT and SIN material

Exposure Parameter	N Geometric Mean, Geometric CV% Mean (SD), CV% Median, Min – Max			
	TAK-755 ORT 40 IU/kg		TAK-755 SIN 40 IU/kg	
	QW	Q2W	QW	Q2W
$C_{max,ss}$ ADAMTS13 Activity (IU/mL)	N=65 1.14, 23.4% 1.17 (0.288), 24.7% 1.11, 0.746 – 2.23	N=65 1.01, 23.0% 1.04 (0.251), 24.2% 0.999, 0.666 – 1.84	N=65 1.23, 23.4% 1.26 (0.311), 24.7% 1.20, 0.806 – 2.41	N=65 1.09, 23.0% 1.12 (0.271), 24.2% 1.08, 0.719 – 1.99
$C_{tough,ss}$ ADAMTS13 Activity (IU/mL)	N=65 0.171, 47.2% 0.195 (0.141), 72.3% 0.160, 0.0746 – 0.853	N=65 0.0533, 62.4% 0.0671 (0.0716), 106.7% 0.0491, 0.0175 – 0.432	N=65 0.185, 47.2% 0.211 (0.152), 72.3% 0.173, 0.0805 – 0.920	N=65 0.0575, 62.4% 0.0724 (0.0773), 106.7% 0.0530, 0.0189 – 0.466
$C_{ave,ss}$ ADAMTS13 Activity (IU/mL)	N=65 0.375, 31.5% 0.396 (0.166), 41.9% 0.356, 0.212 – 1.10	N=65 0.188, 32.9% 0.200 (0.0917), 45.7% 0.178, 0.106 – 0.617	N=65 0.405, 31.5% 0.428 (0.179), 41.9% 0.384, 0.229 – 1.19	N=65 0.203, 32.9% 0.216 (0.0989), 45.7% 0.192, 0.115 – 0.666
AUC_{ss} ADAMTS13 Activity (h.IU/mL)	N=65 62.9, 31.5% 66.6 (27.9), 41.9% 59.8, 35.6 – 185	N=65 63.3, 32.9% 67.4 (30.8), 45.7% 59.8, 35.6 – 207	N=65 68.0, 31.5% 71.9 (30.1), 41.9% 64.5, 38.5 – 200	N=65 68.3, 32.9% 72.7 (33.2), 45.7% 64.6, 38.5 – 224
Duration ADAMTS13 Activity above 10% (day)	N=65 6.96, 3.5% 6.96 (0.216), 3.1% 7.00, 5.34 – 7.00	N=65 8.05, 30.0% 8.41 (2.54), 30.2% 7.92, 4.06 – 14.0	N=65 6.98, 2.4% 6.98 (0.153), 2.2% 7.00, 5.77 – 7.00	N=65 8.66, 28.3% 8.99 (2.52), 28.0% 8.57, 4.41 – 14.0
Percentage of ADAMTS13 Activity above 10% (%)	N=65 99.4, 3.5% 99.5 (3.08), 3.1% 100, 76.4 – 100	N=65 57.5, 30.0% 60.1 (18.2), 30.2% 56.6, 29.0 – 100	N=65 99.7, 2.4% 99.7 (2.18), 2.2% 100, 82.4 – 100	N=65 61.8, 28.3% 64.2 (18.0), 28.0% 61.2, 31.5 – 100

Note: values below the LLOQ were retained for the calculation of the mean $C_{trough,ss}$

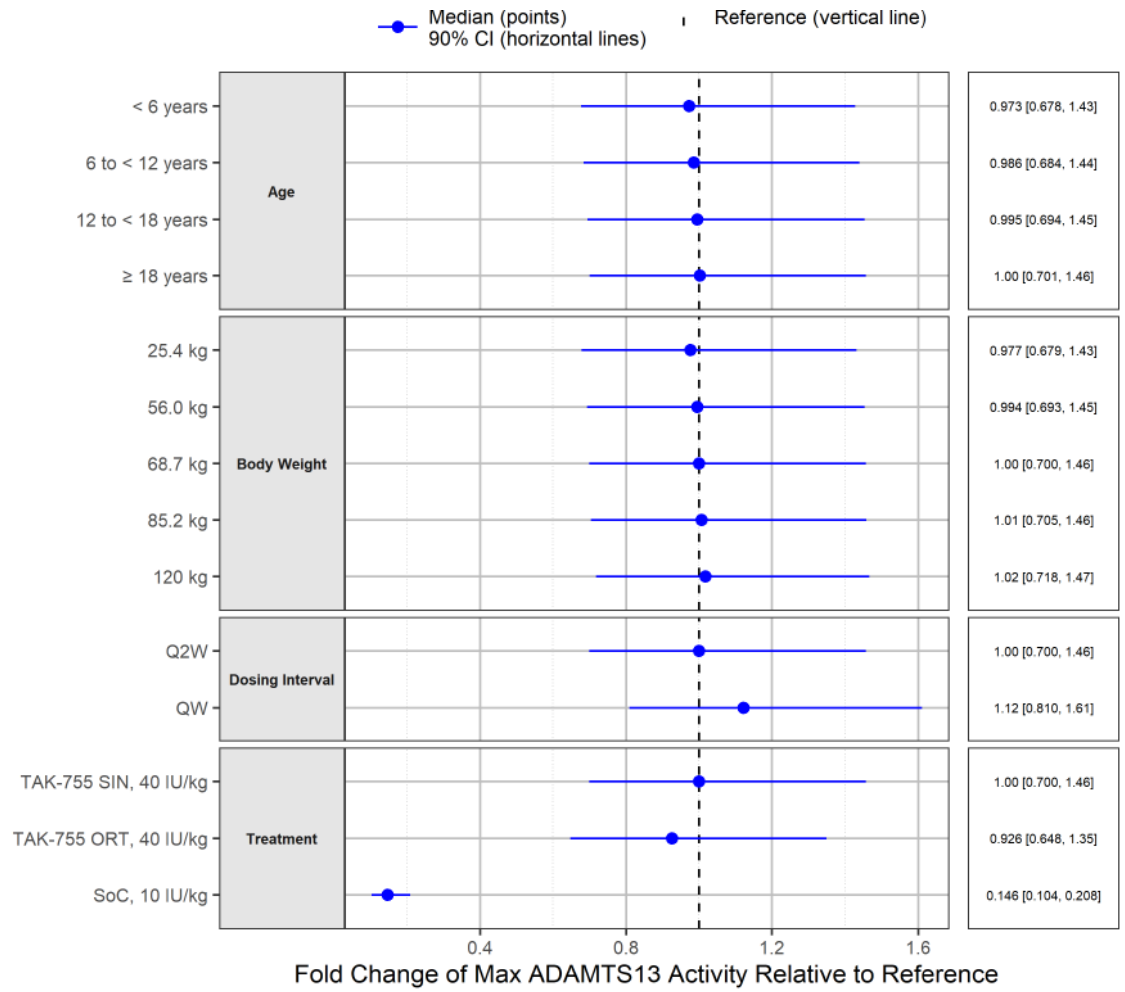
Special populations

TAK-755 was not studied in patients with renal or hepatic impairment. Based on the molecular weight (172 kDa) and absorption, distribution, metabolism, and excretion properties of TAK-755, the PK is not expected to be significantly impacted. In addition, baseline eGFR and bilirubin did not have any impact on CL of ADAMTS13 activity.

In the popPK model, gender did not have any impact on the PK of ADAMTS13 activity. Race was not found to be a significant covariate in the integrated popPK analysis. There is limited data on the use of TAK-755 in patients over 65 years of age.

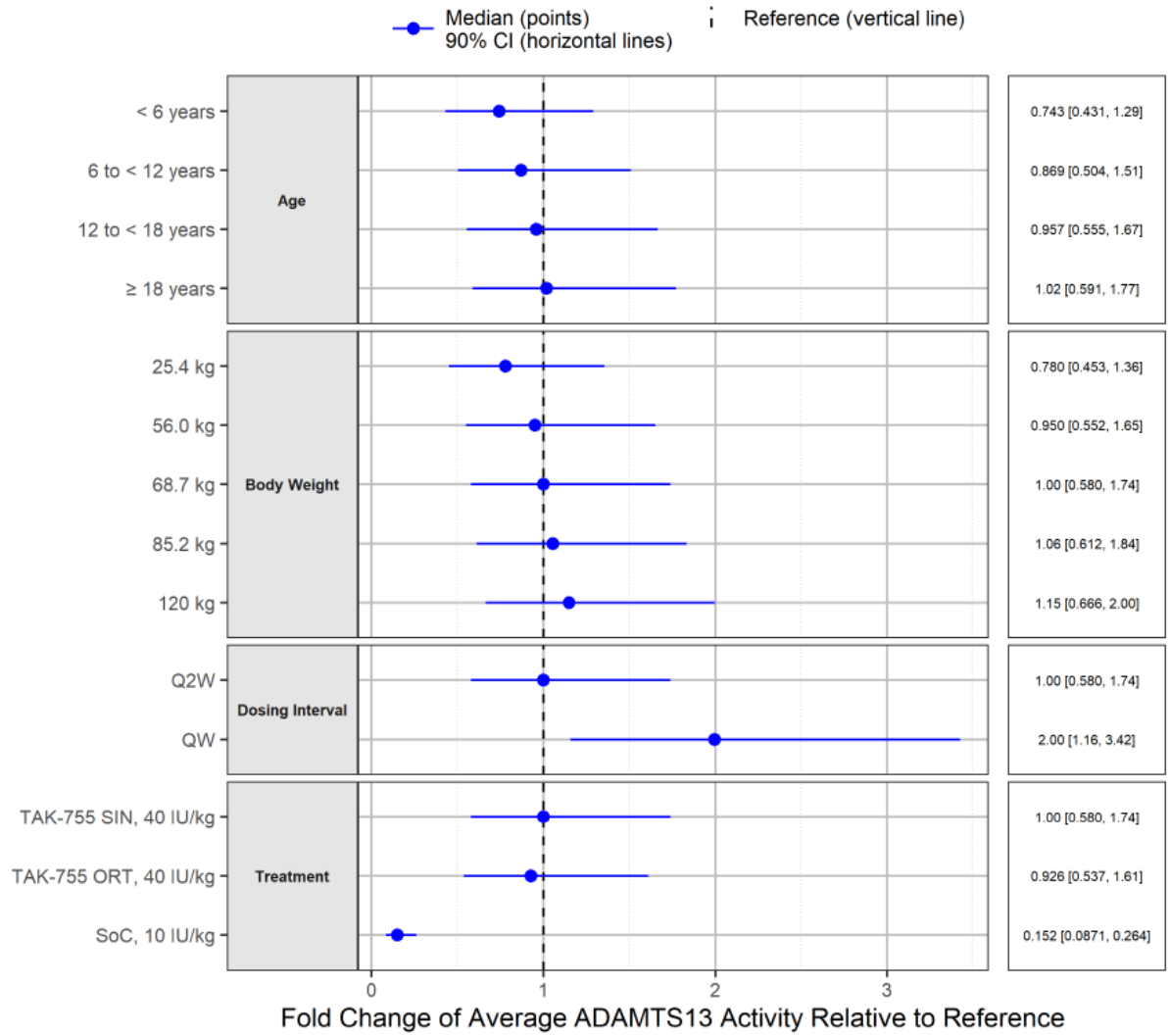
Simulations - Impact of Covariates on Exposure Parameters of ADAMTS13 Activity

Time profiles of ADAMTS13 activity under steady state conditions (descriptive statistics see 2.1.6.2. Time dependency) were simulated in a total of 1000 patients. Forest plots were then derived by changing one covariate at a time while fixing others at the reference value. The effects of age, body weight, dosing intervals (Q2W and QW) and treatment on the maximum (Cmax,ss) and average (Cave,ss) ADAMTS13 activity are presented below. The effects of the covariates on the percentage of time (days) with ADAMTS13 activity above 10% are also presented.



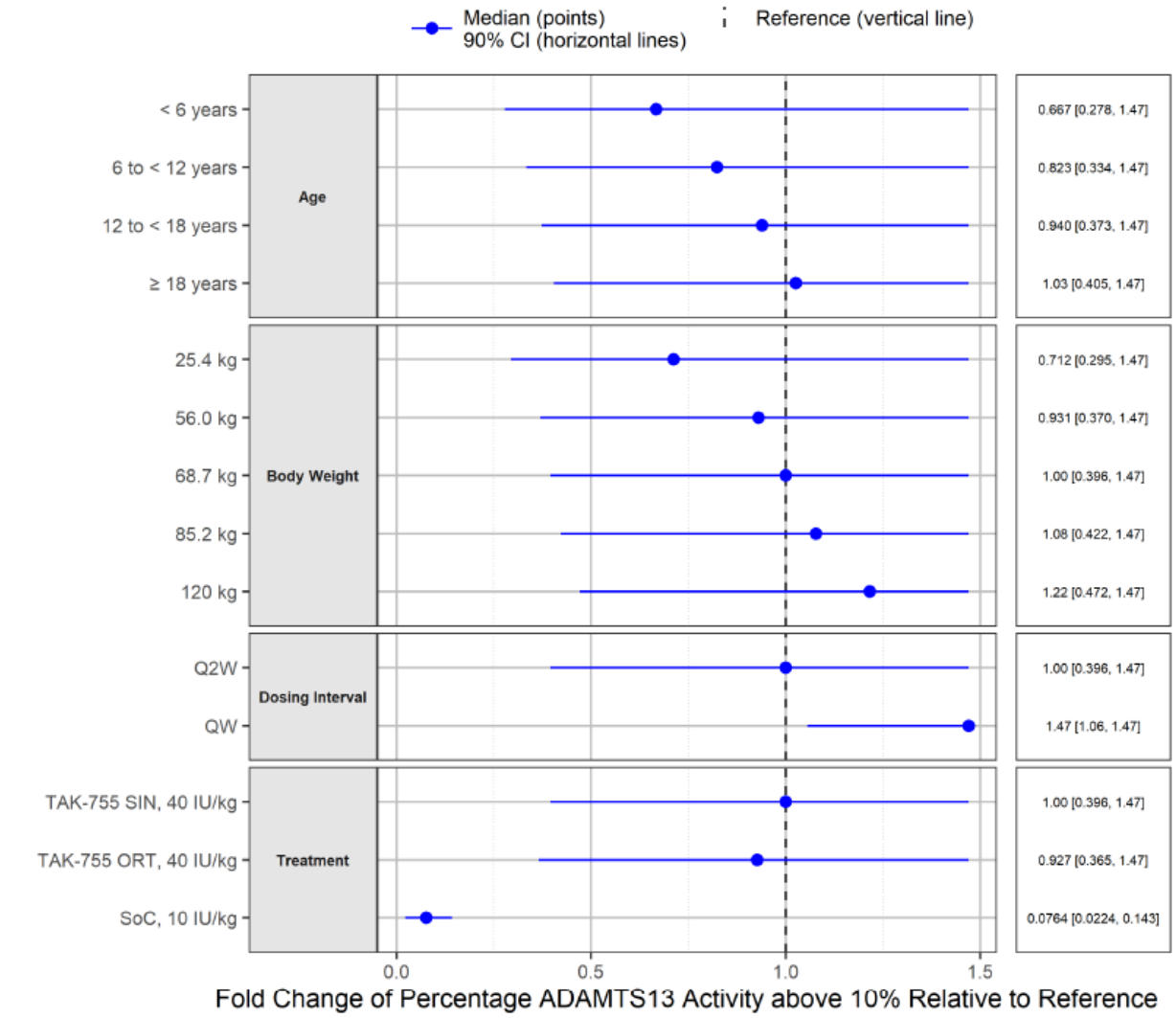
Note: the reference is a 68.7-kg patient who received 40 IU/kg Q2W of the SIN material of TAK-755. The effect of age was derived by selecting the median body weight in patients < 6, 6 to <12, 12 to <18 and ≥18 years (20.8, 39.1, 57.6, and 74 kg, respectively). Body weight values of 25.4, 56.0, 85.2 and 120 kg represent the 5th, 25th, 75th, and 95th percentiles. The right panel presents the numerical values associated with the median and 90% CI.

Figure 7 : Covariate effects on maximum ADAMTS13 activity



Note: the reference is a 68.7-kg patient who received 40 IU/kg Q2W of the SIN material of TAK-755. The effect of age was derived by selecting the median body weight in patients < 6, 6 to <12, 12 to <18 and ≥18 years (20.8, 39.1, 57.6, and 74 kg, respectively). Body weight values of 25.4, 56.0, 85.2 and 120 kg represent the 5th, 25th, 75th, and 95th percentiles. The right panel presents the numerical values associated with the median and 90% CI. The average ADAMTS13 activity (Cave,ss) was derived as the AUC over the dosing interval.

Figure 13: Covariate effects on average ADAMTS13 activity

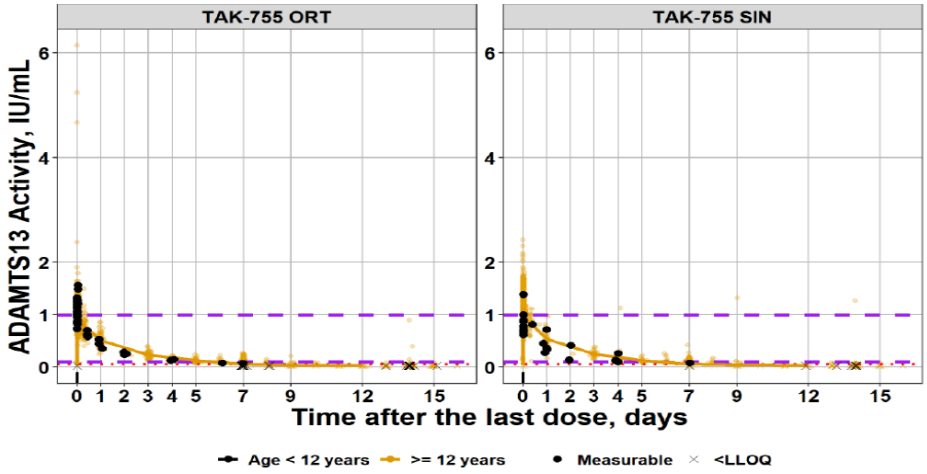


Note: the reference is a 68.7-kg patient who received 40 IU/kg Q2W of the SIN material of TAK-755. The effect of age was derived by selecting the median body weight in patients < 6, 6 to <12, 12 to <18 and ≥18 years (20.8, 39.1, 57.6, and 74 kg, respectively). Body weight values of 25.4, 56.0, 85.2 and 120 kg represent the 5th, 25th, 75th, and 95th percentiles. The right panel presents the numerical values associated with the median and 90% CI.

Figure 8 : Covariate effects on percentage of time of ADAMTS13 activity above 10 % (%)

Children

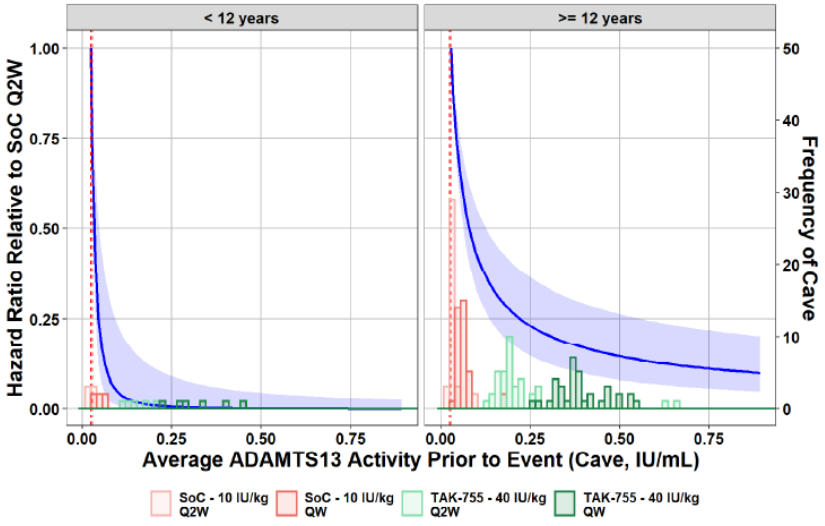
In study 281102, available paediatric PK data in subjects <12 years of age indicate that body weight-based TAK-755 IV dosing provides ADAMTS13 activity exposures similar to that of the older age groups (Figure 15). Particularly, age did not appear to have an overall impact on ADAMTS13 PK distribution.



Note: Solid line represents the mean profile of data using subjects ≥12 years; All available individual data from subjects with <12 years are presented as black solid circles; Two reference horizontal purple lines represent 10% and 100% activity, respectively; red dotted line represents 6.5% activity (assay LLOQ).

Figure 9: mean and individual observed ADAMTS13 activity vs. time following administration of 40 IU/kg of TAK-755 (ORT or SIN) in cTTP subjects with <12 and ≥ 12 years (Study 281102)

The exposure-response relationship of Cave of ADAMTS13 for the hazard ratio of thrombocytopenia by age group is presented in Figure 16. The exposure-response relationship in patients < 12 was steeper than that observed in patients ≥12 years.



Note: hazard ratio were derived relative to the SoC Q2W regimen (HR = 1)

Figure 10: Cox proportional hazard model with recurring events – thrombocytopenia – Exposure-response relationship by age group

Pharmacokinetic interaction studies

TAK-755 is a therapeutic recombinant protein. Drug-drug interaction studies (as a perpetrator or as a victim) were not conducted as they were deemed not required for this therapeutic protein.

Pharmacokinetics using human biomaterials

Not Applicable.

2.6.2.2. Pharmacodynamics

PD analysis included measurements of VWF antigen, von Willebrand factor: ristocetin cofactor (VWF:RCo) activity, VWF multimer patterns, and VWF cleavage products. VWF:RCo reflects the function of VWF multimers as measured by their ability to bind platelet GP1b after ristocetin treatment. PD data are based on 15 cTTP subjects in Phase 1 Study 281101, 47 cTTP subjects in the pivotal Phase 3 study pharmacokinetic full analysis set (PKFAS; Study 281102), and 36 cTTP subjects (including both rollover and non-rollover subjects from Study 281102) in the continuation Phase 3 study PKFAS (Study 3002).

Mechanism of action

ADAMTS13 is a VWF cleaving protease, and cTTP is caused by a severe congenital ADAMTS13 deficiency, which leads to accumulation of ultra-large VWF multimers with high platelet binding activity. The formation of VWF-platelet microthrombi leads to platelet consumption and thrombocytopenia, which is a marker of TTP disease activity. TAK-755 contains a recombinant form of the endogenous ADAMTS13 with similar pharmacokinetic (PK) and pharmacodynamic (PD) properties. The use of TAK-755 in TTP patients with congenital ADAMTS13 deficiency provides targeted ADAMTS13 supplementation, which is expected to reduce or eliminate the spontaneous formation of such VWF-platelet microthrombi and thus, the occurrence of acute TTP events, subacute TTP events, and individual manifestations of TTP.

Nonclinical studies were conducted to support the mechanism of action, pharmacology, PK, and toxicology of TAK-755. A Quantitative Systems Pharmacology (QSP) analysis was conducted to establish a quantitative mechanistic understanding between ADAMTS13 activity, VWF, and platelets by describing the dynamic relationship in subjects with cTTP as a function of treatments (TAK-755 vs SoC). This analysis integrated data from various sources including *in vitro* data, ADAMST13 knockout (KO) mouse experimental data, and literature clinical data, as well as data from the pivotal Phase 3 Study 281102 to calibrate and validate the model. Virtual population simulations using this QSP model were conducted to (1) identify the ADAMTS13 activity exposure metric that correlates best with platelet normalisation or recovery, and (2) establish the relationship between ADAMTS13 activity exposures and thrombocytopenia (platelet count $<150\times10^9$/L) and severe thrombocytopenia (platelet count $<100\times10^9$/L) events.

Primary and Secondary pharmacology

Measurement of plasma VWF:RCo, VWF:Ag and VWF structure analysis was conducted prior to and following a single infusion of rADAMTS13 in Phase 1 Study 281101.

Individual profiles (for 40 IU/kg only) of VWF (%) and VWF multimer pattern over 0-48 hour are shown below. Besides the multimeric sizes typically present in circulating plasma (small, intermediate, and large), ultra-large VWF multimers were also observed in the samples collected prior to dosing, at Screening or pre-dose, in all subjects, and at most timepoints post-dose. Following single-dose administration of BAX 930 at 5 U/kg, 20 U/kg, and 40 U/kg, a trend for decreasing large multimers (including ultra-large multimers) and increasing levels of the intermediate form was observed over the first 24 hours post-dose in individual profiles at the higher doses of 20 U/kg or 40 U/kg.

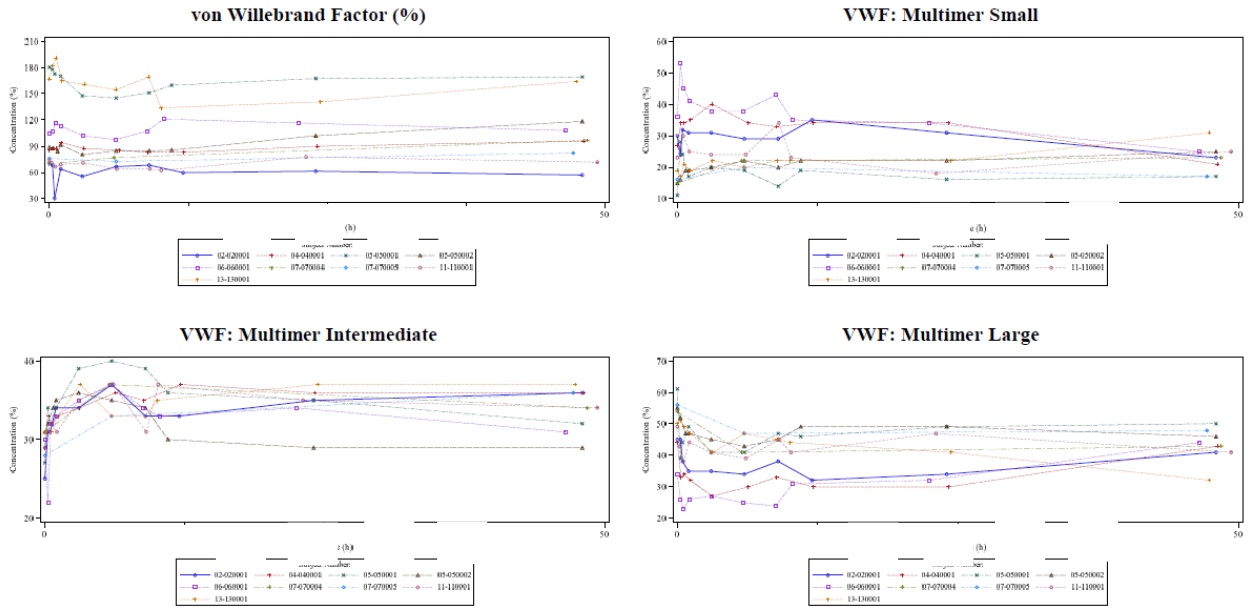


Figure 11: Individual plasma VWF (%) and multimer pattern versus time over 0-48 hour at 40 U/kg dose level

The proportion of subjects (n [%]) in each treatment with detectable ADAMTS13-mediated VWF cleavage products are summarized by scheduled times in Table 16.

Table 9 Summary (n (%) of detectable ADAMST13-mediated VWF cleavage products

Schedule Time (h)	5 U/kg (N=3)	20 U/kg (N=3)	40 U/kg (N=9)	Total (N=15)
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.25	3 (100.0)	3 (100.0)	7 (100.0)	13 (100.0)
0.5	3 (100.0)	3 (100.0)	7 (100.0)	13 (100.0)
1	3 (100.0)	3 (100.0)	7 (100.0)	13 (100.0)
3	3 (100.0)	3 (100.0)	7 (100.0)	13 (100.0)
6	1 (33.3)	3 (100.0)	9 (100.0)	13 (86.7)
9	0 (0.0)	3 (100.0)	7 (100.0)	10 (76.9)
12	0 (0.0)	3 (100.0)	7 (100.0)	10 (76.9)
24	0 (0.0)	3 (100.0)	7 (100.0)	10 (76.9)
48	0 (0.0)	2 (66.7)	9 (100.0)	11 (73.3)
96	0 (0.0)	0 (0.0)	6 (85.7)	6 (46.2)
144	0 (0.0)	0 (0.0)	6 (66.7)	6 (40.0)
168	0 (0.0)	0 (0.0)	3 (42.9)	3 (23.1)
192	0 (0.0)	0 (0.0)	2 (28.6)	2 (15.4)
216	0 (0.0)	0 (0.0)	2 (22.2)	2 (13.3)
240	0 (0.0)	0 (0.0)	1 (14.3)	1 (7.7)
264	0 (0.0)	0 (0.0)	1 (14.3)	1 (7.7)
288	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Mean (SD) and individual profiles (for 40 IU/kg only) of VWF:RCo over 0-48 hours are shown in Figure 18. Over the first 24 hours, the mean post-dose VWF:RCo levels, which reflect the function of VWF multimers as measured by VWF multimers's ability to bind platelet GP1b, were lower than mean

baseline levels at most timepoints across the 3 dose levels. Decreases by almost 30% were observed in the first 9 hours.

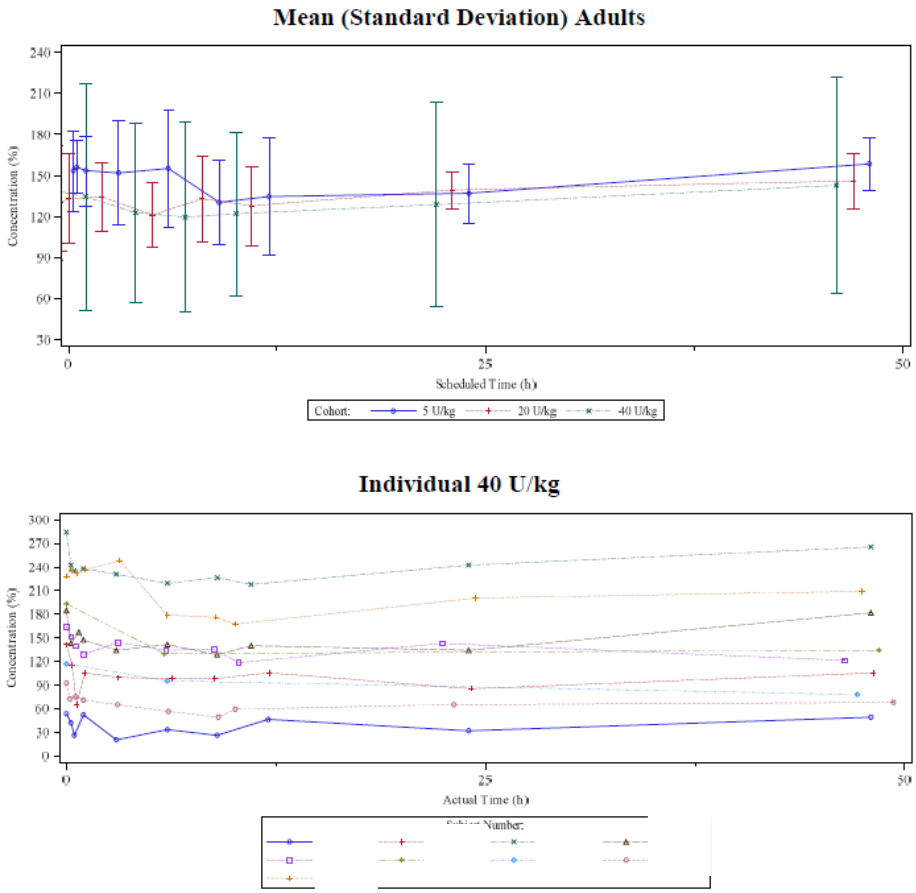


Figure 18: Mean (standard deviation) and individual VWF:RCo versus time over 0-48 hour

Platelet and LDH levels

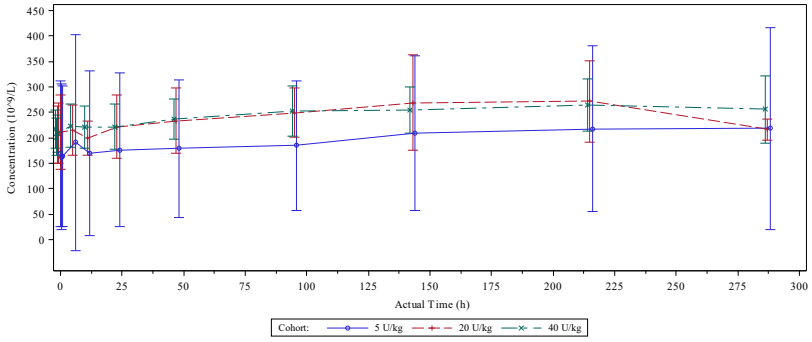
Dose Cohort 1 (5 U/kg): The ***mean platelet count*** decreased slightly from baseline at 15 minutes and 1-hour post-dose, increasing above baseline at 6 hours post-dose, returning to near baseline at 12 hours post-dose, which increased steadily from 12 hours until 96 hours post-dose and showed an upsurge from 144 hours to 288 hours post-dose, returning closer to baseline at the completion visit. The ***mean LDH value*** showed a considerable increase from baseline at 1-hour post-dose, decreasing below baseline from 6 hours post-dose until 24 hours post-dose, returning to near baseline at 48 hours and 96 hours post-dose, and decreasing below baseline from 144 hours to 288 hours post-dose, increasing closer to baseline at the completion visit.

Dose Cohort 2 (20 U/kg): The ***mean platelet count*** increased steadily from baseline from 15 minutes until 6 hours post-dose, decreased to below baseline at 12 hours post-dose, increasing considerably from baseline from 24 hours until the completion visit. Constant but marginal variations from baseline were noted at all timepoints in the ***mean LDH values***, which was slightly above baseline at the completion visit.

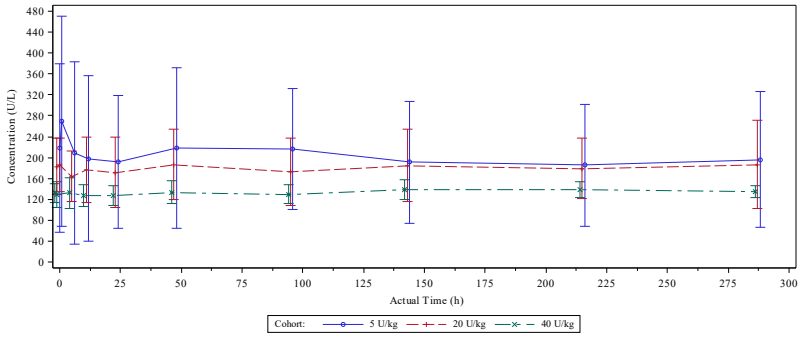
Dose Cohort 3 (40 U/kg): The ***mean platelet count*** decreased from baseline at 15 minutes and 1-hour post-dose and increased from baseline from 6 hours post-dose through 288 hours post-dose and decreased below baseline at the completion visit. The ***mean LDH values*** showed marginal variations

from baseline, decreasing slightly from baseline initially until 24 hours post-dose, increasing marginally from baseline from 48 hours until 288 hours post-dose, and showed an upsurge at the completion visit.

Analyte: Platelets (10^9/L)



Analyte: Lactate Dehydrogenase (U/L)



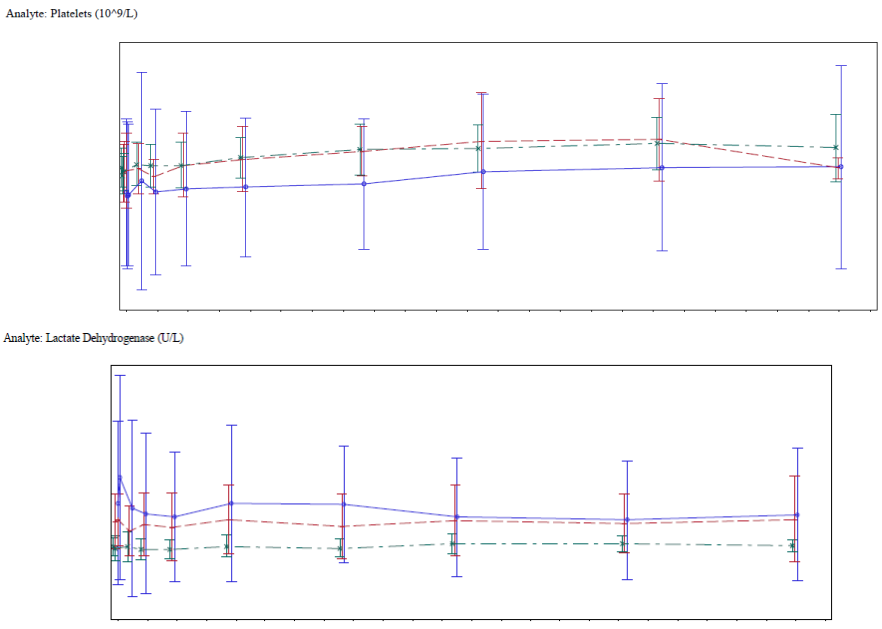
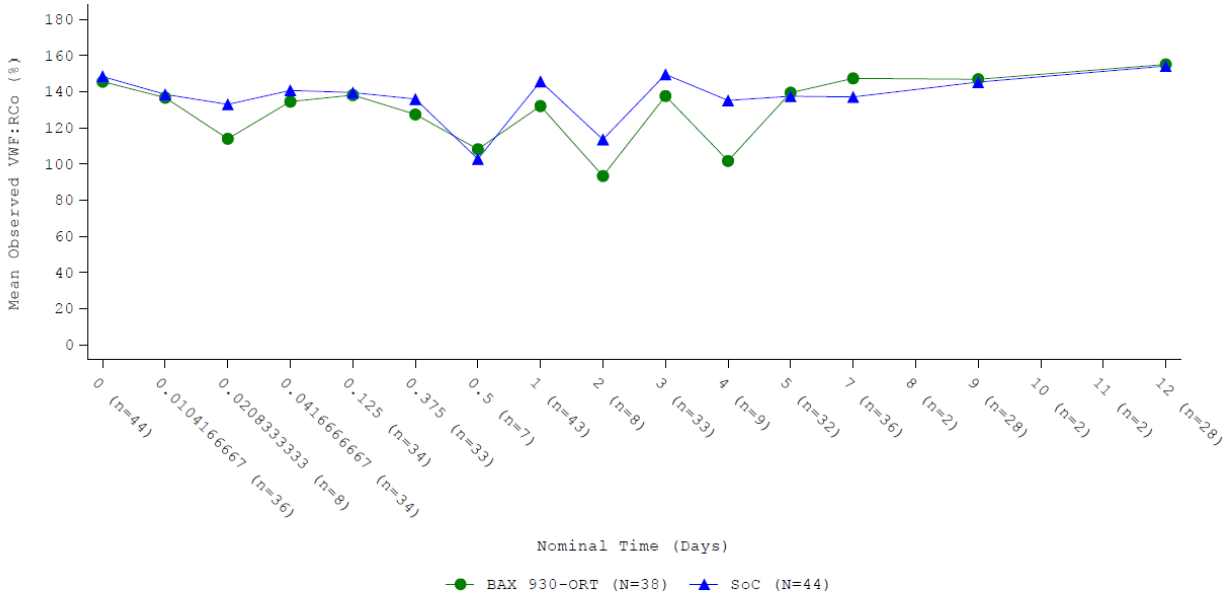


Figure 19: Laboratory Data Summary (Study 281101: Safety Analysis Set)

PD objectives in Phase 3 Study 281102 were to assess VWF:antigen (VWF:Ag), and VWF:ristocetin cofactor activity (RCo) at baseline and following infusion of the SoC agent and TAK-755 treatment during the initial PK assessment in the Prophylactic Cohort. Select VWF parameters were assessed prior to each PK infusion of SoC or TAK-755 in the Prophylactic Cohort. Additional exploratory PD biomarkers, including but not limited to VWF multimer patterns, ADAMTS13-mediated VWF cleavage

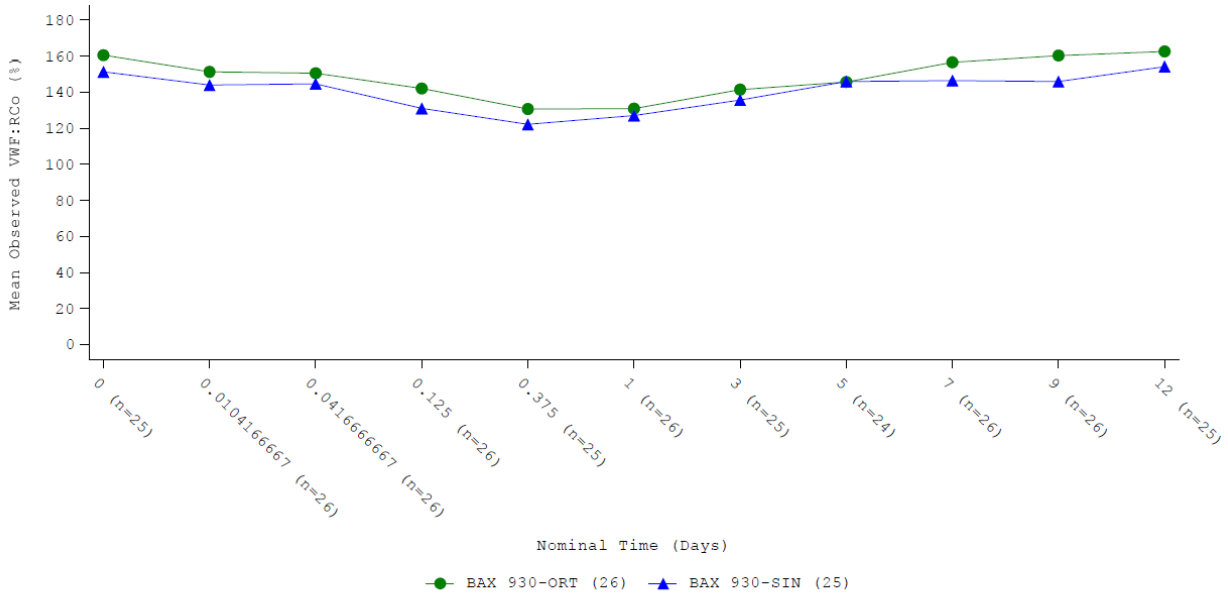
products and coagulation readouts, were evaluated at baseline and following infusion of the SoC agent and TAK-755.

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) (Figure 20 and Figure 21). 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. However, no obvious trend was observed between TAK-755 and SoC when looking at the overall time-series profiles. The data on VWF:RCo levels are not unexpected as the cTTP patients were generally clinically stable and without significantly increased disease activity, during the PK periods when these samples were taken. Therefore, it can be hypothesized that following TAK-755 or SoC administration, there was no major impact on VWF:RCo activity during the PK periods.



Subject passed screening and entered the study more than once and is included as 2 study subjects. All data for each subject ID are included in the analyses.

Figure 20: Mean observed VWF:RCo (%) activity-time profile TAK-755 ORT and SoC for PK-I and PD analysis set



Subject passed screening and entered the study more than once and is included as 2 study subjects. All data for each subject ID are included in the analyses.

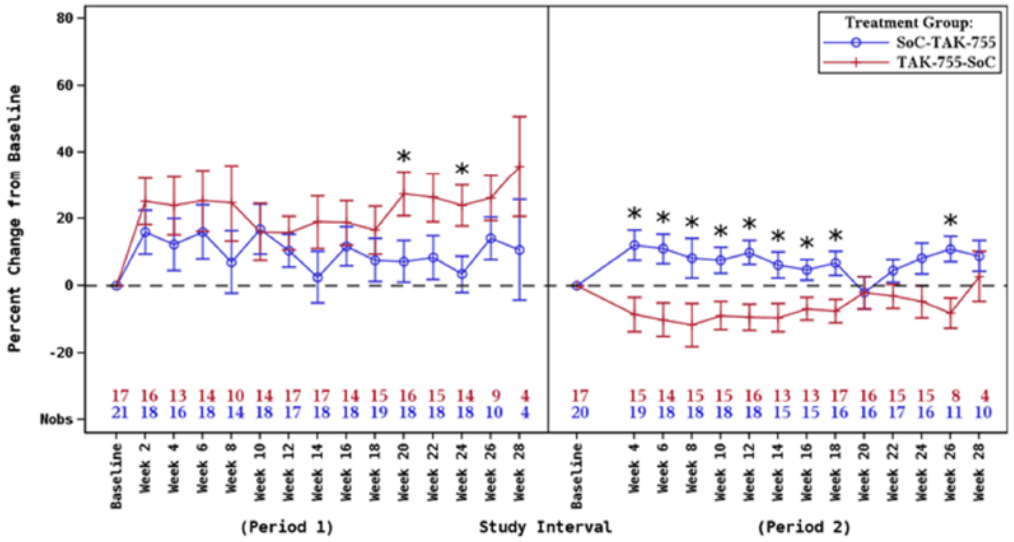
Figure 21: Mean observed VWF:RCo (%) activity time profile following TAK-755 ORT and TAK-755 SIN for PK-II-PD analysis set

During PK-I, immediately following treatment, more subjects receiving TAK-755 tend to show detectable ADAMTS13 mediated VWF cleavage products, compared to SoC administration. However, at later timepoints this difference dissipated. This may be explained by the ADAMTS13 activity PK and overall exposure differences between TAK-755 and SoC which are numerically most different immediately after treatment.

During PK-II, comparing TAK-755 ORT and TAK-755 SIN, the latter provided a numerically higher percentage of subjects with VWF cleavage products. In particular, ADAMTS13 mediated VWF cleavage products were observed during longer period of time for both TAK-755 ORT and TAK-755 SIN, up to 72 hours post dose in >50% evaluable samples. This evidence, in conjunction with VWF antigen and VWF: RCo results, support the PD activity in patients with cTTP. Different factors could have impacted these such as VWF:RCo activity and assay quality.

Exploratory PD objectives in study 281102 were to assess shifts in biomarkers of organ damage, including troponin T (cardiac troponin T [cTnT]) and I (cTnI) (cardiac), creatine kinase myocardial band (CK-MB) fraction (cardiac), neuron-specific enolase (NSE) (brain), S100 calcium-binding protein B (S100B) (brain), and serum creatinine (kidney), during routine prophylaxis with the SoC treatment and TAK-755 as well as during acute TTP events in the Prophylactic Cohort.

As an indicator of TTP disease activity, the relative change in platelet count was analysed over time during the controlled comparison (Period 1 and Period 2). Change in platelet count was calculated relative to the study period baseline. The relative platelet count, indicated as percent change from baseline, was generally higher during TAK-755 prophylactic treatment compared to during SoC treatment. Following the TAK-755-SoC subjects who were on TAK-755 prophylaxis during Period 1, there is a numerical drop in the relative platelet count for these subjects when moving to Period 2 (SoC prophylaxis). For SoC-TAK-755 subjects who were on SoC prophylaxis during Period 1, there is a trend for increased relative platelet count when these subjects switch to TAK-755 prophylaxis in Period 2.



LS=least squares; MFAS=modified full analysis set; Nobs=number of subjects with non-missing value at visit; SE=standard error; SoC=standard of care

Notes: The numbers in red are for TAK-755-SoC and those in blue are for SoC-TAK-755.

Visits are only included where n is at least 3 for both treatments.

Period 1 baseline is the last non-missing measurement prior to the first study dose for prophylaxis subjects and the last nonmissing measurement prior to the first prophylaxis dose for on-demand subjects. Period 2 baseline is the last nonmissing measurement prior to the first dose of Period 2.

* Indicates that the nominal p-value for comparison of treatments is <0.05.

Figure 22: Study 281102 LS mean (SE) percent change from baseline in platelets while on prophylactic treatment by randomised treatment sequence (MFAS adolescents and adults in treatment periods 1 and 2)

Exposure-Response models

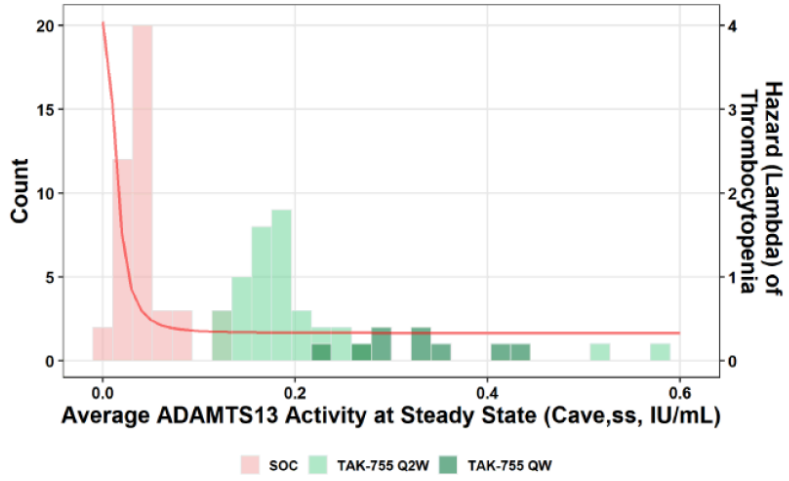
The ER models were developed to determine the relationship between ADAMTS13 activity and the probability of isolated TTP manifestations including a composite TTP manifestations endpoints following administration of treatment (TAK-755 vs SoC). The primary ER analysis consisted of modelling of events count data (1). Additional ER analyses were performed using semi-parametric Cox-proportional-hazards modelling for recurring events (2), and parametric repeated time-to-event (RTTE) models (3). The effect of age was evaluated as part of the above-mentioned ER models to support dosing recommendations in paediatric subjects (<12 years) with cTTP. Additionally, data from Period 3 were also included in the RTTE model. To this end, the intent and objective of the ER analyses is as follows:

- Identify if there is a significant TAK-755 treatment effect to confirm and corroborate the findings from the protocol-specified statistical analyses.
- Focus on laboratory-based objective endpoints, thrombocytopenia and MAHA, to evaluate if TAK-755 reduces the hazard of these endpoints of interest in an ADAMTS13 activity-dependent manner.
- Assess if there is a persistent beneficial effect of TAK-755 using exposure-hazard reduction relationship in 3 efficacy periods from the pivotal Phase 3 study (cross-over Periods 1 and 2 followed by maintenance Period 3).
- Establish and demonstrate the consistent beneficial effect of TAK-755 in the treatment of cTTP using 3 different sets of ER analyses.

1) Primary Exposure-response Results for Count of Isolated TTP Events

This analysis revealed a significant treatment effect of TAK-755 over SoC. The ER relationship for the Cave,ss of ADAMTS13 activity was estimated to be very steep and significant for (a) thrombocytopenia events, (b) MAHA events, and (c) the composite TTP manifestations endpoint.

The ER relationship between the Cave of ADAMTS13 activity and the count (left axis) or hazard (right axis) of thrombocytopenia is depicted in Figure 23.



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_{ave50}: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

Figure 23: Average ADAMST13 activity at steady state (exposure)-hazard of thrombocytopenia (response) relationship using isolated thrombocytopenia event counts (N=41; adults, adolescents and paediatric subjects)

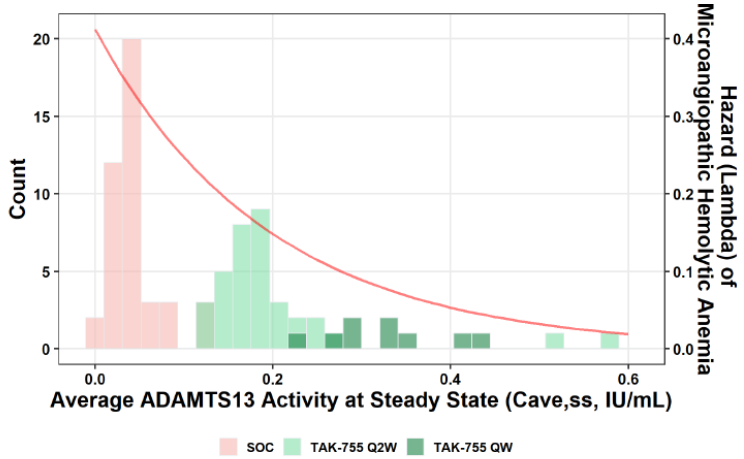
Using the above-described model-based thrombocytopenia count ER relationship, the probability of thrombocytopenia-free (count=0) associated with steady-state ADAMTS13 Cave activity (popPK model predicted) resulting from the TAK-755 and SoC was derived and described in Table 17.

Table 17: Count exposure-response model predicted probability of thrombocytopenia -free (count=0) by predicted percentiles of ADAMTS13 Cave.ss resulting from 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).

Similarly, a consistent and significant ER relationship was found between average ADAMTS13 activity exposures and MAHA counts (Figure 24, Table 18).



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 0.328, 0.147, and 0.0780, respectively.

Figure 24: MAHA count (maha_pois3.ctl)- exposure-response relationship (N=41)

Table 18: MAHA count (maha_pois3.ctl)- predicted probability of MAHA event-free (Count=0) by percentiles of ADAMTS13 Cave,ss for the SoC and TAK-755 (N=41)

Percentiles	SoC (10 IU/kg)		TAK-755 Q2W (40 IU/kg)		TAK-755 QW (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	68.3	0.130	80.9	0.239	88.6
10%	0.0184	68.7	0.137	81.5	0.256	89.5
25%	0.0277	69.9	0.155	83.0	0.288	91.0
50% (Median)	0.0398	71.4	0.176	84.6	0.332	92.7
75%	0.0491	72.6	0.206	86.6	0.351	93.4
90%	0.0863	76.7	0.249	89.1	0.424	95.4
95%	0.121	80.1	0.396	94.7	0.427	95.5

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.

2) Cox-proportional-hazards Exposure-response Results (Recurring Time to Event) for Key Objective Endpoints (Thrombocytopenia and MAHA)

Cox-proportional-hazards analysis used the population PK model to derive individual longitudinal ADAMTS13 activity profiles based on individual post-hoc parameters and actual dosing information. The mean ADAMTS13 average activity (C_{ave}) since the start of treatment up to the first event or between events was included in the dataset in each patient in Period 1 and 2. The effect of treatment on the probability of thrombocytopenia event-free and MAHA event free were evaluated. TAK-755 was associated with a higher probability of thrombocytopenia event-free relative to SoC from approximately Week 2 onwards. These observations suggest that it takes approximately 2 weeks for onset of prophylactic treatment effect. During Period 2, SoC was associated with a slightly higher probability of thrombocytopenia event-free relative to TAK-755, probably mainly due to the residual protective effect of TAK-755 in Period 1.

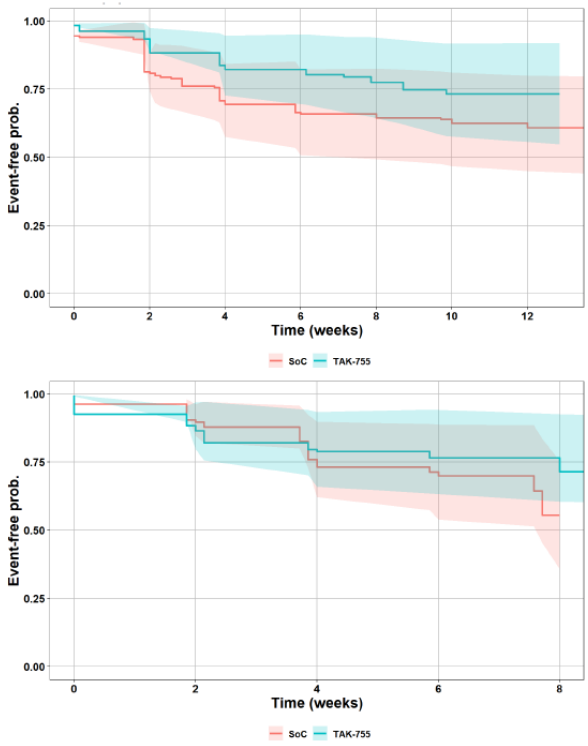
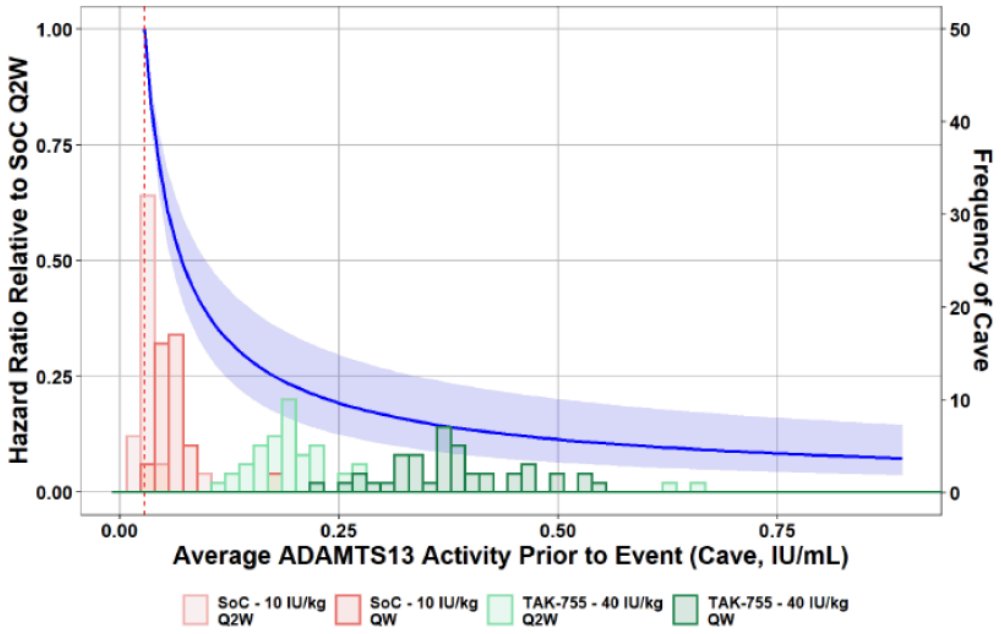


Figure 25: Probability of Thrombocytopenia Event-Free in Period 1 (Top Panel) and Period 2 (Bottom Panel) – Treatment Effect

The ER relationship of Cave of ADAMTS13 activity for the HR of thrombocytopenia using final Cox-proportional-hazards modelling is depicted in Figure 26 and summarized in Table 19.



Note: hazard ratio were derived relative to the SoC Q2W regimen (HR = 1)

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; C_{ave}=average concentration; ER=exposure-response; HR=hazard ratio; popPK=population pharmacokinetics; Q1W=once weekly; Q2W=every 2 weeks; SoC=standard of care

Figure 26: Average ADAMTS13 activity (exposure) hazard ratio (response) of thrombocytopenia relationship using Cox-proportional-hazards exposure-response modelling (N=43)

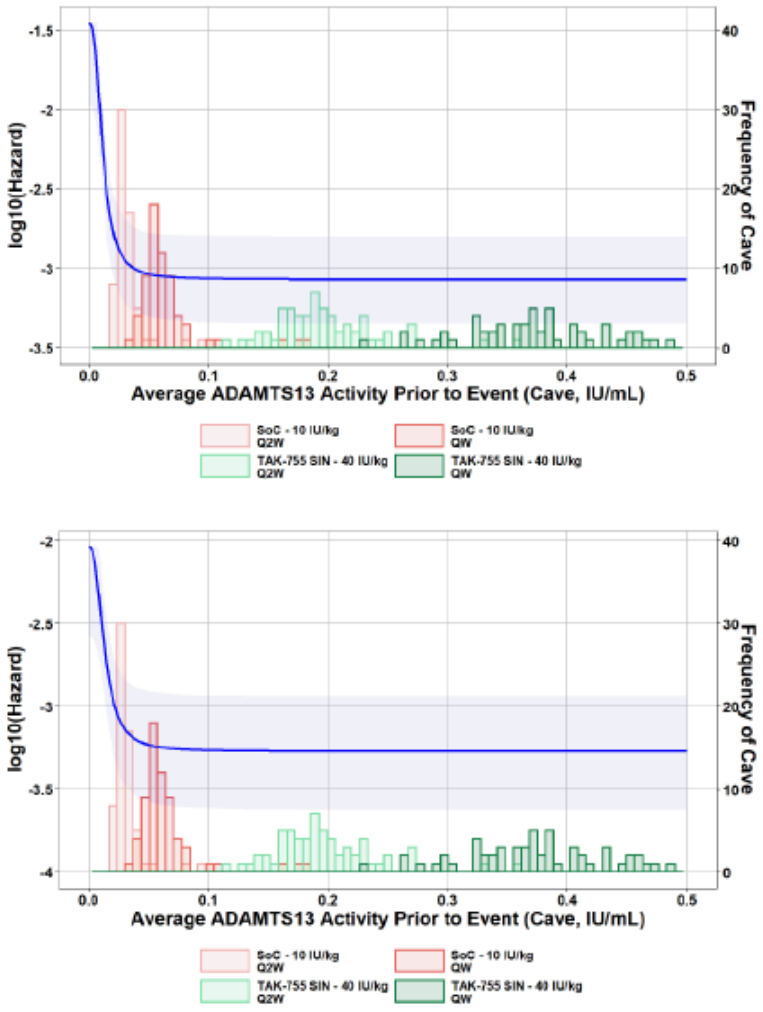
Table 19: Hazard ratio for probability of recurring thrombocytopenia events using Cox-proportional hazards exposure-response analysis (N=43)

Treatment	Dosing Interval	Median $C_{ave,ss}$ ADAMTS13 activity (IU/mL)	Hazard Ratio (95% CI) for Probability of Thrombocytopenia
SoC (10 IU/kg)	Q2W	0.0282	**1 (Reference)**
	QW	0.0563	0.593 (0.680-0.517)
TAK-755 (40 IU/kg)	Q2W	0.187	0.239 (0.348-0.165)
	QW	0.374	0.142(0.237-0.085)

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; $C_{ave,ss}$=average concentration at steady state; CI=confidence interval; ER=exposure-response; popPK=population pharmacokinetics; Q1W=once weekly; Q2W=every 2 weeks; SoC=standard of care
Note: Hazard ratio were derived relative to the SoC Q2W regimen; Individual ADAMTS13 $C_{ave,ss}$ used in the Cox-proportional-hazards modeling (subjects <12 and ≥ 12 years of age) were used to derive the above listed median $C_{ave,ss}$

3) Longitudinal Recurring Time-to-event Exposure-response Results

The ER relationship of ADAMTS13 activity Cave for the hazard of thrombocytopenia (top panel) and MAHA (bottom panel) using the final RTTE approach is depicted in Figure 27. The final RTTE models predicted probabilities of thrombocytopenia and MAHA event-free resulting from TAK-755 40 IU/kg dosing regimen remained high (>70%) at 6 and 12 months (see Table).



ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; C_{ave}=average concentration; E_{max}=maximum effect; ER=exposure-response; MAHA=microangiopathic hemolytic anemia; popPK=population pharmacokinetics; RTTE=repeated time-to-event; SoC=standard of care
Note: Final RTTE model with thrombocytopenia had ADAMTS13 activity EC_{ave50} (effective C_{ave}) of 0.0113 IU/mL (or 1.13% activity) with an E_{max} of 97.5% reduction (inhibition) in hazard of thrombocytopenia; Final RTTE model with MAHA had ADAMTS13 activity EC_{ave50} (effective C_{ave}) of 0.0133 IU/mL (or 1.33% activity) with an E_{max} of 94.2% reduction (inhibition) in hazard of MAHA.

Figure 27: Average ADAMTS13 activity (exposure)-hazard (response) of thrombocytopenia (top panel) and MAHA (bottom panel) relationship using RTTE modelling (N=43)

Table 20: probability of thrombocytopenia and MAHA event free resulting from TAK-755 40 IU/kg administration in subjects with cTTP using final RTTE ER model

Duration	Model Predicted Probability (95% CI)	
	Thrombocytopenia	MAHA
6 months	0.856 (0.921, 0.750)	0.906 (0.957, 0.810)
12 months	0.732 (0.848, 0.563)	0.821 (0.917, 0.656)

CI=confidence interval; cTTP=congenital thrombotic thrombocytopenic purpura; ER=exposure-response; MAHA=microangiopathic hemolytic anemia; popPK=population pharmacokinetics; RTTE=repeated time-to-event

Quantitative Systems Pharmacology (QSP) Analysis

A QSP model was developed to mechanistically describe the PD interaction of ADAMTS13, as either TAK-755 or frozen plasma, for the treatment of cTTP. TAK-755 is a recombinant form of ADAMTS13. The model was developed to supplement the clinical data to improve understanding of ADAMTS13

activity relationship with VWF and platelets, enrich the longitudinal ADAMTS13 and VWF data from pivotal trial, and improve understanding of low prevalence rates of TTP events in relation to ADAMTS13 exposure.

The QSP model structure, shown in Figure 28, describes the interactions between ADAMTS13 (both endogenous and recombinant forms), VWF, and platelets (PLT). These biological interactions were quantitatively and mechanistically integrated into a QSP modeling framework which is supported by literature and the Applicant's in-house data, and all dynamic equations corresponding to the model structure are listed in the Appendix, Section H.6.6. Both endogenous and recombinant forms of ADAMTS13 are accounted for in the model and are assumed to have same reaction rates with other molecules. Individual predictions (IPRED) from a two- compartment model with instantaneous input and first-order elimination represented the pharmacokinetics (PK) of the drug (final popPK and ER report using first IA cutoff data) was used to as inputs for the QSP model.

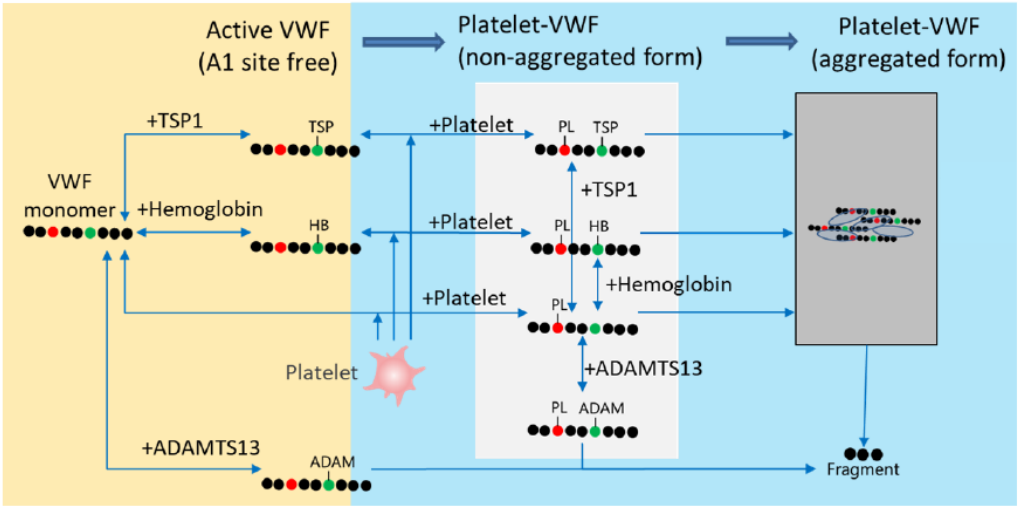


Figure 28: QSP model structure describing the interaction of ADAMTS13 (both endogenous and recombinant forms) and VWF, platelets (PL), thromspondin protein 1 (TSP1), and hemogloin (Hb). The recombinant ADAMTS13 represents the therapeutic drug of this study, TAK-755. The interactions with the active VWF and platelet to form aggregated platelet-VWF complexes are shown in blue.

The overall strategy used to estimate the QSP model parameters is summarized as a flow chart in Figure 29.

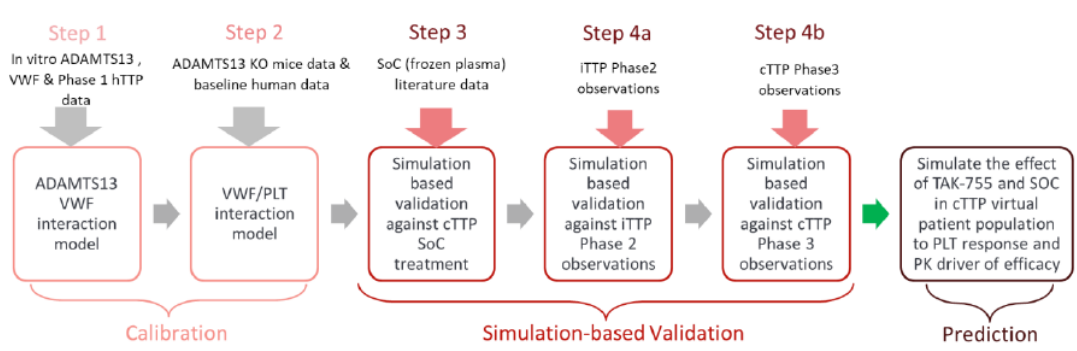
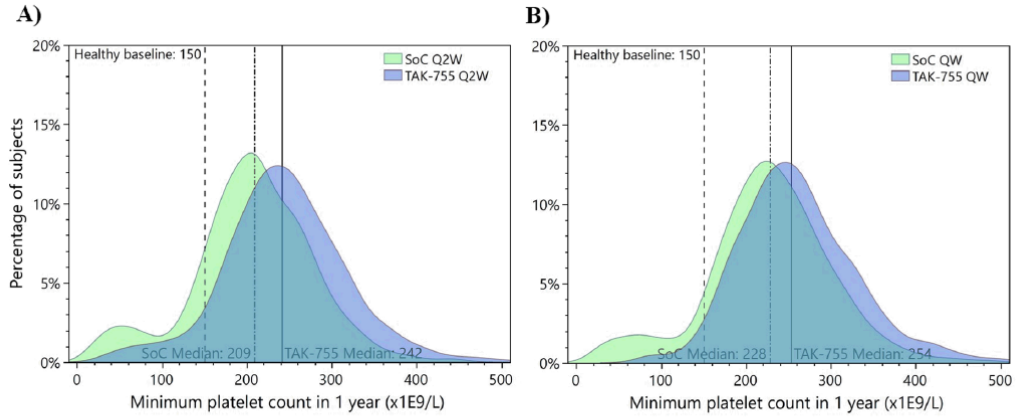


Figure 29: Summary of the overall strategy used to estimate the PD model parameters. The baseline human data in step 2 refers to the data from healthy volunteers and untreated cTTP patients

The PK metrics that correlate most strongly with platelet count increase are Ctrough and the fraction of time above 0.1 IU/mL of ADAMTS13 activity, with Cave having a similar strong positive correlation, and Cmax correlating poorly with platelet response (not shown). This result supports additional justification for using ADAMTS13 activity Cave PK parameter as an exposure input for the ER analysis.

The duration of the carry-over effect after switching treatment arms is approximately 20 days to reach 90% of the new steady-state platelet count after switching treatments or dosing regimens for all subjects, which is consistent with the findings from Cox-proportional-hazards ER results where this effect was found to be approximately 2 weeks.

Higher ADAMTS13 activity exposure results in higher median platelet counts for the virtual population, with fewer virtual subjects having platelet counts below both 100×10^9/L and 150×10^9/L. Following TAK-755 administration (as compared to SoC), the calculated HR of thrombocytopenia was more than 53% lower regardless of dosing interval (Q2W and Q1W). Similarly, when the more stringent criteria of severe thrombocytopenia (defined as platelet count less than 100×10^9/L) was used, the predicted hazard was greater than 59% lower regardless of dosing interval(s). This is generally consistent with the annualized incidence rates results reported per the primary statistical efficacy analysis in the pivotal Study 281102. These positive results are indicative of consistent trends in favor of TAK-755 (over SoC). In other words, despite various quantitative approaches (QSP and ER results) including primary statistical analysis, TAK-755 (over SoC) is expected to provide less occurrences of thrombocytopenia.



IV=intravenous; Q1W=once weekly; Q2W=every 2 weeks; QSP=Quantitative Systems Pharmacology; SoC=standard of care
Solid and dash-dotted lines indicate medians of each treatment group. The vertical line on the left of each panel represents isolated thrombocytopenia manifestation threshold of 150×10^9/L. (A) IV dosing administration of SoC vs TAK-755 with a Q2W dosing interval. B) IV dosing administration of SoC vs TAK-755 with a Q1W dosing interval.

Figure 30: distribution of minimum platelet count in 1 year for virtual population under TAK-755 and SoC treatment with Q1W and Q2W dosing sechdules

Table 21: Summary of the percent of virtual subjects experiencing thrombocytopenia (platelet count <150 *10 /L) and severe thrombocytopaenia (platelet count <100*10⁹ /L) following 1 year of TAK-755 and SoC administration

Platelet Count Threshold	Treatment	Dosing Interval	Median Platelet Count (SD) [$\times 10^9$/L]	% of Virtual Subjects Experiencing Thrombocytopenia Occurrences	Hazard Ratio Point Estimate for Probability of Thrombocytopenia
150×10^9/L (Thromocytopenia)	SoC (10 IU/kg)	Q2W	209 (72)	17.2	**1 (Reference)**
		Q1W	228 (74)	10.6	0.62
	TAK-755 (40 IU/kg)	Q2W	242 (73)	8.1	0.47
		Q1W	254 (70)	3.1	0.18
100×10^9/L (Severe thrombocytopenia)	SoC (10 IU/kg)	Q2W	209 (72)	8.7	**1 (Reference)**
		Q1W	228 (74)	6.7	0.77
	TAK-755 (40 IU/kg)	Q2W	242 (73)	3.6	0.41
		Q1W	254 (70)	0.8	0.09

Q1W=once weekly; Q2W=every 2 weeks; QSP=Quantitative Systems Pharmacology; SD=standard deviation; SoC=standard of care; Note: QSP simulated median platelet count (SD) for the virtual population is 209 (72)$\times10^9$/L for SoC Q2W dosing, 228 (74)$\times10^9$/L for SoC Q1W dosing, 242 (73)$\times10^9$/L TAK-755 Q2W dosing, and 254 (70)$\times10^9$/L for TAK-755 Q1W dosing.

2.6.3. Discussion on clinical pharmacology

The PK/PD of TAK-755 was characterised in cTTP subjects only. This is acceptable as healthy volunteers are expected to have normal ADAMTS13 levels, and therefore the administration of rADAMTS13 would not yield any useful information on the pharmacology of TAK-755. Clinical PK/PD data are based on 15 cTTP subjects from completed Phase 1 Study 281101, 47 cTTP subjects from the pivotal Phase 3 study pharmacokinetic full analysis set (PKFAS; Study 281102), and 36 cTTP subjects (including 29 rollover and 7 non-rollover subjects from Study 281102) from the continuation Phase 3 study PKFAS (Study 3002). Due to the rarity of the disease, the overall small sample size is acceptable. No specific target levels are defined for ADAMTS13 and the accepted normal range varies by clinical center and may be affected by age, gender and genetic variants in different ethnic populations polymorphisms that occur more frequently in certain ethnic populations (Tso et *al,* Singapore Med J, 2022). Since severe deficiency of ADAMTS13 is generally considered to be <10% (0.1 IU/) plasma activity, any level above 0.1 IU/kg is considered a valid treatment target.

The PK parameter estimates for ADAMTS13:Ag were shown to have overall comparable values to ADAMTS13 activity. In general, ADAMTS13 activity (FRETS-VWF73) levels are considered more relevant than ADAMTS:Ag as they allow a conclusion on the functionality of rADAMTS13 after *in vivo* administration in the clinical setting. ADAMTS13 activity showed approximately dose proportionality with respect to Cmax and AUC(0-T). The fold increase in geometric mean Cmax was somewhat higher than expected for the 5 IU/kg to the 20 IU/kg dose (approximately 5-fold instead of expected 4-fold), but as expected for the 20 IU/kg to the 40 IU/kg (approximately 2.4-fold). Available data for AUC(0-inf) showed an approximately 2.8-fold increase in exposure for dose increase from the 20 IU/kg to the 40 IU/kg dose. Greater than proportional increases were observed for lower doses, which could be attributable to concentrations falling below LLOQ earlier at the lower doses. Dose proportionality at steady state was not investigated as steady state parameters are derived from the popPK model (see below) for the 40 IU/kg dose level only.

The determinants of enzymatic activity/potency have been characterised (see Quality Section). Because the actual activity value was used for dosing in the phase 1 and phase 3 studies, the potential variation in specific activity has no impact on the PK analysis, dose proportionality assessment, and exposure-response analysis. Moreover, the potential variation in specific activity is unlikely to affect

the efficacy and safety profile because a rather flat dose response was observed between 20 IU/kg, 40 IU/kg Q2W and 40 IU/kg QW.

In Phase 3 Study 281102 the PK/PD of prophylactic treatment with TAK-755 compared to SoC was assessed. 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), depending on the previous SoC administration scheme. During PK-I, a crossover PK evaluation aimed to characterise ADAMTS13 PK after administration of TAK-755 prior to the first treatment period. Despite the estimated t1/2 of 2-3 days, PK results from PK-I for the Q1W dosing scheme were not substantially different from the Q2W dosing scheme, suggesting that a potentially occurring carry-over effect was not observed. As would be expected from the overall lower exposure, the mean time above 10% ADAMTS13 activity (>0.1 IU/ml) was considerably lower during SoC treatment compared to TAK-755 (1.7 vs 5.2 days) after a single dose. The mean duration above 10% ADAMTS13 activity was predicted to be longer at steady state (up to 9 days), suggesting the Q1W dosing scheme may not be necessary in a proportion of patients. Yet, the Q2W dosing scheme is also not entirely supported by PK data, as the duration above 10% ADAMTS13 activity is shorter than the longer bi-weekly dosing interval. The longer interval might however still be appropriate, as there is likely a delayed effect of accumulating large VWF multimers prolonging the effect after the intended ADAMTS13 activity dropped below 10%. Further, efficacy data support both dosing schemes. The recommended posology for prophylactic treatment is 40 IU/kg of body weight once every other week. In addition, section 4.2 of the SmPC states that the prophylaxis dosing frequency may be adjusted to 40 IU/kg of body weight once weekly based on clinical response.

The recommended posology in section 4.2 of the SmPC does not have age restriction. The applicant proposes the same prophylactic dose for all age groups, after accounting for bodyweight. There are limited data in children. The pop PK model did not include patients with a body weight <15 kg; the youngest patient included in the popPK dataset was 3 years old. Population PK data indicate that body weight-based dosing is considered appropriate, though with a trend for lower exposure for the younger children with a lower body weight. This is consistent with allometric scaling and body-weight based dosing. To support the dose and dose regimen from birth, the Applicant was asked to provide population PK estimates for children with a body weight of 10 kg, 10-20 kg, 20-40 kg, and >40 kg. This analysis showed that AUC and C_{ave} were indeed lower in the 10 kg group. It seems that the dose would cover for about 1 week (~6 days >10% ADAMTS13 activity) for the <10kg subjects compared to around 10 days for adults. Therefore, shorter dosing intervals may be considered more likely for infants <10kg. As no subgroups could be identified for which this would be beneficial (variability seen in the simulations), therefore section 4.2 of the SmPC specifically state that based on the results from population pharmacokinetics analysis, it might be more likely for infants < 10 kg body weight to require adjustment to dosing frequency from every other week to once weekly dosing.

PK-III aimed to assess if any time-dependent PK changes occur due to long-term exposure to TAK-755 SIN at the end of the third treatment period. Results from PK-III appear overall in a comparable range to results from PK-I, with differences in some parameters, in particular higher Cmax (also in continuation study 3002) and AUC. However, due to the very limited number of subjects included (n=5), the results of PK-III should be interpreted with caution. Available Ctrough levels suggest no accumulation as the majority of pre-dose levels were below the LLOQ.

The calculated total volume of distribution of TAK-755 is 6.40 L. Assuming the total blood volume of 5.15 L in a 68.7 kg subject, the conclusion that ADAMTS13 does not distribute into tissues cannot be made with certainty. However, published literature indicates that no substrates of ADAMTS13 other than VWF are known, for which ADAMTS13 has high affinity. Administration of supra pharmacologic doses in non-clinical studies did not result in any hematologic effects or microscopic changes in any bodily organ, with the exception of VWF cleavage. Thus, with the current data available, potential accumulation of TAK-755 is not likely and does not raise a safety concern.

Drug-drug interaction studies (as a perpetrator or as a victim) were not conducted as they were deemed not required for this therapeutic protein. As ADAMTS13 is an endogenous enzyme, no drug interactions are expected. There is currently no evidence that higher concentrations of ADAMTS13 activity pose a safety risk.

Upon request, the Applicant removed the potency correction from Sections 4.2 and 6.6 of the SmPC. Further, the Applicant clarified that actual potency of rADAMTS13 was used for the clinical dose calculation and administration across 3 studies (281101, 281102, and 3002) in the cTTP clinical development program. Moreover, the average ±% difference was <10% (very nominal) between actual and nominal potency across the lots used in these 3 clinical studies, and therefore the use of actual potency as opposed to nominal potency for clinical dose calculations is not expected to impact the clinical efficacy or safety of TAK-755 in patients with cTTP.

Two patients included in study 281102 received on demand treatment. Pharmacokinetic data on these patients were provided upon request and showed that the daily post infusion ADAMTS13 activity values were generally comparable to the observed PK from Study 281102.

PopPK

The applicant integrated data from available studies (Phase 1 study 281101 and 2 ongoing Phase 3 studies 281102 and 3002) in a population PK model, which included a total of 65 unique subjects with a total of 2462 samples. Limited data are available for paediatric patients <12 years of age (n=14), and no data are available for patients with renal or hepatic function impairment. The popPK model is based on ADAMTS13 activity PK parameters (rather than PK of ADAMTS13 antigen), which is considered appropriate, as *in vivo* ADAMTS13 activity is expected to better predict clinical efficacy. No data on healthy volunteers are available, as TAK-755 was only administered to patients with cTTP.

The overall applied methodology for model development, covariate selections and model validation are acceptable. The applicant developed a 2-compartment model with zero-order infusion, first order linear elimination from the central compartment. There was no statistically significant covariate effect of age, body weight and TAK-755 material (SIN vs ORT) on Cmax,ss, Cave,ss, and percentage of time of ADAMTS13 activity above 10%. As expected, SoC was found to be a significant covariate, with significantly lower Cmax,ss, Cave,ss, and percentage of time of ADAMTS13 activity above 10% compared to TAK-755. While Cmax,ss was not significantly impacted by the dosing interval (QW vs Q2W), Cave,ss and percentage of time above 10% ADAMTS13 activity was significantly higher on the QW dosing scheme, which is expected as Cave,ss is directly derived from the dosing interval (AUC over the dosing interval) and a weekly dosing leads to an overall higher exposure.

The model appears to capture the overall trend of the observed data. However, few subjects with exceptionally high observed concentrations (>4 IU/mL) are underpredicted in the individual as well as population predictions, suggesting that values that high are not captured by the model. Furthermore, it appears that the prediction tends to generally underestimate higher values above 1 IU/mL, especially for population predictions. However, these observations are not considered a concern per se, as there is currently no evidence that higher concentrations of ADAMTS13 activity pose a safety risk. This underestimation might however skew any estimates of potential accumulation. Respective analyses should be handled with care and take this into consideration.

Regarding the lower doses of 5 IU/mL and 20 IU/mL, the measured ADAMTS13 activity levels were overall low and predictions are of limited value. For the 40 IU/mL dose, while the median (50th percentile) fits well with the model-predicted median, the observed 5th and 95th percentiles are closer to the mean compared to the model-predicted percentiles, indicating a wider prediction range than the observed data from studies 281101 and 281102 would indicate. During PK-I of study 281102 much

wider 95% CI have been estimated for TAK-755 SIN compared to TAK-755 ORT. This is most likely due to the very limited number of data points are available for TAK-755 SIN.

Overall, the popPK model seems to capture the data rather well but has some limitations regarding the prediction of high values and it seems to have a wider prediction range as indicated by the observed data especially for later timepoints, which seems to be also reflected in wide CIs seen in the results of analysis regarding the covariate effects on different PK parameter. This might be at least partly due to lower sample sizes and might benefit from additional data in the future.

Special Populations

In the popPK model, gender and race did not have any impact on the PK of ADAMTS13 activity (see section 5.2 of the SmPC). Although a trend towards lower exposure with lower body weight and younger patients was observed, body weight or young age was not found to be a significant covariate. Body-weight adjusted dosing is therefore considered appropriate for all weight ranges, including younger patients. Since age and weight are correlated it has to be noted here that some concerns remain regarding the dosing in very light patients (10kg), however as stated above, specific recommendations are given in section 4.2 of the SmPC in this regard. ADAMTS13 activity-time profile of one subject >65 years of age included in the pivotal Phase 3 Study 281102 was above average, but not substantially different from other ADAMTS13 activity-time profiles. Baseline eGFR and bilirubin or age had no impact on ADAMTS13 activity. Therefore, no dose adjustment is considered necessary in patients with impaired renal or hepatic function. Overall, no dose adjustments or restrictions in certain patient groups are currently foreseen. The lack of data or limited data in certain special populations is reflected in the SmPC section 5.2.

Bioequivalence

Due to 2 different manufacturing sites employed for TAK-755 bulk drug substance (BDS) sources used in study 281102 (TAK-755 ORT and TAK-755 SIN), the objective of PK-II in study 281102 was to demonstrate that the ADAMTS13 exposures were comparable between TAK-755 ORT and TAK-755 SIN. The cross-over design during PK-II to assess biosimilarity between TAK-755 SIN vs TAK-755 ORT with IP to be administered 14 days apart is acceptable, as a period of approximately 5 x t1/2 ensures there is no carry-over effect. Although not pre-specified in the protocol, the results suggest biosimilarity between TAK-755 SIN and TAK-755 ORT from a clinical perspective, as the conventional acceptance range for bioequivalence (90% CI of geometric mean ratio between 80%-125% according to the Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) was met for all parameters, including Cmax and AUCinf for ADAMTS13 activity and antigen. Biosimilarity can also be concluded on the quality level (see Quality AR). Yet, in the predicted steady state of ADAMTS13 activity, exposure appears higher in TAK-755 SIN vs TAK-755 ORT, but this difference was deemed not clinically meaningful.

The PK parameters specified in Section 5.1 of the SmPC are derived from TAK-755 SIN during PK-II. This is considered appropriate, as these parameters are observed after extended treatment duration and TAK-755 SIN was mainly used during the later phase of the clinical programme.

Pharmacodynamics

TAK-755 contains a recombinant form of endogenous ADAMTS13, aiming to replace severe congenital ADAMTS13 deficiency in cTTP patients. TAK-755 is considered to act in the same way as the endogenous enzyme ADAMTS13 which is a VWF cleaving protease. It is thus expected to reduce or eliminate the spontaneous formation of VWF-platelet microthrombi and subsequently the occurrence of acute TTP events, subacute TTP events, and individual manifestations of TTP.

In clinical studies 281101 and 281102 plasma VWF:RCo and VWF:Ag (presented as VWF [%]) were analysed, and VWF structure analysis (multimer pattern and cleavage products) was conducted prior to and following a single infusion of TAK-755. The assessed PD markers are considered adequate to capture rADAMTS13-mediated effects, as VWF is the substrate of ADAMTS13. Therefore, the presence of cleaved VWF indicate ADAMTS13 activity and VWF:RCo levels reflect the function of VWF multimer's ability to bind platelet GP1b. However, measuring VWF parameters has limitations, as generally the reference range is wide and no cTTP-specific thresholds are defined. Furthermore, available assays for VWF multimer analysis are semi-quantitative and lack standardisation, hampering a reliable interpretation. Therefore, platelet aggregation tests would be of interest to assess a clinically more relevant downstream marker of VWF activity, and their use was also recommended during Scientific Advice (EMEA/H/SA/1646/1/2010/PA/III), but were finally not included in the clinical programme.

In study 281101, minor transient trends for decreasing large VWF multimers (including ultra-large multimers) and increasing levels of the intermediate form was observed over the first 24 hours post-dose in individual profiles at higher doses. However, no clear dose-dependent effect could be observed and ultra-large VWF multimers were observed in all subjects at most timepoints. Reassuringly, a dose-dependent effect regarding the proportion of subjects (n [%]) with detectable VWF cleavage products over time was observed, i.e. VWF cleavage products were observed over a longer period of time at higher dose levels. The results from study 281102 suggest that more subjects receiving TAK-755 showed detectable ADAMTS13 mediated VWF cleavage products, compared to SoC administration, but at later timepoints no difference between groups was apparent. This observation is in accordance with similarly low exposure between treatment groups after approx. 5.2 days (mean time above 10% ADAMTS13 activity for the TAK-755 group) after a single dose.

Based on findings in Phase I study, the Applicant selected a prophylactic dose of 40 IU/kg to be used in the Phase III study. Based on above PD (and PK findings) the selection of this dose can be supported.

Despite a transient decrease of VWF:RCo during study 281101, significant VWF:RCo modulation was not observed in study 281102 following TAK-755 and SoC treatment, plausibly due to these VWF measurements taken during stable disease state, according to the Applicant. This argument can be followed, but further highlights the limitations of the used PD markers. Reassuringly, the relative change of platelet counts over time suggests higher platelet counts in patients treated with TAK-755 during both treatment periods, confirming also results from the QSP model (see below). Upon request, the Applicant presented the absolute change data in platelets and LDH for both treatment periods separately and patient-level data for the on-demand cohort. Higher increase in platelet count was observed with Adzynma compared to SoC. Subsequently, a decrease in patient counts was observed in patients who switched from Adzynma to SoC in Period 2 and platelet count increased in patients who switched from SoC to Adzynma. LDH levels showed variable results, with overlapping values between Adzynma and SoC.

In the on-demand cohort, patients experienced fast increase in platelet count and decrease in LDH after start with Adzynma or SoC treatment, confirming the effectiveness of both therapies in the on-demand setting.

Taken together, the available PD results are supportive of ADAMTS13 functionality in the clinical setting. However, several aspects hamper a conclusive interpretation and the totality of data (pre-clinical, clinical efficacy), complemented with results from the QSP model, need to be supportive as well to allow a conclusion on the benefit of TAK-755.

E-R and especially QSP modelling, which are described in the following sections, are regarded reasonable approaches for attempting to gain supportive data and to refine the mechanistic understanding. However, as discussed during Scientific Advice (EMA/SA/0000087869), the modelling

approaches and related results are not considered high impact (key data to replace a comparative efficacy analysis).

E-R Models

Based on the popPK model, 3 E-R models were developed: count of isolated TTP events, Cox-proportional-hazards ER and RTTE.

In the primary E-R modelling for count of isolated TTP manifestations, derived endpoints were (a) isolated thrombocytopenia, (b) MAHA, (c) abdominal pain, (d) neurological symptoms, (e) renal dysfunction, (f) "Other" TTP manifestations, and (g) composite TTP manifestations endpoint. The analysed endpoints are considered appropriate.

The model was built to assess the relationship between Cave,ss (derived from the final popPK model) and count of the above endpoints. Upon request, results showing the relationship between time above 10% ADAMTS13 activity and count of TTP endpoints were presented as well. Exposure-response relationship of ADAMTS13 activity and TPP endpoint count shows a similar decline of events upon increasing exposure, irrespective of whether the model is based on Cave,ss or on time above 10%.

Diagnostic plots for the count of isolated TTP events model indicate that the predictions of observed frequency of events appear overall in line with the observed data. However, the data is skewed due to the overall low number of event counts, therefore the predictive value of the presented model is rather limited. This is a major limitation of all three presented E-R models. Furthermore, the additional and especially descriptive value between SOC and TAK-755 of the Cox-proportional-hazards ER and RTTE models is limited since the 95% intervals largely overlap. The provided diagnostic plots for these models allow only limited conclusion on the accuracy of the predictions due to the overall low event rates.

The applicant demonstrated that the effect of age was not statistically significant on the final E-R relationship and magnitude of this effect of age was not clinically meaningful. As stated in section 4.2 of the SmPC, no dose adjustment is required for elderly patients as well as for patients with renal or hepatic impairment. The median Cave,ss of ADAMTS13 activity of SoC, TAK-755 Q2W and Q1W regimens in subjects <12 years were associated with a 69.4%, 81.0%, and 87.9% probability of MAHA event free, respectively. The median C_{ave},ss of ADAMTS13 activity of the SoC, TAK-755 Q2W and Q1W regimens in subjects ≥12 years were associated with a 70.4%, 83.6%, and 91.6% probability of MAHA event free, respectively.

QSP Model

In addition to the popPK and E-R models, a QSP model was developed to mechanistically describe the PD interaction of ADAMTS13 activity with VWF and platelets to support low prevalence rates of TTP events. Data from literature, *in vitro* experiment, adamts13 KO mouse model and baseline human data of healthy volunteers and untreated cTTP patients were used to build this model. Data of TAK-755 treated patients with iTTP and cTTP from clinical studies were used to validate this model. This approach is overall acceptable. As different sources of data were used, uncertainty around certain parameters are to be expected. For example, the inclusion of TSP1 is solely based on literature data as this parameter was not evaluated in the pre-clinical program of the MAA. Sensitivity analyses were provided by the Applicant to study how the model parameters affect the platelet amounts in cTTP patients. Three parameters [fraction of VWF in stretched form (VS_Frac), dissociation constant between stretched VWF and platelets (Kd_VS_Platelet) and platelet synthesis rate (platelet_syn_human)] were identified to show the highest sensitivity, but the relevance of this finding remains unclear.

Due to the high level of noise in the data and empirical nature of the link between LDH and the species in the model, LDH was finally not included in the model. This is acceptable, as LDH is a rather unspecific marker as it can be influenced by a number of factors. In this context, it is noted that the predictive value of platelets as such may be questionable as levels may be influenced by factors other than ADAMTS13 activity as well.

The use of iTTP data for model validation is under the assumption that the dynamic interactions between active ADAMTS13, VWF, and platelets remain constant regardless of the mechanism of ADAMTS13 deficiency. The applicant is of the opinion that the outcomes or conclusions of the simulations would not be altered by this assumption, since the model was validated independently with cTTP patients treated with frozen plasma, cTTP patients treated with TAK-755, and iTTP patients treated with TAK-755. This cannot entirely be followed, since the model predictions did fit with observed values in only in a fraction of patients (both cTTP and iTTP). Reassuringly, the validity of the overall model is supported by the actual platelet counts, showing an increase in platelet count from baseline in subjects treated with TAK-755.

In conclusion, current E-R models are considered supportive, and it seems that exposures after a 40 IU/kg dose are all effective. On-demand treatment/ exposure are missing in these analyses.

2.6.4. Conclusions on clinical pharmacology

Overall, although the PK/PD data of TAK-755 in cTTP patients is limited, ADAMTS13 antigen and activity profiles, complemented by a popPK model, support body weight-adjusted dosing across age ranges. PD markers (VWF:Ag, VWF:RCo and VWF multimer patterns and cleavage products) and platelet counts, complemented by E-R and a quantitative systems pharmacology (QSP) model, indicate trends of beneficial effects after TAK-755 administration in cTTP patients.

The applicant evaluated a Q1W and a Q2W dosing regimen, and pharmacology data suggest that the risk of thrombocytopenia is lower with more frequent dosing, but in clinical studies the performance of both dosing regimens was appropriate. Due to the low incidence of clinical events, frequent dosing is not required in most patients, and could be adjusted based on the clinical response (see efficacy section). The ADAMTS13 activity and corresponding PD response for both dosing regimens is consistently higher than with standard of care. With regards to paediatric population, the following recommendation has been added in section 4.2 of the SmPC: based on the results from population pharmacokinetics analysis, it might be more likely for infants < 10 kg body weight to require adjustment to dosing frequency from every other week to once weekly dosing.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

281101 - A Phase 1, Prospective, Uncontrolled, Open-label, Multi-center, Dose-escalation Study Evaluating the Safety and Pharmacokinetics in Hereditary Thrombotic Thrombocytopenic Purpura (hTTP)

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%).

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 Objective

To assess health-related quality of life (HRQoL) and previous treatment experiences of participating subjects.

Assessment

The assessment of PK, PD, and safety outcomes is presented in the relevant sections of this AR.

2.6.5.2. Main study

TAK-755-281102 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])

Methods

- **Study Participants**

Main Inclusion Criteria

The main criteria for inclusion were subjects between 0 and 70 years of age, with documented diagnosis of severe hereditary ADAMTS13 deficiency, confirmed by genetic testing and ADAMTS13 activity < 10%, and not displaying any severe TTP signs (platelet count <100,000/µL and elevation of LDH >2×ULN) at screening if entering the Prophylactic Cohort, but experiencing an acute TTP event if entering the On demand Cohort. Subjects ≥ 18 years of age were to have a Karnofsky score ≥ 70%, and < 18 years of age have a Lansky score≥ 80%. Female subjects of childbearing potential were to have a negative serum pregnancy test and were to comply with the contraception requirements as specified in the study protocol.

Main Exclusion Criteria

The main criteria for exclusion were subjects diagnosed with any other TTP-like disorder (for e.g., microangiopathic haemolytic anaemia), including acquired TTP. Subjects having a medical history or presence of functional neutralising ADAMTS13 inhibitor at screening, or a medical history of immunological disorders, autoimmune disorders, or significant neurological events were also excluded.

Subjects were also excluded from study participation if they tested positive for human immunodeficiency virus (HIV), or were diagnosed with a cardiovascular disease, or severe liver

disease, or end-stage renal disease requiring dialysis, or were chronically treated with immunomodulatory drugs.

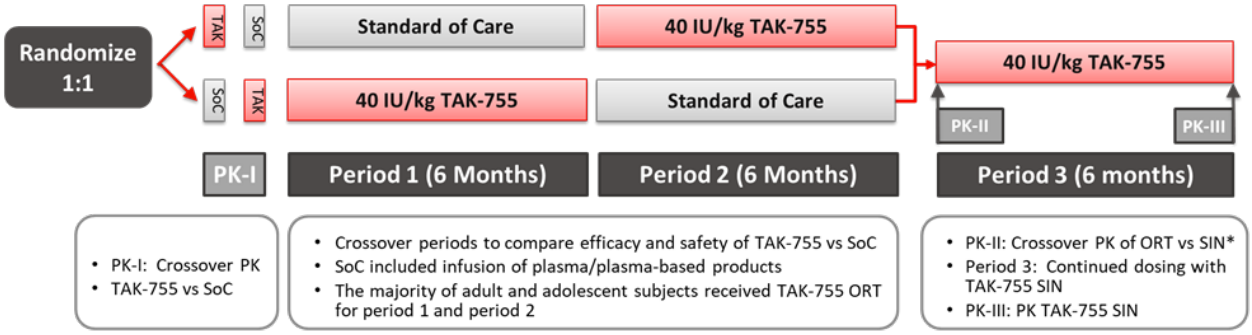
- **Treatments**

Prophylactic Treatments Administered

The prophylactic treatment of cTTP included 3 periods; each period was 6 months in duration. Subjects were randomized to receive either TAK-755 or their SoC in Period 1 and then crossed-over to the alternate treatment in Period 2. All subjects received TAK-755 in Period 3.

During the study the TAK-755 active pharmaceutical ingredient manufacturing process was transferred from Orth, Austria (product: TAK-755-ORT) to Singapore (product: TAK-755-SIN). Subjects screened prior to 01 Oct 2021 initiated the study with the TAK-755 ORT for periods 1 or 2. These subjects were to have a planned assessment of PK comparability (PK-II) between TAK-755 ORT and TAK-755 SIN, before initiating Period 3 with TAK-755 SIN. Subjects screened on or after 01 Oct 2021 were to receive only TAK-755 SIN.

Figure 31: A Study 281102 Design of the Prophylactic cohort



SoC=standard of care; PK=pharmacokinetic
*TAK-755 SIN refers to drug substance from the Takeda Singapore facility and TAK-755 ORT refers to drug substance from the Takeda Orth (Austria) facility.

TAK-755 Prophylactic Treatment Regimen

Subjects were to receive 40 IU/kg [±4 IU/kg] TAK-755 administered by IV infusion at a slow infusion rate between 2.0 mL to 4.0 mL per minute. A subject's SoC treatment prior to study enrolment determined whether they received TAK-755 once weekly (Q1W) or every 2 weeks (Q2W). Subjects who had their SoC Q1W were to start TAK-755 treatment at a dose of 40 IU/kg [±4 IU/kg] administered Q1W. All other subjects were to receive a starting prophylaxis dose of 40 IU/kg [±4 IU/kg] administered Q2W (including those who had received their SoC at alternative dosing frequencies).

Adjustments to the dosing frequency (ie, a change from Q2W to Q1W) were permitted based on clinical events and/or laboratory results.

Standard of Care Prophylactic Treatment Regimen

The SoC dose and treatment regimen was to be determined by the investigator for each subject and was to be defined by the subject's treatment product and dosing regimen at the time of entry into the study. Investigator-recommended standard treatment was to contain ADAMTS13 as a measurable and quantifiable administered dose and comprised all of the plasma-based therapeutic options currently used in clinical practice. The SoC treatment type and dose was to be recorded in the electronic case report forms (eCRFs) and could be any of the following:

- FFP

- Pooled S/D treated plasma
- FVIII:VWF concentrates

All treatments were in liquid form and administered intravenously. The dosing frequency was to be determined by the investigator and SoC treatment at intervals of Q2W or Q1W, while once every 3 weeks (Q3W) was accepted but not encouraged. Adjustments to the dosing frequency were permitted based on clinical events and/or laboratory results.

Adjustments to the Prophylactic Treatment Regimen

Dose modifications to the TAK-755 dosing frequency, or SoC treatment type, dose volume, or frequency, were recommended if any of the following conditions were met:

- One acute TTP event

☐ Two separate occurrences of laboratory deviations:

- Drop in platelet count of ≥25% of baseline or a platelet count <150,000/μL, OR

- Elevation of LDH >1.5× of baseline or >1.5×ULN

☐ Three separate occurrences of organ-specific signs or symptoms, with or without changes in platelet count or LDH

- Neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR

- Abdominal pain; OR

- An increase of serum creatinine >1.5×baseline

Acute and Subacute TTP Event Treatment for the Prophylactic Cohort

☐ Subjects experiencing an acute TTP event during the prophylaxis period were to receive the following dose and dosing regimen:

- TAK-755 Prophylactic Subjects:
    - ◦ Subjects were to receive an initial dose of 40 IU/kg [±4 IU/kg] TAK-755
    - ◦ Subjects were to receive a subsequent dose of 20 IU/kg [±2 IU/kg] TAK-755 on Day 2
    - ◦ Subjects were to receive an additional daily dose of 15 IU/kg [±1.5 IU/kg] TAK-755 until 2 days after the acute TTP event was resolved (acute TTP event resolution defined as platelet count ≥150,000/μL or platelet count within 25% of baseline OR elevation of LDH ≤1.5× baseline or ≤1.5×ULN)
    - ◦ Subjects were to continue prophylactic therapy 1 week after their last acute treatment dose
- SoC Prophylactic Subjects:
    - ◦ Subjects experiencing an acute TTP event during the prophylaxis period were to receive the investigator-recommended standard treatment and dosing regimen during the acute TTP event
    - ◦ Subjects were to continue prophylaxis therapy 1 week after their last acute treatment dose

☐ Additionally, investigators were able to elect to treat a subacute TTP event with 1 or 2 additional daily doses of SoC/TAK-755.

At Home Infusions for Prophylactic Treatment

During prophylactic treatment, and if deemed necessary and acceptable by the investigator, subjects were to be given the option to have their randomized treatment infused by a healthcare provider at home (only available for subjects receiving either TAK-755 or FVIII SoC, as suitable for home administration).

Regimen for On-Demand Treatment of Acute Events

Eligible subjects entering the OD treatment cohort were to be randomized 1:1 to receive either TAK-755 or their current SoC.

After completing the OD treatment, subjects had the choice to complete the study or to enter the Prophylactic Cohort. If they elected to enter the Prophylactic Cohort, they were to receive the same treatment in Period 1 as they received as their randomized OD treatment (and were then to receive the alternate treatment in Period 2). Subjects were permitted to re-enter the OD cohort if experiencing another acute TTP event.

TAK-755 On-Demand Treatment Regimen

For the OD treatment cohort, subjects were to receive 40 IU/kg TAK-755 on Day 1, 20 IU/kg on Day 2, followed by 15 IU/kg on Day 3 and daily thereafter until 2 days after the acute TTP event was resolved.

Standard of Care On-Demand Treatment Regimen

The SoC regimen was to be determined by the investigator for each subject and was to be defined by the subject's treatment product and dosing regimen at the time of entry into the study. SoC was to be either FFP, pooled S/D treated plasma, or FVIII:VWF concentrates. Investigator recommended SoC treatment was to contain ADAMTS13 as a measurable and quantifiable administered dose. The SoC treatments were in liquid form and administered intravenously.

- **Objectives**

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

Secondary and exploratory objectives covered a large range of investigations concerning sub-acute TTP events, more granular isolated TTP manifestations, success in treating TTP events, safety, tolerability, immunogenicity, PK- and PD-response, Health Related Quality of Life and Resource Utilisation.

- **Outcomes/endpoints**

Primary Efficacy Outcome Measure

The incidence of acute TTP events (see Table 19 for event definitions) among subjects receiving either TAK-755 or SoC prophylactically during the corresponding treatment periods.

Secondary Efficacy Outcome Measures

1. Proportion of acute TTP events responding to TAK-755, defined as not requiring the use of another ADAMTS13-containing agent
2. Time to resolution of acute TTP events following initiation of treatment with TAK-755 or SoC agent
3. Incidence of thrombocytopenia defined as a drop in platelet count ≥25% of baseline or a platelet count <150,000/μL
4. Incidence of MAHA defined as an elevation of LDH >1.5× of baseline or >1.5×ULN
5. Incidence of neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures)
6. Incidence of renal dysfunction defined as an increase in serum creatinine >1.5×baseline
7. Incidence of abdominal pain
8. Incidence of supplemental doses prompted by subacute TTP events (see Table above for event definitions)
9. Incidence of dose modification not prompted by an acute TTP event
10. Incidence of acute TTP events while subjects are on their final dose and dosing regimen in the study

Exploratory Outcome Measures

1. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7, Section 9.5.1.2), while receiving prophylactic treatment with TAK-755 or SoC during the 6 months of the corresponding treatment

2. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), while receiving the final prophylactic treatment regimen with TAK-755 or SoC

3. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), requiring supplemental dose treatment

4. Incidence of the subacute TTP events in subjects receiving prophylactic treatment.

[a] Composite of the secondary outcome measure is defined as the occurrence of at least one of the secondary outcome measures 3 to 7

Table 22: 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

LDH=lactate dehydrogenase; TTP=thrombotic thrombocytopenic purpura; ULN=upper limit of normal.

[a] In this instance, a laboratory measure refers to platelet counts or an LDH measurement.

• Patient reported outcomes: SF-36v2, EQ-5D, PedsQL, TSQM-9, cTTP Patient Experience Questionnaire.

• Healthcare Resource Utilization Analyses

- **Sample size**

The sample size for this study was not selected as a result of a power calculation, in particular due to the fact that the primary outcome measure was not planned to be assessed by a formal significance test. Approximately 42 adult (≥18 years old) subjects and 15 adolescent (>12-≤17 years old) or paediatric (<12 years old) subjects were to be enrolled in this study, including approximately 36 adult subjects and 12 adolescent or paediatric subjects starting in the prophylaxis cohort, and approximately 6 adult subjects and 3 adolescent or paediatric subjects, in the on-demand cohort.

- **Randomisation and Blinding (masking)**

This study was planned and carried out as randomized, open-label, active-controlled clinical study. Subjects in the prophylaxis cohort were to be randomized equally using a permuted block algorithm to randomly assign treatment order (BAX 930 – SoC or SoC – BAX 930). Subjects in the on-demand cohort were to be randomized equally using a permuted block algorithm to either BAX 930 or SoC.

After the Period 2, subjects in the prophylaxis cohort who undergo PK-II assessment, were to be randomized to the infusion sequence for PK-II (BAX 930 ORT followed by BAX 930 SIN, or BAX 930 SIN followed by BAX 930 ORT) in a 1:1 ratio stratifying for the sequence for PK-I. Subjects in each sequence at PK-1 were to be randomized evenly between the two sequences: ORT-SIN, SIN-ORT.

- **Statistical methods**

Analyses of the primary endpoint was to be based on the modified full analysis set (MFAS). This set was to include 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 they were instead treated on SoC because TAK-755 was not available, the subjects were to be excluded from MFAS.

- For subjects enrolled prior to the study hold in November 2017, if SoC was the randomized treatment for Period 1 and 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 to be used in the MFAS-based efficacy analysis. The period over which the endpoint was to be 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 to be included in the MFAS-based efficacy analyses.

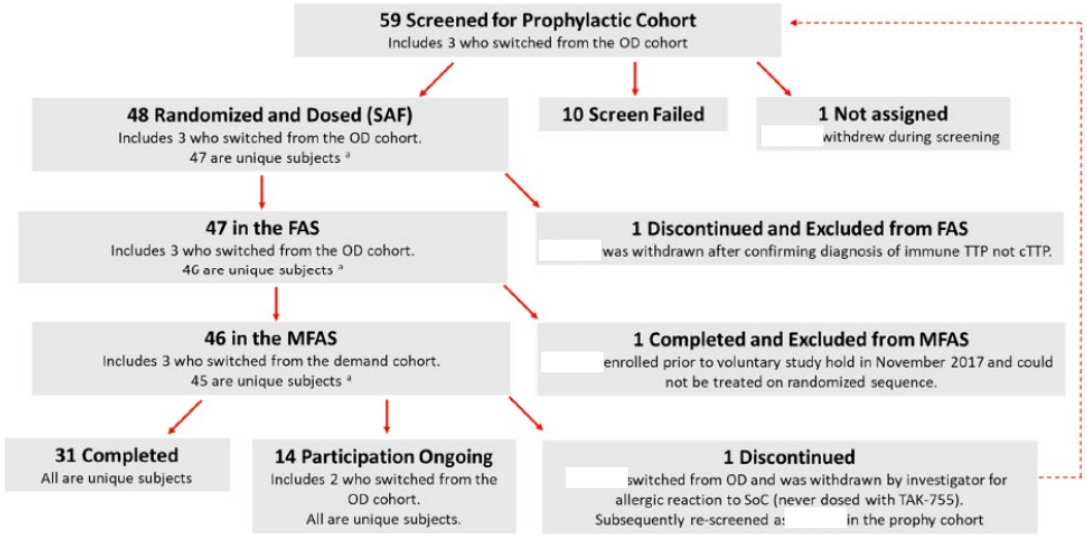
The number of acute TTP events per subject overall and by treatment and period was to be determined as the count of acute TTP events a subject had overall on the study. The annualised acute TTP event rate was to be derived according to detailed descriptions in the SAP.

Sensitivity analysis were performed over the FAS, the Per-Protocol Analysis Set (PPAS) and Safety Analysis set (SAF), if different. Within-subject difference of the annualized acute TTP event rates between the 2 study treatments SoC and TAK-755 were to be summarised for all subjects and the adolescent and adult subjects (≥12 years).

Analysis of secondary and other efficacy endpoints were to be conducted over the FAS with sensitivity analyses performed over the SAF, MFAS, and PPAS. For the analyses of incidences of subacute TTP events and TTP manifestations similar analyses and summaries were to be performed as described for acute TTP events. For the separate analyses of incidences of thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurologic symptoms, abdominal pain, and other TTP manifestations also similar analyses and summaries were to be performed as described for acute TTP events.

Results

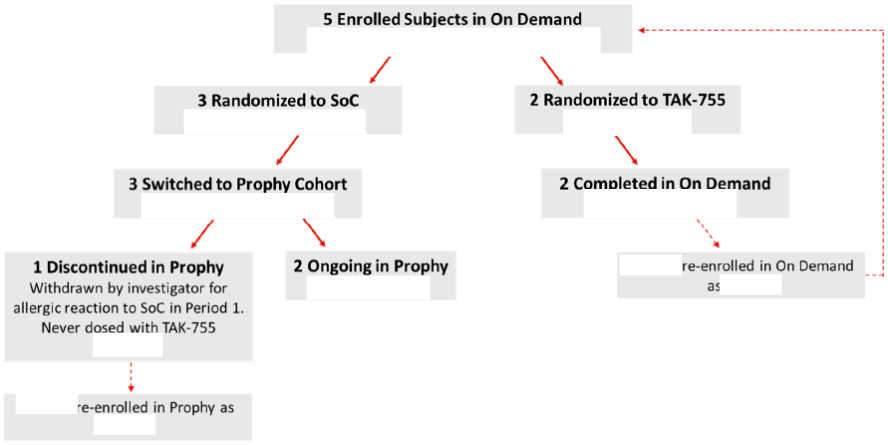
- **Participant flow**



FAS=full analysis set; MFAS=modified full analysis set; OD=on-demand; prophy=prophylactic; SAF=safety analysis set; SoC=standard of care

[a] is 1 person who enrolled in the study twice.

Figure 32: By subject disposition for the prophylactic cohort – all subjects enrolled set



Prophy=prophylactic; SoC=standard of care

Subjects are the same person who enrolled twice.

Figure 33: By subject disposition for the on-demand cohort -all subjects enrolled set

- **Recruitment**

Studied Period: This interim study report presents an interim analysis for subjects enrolled from 13 Oct 2017 (first subject enrolled) to 12 Aug 2022, the date of the interim data cutoff. Subjects were enrolled by 34 study sites in Austria, France, Germany, Italy, Japan, Poland, Spain, UK, and US.

- **Conduct of the study**

Protocol Amendments

The original global protocol was amended 7 times. Where required, local (country-specific) amendments were implemented (8 local amendments), for a total of 15 amendments. Protocol amendments are summarised in the table below.

The original protocol version dated 13 Feb 2017 was submitted to global regulatory authorities as part of meetings for Clinical Protocol Assistance and Scientific Advice; Amendment 2 was the first protocol version formally submitted to Competent Authorities under a clinical trial application; Amendment 3 was the active protocol when the first subject was screened on 13 Oct 2017. Thus, there were 5 global amendments over the study active recruitment period.

The primary reasons for global amendments were: the discovery of a protein variant of TAK-755 from emerging data (this resulted in a voluntary study halt from November 2017 until July 2019, the period in which this issue was investigated); transfer of the manufacturing site (which required addition of a PK comparability component to be added to the study) and changes to the sponsor (from Baxalta US Inc. to Shire Plc. to Takeda Development Center Americas, Inc.).

Changes to Study Procedures Due to COVID-19 Pandemic

The following information summarises changes to study procedures that were implemented for study subjects or study sites affected by the COVID-19 pandemic. This was aligned with the US FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators, and IRBs, March 2020, updated 27 January 2021; the EMA Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 4 (04 February 2021); and the EMA Points to consider on implications of COVID-19 on methodological aspects of ongoing clinical trials, dated 26 June 2020.

Because a pandemic (eg, COVID-19) may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes were to be made on a case-by-case basis by the PI in consultation with the study team and the medical team as needed, while maintaining subject safety and confidentiality as the priority.

Procedural changes due to COVID-19 included the following:

- Activation of new study sites and the enrollment of new subjects into the Prophylactic Cohort were put on hold for a minimum of approximately 3 weeks beginning on approximately 02 Apr 2020. The enrollment hold was lifted on a site-by-site basis after it was determined that local regulations and/or site restrictions would no longer inhibit subject participation in the study and that adequate precautions were in place to limit a potential subjects' exposure to COVID-19. Sites were provided a questionnaire and once returned to Takeda and reviewed by the study team, a decision was made on whether the site could re-open. Enrollment into the OD Cohort remained open.
- Subjects that were in screening for the Prophylactic Cohort at the time the enrollment pause went into effect would be allowed to be enrolled into the study after the enrollment pause was lifted. All the screening tests were to be repeated once the protocol-specified screening period elapsed.

- Throughout the pandemic, different monitoring approaches were implemented as documented in the Clinical Operations Plan. Remote site initiation visits and remote interim monitoring visits were implemented. In addition, remote data verification, audio data verification, remote source data monitoring, and remote source data verification were all implemented as country-specific restrictions allowed.
- If central laboratory samples could not be collected due to site restrictions, the sites were advised to collect laboratory samples instead and report a protocol deviation accordingly.

Protocol Violations/Deviations

There was one critical protocol deviation in the study (one subject). This deviation was reported as critical because the site administered expired IP to the subject (one batch expired 31 May 2022 and was administered to the subject on 01 June 2022). There were no safety concerns reported due to this administration, and after this occurred, expiration of this IP lot was extended based on updated stability data.

One deviation in exclusion criteria was for one who was incorrectly diagnosed with cTTP and terminated early from the study when it was determined that the subject had immune-mediated TTP (iTTP).

One protocol schedule deviation was for another subject who moved from the OD Cohort to the Prophylactic Cohort without having a confirmed acute event.

The most common major protocol deviations in the study were related to Protocol Schedule and included deviations from the lab assessment schedule, dosing schedule, protocol visit schedule, and study procedure schedule, occurring in a majority of subjects for both cohorts.

Due to the long-term study duration and the number of study visits (occurring every other week or weekly) required for each subject, combined with study conduct during the global COVID-19 pandemic and the low threshold for categorising a deviation as 'major' (e.g., instance of a single missed visit), it is not unexpected for the majority of the subjects to have had at least 1 major protocol deviation.

<u>COVID-19–Related Protocol Deviations</u>

Changes to study procedures due to the COVID-19 pandemic were instituted to maintain subject safety and preserve study integrity, as described in Section 9.8.2. Protocol deviations that were deemed related to the COVID-19 pandemic were indicated as such in the protocol deviation review. The most common category of protocol deviations deemed related to COVID-19 was Protocol Schedule (Listing 16.2.2.1). Within this category, the following protocol deviations occurred most often:

☐ All or some of the central labs not being collected during local COVID restrictions. Local labs were collected in lieu of central labs during this time period to ensure that critical safety and efficacy data required for evaluation of subject safety and the study endpoints were collected.

☐ Missing study visits due to COVID-19 restrictions at the site (mainly for Subject at Sitein the). While Subject did not receive IP during clinical visits due to COVID-19 restrictions, this subject received SoC infusions of the FVIII product at home during this time (from), although some study assessments, including laboratory assessments, were not collected. There were no subject discontinuations from the study as a result of COVID-19-related deviations.

These changes were deemed necessary and adequate to monitor subject safety over the course of the study. Following an assessment by the sponsor, neither the number nor the type of deviations related

to the COVID-19 pandemic were judged to have had an impact on the overall analysis of data in this study or the study conclusions.

Study sites non-compliance

All study sites were reported to be in GCP compliance with the exception of the following where non-compliance events (NCE) were identified:

Site

- One NCE was identified on 28 Feb 2023 for Study 281102: 2 subjects are affected; data from these two subjects are part of the MAA. For these two subjects, timing of assessments for select physical examinations, vital signs, pregnancy tests, blood sample collection and study drug infusions were retrospectively recorded in the source data by the Study Coordinator (SC). The SC confirmed that the timepoints were estimated based on when these activities were performed within the clinic. CAPAs are being implemented and these NCE were reported to the relevant Competent Authority: PEI.
- Impact assessment: As the actual timestamps for the above-mentioned assessments are not used for any data analysis, there is no data integrity or scientific value impact from this NCE.

Site

- Two NCE were identified on 13 Mar 2023 for continuation Study 3002: NCE (1) 4 subjects and NCE (2) 10 subjects are affected; data from all of these subjects are not part of the MAA; that is, the data from these subjects are not part of the Clinical Study Report comprising the MAA, however the study is ongoing and thus being reported here for completeness. NCE (1): There was lack of safety follow-up telehealth visits/calls for four subjects on Self/Caregiver-Infusion. NCE (2): Delayed reconsenting for ten subjects. Of note, these findings occurred after the August 2022 interim analysis. CAPAs are being implemented and these NCE were reported as a potential serious breach to the relevant Competent Authority: MHRA.
- Impact assessment: Paper diaries were used by the site to follow-up subjects on Self/Caregiver-infusion as opposed to telehealth visits per protocol, which is considered a potential risk to subject safety and the delayed reconsenting is considered a potential risk to subjects' rights. There is no impact to data integrity and scientific value of the study. As Site was also the highest enrolling site, sensitivity analyses of efficacy and safety results with and without Site were conducted and presented.

- **Baseline data**

Table 23: Demographics by Treatment Cohort — Safety Analysis Set

Characteristics	Total Prophylactic Cohort[a]			On-Demand Cohort[b]		
	TAK-755 – SoC[c]	SoC - TAK-755[d]	Total	TAK-755	SoC	Total
Age (years)[e]						
n	21	27	48	2	3	5
Mean (SD)	33.5 (16.51)	29.1 (16.89)	31.0 (16.69)	NC	28.3 (8.02)	25.0 (7.28)

Median	42.0	27.0	32.5	NC	29.0	20.0
Min, Max	3, 54	5, 68	3, 68			20, 36
Age Group [n (%)]						
≥18 years	16 (76.2)	20 (74.1)	36 (75.0)	2 (100)	3 (100)	5 (100)
12 to <18 years	1 (4.8)	3 (11.1)	4 (8.3)	0	0	0
6 to <12 years	1 (4.8)	3 (11.1)	4 (8.3)	0	0	0
<6 years	3 (14.3)	1 (3.7)	4 (8.3)	0	0	0
Sex [n (%)]						
Male	9 (42.9)	11 (40.7)	20 (41.7)	1 (50.0)	2 (66.7)	3 (60.0)
Female	12 (57.1)	16 (59.3)	28 (58.3)	1 (50.0)	1 (33.3)	2 (40.0)
Childbearing Potential[f] [n %)]	9 (75.0)	12 (75.0)	21 (75.0)	1 (100)	0	1 (50.0)
Ethnicity [n (%)]						
Hispanic or Latino	1 (4.8)	0	1 (2.1)	0	0	0
Not Hispanic or Latino	16 (76.2)	23 (85.2)	39 (81.3)	2 (100)	3 (100)	5 (100)
Not Reported	4 (19.0)	4 (14.8)	8 (16.7)	0	0	0
Race[g] [n (%)]						
Asian	2 (9.5)	3 (11.1)	5 (10.4)	1 (50.0)	0	1 (20.0)
Black or African American	0	1 (3.7)	1 (2.1)	0	0	0
White	15 (71.4)	17 (63.0)	32 (66.7)	1 (50.0)	2 (66.7)	3 (60.0)
Multiple	0	1 (3.7)	1 (2.1)	0	1 (33.3)	1 (20.0)
Not Reported	4 (19.0)	5 (18.5)	9 (18.8)	0	0	0
Height (cm)						
n	21	27	48	2	3	5
Mean (SD)	159.62 (24.283)	162.92 (16.435)	161.48 (20.077)	NC	175.33 (13.317)	167.80 (14.940)
Weight (kg)						
n	21	27	48	2	3	5
Mean (SD)	68.30 (25.969)	65.06 (17.865)	66.48 (21.591)	NC	67.87 (5.445)	63.08 (9.960)
BMI (kg/m^2)						
n	21	27	48	2	3	5
Mean (SD)	25.46 (5.823)	24.09 (4.726)	24.69 (5.221)	NC	22.18 (2.104)	22.36 (1.861)

eCRF=electronic case report form; Max=maximum; Min=minimum; NC=not calculated; OD=on-demand; SD=standard deviation; SoC=standard of care
One subject in the safety analysis set (Subject #) had randomized treatment sequence TAK-755 - SoC but actual treatment sequence SoC - TAK-755.
Percentages are based on all subjects in the Safety Analysis Set within each column.
Two rescreened subjects passed screening and entered the study more than once (Subject #and Subject #). For each subject, all data collected are included into the analysis.

[a] Total Prophylactic Cohort includes the subjects who were originally enrolled in the Prophylactic Cohort and the subjects who moved to the Prophylactic Cohort from the OD Cohort.

[b] OD Cohort includes the subjects who enrolled in the OD Cohort.

[c] Subjects in TAK-755 - SoC took TAK-755 in Period 1 and SoC in Period 2.

[d] Subjects in SoC - TAK-755 took SoC in Period 1 and TAK-755 in Period 2.

[e] Age was obtained from the eCRF.

[f] Percentage of female subjects.

[g] s as race question is not permitted.

- **Numbers analysed**

All subjects that were randomized to treatment (RND) received at least 1 dose of study treatment (either TAK-755 or SoC) and were included in the SAF (Table 24). Descriptions of all other analysis populations are defined per the footnotes in Table 24.

Table 24: Analysis Sets

Analysis Set	Total Prophylactic Cohort[a]			On-Demand Cohort[b]		
	TAK-755 – SoC[c] n (%)	SoC - TAK-755[d] n (%)	Total n (%)	TAK-755 n (%)	SoC n (%)	Total n (%)
All Subjects Enrolled Set[e]	NA	NA	59	NA	NA	5
Randomized Analysis Set[f]	22	26	48	2	3	5
Safety Analysis Set[g]	22 (100)	26 (100)	48 (100)	2 (100)	3 (100)	5 (100)
Full Analysis Set[h]	22 (100)	25 (96.2)	47 (97.9)	2 (100)	3 (100)	5 (100)
Modified Full Analysis Set[i]	21 (95.5)	25 (96.2)	46 (95.8)	2 (100)	3 (100)	5 (100)
Per Protocol Analysis Set[j]	20 (90.9)	22 (84.6)	42 (87.5)	2 (100)	2 (66.7)	4 (80.0)
Pharmacokinetic Full Analysis Set[k]	22 (100)	25 (96.2)	47 (97.9)	2 (100)	3 (100)	5 (100)
Pharmacodynamics Analysis Set[l]	22 (100)	24 (92.3)	46 (95.8)	0	2 (66.7)	2 (40.0)

cTTP=congenital thrombotic thrombocytopenic purpura; ENR=all subjects enrolled set; FAS=full analysis set; IP=investigational product; MFAS=modified full analysis set; n=number of subjects; NA=not applicable; OD=on-demand; PD=pharmacodynamic; PDAS=pharmacodynamic analysis set; PK=Pharmacokinetic; PKFAS=pharmacokinetic full analysis set; PPAS=per-protocol analysis set; RND=randomized analysis set; SAF=safety analysis set; SoC=standard of care

Percentages are based on all subjects that were randomized within each column except otherwise specified. Subjects are presented according to the treatment group they were randomized to for Period 1.

[a] Total Prophylactic Cohort includes the subjects who were originally enrolled in the Prophylactic Cohort and the subjects who moved to the Prophylactic Cohort from the OD Cohort.

[b] OD Cohort includes the subjects who enrolled in the OD Cohort.

[c] Subjects in TAK-755 - SoC were randomized to take TAK-755 in Period 1 and SoC in Period 2.

[d] Subjects in SoC - TAK-755 are randomized to take SoC in Period 1 and TAK-755 in Period 2.

[e] The ENR includes all subjects that signed informed consent. Subjects that enrolled but were not randomized are included in the Prophylactic Total column.

[f] The RND includes all subjects that were randomized into 1 of the treatment sequences for the Prophylactic Cohort or one of the treatment arms for the OD Cohort.

[g] The SAF includes all subjects treated with at least 1 dose of TAK-755 or SoC treatment after randomization. One subject in the safety analysis set (Subject #) was randomized to treatment sequence TAK-755 - SoC but the actual treatment sequence was SoC - TAK-755.

[h] The FAS includes all subjects with a confirmed cTTP diagnosis receiving at least 1 dose of TAK-755 or SoC treatment after randomization. Subject was excluded from the FAS.

[i] The MFAS includes all subjects from FAS with the following modifications:

- For subjects enrolled prior to November 2017, if TAK-755 was the randomized treatment for Period 1 and they were instead treated with SoC because TAK-755 was not available, the subjects were excluded from MFAS.
- For subjects enrolled prior to November 2017, if SoC was the randomized treatment for Period 1 and they were treated with SoC beyond the 6-month period specified in the protocol because TAK-755 was not available, only the primary efficacy data for Period 1 collected prior to the Month 6 visit were used in the MFAS-based primary efficacy analysis.
- Subjects and were excluded from the MFAS.

[j] The PPAS includes all subjects in the MFAS who had no major deviations from the protocol affecting the efficacy outcome or treatment of the subject. Subjects, and from the Prophylactic Cohort and Subject from the OD Cohort were excluded (described below).

[k] The PKFAS includes all subjects in the FAS who received at least 1 dose of IP and provided adequate postdose PK measurements at a scheduled PK timepoint for at least 1 of the PK analytes without major protocol deviations or may have affected the integrity of the PK data. Subjectwas excluded from the PKFAS.

[l]The PDAS includes all subjects in the FAS who received at least 1 dose of IP andand provided at least 1 valid data point post dose of the respective infusion for at least 1 PD measurement for any of the PD outcome measures and had no major protocol deviations or events that may have affected the integrity of the PD data. Subject from the Prophylactic Cohort and Subjects from the OD Cohort were excluded from the PDAS.

- **Outcomes and estimation**

Primary Efficacy Endpoint

The primary efficacy outcome measure was the incidence of acute TTP events among subjects receiving either TAK-755 or SoC prophylactically during the corresponding treatment periods.

The primary endpoint analyses for the IA are presented for adult and adolescent subjects (aged ≥12 years) based on the MFAS. Sensitivity analyses for the primary endpoint were performed over the FAS, PPAS, and SAF with the iTTP confirmed subject excluded (one subject).

No acute TTP events occurred in 37 adult or adolescent subjects while receiving TAK-755 prophylaxis during the cross-over treatment period and throughout the duration of the study including in 35 subjects in Period 3 (Table 25) at the time of IA data cutoff. The longest duration of TAK-755 exposure was 22.6 months. As this trial is ongoing, all subjects remaining in the trial, including the fully enrolled paediatric age cohorts, will be closely monitored and their duration of exposure will continue to increase.

One acute TTP event occurred in 1 adult subject while receiving SoC (FFP) prophylactically during the cross-over treatment Period 1. The event was confirmed to be an acute event by laboratory abnormalities (investigator reported as due to a viral infection) including a decrease in platelets to 104×10^9/L that was a ≥50% drop from the baseline of 239×10^9/L, and LDH 454 U/L that was a >2-fold elevation from the baseline of 188 U/L.

Table 25: Summary of Acute TT Study Period in the Prophylactic Cohort -MFAS (Age ≥12 Years)

Parameter Statistic	SoC	TAK-755	
	Period 1 and 2 (N=38)	Period 1 and 2 (N=37)	Period 3 (N=35)
Number of subjects with acute TTP event	1	0	0
Number of acute TTP events	1	0	0
Annualized acute TTP event rate[a]			
Mean (SD)	0.05 (0.280)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00
Min, Max	0.0,1.7	0.0,0.0	0.0,0.0

Duration of observation period (years)[b]			
Mean (SD)	0.54 (0.113)	0.53 (0.106)	0.58 (0.219)
Median	0.54	0.55	0.54
Min, Max	0.1,1.0	0.0,0.6	0.0,1.3
Q1, Q3	0.50,0.58	0.50,0.58	0.46,0.63

Max=maximum; MFAS=modified full analysis set; Min=minimum; N=total number of subjects per treatment arm and period in the MFAS; Q=quartile; SD=standard deviation; SoC=standard of care; TTP=thrombotic thrombocytopenic purpura
Data from Periods 1, 2 and 3 are used for subjects in the Prophylactic Cohort and those who switched from On-Demand to Prophylactic Cohort.
A unique subject~~)~~ passed screening and entered the study more than once and is included in the MFAS as 2 study subjects.

Because of the sparse number of events, only descriptive statistics on acute event rates are reported. The mean annualised 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 cross-over periods and Period 3.

There were no acute events in paediatric subjects (albeit with a more limited study duration), thus similar results were observed in the all-age group analysis. All sensitivity analyses showed similar results in FAS, PPAS, and SAF.

Exploratory endpoint

Subacute TTP Events During the Prophylactic Treatment Period

During crossover treatment Periods 1 and 2, 4 subjects had 5 subacute TTP events while taking SoC prophylactic treatment (all during Period 1); 1 of these subacute events was also classified as an SAE because of hospitalization. No subject had a subacute event while on TAK-755 prophylactic treatment in Periods 1 and 2. Then, in Period 3, 2 subjects had 1 subacute event each while taking TAK-755 prophylactic treatment; 1 of these subacute events was also classified as an SAE because of hospitalization. Both of the subacute TTP events that were classified as SAEs occurred in the context of an infection (COVID-19 for the subject on TAK 755 and a gastrointestinal infection for the subject on SoC).

Table 26: Study 281102 Prophylactic Cohort Subacute TTP Events (MFAS)

Demographic Group Parameter	SoC	TAK-755	
	Periods 1 and 2 Combined	Periods 1 and 2 Combined	Period 3
Adolescents and Adults (≥12 years)			
Number of Subjects	38[a]	37	35
Subjects with Event, n (%)	4 (10.5)	0	2 (5.7)
Number of Events	5	0	2
Non-model Based Annualized Event Rate, Mean (SD)	0.25 (0.778)	0	0.07 (0.291)
All Subjects			
Number of Subjects	42[a]	43	35
Subjects with Event, n (%)	4 (9.5)	0	2 (5.7)
Number of Events	5	0	2
Non-model Based Annualized Event Rate, Mean (SD)	0.23 (0.743)	0	0.07 (0.291)

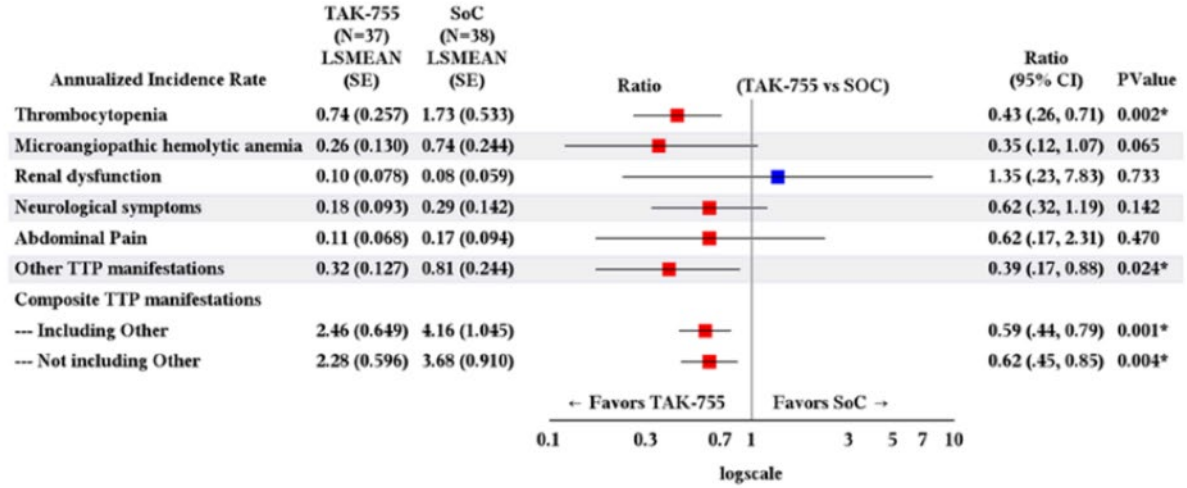
iCSR=interim clinical study report; MFAS=modified full analysis set; SD=standard deviation; SoC=standard of care; TTP=thrombotic thrombocytopenic purpura

[a] One adult subject was double-counted

Secondary Efficacy Endpoints

Incidence of Isolated TTP Manifestations During Prophylaxis

Several secondary endpoints of this study evaluated the incidence of TTP clinical signs and symptoms, including manifestations of thrombocytopenia, MAHA, renal dysfunction, neurologic symptoms (e.g., headache and migraine), and abdominal pain during the prophylactic treatment Periods 1, 2, and 3. As platelet consumption is a hallmark of cTTP disease activity, a drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/μL was considered a thrombocytopenia manifestation. Adverse events reported by investigators as related or possibly related to TTP and that were not captured as either neurological symptoms, abdominal pain, thrombocytopenia, increased LDH, or increased creatinine were classified as “Other” TTP manifestations. The most commonly reported "Other" TTP manifestations were platelet count decreased (8 events in 4 subjects), fatigue (8 events in 5 subjects), and nausea (4 events in 3 subjects) noting the potential for some overlap with laboratory based TTP manifestations.



The figure is based on >=12 yrs old data, not from all subjects results.
'TAK-755' and 'SoC' columns show LS mean (SE) of annualized event rate.
From a generalized linear mixed-effects model with a negative binomial distribution as a family and a logarithmic link function with treatment as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset.
Data from Periods 1 and 2 are used for subjects in the Prophylactic Cohort and those who switched from On-Demand to Prophylactic Cohort.

CI=confidence interval; LSMEAN=least squares mean; MFAS=modified full analysis set; SE=standard error; SoC=standard of care; TTP=thrombotic thrombocytopenic purpura

Note: p-values are nominal.

*Nominal p-value <0.05.

Source: Study 281102 iCSR ISS/ISE Figure st00957_14.2.2.2.11.ge12

Figure 34: study 281102 prophylactic cohort forest plot of ratio (TAK-755 to SoC) of model-based annualised event rates for TTP manifestations (MFAS adolescents and adults)

Acute TTP Events Responding to TAK-755 Treatment

The secondary endpoint analysis of the proportion of acute TTP events responding to TAK-755 treatment was performed in the MFAS for both the Prophylactic and the OD Cohorts. No subjects receiving TAK-755 in the Prophylactic Cohort, including during Period 3, had any acute TTP events. Only 1 acute TTP event treated with TAK-755 in the OD Cohort was confirmed to meet the protocol definition of an acute event. The acute TTP event was resolved and thus the proportion of acute TTP events responding to TAK-755 was 100% (Table 24). One additional acute event treated with TAK-755 in the OD Cohort was not confirmed by the central laboratory as an acute event, and therefore is not included in this endpoint analysis, although it met the criteria for being resolved by TAK-755 treatment.

Table 27: treated acute TTP events responding to TAK-755 by treatment cohort MFAS (age ≥ 12 years)

	Total Prophylactic Cohort	On-Demand Cohort	Total
Number of acute TTP events treated with TAK-755 (N)	0	1	1
Number of acute TTP events responding to TAK-755 (n[%]) [a]	0	1 (100.0)	1 (100.0)

TTP=thrombotic thrombocytopenic purpura

[a] 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.

Time to Resolution of Acute TTP Events

The secondary endpoint analysis of time to resolution of acute TTP events was performed in the MFAS in both the Prophylactic and the OD Cohorts.

One subject receiving SoC in the Prophylactic Cohort had an acute TTP event; this event was reported as resolved after 14.8 days. It should be noted that for this event, after 3 days the subject had no additional unscheduled visits; at the next scheduled visit at 14.8 days post-event the Investigator considered the event resolved. No subjects receiving TAK-755 in the Prophylactic Cohort, including during Period 3, had any acute TTP events.

In the OD Cohort, 1 confirmed acute TTP event was treated with SoC; the time to resolution was reported as 1.5 days. It should be noted that the Investigator-reported end date of 1.5 days did not meet the protocol definition for a resolved acute event.

One confirmed acute event was treated with TAK-755, and the reported time to resolution of the acute TTP event was 3.0 days. The Investigator-reported end date of 3.0 days met the protocol definition for a resolved acute event.

For SoC, 3 events that did not meet the protocol defined criteria for acute event resolved within 2, 4 and 5 days. For TAK-755, the event that did not meet the protocol defined criteria for acute event resolved within 5 days.

In conclusion, time to resolution of acute events appeared to be comparable for TAK-755 and SoC.

Incidence of supplemental doses prompted by subacute TTP events

Supplemental doses were defined in Study 281102 as supplemental doses prompted by subacute TTP events and are summarised for the MFAS in the table below.

Table 28: Study 281102 Prophylactic Cohort Incidence of Supplemental Dose Prompted by Subacute TTP Events (MFAS)

Supplemental doses prompted by subacute TTP events	SoC	TAK-755	
	Period 1 and 2	Period 1 and 2	Period 3
Adolescents and Adults (Age ≥12 years), n	38[a]	37	35
Number of subjects with event	2	0	1
Number of supplemental doses	6[b]	0	4
Mean annualized event rate (SD)	0.29 (1.477)	0	0.13 (0.770)
All Subjects, n	42[a]	43	35
Number of subjects with event	2	0	1
Number of supplemental doses	6[b]	0	4
Mean annualized event rate (SD)	0.1 (0.78)	0	0.1 (0.68)

iCSR=interim clinical study report; MFAS=modified full analysis set; SD=standard deviation; SoC=standard of care; TTP=thrombotic thrombocytopenic purpura

[a] Adult Subject was double-counted as bothin the SoC Periods 1 and 2 Combined column

[b] Does not include Subject who received an additional dose of 820 mL of SoC on to treat a subacute event in Period 1 because the dose was received the day after the end of the subacute event (Narrative, Study 281102 iCSR Section 14.3.3).

Of note, one subject in SoC group, received 1 supplemental SoC dose and second subject in the SoC group received 1 supplemental dose of SoC and then switched to 4 supplemental TAK-755 doses. One subject in the TAK-755 group received one supplemental dose of SoC (due to the absence of TAK-755 in the non-study site hospital where the subject was admitted) and then received 2 additional doses of TAK-755.

In total, 3 subjects on SoC prophylaxis received additional dose(s) in the context of a TTP manifestation (5 doses in total). Additionally, 5 subjects received additional dose(s) of TAK-755 or SoC for other reasons (7 doses in total), such as surgery, vaccination, infection or hospitalisation.

Incidence of dose modification not prompted by an acute TTP event

There were no dose modifications prompted by an acute TTP event during this study.

Two adult subjects in the MFAS had dose modifications for other reasons:

- Subject on SoC: The dose of SoC was increased from 11 to 13 mL/kg (800 mL to 1000 mL) in Period 2 due to recurrent headache and fatigue.
- Subject on TAK-755: The frequency of TAK-755 infusions was increased from Q2W to Q1W in Period 3 due to recurrent headaches and migraines.

Incidence of acute TTP events while subjects are on their final dose and dosing regimen in the study

There was 1 acute event from 1 subject while receiving SoC, which occurred during the final dose and dosing regimen period for that subject. There were no acute TTP events from any subjects within the final dose and dosing regimen period while receiving TAK-755.

Patient reported outcomes: SF-36v2, EQ-5D, PedsQL, TSQM-9, cTTP Patient Experience Questionnaire

In Study 281102, patient reported cTTP-related symptoms, impacts, and health related quality of life (HRQOL) as assessed using the cTTP Patient Experience Questionnaire (PEQ), the 36-Item Short Form Health Survey Version 2.0 (SF-36v2), and EuroQol 5 Dimensions Questionnaire 3 Level (EQ 5D-3L) questionnaires remained consistent across study assessment time points for subjects receiving prophylactic TAK-755 and prophylactic SoC.

For the Treatment Satisfaction Questionnaire for Medication (TSQM-9), a PRO developed to measure key dimensions of treatment satisfaction (effectiveness, convenience, and satisfaction with treatment), subjects consistently reported higher scores across all dimensions after receiving TAK-755 prophylactic treatment compared to after receiving SoC prophylactic treatment.

Healthcare Resource Utilization Analyses

Healthcare resource utilisation including annualised rates of hospital visits, hospitalisation duration, emergency room visits, and absence from school/work duration were lower while subjects were taking prophylactic TAK 755 treatment compared to while subjects were taking prophylactic SoC treatment (Study 281102 iCSR Table 14.2.4.7). For example, mean annualized number of hospital visits (SD) was 0.47 (1.073) for TAK-755 and 3.13 (7.418) for SoC.

- **Ancillary analyses**

Incidence of Other TTP Manifestations

For completeness of reporting, the "Other" category of TTP manifestations included an ad hoc analysis of all AEs reported by investigators that were considered related or possibly related to cTTP and were not captured as neurological symptoms, abdominal pain, thrombocytopenia, increased LDH, or increased creatinine. The most commonly reported "Other" TTP manifestations were fatigue, platelet count decreased, and nausea.

The model-based estimate of mean annualized incidence rate during the controlled cross-over (Periods 1 and 2) was approximately 60% lower for TAK-755 than SoC treatment (0.32 versus 0.81, respectively; 2-sided nominal p-value=0.024.

In Periods 1 and 2, 14 out of 38 adult and adolescent subjects experienced 24 "Other" TTP manifestations while receiving SoC, with a mean (SD) annualized event rate of 1.17 (2.030); 6 out of 37 subjects experienced 9 "Other" TTP manifestations while receiving TAK-755, with a mean (SD) annualized event rate of 0.45 (1.175).

This post hoc analysis of all AEs considered related or possibly related to cTTP also shows a trend towards a reduced incidence while being on rADAMTS13 prophylactic treatment compared to SoC prophylaxis.

TTP Manifestations by Treatment Frequency (Q2W and Q1W)

Study 281102 allowed subjects to receive prophylaxis treatment based on their SoC treatment frequency at the time of enrollment (Q2W or Q1W). Subjects were not randomized to a dosing frequency in the study and, for the most part, continued based on the SoC frequency they were receiving prior to the study. Approximately 20% of subjects received Q1W treatment during the study.

An ad-hoc subgroup analysis was performed on the MFAS subjects with age $\geq$ 12 to evaluate the incidence of TTP manifestations by TAK-755 dosing frequency.

TAK-755 prophylaxis treatment in adult and adolescent subjects in the MFAS resulted in consistently lower annualized event rates of thrombocytopenia compared to SoC treatment for both the Q1W regimen (0.5 versus 1.79) and the Q2W regimen (2.29 versus 4.50). A similarly low annualized event rate of thrombocytopenia was maintained in Period 3 with TAK-755 treatment.

The annualised event rate of TTP manifestations with TAK-755 treatment was also consistently lower compared to SoC treatment within the Q2W regimen in Periods 1 and 2 for MAHA, neurological symptoms, abdominal pain, and "Other" events; the only exception was the renal dysfunction event rate, which was consistent with the results based on the overall adult and adolescent population. The same trend favouring TAK-755 treatment was demonstrated in neurological symptoms, abdominal pain, and "Other TTP manifestations" in the Q1W group.

The post hoc analysis of treatment effect by treatment frequency cannot be meaningfully interpreted, as subjects were not randomised to Q1 or Q2 treatment schemes but continued their previous prophylactic dosing, which could be prompted either by a subject's frequent symptoms or by a more stringent prophylactic regimen in use at their particular treatment centre.

TTP Manifestations by SoC Treatment Received

During SoC treatment, Study 281102 allowed subjects to receive any of the commercially available plasma-based therapies commonly used to treat cTTP (FFP, SDTP, FVIII) per the investigator's decision and subjects' cTTP treatment history. An *ad-hoc* subgroup analysis was performed on the MFAS for ≥12 years of age subjects to evaluate the incidence of TTP manifestations among subject groups per different SoC types. This evaluation allowed a direct comparison of TTP manifestations for the same subjects that had received TAK-755 and SoC by SoC type in the controlled crossover period.

This *post hoc* analysis of the treatment effect of TAK-755 compared to each SoC modality shows that the incidence of TTP manifestations with TAK-755 is likely lower than with any specific SoC modality.

TTP Manifestations by Age Group

As of the IA data cutoff date on 12 Aug 2022, mean duration of exposure is limited for paediatric subjects relative to adults and adolescents.

Due to the small sample size and the sparse thrombocytopenia events reported in each of the subgroups aged <18 years, the interpretation and the comparison between TAK-755 and SoC treatment is limited. Of note, there was 1 "Other" TTP manifestation reported in 1 subject in the 6 to <12 years age group (one child: in Period 1 while receiving TAK-755, experienced 1 "Other" TTP manifestation which was platelet count decreased coincident with a thrombocytopenia manifestation on the same day).

As paediatric subjects could only be enrolled into the pivotal trial after some experience had been gained in adult patients (staggered enrolment), their exposure to TAK-755 is limited.

There were no obvious trends across the races, between male and female subjects, or across geographic regions.

Update of the Effacy Outcomes

With the responses to the D120 LoQ, the Applicant submitted updated efficacy data for the pivotal trial with a data cutoff of 11 Aug 2023, representing an additional year on study.

For this Day 120 response data cut, there were 38 adolescent and adult subjects and 8 paediatric subjects (4 subjects aged <6 years and 4 subjects aged 6 to <12 years), for a total of 46 subjects in the prophylactic cohort of the Study 281102 MFAS, which was the same number of subjects included in the prophylactic cohort for the initial marketing authorisation application.

In the prophylactic cohort, 45 (97.8%) of 46 subjects completed the main comparative crossover portion of the study, ie, Period 1 and 2, and 40 (87.0%) subjects completed the study. There are 5 (10.9%) subjects still on study in Period 3, and 1 (2.2%) subject discontinued the study during Period 1. All 8 (100%) paediatric subjects had completed the main comparative crossover portion of the study (ie, Periods 1 and 2) and 3 of the 8 paediatric subjects had completed the study.

In the OD cohort, 6 subjects were enrolled and 5 subjects (83.3%) completed the OD cohort, with 3 of these subjects (50%) then switching to the prophylactic cohort; 1 paediatric subject (16.7%) completed OD treatment with SoC and then discontinued the study after the event resolution.

The main efficacy outcomes are presented below:

Acute Thrombotic Thrombocytopenic Purpura Events During Prophylactic Treatment

During Study 281102, up until the Day 120 response data cut of 11 Aug 2023, no subject (paediatric, adolescent, or adult) in the MFAS had an acute TTP event while on prophylactic treatment with TAK-755 (Periods 1, 2, or 3).

As previously reported for the initial MAA, 1 subject, a woman in the MFAS, had 1 acute TTP event while on prophylactic treatment with SoC (mean [SD] annualised event rate of 0.05 [0.280] per subject-year for 38 subjects with age ≥12 years and an annualized event rate of 0.04 [0.254] per subject-year for the 46 subjects of all ages while receiving SoC during Periods 1 and 2 combined).

Subacute Thrombotic Thrombocytopenic Purpura Events During the Prophylactic Treatment Period

Subacute Events in Adolescents and Adults

Six subjects in the adolescent and adult subgroup of the prophylactic cohort of the Study 281102 MFAS had 7 subacute TTP events. Four of these subjects reported 5 subacute events while on SoC prophylactic treatment (all were during Period 1). Two subjects had 2 subacute events while on TAK-755 prophylactic treatment (both events occurred during Period 3).

The mean annualized event rate of subacute events for the adolescent and adult population was 0 per subject-year during TAK-755 treatment vs 0.25 (0.783) per subject-year during SoC treatment in the controlled comparison portion of the study, ie, Periods 1 and 2. The mean annualized event rate of subacute events for the adolescent and adult population was 0.07 (0.284) per subject-year during TAK-755 treatment in Period 3. These outcomes are identical to those submitted with the earlier data cut.

Subacute Events in Paediatric Subjects

Three paediatric subjects in the prophylactic cohort of the Study 281102 MFAS had 3 subacute TTP events. These subacute TTP events occurred in the time between the initial MAA and the Day 120 response data cut. All occurred during the controlled comparison Period 1 and 2, and all were preceded by infections.

Two of these events occurred while the subjects were receiving prophylactic treatment with SoC; these 2 paediatric subjects (both aged <6 years) each had 1 subacute TTP event. One subject had a subacute event during Period 1, which was also classified as an SAE of thrombocytopenia. The second subject had a subacute event during Period 2.

The other subacute TTP event occurred during prophylactic treatment with TAK-755; this paediatric subject (aged 6 to <12 years) had a subacute event during Period 2.

The mean annualised event rate of subacute TTP events for the *paediatric population (aged <12 years)* was 0.23 (0.653) per subject-year during TAK-755 treatment vs 0.51 (0.946) per subject-year during SoC treatment in the controlled comparison portion, ie, Period 1 and 2, and 0 per subject-year during TAK-755 treatment in Period 3.

For *paediatric subjects aged <6 years*, the mean annualised event rate of subacute TTP events was 0 per subject-year during TAK-755 treatment vs 1.02 (1.180) per subject-year during SoC treatment in the controlled comparison Period 1 and 2.

For *paediatric subjects aged ≥6 to 12 years*, the mean annualised event rate of subacute TTP events was 0.46 (0.923) per subject-year during TAK-755 treatment vs 0 per subject-year during SoC treatment in the controlled comparison Period 1 and 2.

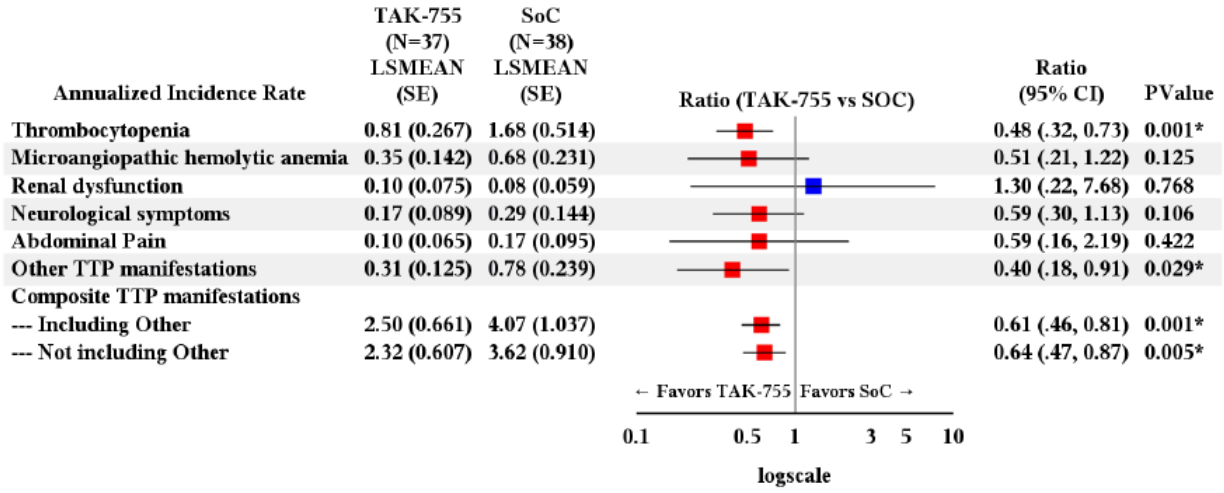
Summary of Subacute Thrombotic Thrombocytopenic Purpura Events During the Prophylactic Treatment Period, All Subjects

For the overall MFAS population, there were a total of 9 subjects with 10 subacute TTP events that occurred during the prophylactic period. The mean annualised event rate of subacute events was numerically lower during TAK-755 prophylactic treatment (during Periods 1 and 2 and during Period 3) compared with during SoC prophylactic treatment. The mean annualised event rate was 0.04 (0.275) per subject-year while receiving TAK-755 treatment vs 0.30 (0.809) per subject-year while receiving SoC prophylactic treatment during Period 1 and Period 2 combined, and 0.05 (0.258) per subject-year while receiving TAK-755 treatment in Period 3.

Thrombotic Thrombocytopenic Purpura Manifestations During Prophylactic Treatment

Thrombotic Thrombocytopenic Purpura Manifestations in Adolescent and Adult Subjects in the Modified Full Analysis Set

Aligned with the findings reported in the initial MAA, the results from this Day 120 response data cut demonstrate TAK-755 treatment was associated with consistently lower annualized event rates of TTP manifestations compared to SoC. For the TTP manifestations of thrombocytopenia, MAHA (increased LDH), abdominal pain, neurologic symptoms, and other TTP manifestations in adolescent and adult subjects, both the non–model-based and the model-based annualized event rates were numerically lower during TAK-755 prophylactic treatment compared with SoC prophylactic treatment (presented visually for the model-based event rates).



The figure is based on >=12 yrs old data, not from all subjects results.
'TAK-755' and 'SoC' columns show LS mean (SE) of annualized event rate.
From a generalized linear mixed-effects model with a negative binomial distribution as a family and a logarithmic link function with treatment
as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset.
Data from Periods 1 and 2 are used for subjects in the Prophylactic Cohort and those who switched from On-Demand to Prophylactic Cohort.

CI=confidence interval; LSMEAN=least squares mean; SE=standard error; SoC=standard of care
Note: p-values are nominal.
*Nominal p-value <0.05.
Source: Study 281102 Day 120 response Figure st00957_14.2.2.2.11.ge12

Figure 35: Study 281102 prophylactic cohort forest plot of ratio (TAK-755 to standard of care) of model-based annualised event rates for thrombotic thrombocytopenic purpura manifestations (adolescents and adults, modified full analysis set)

Thrombotic Thrombocytopenic Purpura Manifestations in Paediatric Subjects in the Modified Full Analysis Set

For paediatric subjects, the non–model-based annualised event rates of thrombocytopenia, abdominal pain, and other TTP manifestations numerically favoured TAK-755 treatment over SoC treatment in the combined Period 1 and 2, and consistently lower incidence rates were observed in Period 3. No neurological manifestations occurred in paediatric subjects during either TAK-755 or SoC treatment periods. The non–model-based annualised event rates of MAHA (increased LDH) and renal dysfunction were numerically higher with TAK-755 treatment than SoC in the combined Period 1 and 2. The model-based analysis showed a slightly favourable incidence rate in thrombocytopenia with TAK-755 treatment and in MAHA with SoC treatment during Period 1 and 2; however, the model failed to converge for other manifestations endpoints because of sparse number of events. Notably, the annualised event rate (non-model based) in period 3 (0.69) was numerically much lower than during the combined period 1 and 2 (2.98). Importantly, as the total number of paediatric subjects and TTP manifestations were relatively few on TAK-755 or SoC prophylaxis, these analyses are prone to be influenced by individual subject outliers, which limits the interpretation of comparison to SoC.

Results were similar for paediatric subjects aged <6 years; the mean annualised event rate of TTP manifestations, including thrombocytopenia, MAHA, abdominal pain, and other TTP manifestations, numerically favoured TAK-755 treatment over SoC treatment in the combined Period 1 and 2. In the paediatric subjects aged <6 years, the only TTP manifestation with a higher mean annualised event rate during TAK-755 treatment was renal dysfunction.

For paediatric subjects aged ≥6 to 12 years, no subjects in either treatment group had any TTP manifestations of neurological symptoms or abdominal pain during Period 1 or Period 2. The annualised

event rate of TTP manifestations of thrombocytopenia in Periods 1 and 2 was nearly identical during TAK-755 treatment and SoC treatment (mean [SD] annualized event rates of 5.50 [8.682] and 5.54 [11.077], respectively), and the annualized event rates of MAHA and renal dysfunction were numerically higher during TAK-755 treatment compared with SoC treatment during Period 1 and Period 2 (mean [SD] annualised event rate for MAHA was 0.46 [0.923] during TAK-755 treatment vs 0 during SoC treatment and for renal dysfunction was 0.84 [1.688] during TAK-755 treatment vs 0 during SoC treatment).

Treatment of Confirmed and Suspected Acute Thrombotic Thrombocytopenic Purpura Events in the Prophylactic and On-demand Cohorts

This section includes data from all confirmed and suspected (not laboratory-confirmed to meet protocol definition of acute event) acute TTP events in Study 281102 (all enrolled subjects with cTTP in both the prophylactic cohort and the OD cohort). For the OD cohort, subjects were provisionally enrolled if an investigator suspected the subject was undergoing an acute TTP event, pending central laboratory (platelet and LDH values) confirmation; thus, the event was a suspected acute TTP event until confirmed by laboratory data. Some suspected acute TTP events were not confirmed by central laboratory data (either the central laboratory values did not meet protocol-defined criteria or only a local laboratory was used). Subjects who were randomized to TAK-755 were administered the TAK-755 OD dosing regimen for acute events.

All confirmed and suspected acute TTP events in Study 281102, including event start and stop dates, treatment for the event, and associated laboratory data, are listed by subject in Table 29.

Table 29: Study 281102 All suspected and treated acute thrombotic thrombocytopaenia purpura events (modified full analysis set)

Unique Subject ID Sex/age (years)	Cohort	Treatment for the 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]
	Prophylactic [redacted] SoC W)	FFP		104 (56.5% ↓ from baseline)[a]	454 (2.41 × baseline)[a]	YES	279[c]	194 (1.03 × baseline)[c]
	OD	TAK-755		84	236 (1.10 × ULN)	NO	270 [c]	205 (0.96 × ULN)[c]
	OD	TAK-755		24[a]	598 (2.43 × ULN)[a]	YES	155[c]	278 (1.13 × ULN)[c]
	OD	SoC (FFP)		23[a]	685 (2.78 × ULN)[a]	YES	62	320 (1.30 × ULN)
	OD	SoC (FFP)		23	652 (2.65 × ULN)	NO	101	323 (1.31 × ULN)
	OD	SoC (S/DTP)		20	458 (2.04 × ULN)	NO	276[c]	263 (1.17 × ULN)[c]
	OD	SoC (S/DTP)		65	211 (1.06 × ULN)	NO	150[e]	187 (0.94 × ULN)
	OD	SoC (FFP)		37	674 (3 × ULN)	NO	257[f]	453 (2.01× ULN)

FFP=fresh frozen plasma; iCSR=interim clinical study report; ID=identification; LDH=lactate dehydrogenase; OD=on-demand; Q2W=every 2 weeks; S/DTP=solvent/detergent treated plasma; SoC=standard of care; TTP=thrombotic thrombocytopenic purpura; ULN=upper limit of normal

*Subject No. 061001/061002 passed screening and entered the study twice.

[a] Events confirmed by the central laboratory to meet protocol acute TTP event criteria.

[b] Local laboratory results are presented. Additional laboratory results are provided in the individual subject narratives in the Study 281102 Day 120 response Narratives and in Study 281102 iCSR Section 14.3.4).

[c] The laboratory 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% of baseline, whichever occurred first, and (b) elevation of LDH ≤1.5×baseline or ≤1.5×ULN. The investigator-reported date of resolution did not always coincide with the protocol definition of resolution.

[d] Second acute event occurred during OD cohort and was not included in time to resolution endpoint analysis.

As previously reported for the initial MAA, there was 1 subject (an adult) who had an acute TTP event during prophylactic study treatment while receiving SoC. There was an additional acute event in the prophylactic cohort that is not included in these analyses on the MFAS, as the subject was found to have immune-mediated TTP (Subject) and was discontinued from the study for not meeting enrolment criteria. No new acute TTP events occurred in the prophylactic cohort after the IA (ie, in the period of time between 12 Aug 2022 and 11 Aug 2023).

During the period of 12 Aug 2022 through 11 Aug 2023 (data cut-off date for this Day 120 response data cut), male subject with an acute TTP event enrolled in the OD cohort and was randomized to receive SoC treatment.

Therefore, as of 11 Aug 2023, the OD cohort enrolled a total 6 subjects (5 unique subjects) with 7 acute TTP events (both confirmed and suspected). These included 1 paediatric subject and 5 unique adult subjects [1 subject enrolled twice, with 2 different Study 281102 ID numbers], and 2 of these events were confirmed as acute TTP events by central laboratory results. Two subjects were randomized to receive TAK-755 treatment, and 4 subjects were randomized to receive SoC treatment. All these laboratory-confirmed and suspected acute TTP events resolved after treatment with either

TAK-755 or SoC. Both acute TTP events (1 laboratory confirmed and 1 suspected) treated with TAK-755 responded to TAK-755 treatment (ie, resolved without requiring the use of another ADAMTS13-containing agent).

As of 11 Aug 2023, all 6 subjects completed the OD treatment in the OD cohort and 5 subjects completed the study in either the OD cohort (2 subjects) or prophylactic cohort (3 subjects). The paediatric subject was randomized to SoC and was discontinued early from the OD cohort based on the investigator's decision.

Treatment and time to resolution for the 3 confirmed acute TTP events (all reported in the initial MAA) are listed below. One of these events occurred in the prophylactic cohort in a subject who was receiving prophylactic treatment with SoC, and the other 2 confirmed acute TTP events occurred in subjects in the OD cohort and received SoC and TAK-755, respectively:

- One subject (young woman/prophylactic cohort): Acute TTP event treated with 2 doses of FFP on Day 1 and an unscheduled visit on Day 3 of the event. The event was reported as resolved in 14.8 days based on laboratory data at the next scheduled visit. Notably, the subject had no visits between Day 3 of the event and the next scheduled visit. Thus, the time to resolution of the acute event is not precisely determined.
- One subject (young man/OD cohort enrolled): First acute TTP event treated with TAK-755 (40 IU/kg on Day 1, 20 IU/kg on Day 2, followed by 15 IU/kg Q1D on Day 3 and 4) and resolved in 3.0 days. Platelets increased and LDH decreased incrementally with each dose of TAK-755.
- One subject (young man/OD cohort re-enrolled): Second acute TTP event treated with FFP (Q1D doses for 3 days) and resolved in 1.5 days per investigator-reported date of resolution. Notably, at the time when this event was reported as ended, platelet and LDH values did not meet the protocol definition for a resolved acute event. However, the subject did not receive any more doses of FFP for this acute event.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of efficacy for trial 281102

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 TAK755 (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])		
Study identifier	TAK-755-281102 (EudraCT Number: 2017-000858-18)	
Design	Study 281102 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 (formerly called BAX930 or SHP655) in the prophylactic and on-demand (OD) treatment of subjects with severe cTTP. This is an ongoing study for which an interim analysis and report were generated, based on a data cutoff date of 12 August 2022. At the time of cut-off, 32 subjects ≥12years had completed all three study periods. Available data from subjects <12 years is included in subgroup analyses. A total of 48 subjects entered the Prophylactic cohort, in which subjects were randomized to receive 40IU/kg TAK-755 (every 2 weeks [Q2W] or once every week [Q1W]) or standard of care (SoC) (Q2W or Q1W) for 6 months in Period 1. Subjects then switched to the opposite treatment for an additional 6 months in Period 2. All subjects then continued to receive TAK-755 for another 6 months in Period 3. 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 SoC or TAK-755. For on-demand subjects randomized to TAK-755, subjects received an initial dose of 40 IU/kg [±4 IU/kg] TAK-755, a subsequent dose of 20 IU/kg [±2 IU/kg] TAK-755 on Day 2, and an additional daily dose of 15 IU/kg [±1.5 IU/kg] TAK-755 until 2 days after the acute TTP event is resolved.	
	Three Pharmacokinetics/Pharmacodynamics (PK/PD) periods were also included in this study: PK-I: to characterise the baseline PK of ADAMTS13 activity after administration of TAK-755 ORT (Orth, Austria) or TAK-755 SIN (Singapore) and SoC prior to the first treatment period, PK-II; to assess the PK comparability between TAK-755 SIN and TAK-755 ORT in subjects who received TAK-755 ORT in PK-I, and PK-III; to assess if any time-dependent PK changes occur due to long-term exposure to TAK-755 SIN at the end of the third treatment period (Period 3).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approximately 22 months (Prophylactic cohort) Approximately 1 month (OD cohort) NA NA
Hypothesis	No formal hypothesis testing was performed. Assessment was based on totality of evidence for both safety and efficacy.	
Treatments groups		
	TAK-755	Prophylactic cohort- TAK-755 40 IU/kg, Q2W or Q1W. 12 months + minimal exposure time in two PK periods, N=48 On-demand cohort-40 IU/kg TAK-755 on Day 1, 20 IU/kg on Day 2, followed by 15 IU/kg on Day 3 and daily thereafter until 2 days after the acute TTP event was resolved

	SoC		SoC treatment type, per Investigator discretion (Fresh, frozen plasma, pooled solvent/detergent treated plasma, FVIII:Von Willebrand Factor concentrates) Prophylactic cohort- Q2W or Q1W. 6 months + minimal exposure in a single PK period, N=47 On-demand cohort- to be determined by the investigator for each subject and was to be defined by the subject's treatment product and dosing regimen at the time of entry into the study
Endpoints and definitions	**Primary endpoint**	Incidence of acute TTP events among subjects during the corresponding treatment periods	Annualised acute TTP event rate was reported. An acute event defined as having both of the following laboratory measures: • Drop in platelet count ≥50% of baseline or a platelet count <100,000/µL • Elevation of LDH >2 × of baseline or >2 × ULN
	Subgroup analysis of primary efficacy endpoint	Age group	Age groups (≥12 years, ≥ 18 years, 12 to <18 years, 6 to <12 years, <6 years)
	Subgroup analysis of primary efficacy endpoint	Sex	Sex (Male or Female).
	Subgroup analysis of primary efficacy endpoint	Geographic region	Geographic region (US, Europe, Japan)
	Subgroup analysis of the exploratory efficacy endpoints were the same as the primary endpoint.	Age group Race group Sex Geographic Region	**Age group:** ≥12 years , ≥ 18 years, 12 to <18 years, 6 to <12 years, and <6 years **Race group**: White, Japanese, Other (neither White nor Japanese) **Sex**: Male, Female **Geographic Region**: US, Europe, Japan
	Relevant Secondary Endpoint	Incidence of thrombocytopenia	Thrombocytopenia is defined as a drop in platelet count ≥25% of baseline or a platelet count <150,000/µL.
	Subgroup analyses of the secondary efficacy endpoint, incidence of Thrombocytopenia were the same as	Age group Race group Sex Geographic Region	**Age group:** ≥12 years, ≥ 18 years, 12 to <18 years, 6 to <12 years, and <6 years **Race group**: White, Japanese, Other (neither White nor Japanese) **Sex**: Male, Female

	the primary endpoint.		**Geographic Region**: US, Europe, Japan
	Secondary Endpoint	Incidence of MAHA	MAHA is defined as an elevation of LDH >1.5 × baseline or >1.5 × ULN
	Secondary Endpoint	Incidence of renal dysfunction	Renal dysfunction is defined as an increase in serum creatinine >1.5 × baseline.
	Secondary Endpoint	Incidence of neurological symptoms	Neurological symptoms are derived from Adverse Events (AEs) related or possibly related to TTP and include, e.g., headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures.
	Secondary Endpoint	Incidence of abdominal pain	The incidence of abdominal pain was derived from AEs related or possibly related to TTP.
	Exploratory Endpoint	The incidence of TTP manifestations, defined as a composite of secondary outcome measures	Composite secondary outcomes measure is defined as: Occurrence of at least one of the isolated TTP manifestations including thrombocytopenia, MAHA, renal dysfunction, neurological symptoms, and abdominal pain (excludes "Other TTP manifestations"), while receiving prophylactic treatment with TAK-755 or SoC during the crossover treatment period, limited to the first 6-months in each treatment period
Database lock	30-Sep-2022		

Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified Full Analysis Set **(MFAS)-** includes all subjects who were included in the Full Analysis Set (FAS; see definition below under Secondary Analysis) 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 they were instead treated on SoC because TAK-755 was not available, the subjects were to be excluded from MFAS. For subjects enrolled prior to the study hold in November 2017, if SoC was the randomized treatment for Period 1 and 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 to be used in the MFAS-based efficacy analysis. The period over which the endpoint was to be 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 to be included in the MFAS-based efficacy analyses. The subgroup analyses for the listed primary, secondary, and exploratory endpoints were conducted for age, sex, race, and geographic region. Due to the low event rates and prioritization of the most relevant data, subgroup analyses for race was omitted for the purpose of this document. For secondary endpoints MAHA, neurological symptoms, abdominal pain, and renal dysfunction, no subgroup analyses are reported here due to low event rates.			
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Primary analysis: Annualized acute TTP event rate (MFAS) **Age ≥ 12 years** **[number of subjects: mean (SD)]**)	38: 0.05 (0.280)	37: 0	35: 0
	• **≥ 18 years** • **12 to <18 years** • **6 to <12 years** • **<6 years**	34: 0.05 (0.296) 4: 0 4: 0 0: NA	33: 0 4: 0 3: 0 3: 0	31: 0 4: 0 0: NA 0: NA
	• **Male** • **Female**	17: 0 25: 0.07 (0.345)	18: 0 25: 0	13: 0 22: 0
	• **US** • **Europe** • **Japan**	10: 0 27: 0.06 (0.332) 5: 0	10: 0 28: 0 5: 0	9: 0 21: 0 5: 0

Analysis description		**Secondary Analysis**		
Analysis population and time point description		**MFAS-** as defined above		
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Mean annualised event rate of **thrombocytopenia** (MFAS) **Age ≥ 12 years** **[number of subjects: mean (SD)])**	38: 4.10 (5.806)	37: 1.84 (4.329)	35: 1.44 (4.501)
	• ≥ 18 years • 12 to <18 years • 6 to <12 years • <6 years	34: 4.14 (5.855) 4: 3.73 (6.200) 4: 3.0 (6.00) 0: NA	33: 1.72 (4.249) 4: 2.78 (5.569) 3: 1.7 (2.08) 3: 0	31: 1.56 (4.767) 4: 0.54 (1.077) 0:NA 0: NA
	• Male • Female	17: 4.64 (6.230) 25:3.96 (6.445)	18: 1.73 (3.760) 25: 2.31 (5.531)	13: 1.43 (4.210) 22: 1.45 (4.762)
	• US • Europe • Japan	10: 5.25 (7.497) 27: 4.03 (6.212) 5: 3.32 (4.954)	10: 4.06 (7.069) 28: 1.60 (4.143) 5: 0.68 (1.518)	9: 4.46 (8.360) 21: 0.49 (0.964) 5 (0.00 (0.000)
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Secondary analysis: Annualized event rate- **MAHA** (MFAS) **Age ≥ 12 years** **[number of subjects: mean (SD)])**	38: 1.36 (3.019)	37: 0.35 (0.946)	35: 0.53 (0.829)
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Secondary analysis: Annualized event rate-**renal dysfunction** (MFAS) **Age ≥ 12 years**			

	[number of subjects: mean (SD)])	38: 0.25 (1.094)	37: 0.41 (1.551)	35: 0.06 (0.378)
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Secondary analysis: Annualised event rate-**neurological symptoms** (MFAS) **Age ≥ 12 years** **[number of subjects: mean (SD)])**	38: 1.35 (4.483)	37: 0.88 (3.214)	35: 1.06 (2.587)
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Secondary analysis: Annualized event rate-**abdominal pain** (MFAS **Age ≥ 12 years** **[number of subjects: mean (SD)])**	38: 0.34 (0.940)	37: 0.20 (0.832)	35: 0.22 (1.069)
Descriptive statistics and estimate variability	**Treatment group**	**SoC** Period 1 and 2	**TAK-755** Period 1 and 2	**TAK-755** Period 3
	Mean annualised event rate of **composite TTP manifestations** in the Prophylactic Cohort (MFAS) **Age ≥12 Years** **[number of subjects: mean (SD)]**	38: 6.87 (8.160)	37: 3.88 (5.623)	35: 3.23 (5.234)
	• ≥ 18 years • 12 to <18 years • 6 to <12 years • <6 years	34: 7.21 (8.332) 4: 4.00 (6.733) 4: 5.00 (10.000) 0: NA	33: 3.99 (5.665) 4: 3.00 (6.000) 3: 6.98 (10.400) 3: 0.00 (0.000)	31: 3.51 (5.494) 4: 1.04 (1.201) 0:NA 0: NA
	• Male • Female	17: 6.40 (8.650) 25: 6.89 (8.105)	18: 2.71 (3.925) 25: 4.63 (6.855)	13: 2.45 (4.699) 22: 3.69 (5.579)
	• US • Europe	10: 7.63 (9.314) 27: 6.77(8.314)	10: 4.50 (6.945) 28: 3.84(5.864)	9: 5.78 (8.502) 21: 2.81(3.518)

	• Japan	5: 4.40 (6.387)	5: 2.40 (3.578)	5: 0.40 (0.894)

Analysis description	**Model-based inferential analysis**
Analysis population and time point description	As a comparison between TAK-755 and SoC, the model-based estimate of mean annualized incidence rate of TTP manifestations in adult and adolescent subjects in the **MFAS** (Age ≥12 Years) is presented for each treatment group for the Prophylactic Cohort specifically during Period 1 and Period 2, as well as the ratio of the 2 treatment group incidence rates accompanied by 95% CI and 2-sided nominal p-value. The secondary and exploratory endpoint measures mentioned above, including thrombocytopenia events, MAHA events, renal dysfunction, neurological symptoms, abdominal pain, and composite TTP manifestations (not including 'Other') are presented in this model-based comparative analysis between treatment groups in Period 1 and Period 2.

Event	**TAK-755 (N=37)**	**SoC (N=38)**	**Ratio TAK-755/SoC (95% CI of ratio) p-value of ratio**
	Annualized Event Rate (LS Means [SE])		
Thrombocytopenia events	0.74 (0.257) [a]	1.73 (0.533) [a]	0.4 (0.3, 0.7) 0.002
Microangiopathic hemolytic anemia events	0.26 (0.130) [a]	0.74 (0.244) [a]	0.4 (0.1, 1.1) 0.065
Renal dysfunction events	0.10 (0.078) [b]	0.08 (0.059) [b]	1.3 (0.2, 7.8) 0.733
Neurological symptoms events	0.18 (0.093) [a]	0.29 (0.142) [a]	0.6 (0.3, 1.2) 0.142
Abdominal Pain events	0.11 (0.068) [a]	0.17 (0.094) [a]	0.6 (0.2, 2.3) 0.470
Composite TTP manifestations not including "Other"	3.68 (0.910)	2.28 (0.596)	0.6 (0.5, 0.9) 0.004

CI=confidence interval; LS=least squares; MFAS=modified full analysis set; N=total number of subjects per treatment arm in the MFAS ≥12 years; SE=standard error; SoC=standard of care; TTP=thrombotic thrombocytopenic purpura

From a generalised linear mixed-effects model with a negative binomial distribution as a family and a logarithmic link function with treatment as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset. Period (1 and 2) and sequence (TAK-755 - SoC, SoC - TAK-755) were included in the model as categorical variables.

Due to sparse events, the full model did not converge. Therefore, these results are from a generalised linear mixed effects model that did not include the treatment sequence as a covariate.

Results and Analysis	
Notes	Two subjects discontinued during the study. One subject discontinued following diagnosis with immune-mediated TTP. One other subject discontinued due to Principal Investigator decision following an allergic reaction to SoC. Overall, TAK-755 prophylaxis in the controlled comparison (Periods 1 and 2 combined) resulted in consistently lower annualised event rates of TTP events and manifestations compared to SoC prophylaxis. For the TTP manifestations of thrombocytopenia, MAHA, neurological symptoms, abdominal symptoms, and composite TTP manifestations, the annualised event rate was lower during TAK-755 prophylactic treatment compared with SoC prophylactic treatment. The treatment group difference in model-based annualised event rates reached a nominal p-value <0.05 in favor of TAK-755 for thrombocytopenia manifestations, "Other" TTP manifestations, and composite manifestations – which included all the pre-specified manifestations (except "Other").

	For renal dysfunction manifestations, the model based annualized event rates were low and numerically similar for TAK-755 and SoC prophylactic treatments. There were a sparse number of events in this category.

2.6.5.3. Clinical studies in special populations

The age range of subjects included into the pivotal trial was 3 to 68 years, and for subjects taking part in the continuation study 3002 17 to 61 years. No paediatric subjects had rolled over yet.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not Applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Integrated Analysis of Efficacy

A pooled analysis of the efficacy outcomes of pivotal trial 281102 and continuation trial TAK 755-3002 supports the notion that prophylactic use of rADAMTS13 is likely to be beneficial for preventing TTP related acute and subacute events. No subject experienced an acute TTP event during the available observation period of a median of 422 and a maximum of 1108 days. All additional analyses with regards to isolated TTP related manifestations and organ damage support this conclusion.

Updated Pooled Analysis submitted with D120 responses

The efficacy analyses for the EAS Pool I (which included subjects of all ages) and Pool II (a subset of Pool I with subjects with longer exposure to study drug that included only adolescents and adults because adults were enrolled before adolescents, followed by paediatric subjects in Study 281102) were based on the incidence of acute TTP events, subacute TTP events, and TTP manifestations while on TAK-755 prophylactic treatment as of the data cutoff dates (11 Aug 2023 [for Study 281102] and 20 Jun 2023 [for Study 3002]).

One acute TTP event occurred in Pool I while subjects received TAK-755 prophylaxis. The overall mean annualized acute event rate for Pool I was 0.02 (0.154).

Eight subjects in EAS Pool I had 1 subacute event each. Five of these subjects were also in Pool II. The mean annualized event subacute rate was 0.07 for both Pool I and Pool II. All subacute TTP events resolved: without any supplemental dose (3 events), with supplemental doses of both SoC and TAK-755 because the event was first treated at a non–study hospital (2 events), or with supplemental doses of TAK-755 only (3 events).

Results for TTP manifestations were similar for EAS Pool I and Pool II despite Pool I including more subjects (70 vs 29) and paediatric subjects (13 vs 0). For EAS Pool I, the mean annualized event rate for composite TTP manifestations was 2.61. For EAS Pool II, the mean annualized event rate for the composite TTP manifestation endpoint was 2.99.

Table 31: Pooled studies 281102/3002 subject disposition (efficacy analysis set)

Number (%) of Subjects	Pool I (N=70)	Pool II (N=29)
Total	70 (100)	29 (100)
Completed the program (ie, both studies)	1 (1.4)	0
Number of subjects whose participation is ongoing in the prophylactic cohort	67 (95.7)	27 (93.1)
Ongoing in Study 281102	5 (7.1)	0
Ongoing in Study 3002	62 (88.6)	27 (93.1)
Completed Study 281102 and Continued into Study 3002 (ie, rollover subjects)	40	29
Number of subjects who completed the prophylactic cohort	1 (1.4)	0
Discontinued from the prophylactic cohort (both because of pregnancy)	2 (2.9)	2 (6.9)

ISE=integrated summary of efficacy (program includes 2 studies, Studies 281102 and TAK-755-3002); ISS=integrated summary of safety; N=number of subjects.

The 2 EAS pools had similar demographic and baseline characteristics. All subjects were under age 65 years (as expected, the mean age for Pool I was younger than for Pool II; 29 years for Pool I compared with 36 years for Pool II) at the start of the first study in which they participated and confirmed diagnosis with cTTP. Most subjects were white (>50%), female (>60%), and located in either the US or Europe (>75%). Almost all subjects (approximately 90%) were already taking prophylactic treatment with either FFP or S/DTP; the most common dosing interval was Q2W (approximately 50% of subjects).

Post hoc analysis with /without site

A *post hoc* analysis of TTP events (acute, subacute) and TTP manifestations by study site (the highest enrolling site) vs Not Site was conducted, as non GCP compliance events were found at this site. It is agreed with the Applicant that site specific higher reporting of abdominal and neurological TTP manifestations for site 1 is likely due to the individual illness manifestations of specific patients and / or the more stringent therapeutic approach of the centre. An impact of the identified GCP non-compliance events (use of paper diaries instead of telehealth visits for home infusions) on the outcomes is unlikely.

2.6.5.6. Supportive study

TAK-755-3002

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)

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. The submitted interim study report presents an interim analysis for subjects enrolled from 14 Apr 2021 (first subject enrolled) to 12 Aug 2022, the date of the interim data cutoff.

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.

The primary safety outcome was the incidence of related treatment-emergent adverse events and serious adverse events in both the prophylactic and on-demand cohorts. The efficacy outcome was secondary and included the number and incidence of acute TTP events, subacute TTP events, and isolated TTP manifestations while receiving TAK-755 prophylaxis.

Efficacy Results:

The efficacy results from the Study 3002 interim analysis evaluating long-term TAK-755 prophylaxis for up to 1.4 years (mean duration of 0.58 years) are shown in the table below and are summarized as follows:

- At the time of interim analysis, no acute TTP events occurred while subjects received TAK-755 prophylaxis for a mean duration of 0.58 years and for up to 1.4 years.
- One acute TTP event occurred during Screening in a non-rollover subject, just prior to initiating dosing with TAK-755. The acute event was resolved by treatment with TAK-755 in 6 days, using a

total of 13632.70 IU of TAK-755 (comprising daily doses ranging from 40.2 to 14.4 IU/kg) to treat the event.

- Three subjects experienced 3 subacute TTP events during the study, resulting in a study mean rate of 0.13 events per subject per year. The 3 subacute events prompted administration of a total of 5 supplemental doses of TAK-755 at 40 IU/kg.
- More than half of the subjects (58.3%) did not experience any of the protocol defined TTP manifestations (thrombocytopenia, microangiopathic hemolytic anemia [MAHA], neurological symptoms, renal dysfunction, or abdominal pain) while receiving TAK-755 prophylaxis. Overall, the mean rate of TTP manifestations was 3.05 per subject per year.
    - Seven subjects (19.40%) experienced 12 thrombocytopenia manifestations, resulting in a study mean rate of 0.62 events per subject per year; 7 of the 12 thrombocytopenia manifestations were observed in 3 subjects during the non-treatment-emergent acute event and 2 subacute TTP events.
    - Three subjects (8.30%) experienced 9 MAHA manifestations, resulting in a study mean rate of 0.54 per subject per year; 7 of the 9 MAHA manifestations occurred in 2 subjects during the non-treatment-emergent acute event and 1 of the subacute TTP events.
    - No subject experienced a renal dysfunction manifestation while receiving TAK-755 prophylaxis.
    - Eight subjects (22.20%) experienced 59 neurological symptom manifestations (headache was the most common), resulting in a study mean rate of 1.57 per subject per year.
    - Three subjects (8.3%) experienced 8 abdominal pain manifestations, resulting in a study mean rate of 0.33 per subject per year.
- For rollover subjects, the incidence rates of acute and subacute TTP events and TTP manifestations were maintained at rates generally consistent with those observed during TAK-755 prophylaxis in the parent Phase 3 Study 281102.
- One subject (2.80%) had 2 TAK-755 dose modifications (change in dosing frequency) not prompted by an acute event.
- While subjects were receiving their final prophylactic treatment regimen (ie, final dose frequency [Q2W or Q1W]), 15 subjects (41.70%) experienced at least 1 TTP manifestation, resulting in a study mean rate of 3.00 per subject per year.
- One subject was treated with TAK-755 in the home setting. This subject experienced 3 TTP manifestations while receiving TAK-755 in the home setting for 112 days.

The long-term continuation study 3002 enrolls subjects who have completed participation in the pivotal trial 281102 as well as new subjects. The in- and exclusion criteria are identical to those of the pivotal trial, which is not optimal as pregnancy is one of the most frequent triggers for TTP events. Furthermore, should subjects become pregnant during participation in study 3002, they were planned to be discontinued from treatment.

Overall, the annualised incidence of isolated TTP manifestations was 3.05. Three subjects experienced 3 subacute TTP events during the study, resulting in an annualised incidence of 0.13. These outcomes are comparable to those from the pivotal trial 281102 and provide supportive evidence of the continued efficacy of apadamtase in the prophylactic setting.

Updated Efficacy Data

With the responses to the D120 LoQ, the Applicant submitted an update of study 3002 with a data cut-off of 20 Jun 2023.

The Day 120 response data cut analysis includes a total of 65 subjects with a confirmed cTTP diagnosis who consented to participate in the study, received any amount of TAK-755, and were included in the FAS for efficacy analyses. All subjects were in the prophylactic cohort, with one of the paediatric subjects starting in the OD cohort. Subjects enrolled comprised: 6 paediatric subjects (aged <12 years), 10 adolescents (aged 12 to <18 years), and 49 adults (aged ≥18 years). For this study, the FAS is the same as the safety analysis set, consisting of all subjects who received any amount of TAK-755.

Disposition and Study Populations

There were 59 adolescent and adult subjects and 6 paediatric subjects, for a total of 65 unique subjects in the FAS of Study 3002. Most (40 of 65) subjects were rollover subjects who completed Study 281102 and continued into Study 3002.

Table 32: Study 3002 subject disposition (full analysis set)

	Prophylactic Cohort		
Category	**Rollover n (%)**	**Non-rollover n (%)**	**Total n (%)**
Number of subjects in the full analysis set	40 (100.0)	25 (100.0)	65 (100.0)
Number of subjects ongoing	38 (95.0)	25 (100.0)	63 (96.9)
Number of subjects who discontinued the study	2 (5.0)	0	2 (3.1)
Primary reason for discontinuation			
Pregnancy	2 (100)	0	2 (100)

cTTP=congenital thrombotic thrombocytopenic purpura; FAS=full analysis set
Rollover: A subject who completed Study 281102.
Non-rollover: A subject who did not complete Study 281102 (regardless of prior exposure to TAK-755).
Percentages are based on all subjects in the FAS within each column.
The FAS includes all enrolled subjects with a confirmed cTTP diagnosis receiving at least 1 dose of TAK-755.

Twenty-five subjects (including all 6 paediatric subjects) were non–rollover subjects. As of the data cutoff date, 63 (96.9%) subjects remain on study, receiving TAK-755 prophylactic treatment. Two rollover subjects discontinued TAK-755 treatment and Study 3002 because of pregnancy.

Demography for the Study 3002 FAS is summarised in Table 33. All subjects were under age 65 years. Most (49 of 65) subjects were adults (aged ≥18 years); 10 subjects were adolescents (aged ≥12 years), and 6 subjects were paediatric (aged <12 years). Most subjects were females located in either the US or Europe.

Table 33: Study 3002 demographics (full analysis set)

Characteristic	Rollover (N=40)	Non-rollover (N=25)	Total (N=65)
Age (years)			
Mean (SD)	35.6 (14.15)	26.2 (16.85)	31.9 (15.81)
Median (Min, Max)	36.0 (13, 61)	24.0 (2, 61)	34.0 (2, 61)
Age Group [n (%)]			
<6 years	0	3 (12.0)	3 (4.6)
6 to <12 years	0	3 (12.0)	3 (4.6)
12 to <18 years	7 (17.5)	3 (12.0)	10 (15.4)
≥18 years	33 (82.5)	16 (64.0)	49 (75.4)
≥12 years	40 (100)	19 (76.0)	59 (90.8)
Sex [n (%)]			
Male	15 (37.5)	8 (32.0)	23 (35.4)
Female	25 (62.5)	17 (68.0)	42 (64.6)
Ethnicity [n (%)]			
Hispanic or Latino	1 (2.5)	0	1 (1.5)
Characteristic	**Rollover (N=40)**	**Non-rollover (N=25)**	**Total (N=65)**
Not Hispanic or Latino	33 (82.5)	22 (88.0)	55 (84.6)
Not Reported	6 (15.0)	3 (12.0)	9 (13.8)
Race [n (%)]			
Asian	5 (12.5)	12 (48.0)	17 (26.2)
Japanese	5 (12.5)	1 (4.0)	6 (9.2)
Chinese	0	11 (44.0)	11 (16.9)
Black or African American	0	2 (8.0)	2 (3.1)
White	28 (70.0)	8 (32.0)	36 (55.4)
Multiple	1 (2.5)	0	1 (1.5)
Not Reported	6 (15.0)	3 (12.0)	9 (13.8)
Height (cm)			
Mean (SD)	168.02 (11.441)	153.17 (27.481)	162.45 (20.229)
Weight (kg)			
Mean (SD)	72.22 (16.589)	65.58 (31.900)	69.73 (23.502)
BMI (kg/m^2)			
Mean (SD)	25.47 (4.841)	26.00 (8.853)	25.67 (6.572)

BMI=body mass index; Max=maximum; Min=minimum; SD=standard deviation

The observation period for prophylactic TAK-755 treatment in the Study 3002 FAS is summarized through the additional 10 months from the initial MAA until the Day 120 response data cut date (20 Jun 2023).

For the Study 3002 FAS, treatment compliance (percentage of infusions with actual dose between 90% and 110% of the planned dose) was high throughout the study. For the prophylactic cohort, the mean percent compliance for all subjects was 98.2% (range: 80% to 100%) for rollover subjects and 96.7% (range: 84% to 100%) for non–rollover subjects; for all subjects combined, the mean percent compliance in the prophylactic cohort was 97.6% (range: 80% to 100%).

One **acute TTP event** occurred in a paediatric subject while receiving TAK-755 prophylaxis in the context of COVID-19. Another 2 acute TTP events, 1 in an adult and 1 in a paediatric subject, both occurred before dosing with TAK-755 and were resolved by treatment with TAK-755.

Six subjects (4 adult and 2 paediatric subjects) experienced 6 **subacute TTP events**, resulting in a mean annualized event rate of 0.04 (0.164) per subject-year for adolescent and adult subjects and a mean annualized event rate of 0.41 (0.639) per subject-year for paediatric subjects. The overall annualized event rate for subacute events was 0.08 (0.261) per -subject year for the overall FAS population. The 6 events resolved with the administration of a total of 6 supplemental doses of TAK-755.

For adolescent and adult subjects, the mean annualized event rate of **TTP manifestations** was 1.74 (3.223) per subject-year. with thrombocytopenia (53 events in 14 subjects), MAHA (14 events in 5 subjects), neurological symptoms (94 events in 8 subjects), and abdominal pain (15 events in 3 subjects) reported. No renal dysfunction manifestations occurred on study. These rates are similar with the results reported in the initial MAA. For paediatric subjects, the mean annualized event rate of TTP manifestations (composite endpoint not including other TTP manifestations was 2.69 (2.991) per subject-year, with thrombocytopenia (9 events in 3 subjects), MAHA (3 events in 2 subjects), and abdominal pain (1 event in 1 subject) reported. Most of the thrombocytopenia and MAHA manifestations occurred in conjunction with an acute or subacute TTP event. No neurological symptoms or renal dysfunction manifestations occurred on study. These rates are similar to the results reported for the adolescent and adult population. The rates across all outcome measures are numerically higher than those seen in the adolescent and adult population, likely a reflection of the small sample size of paediatric subjects and the shorter time with prophylactic treatment.

Overall (for all subjects), the mean annualized event rate of TTP manifestations (composite endpoint not including other TTP manifestations was 1.83 (3.192) per subject-year, with thrombocytopenia (62 events in 17 subjects), MAHA (17 events in 7 subjects), neurological symptoms (94 events in 8 subjects), and abdominal pain (16 events in 4 subjects) reported. No renal dysfunction manifestations occurred on study.

For rollover subjects, the annualized event rates of acute and subacute TTP events and TTP manifestations were maintained at rates generally consistent with those observed during TAK-755 prophylaxis in the parent Phase 3 Study 281102.

Compassionate Use Report

Nine patients with cTTP have received TAK-755 (rADAMTS13) on the grounds of compassionate use. All patients are being treated outside of a clinical trial.

All nine patients are female and were aged between 36 hours-old to 72-years-old at the time of treatment initiation. Four patients were pediatric and five were adults. Two patients started treatment during pregnancy.

Table 34: Demographics and baseline characteristics of patients with cTTP treated with TAK-755 on compassionate grounds

Characteristic	Patients Treated with TAK-755 Total (N=9)
Age at the start of treatment (years, unless specified otherwise)	
Min, Max	36 hours – 72 years
0 to <6 years old	1
6 to <12 years old	2
12 to <18 years old	1
18 to <65 years old	4
≥65 years old	1
Sex	
Male	0
Female	9
Country	
Switzerland	2
England	3
United States	3
Singapore	1

Treatment During Pregnancy

Two patients received treatment with TAK-755 40 IU/kg administered Q1W during pregnancy. Both patients received TAK-755 on compassionate grounds due to experiencing repeated strokes during pregnancy, with insufficient benefit of standard therapy from plasma-based products, and plasma exchange and imminent concern for the health of the mother and the foetus. Both patients responded well to TAK-755 treatment during their pregnancy, neither experienced any further cTTP relapses, and both delivered healthy babies.

Treatment in Pediatrics

Of the nine patients with cTTP treated with TAK-755, four are pediatric patients. The age of these patients at the start of treatment was: 36 hours-old (a neonate) and 3 teenagers.

Treatment in Adult Patients with cTTP

In addition to the two pregnant adults described above, an additional three adult patients with cTTP have received TAK-755 treatment on compassionate grounds.

TTP Chart Review Study (TAK-755-3003)

To complement data from clinical trials in cTTP with real-world data and to address existing knowledge gaps in TTP, a retrospective chart review study (Study 3003, Protocol Number: TAK-755-3003) was conducted by the sponsor to assess the health impacts of cTTP and iTTP and disease management strategies in the real-world clinical practice.

The TTP chart review study was an international, multi-center, retrospective study. The source of all data collected was the medical charts of patients with confirmed diagnosis of cTTP and iTTP. Eligible cTTP patients were included in the study if they had experienced an index event (see the definition below) between January 1, 2009, to December 31, 2017. The study period spanned from January 1, 2009 (or the earliest available data point on or after 01JAN09), to loss to follow-up, death, enrollment in a clinical trial, or December 31, 2020, whichever occurred first. For patients who were involved or enrolled in a clinical trial, only data generated before enrollment in the clinical trial was abstracted,

(i.e., patients were censored on the date they enrolled in a clinical trial). Data abstraction occurred between February 2021 and September 2022. The study design is shown in Figure 1.

The index event was defined as the earliest event during the Identification/Index period when one or more of the following occurred:

☐ The patient was diagnosed with TTP (if within the index period);

☐ The patient first received treatment for management of an acute episode, a sub-acute manifestation, or the prevention of TTP;

☐ The patient experienced a TTP-related clinical event (e.g., stroke, thromboembolic events, etc.) (if within the index period).

Convenience sampling from the target population (patients with a confirmed diagnosis of cTTP) was employed with a goal to reach 80 cTTP patients. No other sampling method was used. In this report, a subset of cTTP patients with similar characteristics to patients enrolled in TAK-755-281102 clinical trial and who received regular prophylaxis treatment were included.

Outcome definitions

The primary outcome of this post hoc analysis was the incidence rate of acute TTP episodes, which is a continuous variable derived based on the number of acute episodes while on prophylaxis and the person-years on prophylaxis during the study period.

The following secondary outcomes were described for acute episodes:

1. cTTP patients who had an acute episode while on prophylaxis during the study period

2. Precipitating factors for acute episodes (categorical, Yes/No):

3. Symptoms presented at acute episodes.

4. Hospitalizations at acute episodes:

Patient characteristics

A total of 78 cTTP patients from France (50), Germany (5), Italy (2), Spain (6), Switzerland (6), the UK (8), and the US (1) were included in the original chart review study. Among these 78 patients, 47 (60.3%) patients had ever received any prophylaxis or pre-emptive treatments (a total of 65 treatments based on different regimens). After excluding patients who did not meet eligibility criteria stated in Section 3.3.3, the final sample size for this post hoc analysis includes a total of 25 patients (17 from France, 4 from UK, 2 from Switzerland, and 1 each from Italy and US) who had similar characteristics to subjects enrolled in TAK-755-281102 clinical trial and had received regular prophylaxis (34 treatments).

In this subset of cTTP patients, female patients were predominant (68%). The majority of patients were children (40%) and young adults under 30 years of age (24%). respectively. Most patients were diagnosed under 18 years of age (64%). The missing race data was mainly due to restrictions from certain countries on reporting race. Prophylactic treatment and diagnosis of cTTP were the top two index events.

Real-world Prophylaxis Treatment Patterns

Among 25 patients who had received a total of 34 individual prophylaxis treatments during the study period, the most common prophylaxis treatment was FFP (32 treatments; 94.1%), and FVIII products were used in 2 treatments. The average duration of prophylaxis use was 6.6 years (median: 6.3; SD: 4.1; range: 0.3-12 years; IQR: 3.5-11.3 years). Clinical symptomatology (40%) was the top reason for starting prophylaxis, followed by TTP episodes frequency (28%).

Regarding the frequency of prescribed/scheduled prophylaxis treatment, there was not a standard frequency, but the vast majority of treatments were administered every 2-3 weeks.

Acute Episodes During Regular Prophylaxis

During the study period (2009-2020), 4 patients experienced a total of 9 acute episodes while on regular prophylaxis. Infection was the precipitating factor for 5 episodes (there was no precipitating factor reported for the remaining 4 episodes). 25 patients contributed to a total of 164.4 person-years on prophylaxis, thus, the incidence rate of acute episodes was 0.0548/person-year (9/164.4) in the subset of cTTP patients who received regular prophylaxis.

Among those 9 acute episodes, GI-related symptoms were the most common presenting symptoms (in 5 episodes), followed by systemic manifestations (in 3 episodes). Chest pain and dizziness were also recorded in 1 episode.

All 9 acute episodes resulted in hospitalizations: 5 of them were at in-patient wards and 4 required an ICU stay.

Several important limitations of this *post hoc* analysis need to be noted when interpreting the results. Firstly, the sponsor definition of an acute episode was based on previously established laboratory evidence for microangiopathic haemolytic anemia and thrombocytopenia (MAHAT), which may be different from other studies. Secondly, pregnancy and certain medications are known triggers for acute TTP episodes, but the study excluded prophylaxis use during pregnancy and patients with certain medical conditions (eg. HIV) from the analysis. Additionally, the study participating sites included mainly well-established specialty treatment centers, thus, some high-risk patients may be monitored more frequently by experienced TTP physicians to prevent the occurrence of acute episodes. As this is a real-world study, the criteria for defining the subset of cTTP patients in this *post hoc* analysis may not be fully comparable with the clinical trial's inclusion/exclusion criteria and can also result in selection bias (e.g., more patients with better treatment adherence).

Because the precise dates of acute TTP events were not available, the method to calculate person-year based on quarters may slightly overestimate the total person-years on prophylaxis. All the above factors could lead to an underestimation of acute episodes in this *post hoc* analysis. Lastly, the small sample size of cTTP patients limits the generalisability of the study findings to other cTTP populations.

In conclusion, the retrospective chart review study offers insights about real-world treatment of patients with cTTP. Most patients received FFP approximately every two weeks, and the incidence of acute TTP events was very low, illustrating the difficulties a comparative clinical trial is set to encounter with regards to sparse clinically meaningful outcome events.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

With this marketing authorisation application Takeda is seeking approval for Adzynma for the following indication: *Adzynma is an enzyme replacement therapy (ERT) indicated for the treatment of*

ADAMTS13 deficiency in children and adult patients with congenital thrombotic thrombocytopenic purpura (cTTP). Adzynma can be used for all age groups..

The clinical efficacy dataset supporting this dossier is based on the results of the pivotal phase 3 trial **281102**. Supportive data are available from continuation phase 3b study **TAK-755-3002** and from the compassionate use programme.

Phase 3 trial 281102 is a randomised, controlled, open-label, 2 period crossover study with a single arm continuation phase evaluating the safety and efficacy of TAK-755 in the prophylactic and on-demand setting. Subjects with severe congenital thrombotic thrombocytopenic purpura (ADAMTS13 activity <10%) on routine prophylaxis with no acute event could enter the trial via the prophylactic cohort and be randomised to 6 months of treatment either with standard of care or TAK-755 followed by 6 months of treatment with the other treatment modality and subsequently enter the continuation phase of another 6 months of TAK-755 treatment. In the case of an acute TTP event, subjects could enter the trial via the on-demand cohort for a randomised treatment of the acute event with either SoC or TAK-755. Subjects could then proceed to the prophylactic cohort, re-enroll for another acute event or leave the trial.

The cross-over design of the prophylactic cohort was discussed and supported in the previous scientific advices. This also allows intra-patient data comparison and accounts for possible imbalance between cohorts in this small study. There was no wash-out period before treatment initiation in Period 1 or 2. Even though this somewhat complicates PK/PD and efficacy assessment, the design is accepted given the risks of low ADAMTS13 levels. To account for this, a sensitivity analysis was performed with exclusion of the first 14 days of the treatment period.

The prophylactic treatment consisted of 40 IU/kg apadamtase Q1W or Q2W (depending on the subjects' pretrial SoC regimen). Thus, the dosing interval Q1W and Q2W was assigned based on the individual subject's SoC dosing frequency before entering the main study. This strategy does not allow proper evaluation of the dosing interval efficacy, as two populations might differ, e.g. subjects who received SoC Q1W before the study display likely a more severe phenotype than subjects on Q2W. The applicant was asked to present the baseline characteristics data and discuss the differences between two groups and possible impact on the efficacy data assessment. In the response to the D120 LoQ, it became apparent that baseline characteristics of the patients who received Q1W or Q2W dosing were rather similar, including their history of acute TTP events. Therefore, based on the data presented it is not possible to conclude that patients with more severe disease had received Q1W dosing with SoC, even though the history details on other TTP manifestations were not provided. Section 4.2 of the SmPC recommends that the prophylaxis dosing frequency may be adjusted to 40 IU/kg of body weight once weekly based on clinical response.

The prophylactic SoC dose and treatment regimen was to be determined by the investigator and could be any of the following: FFP; Pooled S/D treated plasma; FVIII:VWF concentrates. If an acute TTP event occurred during prophylaxis, subjects were to receive an initial dose of 40 IU/kg TAK-755, a subsequent dose of 20 IU/kg TAK-755 on Day 2 and additional daily doses of 15 IU/kg TAK-755 until 2 days after the acute TTP event was resolved (acute TTP event resolution defined as platelet count $\geq$ 150,000/µL or platelet count within 25% of baseline OR elevation of LDH $\leq$1.5$\times$ baseline or $\leq$1.5$\times$ ULN). Subjects with an acute event who entered the on-demand treatment cohort received the same dosing regimen for the treatment of their acute TTP event.

The *primary efficacy outcome* was the incidence of acute TTP events among subjects receiving either TAK-755 or SoC prophylactically during the corresponding treatment periods. *Secondary efficacy endpoints* were defined to inform on the *prophylactic effect* of treatment with rADAMTS13 via the incidence of isolated TTP manifestations during prophylaxis: thrombocytopenia, MAHA, renal dysfunction, neurologic symptoms (e.g., headache and migraine), and abdominal pain. Additional

secondary endpoints were defined to investigate the effect of rADAMTS13 in the *on demand treatment* of acute TTP events: proportion of acute TTP events responding to TAK-755 treatment and time to resolution of acute TTP events following initiation of treatment with TAK-755 or SoC. In addition, the incidence of dose modifications, both prompted by a subacute event and not prompted by such an event, were investigated.

Phase 3b trial TAK-755-3002 is a single arm, open label continuation study investigating the efficacy and safety of prophylactic and on demand treatment with rADAMTS13 treatment up to 3 years. Subjects completing pivotal trial 28102 were eligible to roll over into the continuation trial, and non-rollover subjects fulfilling the in- and exclusion criteria could also enter this trial. The primary objective of this study is safety, and the key secondary efficacy outcome is the number and incidence rate of acute TTP events in subjects with cTTP undergoing prophylactic treatment with TAK-755. In addition, time to resolution of a treated acute TTP event as well as incidence of isolated TTP manifestations and the incidence of dose modifications were defined as secondary endpoints. Prophylactic and on demand doses of TAK-755 were identical to those employed in the pivotal trial.

Limited supportive data are available from the **compassionate use programme**, through which patients who were not eligible for a clinical trial could receive treatment with rADAMTS13.

The **in- and exclusion criteria** select for generally healthy subjects with severe congenital thrombotic thrombocytopenic purpura (ADAMTS13 activity <10%) aged 0 - 70. Importantly, pregnant patients were excluded from participation in the clinical investigation programme, and female subjects experiencing a pregnancy during participation in trial 281102 or 3002 had to discontinue from the respective study. As pregnancy is a major trigger of acute TTP episodes and the use of rADAMTS13 in pregnant patients is highly likely after a potential marketing authorisation, this is an important limitation of the available dataset supporting the efficacy and safety of TAK-755. Taking into account the accumulated clinical trial experience in adult and paediatric subjects as well as the favourable outcomes of two pregnant patients treated within the compassionate use programme, the corresponding exclusion criterion in continuation study 3002 is reconsidered by the Applicant in order to allow closing of this significant information gap. The required ADAMTS13 activity levels are not mentioned in the indication. This can be agreed, since cTTP is by definition characterised by severe ADAMTS13 deficiency with activity levels <10%, as per various guidelines. Patients with acquired TTP were excluded from the study, which is agreed. It is however noted that a study in iTTP patients has recently been completed.

The choice of standard of care prophylaxis as **comparator** in the pivotal trial is considered adequate, as depending on availability and experience of the treatment centre different medicinal products can be used for the prophylactic and on demand treatment of patients with cTTP. Most frequently, FFP is the treatment of choice, but also S/D plasma and plasma derived FVIII:VWF concentrates are used to provide the missing ADAMTS13 activity.

By solely defining 'determination of the incidence of acute TTP events under SoC and TAK-755 prophylactic treatments' as the **primary trial objective**, the methodological options for the comparative assessment of prophylactic treatment benefit of TAK-755 vs SoC remain vague from the planning perspective. In this context, it needs to be noted that in former EMA-SA interaction, the Applicant was strongly advised to prospectively explore relevant effect sizes and precision of the effect estimates for treatment differences. In the advice letter from 2016 CHMP acknowledged that a strict test for superiority might not be feasible in a situation with such few patients. However, it was pointed out that the study nonetheless needed to provide compelling evidence of the clinical benefit. Now, in retrospect, the main issue in this context is the lack of a thorough suitability-check of 'acute TTP event incidence' as primary efficacy endpoint, in particular in light of the chosen (primary) 6 months observation periods. During SA interaction, substantial heterogeneity among patients for acute event

incidences was discussed as potential limiting factor, which led to recommendations to either implement longer (than 6 months) observation periods or to enrich the study population to target expectedly higher incidences.

As neither of these recommendations was followed, the primary trial objective to go for a side-by-side incidence estimation appears as cautious consequence. The lack of an attempt to formalise the primary objective following a non-inferiority approach is seen as missed opportunity to better inform regulatory assessment and decision making. In order to inform such an approach, it would have been necessary to make some assumptions regarding expected incidence of acute TTP events in patients not receiving prophylactic treatment (corresponding to a natural disease course). As such considerations were not presented in the dossier (and as actually observed incidences in both treatment arms were uninformatively low), the Applicant was asked to provide further background information on available knowledge and corresponding expectations concerning the natural disease course with focus on acute TTP-event incidence. The applicant has summarised the available sparse data on incidence of TTP events and natural course of the disease. There is major uncertainty with regards to the reliability of incidence data, as it is likely that due to its manifold presentation the diagnosis of cTTP is often delayed or such events are not adequately diagnosed (Kremer Hovinga et al; Hämostaseologie 2020). It is agreed with the Applicant that incidence rates as presented by Schraner *et al,* 2023 ASH Annual Meeting) can be considered a more accurate estimate of disease activity, especially as it uses an intra-patient comparison. The reported event rates [(95% CI) for acute episodes during prophylaxis exposure and non-exposure periods were 272.4 (230.8-319.3) per 1000 person-years and 520.4 (401.6-663.3) per 1000 person-years, respectively] correspond to the low rate of cTTP events observed in the clinical trial programme. Thus, the importance of taking the outcomes of the secondary endpoints in account and assessing the totality of the presented data is emphasised.

Sample size estimation was not performed, as no formal statistical testing was planned. The sample size was rather driven by practical considerations and feasibility in this rare disease, which is acknowledged and was agreed within the Scientific Advices. In total approximately 48 subjects (36 adults and 12 adolescent or paediatric subjects) were to be enrolled in the prophylactic cohort. For the OD cohort approximately 6 adult subjects and 3 adolescent or paediatric subjects, were to be enrolled, which is considered very limited. Initially, up to 20 subjects were planned to be enrolled in the OD cohort based on Scientific Advice communication. The applicant was asked to comment on the low enrolment rate in the OD cohort in both phase 3 studies. The applicant has explained that these difficulties in finding on-demand patients are likely due to the fact that patients with TTP who suffer from acute TTP events usually are on prophylaxis, as also evident from the registry data. Patients with a milder presentation are less likely to develop acute TTP. So, in general on-demand use of this drug is expected to be limited.

The primary endpoint was defined in accordance with the primary objective of this study, and the critical comments above regarding the methodological weaknesses of this "side-by-side investigation" of TAK-755 and SoC instead of a more direct comparative analysis are valid for both primary objective and primary endpoint in a similar fashion. The secondary and exploratory efficacy endpoints are considered meaningful and clinically relevant.

The original global protocol was amended 7 times, but these amendments are not expected to have influenced the conduct of the study in a negative way. A significant number (60%) of the subjects had at least one major protocol deviation that were related to the protocol schedule. The applicant was asked to discuss the possible reasons for this high number of protocol schedule deviations. The applicant provided the underlying reasons for the high number of protocol schedule deviations. Among others, these include the low threshold for classifying something as a major deviation, the complexity of the protocol schedule (including frequent study visits and study duration) and impact of COVID

pandemic. These are considered valid reasons and are unlikely to impact the study results in a significant way.

The identified protocol deviations concern most frequently the timing and schedule of laboratory or other assessments and are not considered to impact on the efficacy evaluation. A *post-hoc* analysis of acute and subacute TTP events with/without high test enrolling site was presented. An impact of the identified GCP non-compliance events (use of paper diaries instead of telehealth visits for home infusions) on the outcomes is unlikely.

Efficacy data and additional analyses

Efficacy data for the proposed prophylactic dosing scheme are available from the **ongoing pivotal trial 281102** from a planned interim analysis which was to be performed after 30 evaluable adult or adolescent subjects had completed Period 3 of the Prophylactic Cohort. The data cut-off was on 12 Aug 2022, and data from 47 subjects are available in the FAS of the prophylactic cohort. For the on-demand cohort, data from 5 subjects are included in the FAS. Subjects were not randomized to a dosing frequency in the study and, for the most part, continued based on the SoC frequency they were receiving prior to the study. Approximately 20% of subjects received Q1W treatment during the study and the majority received Q2W prophylaxis. Those data therefore support the initially proposed posology in section 4.2, even though the PK outcomes appear to favour the Q1W scheme. However, an adjustment of the treatment interval based on individual response is further recommended in the SmPC, which may overcome uncertainties with regards to the duration of the PK response.

Due to the very low number of acute TTP events, no inferential statistical analysis but only descriptive statistics are presented for the primary endpoint, i.e. the incidence of acute TTP events among subjects receiving either TAK-755 or SoC prophylactically during the corresponding treatment periods. Before study start, the expected low number of observable acute events was repeatedly addressed by CHMP in the EMA SA procedures in 2016 and 2018 and a longer observation period than 6 months, at least 12 months, was strongly advised. However, even if the treatment periods of TAK-755 ORT and TAK-755 SIN are taken together for a full 12 months of prophylactic ERT, no acute event could be observed. In the SoC cohort, during 6 months of prophylactic treatment, one acute TTP could be observed. Even after doubling this observation period, incidence of acute TTP events would likely remain very low and no relevant gain in precision in the estimates of the treatment effect could be expected. At the end, the outcome of 0 events can either be seen as a direct consequence of satisfactory efficacy of ERT using rDAMTS13, or as a result of the unpredictable natural disease course of hereditary TTP featuring discontinuous event incidence, or (most likely) a mixture of both. Thus, no firm conclusions regarding the efficacy of TAK-755 in the prophylactic setting can be drawn from the primary outcome of the pivotal study.

In light of the uninformative nature of the primary efficacy outcome, the analyses for the secondary efficacy endpoints pertaining to the **effect of rADAMTS13 as a prophylactic treatment** increase in importance. Of note, secondary analyses were prespecified in the SAP to be performed in the FAS, however, analysis was actually done in the MFAS. As these two analysis sets diverge by one patient only, this issue is not further pursued. The incidence of isolated TTP events, i.e. thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), renal dysfunction, neurological symptoms and abdominal pain during prophylactic treatment favours TAK-755 with an overall annualised incidence of 2.28 for rADAMTS13 and 3.68 for SoC. Similar TAK-755 trends were seen for each investigated sign or symptom except for renal dysfunction. A numerically lower proportion of subjects being treated with TAK-755 than SoC experienced subacute events and received additional doses of the respective medicinal product, resulting in an annualised event rate of 0.13 for rADAMTS13 and 0.29 for SoC. The number of dose modifications not prompted by an acute TTP event was low and evenly distributed

across treatments. One acute TTP event occurred in a subject being treated with SoC on the final dose and dosing frequency after any dose and/or schedule modifications occurred.

In order to provide more in-depth assessment of secondary outcomes, the Applicant was asked to provide efficacy outcome data on (sub)acute events, TTP manifestations for Period 1 and Period 2 separately. A direct comparison of each isolated TTP manifestation during period 1 and 2 for each subject of the pivotal trial was submitted by the Applicant. These data show that subjects experienced a lower rate of disease manifestations while receiving TAK-755 than while receiving standard of care, further supporting the efficacy of rADAMTS13 in the prophylactic setting.

Comparison of Q1W and Q2W dosing regimens is difficult due to the low number of subjects who received a Q1W regimen, as well as likely differences between two populations, as the regimen was not randomised. In the light of this, the Applicant was asked to reflect upon the observed higher incidence of neurological symptoms and abdominal pain in the Q1W group compared to the Q2W group. In response, the Applicant states the difficulties in drawing conclusions on possible reasons given the small sample size. Subjects that reported frequent neurological events were all female and from the same site in the UK. No clear conclusions can be drawn and the issue is not pursued further. Section 4.2 of the SmPC recommends that a posology of 40 IU/kg of body weight once every other week and that the prophylaxis dosing frequency may be adjusted to 40 IU/kg of body weight once weekly based on clinical response.

The efficacy endpoints investigating the **effect of TAK-755 in the on demand treatment of acute TTP events** were 1) the proportion of acute TTP events responding to TAK-755 treatment and 2) the time to resolution of acute TTP events following initiation of treatment with TAK-755 or SoC, in both the Prophylactic and the OD Cohorts throughout the duration of the study.

Efficacy for this treatment modality is difficult to assess due to the very limited data available. No acute events with TAK-755 occurred in the prophylaxis cohort. Only 1 out of 2 subacute events reported on TAK prophylaxis needed to be treated.

One acute TTP event which met the protocol definition in the on-demand cohort was treated with rADAMTS13, did respond to treatment and was resolved after a treatment duration of 3 days. The one acute event treated with SoC in the prophylactic cohort appears to have been resolved after 3 days as there were no further study visits. An additional SoC-treated acute event in the OD cohort was reported resolved after 3 days but did not meet the definition of a resolved event. In conclusion, time to resolution of acute events appeared to be comparable for TAK-755 and SoC.

Overall, the proposed on-demand posology was considered to be insufficiently substantiated. The applicant was asked to further justify the proposed posology across the age groups, using e.g. popPK modeling and ADAMTS13 levels reported in literature with FFP use for the treatment of acute events. In the response to the D120 LoQ, the Applicant clarified that the selection of the OD dose was based on the goal to achieve normal levels of ADAMTS13 activity as soon as possible and maintain them during the ongoing acute event until it is resolved. The target threshold of 80% was chosen. Definition of "normal" levels of ADAMTS13 may vary per country/region, but 80% is within these norms in any case. Therefore, the approach is supported. Based on the PopPK modelling and (scarce) data from the main study, it can be concluded that the loading dose allows reaching 80% of ADAMTS13 activity fast and maintenance dose allows keeping it stable. For treatment of acute or suspected acute events in the on-demand (OD) cohort, while SoC administration resulted in peak post-infusion ADAMTS13 activity between 0.1 to 0.4 IU/mL, TAK-755 administration resulted in ADAMTS13 activity levels that were always higher and in the normal range (>80% activity or >0.8 IU/mL). Of note, two acute events treated on demand with TAK-755 (one event met protocol-defined criteria for an acute event and the second one not) were resolved within 3 and 5 days. One paediatric subject on prophylaxis with Adzynma experienced acute TTP in the OLE study which was considered resolved two days later.

To support the proposed ADAMTS13 target range and TAK-755 dosing, the Applicant also cited literature that showed that the levels of ADAMTS13 activity achieved after treatment with FFP appear to be very variable, but about the ranges of 30-60%. These ranges are lower compared to the ADAMTS13 activity achieved after TAK-755 administration. However, the provided literature seems to refer to the prophylactic treatment with FFP and not on-demand.

Overall, even though the data is limited, available PK/PD data and scarce data from the OD cohort and literature data support the on-demand dosing. In general, OD use is expected to be very limited, as patients with active disease are usually on prophylaxis, as evident from the registry data.

Supportive efficacy data are available from a planned interim analysis of **ongoing continuation trial 3002.** Data from 36 new and rollover subjects were included in the FAS of the prophylactic cohort and zero subjects were enrolled in the on-demand cohort at the data cut-off. The primary outcome of study 3002 is safety, and the secondary efficacy endpoints investigate the effect of rADAMTS13 for both prophylaxis and treatment of cTTP. No acute TTP events occurred while subjects received TAK-755 prophylaxis for a mean exposure of 0.58 years and up to 1.4 years. One acute TTP event occurred during screening in a non-rollover subject, prior to initiating dosing with TAK-755. The acute event was resolved by treatment with TAK-755 in 6 days. More than half of the subjects (58.3%) did not experience any of the protocol defined TTP manifestations (thrombocytopenia, microangiopathic haemolytic anaemia [MAHA], neurological symptoms, renal dysfunction, or abdominal pain) while receiving TAK-755 prophylaxis. Overall, the annualised incidence of isolated TTP manifestations was 3.05. Three subjects experienced 3 subacute TTP events during the study, resulting in an annualised incidence of 0.13. These outcomes are comparable to those from the pivotal trial 281102 and provide supportive evidence of the continued efficacy of rADAMTS13 in the prophylactic setting.

Further supportive data can be gained from the experience of patients receiving rADAMTS13 through **compassionate use**. Nine female patients were treated with TAK-755, ranging in age from 36 hours to 72 years.

Importantly, outcomes from two pregnant patients are available, as pregnancy was an exclusion criterion in the clinical trial programme. One pregnant female experienced thrombocytopenia that was unresponsive to plasmapheresis and had suffered an ischaemic stroke during the current pregnancy. The patient delivered a healthy infant and continues on Q2W rADAMTS13 prophylaxis. The second female patient suffered a stroke during the second trimester of her pregnancy and was managed with plasma exchanges but soon relapsed into another acute TTP event. With Q1W rADAMTS13 treatment, the patient achieved remission with an intact pregnancy. The compassionate use report states that the pregnancy of the patient was intact and ongoing during the last communication with the investigator. The baby was delivered by an emergency caesarean section at because of pathological foetal doppler ultrasound, cardiotocography findings, and intrauterine growth retardation. The physician administered an additional dose of 3000 IU of TAK-755 to the mother. No cTTP relapse has occurred in the patient, and the preterm child is alive. The treating physician planned to continue weekly TAK-755 administration, to prevent cTTP relapses.

The neonate who started with TAK-755 treatment at an age of 36 hours has been receiving rADAMTS13 at a dose of 40 U/kg every 10 days and has reached all developmental milestones at 2 years of age. This patient has since joined Study 3002. As of the Day 120 response data cut, the subject had received regular prophylaxis averaging every 10 days from 36 hours old until approximately 3 years of age, without development of anti-ADAMTS13 antibodies. On the 3002 study, the subject experienced 8 AEs, all mild in severity, and one subacute event (in association with an influenza A infection) which was treated with a supplemental dose of TAK-755.

Twelve **paediatric patients** are enrolled in pivotal trial 281102, 4 subjects each are <6, 6-<12 and 12-<18, respectively. As younger subjects could only enter the trial after some experience was

accrued with adult subjects, the efficacy outcomes are mostly driven by adult and adolescent subjects. As the Applicant aims for an indication without a lower age limit, it was asked to provide updated paediatric efficacy and safety data to support the currently proposed indication. As requested, the MAH provided efficacy and safety data on paediatric subjects from an updated data cutoff date of 11 August 2023 for Study 281102 and 20 June 2023 for Study 3002 as well as the pooled analysis. The Day 120 response data cut provides safety and efficacy data from Study 281102 from 8 paediatric subjects, 4 subjects <6 years old and 4 subjects 6 to 12 years old who have all completed the main comparative cross-over portion of the study (ie, Periods 1 and 2). A total of 3 paediatric subjects (age 6-12 years old) have completed Period 3, 4 paediatric subjects (age <6 years old) completed 4 weeks of Period 3, and one paediatric subject (age <6 years old) completed the OD cohort. Study 3002 contributes to the paediatric dataset with the addition of 6 pediatric non-rollover patients <12 years old, and 7 rollover and 3 non-rollover patients 12 to <18 years of age. The paediatric population in Studies 281102 and 3002 now make up over 27% of the total subject population (20/72 subjects in ISS are <18 years of age). In general, the efficacy outcomes of the paediatric patients are consistent with the adolescent and adult data and support the efficacy of TAK-755 in paediatric subjects.

Based on the popPK modelling, a higher dosing frequency might be needed in younger paediatric subjects due to the higher clearance. The applicant was asked to discuss the appropriateness of the same prophylactic dosing frequency for all age categories. In response, the Applicant provided additional popPK model-based simulations for the target cTTP paediatric patients with typical body weight assumption of 10, 20, and 40 kg, respectively. AUC and Cave were considerably lower in the 10kg group (at both dosing frequencies QW and Q2W). With the response to the D120 LoQ, the Applicant submitted efficacy data for all subjects based on an updated data cutoff date of 11 August 2023 for Study 281102 and 20 June 2023 for Study 3002. This new data cut provides an additional 12 months of data for Study 281102 and an additional 10 months of data for Study 3002. The updated efficacy outcomes are generally consistent with the data provided in the initial MAA. The efficacy of TAK-755 is shown to be durable in a prophylactic setting.

Additional efficacy data needed in the context of a MA under exceptional circumstances

The marketing authorisation application for Adzynma had initially aimed for a full approval of this medicinal product for the enzyme replacement therapy of congenital TTP. However, cTTP is an ultra-rare orphan disease with an unpredictable nature featuring discontinuous event incidence, which renders the provision of firm clinical evidence for efficacy unfeasible. Due to the extremely low patient numbers and the rare and unpredictable incidence of TTP events it is not considered reasonable to expect sufficient data that could inform a non-inferiority or superiority approach versus standard of care within a reasonable timeframe post-marketing. Data from the Hereditary TTP Registry in 123 patients with confirmed cTTP resulted in an estimate of a median rate of 0.10 (range: 0.02-8.91) acute episodes per year (van Dorland, 2019). Therefore, the totality of data has to be taken into account for the benefit risk consideration for Adzynma, and the Applicant was asked to provide a justification for a marketing authorisation under exceptional circumstances according to Article 14(8) of Regulation (EC) 726/2004, as already discussed in the scientific advice procedure EMEA/H/SAH/068/1/2016/PA/III. With the responses to the D180 LoOI, the Applicant has agreed to apply for MAEC and has submitted a justification why Adzynma fulfils the requirements laid down part II.6 of Annex I of Directive 2001/83/EC. The justification based on the ultra-rarity of the disease, the very limited data with regards to the natural history and the consequential non-comprehensiveness of the dossier is considered acceptable from a regulatory point of view.

In addition, the Applicant has agreed to commit to the following SOBs:

- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.
- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.
- In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.

In addition, a PASS is also requested (please see safety section).

2.6.7. Conclusions on the clinical efficacy

The interpretability of submitted data supporting the efficacy of Adzynma in the treatment of cTTP in the prophylactic and on-demand setting is limited due to very low event occurrence in the primary outcome measure. In this situation, the outcomes from the secondary efficacy endpoints take an increased importance, and for the consideration of the benefit risk balance, the totality of data, including preclinical data, has to be taken into account.

Due to the exclusion of pregnant women from the clinical trial population the external validity of the observed results is negatively impacted, as pregnancy is a relevant trigger for acute TTP events and the use of TAK-755 in pregnant women is highly likely after the granting of a MA. Data from the compassionate use programme provide reassuring supportive evidence of the beneficial effects of treatment during pregnancy whereas other measures (plasma derived treatments, plasma exchange) were insufficient.

Taking into account the rarity of the disease and the low incidence of TTP events during the clinical trial period, no inferential statistical analyses but presentation of data via descriptive statistics only were planned and presented for the primary endpoint. As no firm conclusions regarding the efficacy of the product to prevent the acute attacks can be drawn, the totality of the data has to be taken into account in order to support a positive benefit-risk evaluation, and uncertainties remain with regard to efficacy, safety and dosing, which cannot realistically be addressed via longer follow-up or another clinical trial in the post marketing setting.

Therefore, the Applicant agreed that a marketing authorisation under exceptional circumstances is the appropriate way forward for the Adzynma dossier and has submitted a justification for fulfilling the requirements laid down part II.6 of Annex I of Directive 2001/83/EC.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a MA under exceptional circumstances:

- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.
- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.
- In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

By the cut-off date of 12 Aug 2022 for this interim analysis, 65 unique subjects have been exposed to TAK-755 through clinical trials. In addition, 9 patients with cTTP have been exposed to TAK-755 through CPU.

The applicant provided updated safety data with a cut-off date of 11 Aug 2023 for study 281102 and 20 Jun 2023 for study TAK-755-3002. No new data have been provided for the completed Phase 1 study (Study 281101) since the initial MAA.

In the phase 1 study 281101, a total of 15 subjects received an infusion of either 5 IU/kg (n=3), 20 IU/kg (n=3), or 40 IU/kg (n=9) TAK-755; were hospitalised for at least 96 hours of post-dose inpatient monitoring; and completed the study with a final visit at 28±3 days after TAK-755 infusion. In the phase 3 study 281102, 48 subjects received at least one dose of TAK-755 (40 IU/kg). In the phase 3b continuation study 3002, 36 subjects received at least one dose of TAK-755 (40 IU/kg).

TAK-755 exposure in cTTP clinical trials has ranged from a single infusion of 5 IU/kg (international units per kg) to repeated infusions of 40 IU/kg once every 2 weeks (Q2W) or once a week (Q1W) for over 3 years. This marketing application, updated with the data of the D120 responses, includes cTTP safety data from 2 subjects that have been exposed to TAK-755 for more than 4 years, 12 subjects have been exposed for 36 to <48 months, 16 subjects have been exposed for 24 to <36 months, 17 subject have been exposed for 12 to <24 months, 19 subjects have been exposed for 6 to <12 months, and 5 subjects have been exposed to TAK-755 for <6 months, all at the planned commercial dose of 40 IU/kg IV Q2W or Q1W. Three subjects were exposed to on-demand TAK-755 and had a total exposure of 0.05 subject years. With the cut-off date for Day 120 responses, in pooled data from Studies 281102 and 3002, 72 subjects received prophylactic treatment (71 subjects on TAK-755 and 48 subjects on SoC; 1 subject enrolled twice in the prophylactic cohort). In addition, there were 7 subjects (6 unique subjects) treated in the on-demand cohort in Study 281102 and Study 3002, 3 of these subjects were exposed to TAK-755 on-demand treatment.

The prophylactic cohort was composed of 52 adult subjects (72.2%) and 20 paediatric subjects (27.7%) (7 subjects [9.7%] each in the age groups of 6 to <12 years and 12 to <18 years and 6 (8.3%) subjects in the age group of 2 to <6 years).28 males (38.9%) and 44 females (61.1%); 40 white subjects (55.6%), 17 Asian subjects (23.6%), 2 black or African-American subjects (2.8%), 1 subject of multiple races (1.4%), and 12 subjects for whom race was not reported (16.7%). The on-demand cohort was composed of 7 adults (100%); 4 males (57.1%) and 3 females (42.9%); 2 Asian subjects (28.6%), 3 white subjects (42.9%), and 1 subject of multiple races (14.3%).

Table 35: Extent of exposure to study design in pooled studies 281102 and 3002

	Prophylactic Cohort		On-demand Cohort	
Parameter	**TAK-755** (N=71)	**SoC** (N=48)	**TAK-755** (N=3)	**SoC** (N=4)
Total exposure, subject-years	124.4	29.9	0.05	0.04
Total duration of exposure, days				
Mean (SD)	588.8 (359.79)	209.6 (91.88)	5.7 (1.53)	3.8 (0.96)
Median (min, max)	556.0 (1, 1429)	196.0 (22, 626)	6.0 (4, 7)	3.5 (3, 5)

Parameter	Prophylactic Cohort		On-demand Cohort	
	TAK-755 (N=71)	**SoC** (N=48)	**TAK-755** (N=3)	**SoC** (N=4)
Total duration of treatment, n (%)				
0 to <6 months	5 (7.0)	2 (4.2)	N/A	N/A
6 to <12 months	19 (26.8)	44 (91.7)	N/A	N/A
12 to <24 months	17 (23.9)	2 (4.2)	N/A	N/A
24 to <36 months	16 (22.5)	0	N/A	N/A
36 to <48 months	12 (16.9)	0	N/A	N/A
≥48 months	2 (2.8)	0	N/A	N/A
Total number of infusions				
Mean (SD)	51.1 (39.00)	16.9 (6.48)	5.3 (1.15)	3.8 (0.96)
Median (min, max)	44.0 (1, 162)	15.0 (2, 30)	6.0 (4, 6)	3.5 (3, 5)
Average body weight-adjusted dose, IU/kg[a]				
Mean (SD)	40.29 (1.212)	-	19.46 (3.301)	-
Median (min, max)	40.01 (36.5, 45.2)	-	19.90 (16.0, 22.5)	-
Average actual/planned dose ratio				
Mean (SD)	1.012 (0.0387)	0.998 (0.0191)	1.003 (0.0058)	1.000 (0.0000)
Median (min, max)	1.000 (0.987, 1.254)	1.000 (0.933, 1.066)[b]	1.000 (1.000, 1.010)	1.000 (1.000, 1.000)

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; FFP=fresh frozen plasma; IU=international unit; ISE=integrated summary of efficacy; ISS=integrated summary of safety; max=maximum; min=minimum; N/A=not applicable; PKI=pharmacokinetics assessment period 1; SD=standard deviation; SoC=standard of care

[a] The average weight-adjusted dose was derived differently for TAK-755 and SoC. The TAK-755 values were calculated from actual potency of ADAMTS13 activity for TAK-755. The SoC values were calculated from measurement of ADAMTS13 activity in the FFP infused prophylactically in n=30 subjects before start of PK-I in Study 281102.

2.6.8.2. Adverse events

Study 281101 (single-dose phase I first in human study)

In total 12/15 (80.0%) subjects reported 39 TEAEs (treatment emergent adverse events). In Cohort 1 (5 IU/kg BW) 3/3 (100.0%) subjects experienced 17 TEAEs, every subject reported at least one TEAE. In Cohort 2 (20 IU/kg BW) 2/3 (66.7%) subjects experienced 9 TEAEs. One subject reported TEAEs that were considered related to the study procedure. In Cohort 3 (40 IU/kg BW) 7/9 (80.0%) subjects reported 13 TEAEs. A total of five TEAEs were considered related to the investigational product. Two subjects of Cohort 3 reported TEAEs that were considered related to the study procedure.

Table 36: Overview of treatment emergent adverse events (study 281101: safety analysis set)

	Statistic	5 U/kg (N=3)	20 U/kg (N=3)	40 U/kg (N=9)	Total (N=15)
TEAEs	n (%) E	3 (100.0) 17	2 (66.7) 9	7 (77.8) 13	12 (80.0) 39
	[95% CI]	[0.29,1.00]	[0.09,0.99]	[0.40,0.97]	[0.52,0.96]
Severe TEAEs	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]
TEAEs Related to Investigational Product	n (%) E	0 (0.0) 0	0 (0.0) 0	3 (33.3) 5	3 (20.0) 5
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.07,0.70]	[0.04,0.48]
TEAEs Related to Study Procedure	n (%) E	0 (0.0) 0	1 (33.3) 1	2 (22.2) 3	3 (20.0) 4
	[95% CI]	[0.00,0.71]	[0.01,0.91]	[0.03,0.60]	[0.04,0.48]
TESAEs	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]
TEAEs Leading to Discontinuation of Study	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]
TEAEs Leading to Discontinuation/Interruption of Study IP	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]
TEAEs Leading to Death	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]
Breakthrough TEAEs	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]
TESAEs Related to Investigational Product	n (%) E	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.00,0.71]	[0.00,0.71]	[0.00,0.34]	[0.00,0.22]

CI = Confidence interval. IP = Investigational Product. TEAE = Treatment emergent adverse event. TESAE = Treatment emergent serious adverse event.
n = Number of subjects with at least one TEAE in each category. N = Total number of subjects in the relevant analysis population. E = Number of mentions of TEAEs in each category. % = Percentage of subjects in each category relative to the number of subjects in the relative analysis population.
A TEAE is defined as any AE that started or worsened in severity on or after study IP administration and prior to the Study Completion Visit.
A 'related' TEAE is defined as a TEAE with relationship to investigational product as 'possibly related' or 'probably related'.
95% confidence interval obtained from an exact Clopper-Pearson test.
TEAEs leading to discontinuation of study determined from the Completion/Termination eCRF form.
TEAEs leading to discontinuation/interruption of study IP determined from the Adverse Event eCRF form.
Generated by: T16.sas

Considering the System Organ Classification (SOC), 4/15 (26.7%) subjects reported 18 TEAEs of the nervous system disorders, 6 gastrointestinal disorders, 4 infections and infestations. 3/15 (20.0%) subjects reported 3 events of nasopharyngitis, 2/15 subjects (13.3%) reported 9 events of headache and 2/15 subjects (13.3%) reported 2 events of dizziness.

In Cohort 1 (5 IU/kg BW) a majority of the TEAEs reported by 1 of the 3 subjects were in the SOC nervous system disorders (13 events), headache (6 events) and paraesthesia (4 events). In Cohort 2 (20 IU/kg BW) 1 of the 3 subjects reported 3 events of headache under the SOC nervous system disorders. In Cohort 3 (40 IU/kg BW) a majority of the TEAEs reported were in the SOC gastrointestinal disorders (3/9 (33.3%) subjects, 4 events), nervous system disorders (2/9 (22.2%) subjects, 2 events), and general disorders and administration site conditions (3 events).

All TEAEs considered related to IP (investigational product) occurred in Cohort 3 (40 IU/kg). 2/9 (22.2%) subjects experienced TEAEs of the SOC "Gastrointestinal Disorders" (flatulence, nausea) each experienced by one subject (11.1%). 1/9 (11.1%) subject experienced "Von Willebrand's Factor Activity Decreased" and "Von Willebrand's Factor Antigen Decreased".

All of the reported TEAEs were mild or moderate in severity.

Pooled Studies 281102 (phase 3 study) and TAK-755-3002 (single-arm continuation study)

The Integrated Summary of Safety (ISS) set (pooled database of Studies 281102 and 3002) updated by the data of the D120 responses consisted of 52 adult subjects (72.2%) and 20 paediatric subjects (27.7%) (7 subjects [9.7%] each in the age groups of 6 to <12 years and 12 to <18 years and 6 (8.3%) subjects in the age group of 2 to <6 years). The incidence of TEAEs was reported using an exposure-adjusted event rate (EAER) approach, to account for the difference in exposure duration between TAK-755 and SoC.

The prophylactic cohort of pooled studies 281102 and 3002 had an average exposure time of 588.8 days for TAK-755 and 209.6 days for SoC. 66/71 (93.0%) subjects experienced 1028 TEAEs (826.2 events/100 subject-years (SY)) when treated with TAK-755. 44/48 (91.7%) subjects experienced 332 TEAEs (1108.8 events/100SY) when treated with SoC.

6/71 (8.5%%) subjects experienced 24 TEAEs considered related to TAK-755 (19.3 events/100SY). 23/48 (47.9%) subjects experienced 40 TEAEs considered related to SoC (133.6 event/100SY). Most of the TEAEs were considered of mild or moderate. However, 35 severe TEAEs occurred in 10/74 (14.1%%) subjects when treated with TAK-755 (28.1 events/100SY). 7/48 (14.6%) subjects experienced 14 severe TEAEs (46.8 events/100SY) when treated with SoC.

Table 37: Overall Summary of Treatment-emergent Adverse Events During Prophylactic Treatment in Individual Studies 281102 and 3002, n (%)

	Study 281102			Study 3002		
	Periods 1 & 2		Period 3			
Parameter	**SoC** (N=48)	**TAK-755** (N=47)	**TAK-755** (N=46)	**Rollover** (N=40)	**Non-rollover** (N=25)	**Total** (N=65)
All TEAEs	44 (91.7) 303	39 (83.0) 276	32 (69.6) 226	33 (82.5) 367	21 (84.0) 124	54 (83.1) 491[a]
Excl. related/possibly related to cTTP[b]	43 (89.6) 207	38 (80.9) 229	31 (67.4) 171	33 (82.5) 245	20 (80.0) 96	53 (81.5) 341
Related/possibly related to cTTP	20 (41.7) 96	13 (27.7) 47	13 (28.3) 55	9 (22.5) 122	6 (24.0) 28	15 (23.1) 150
TEAEs related to study drug	22 (45.8) 37	2 (4.3) 8	1 (2.2) 6	1 (2.5) 2	3 (12.0) 7[c]	4 (6.2) 9[c]
Severe TEAEs	6 (12.5) 13	3 (6.4) 5	5 (10.9) 10	7 (17.5) 17	2 (8.0) 2	9 (13.8) 19
Severe TEAEs related/ poss. related to cTTP	3 (6.3) 7	1 (2.1) 2	3 (6.5) 6	3 (7.5) 10	1 (4.0) 1	4 (6.2) 11
Severe TEAEs related to study drug	1 (2.1) 1	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0
Serious TEAEs	7 (14.6) 7	1 (2.1) 1	5 (10.9) 6	4 (10.0) 4	1 (4.0) 1	5 (7.7) 5
Serious TEAEs related /poss. related to cTTP	4 (8.3) 4	0	2 (4.3) 2	1 (2.5) 1	0	1 (1.5) 1
Serious TEAEs related to study drug	1 (2.1) 1	0	0	0	0	0
TEAEs leading to:						
Study drug discontinuation	1 (2.1) 1	0	0	0	0	0
Study withdrawal	0	0	0	0	0	0

cTTP=congenital thrombotic thrombocytopenic purpura; E=number of events; excl.=excluding; iCSR=interim clinical study report; n=number of subjects experiencing the event; N= number of subjects included in the analysis within each period; %=percentage is calculated with N as the denominator; poss.=possibly; SoC=standard of care; TEAE=treatment-emergent adverse event

[a] Of these, 25 TEAEs in 14 subjects had started during a previous TAK-755 study and were reported as ongoing at the time of enrolment in Study 3002 (Study 3002 iCSR Listing 16.2.7.4).

[b] The count for TEAEs, excluding events related or possibly related to cTTP, includes events with missing values for relatedness to cTTP.

[c] All 5 TEAEs considered related to TAK-755 in Study 3002 were mild in severity (Study 3002 Day 120 response Table 14.3.1.6.1 and Listing 16.2.7.1).

Most common adverse events

In the Phase 3 Study 281102, in the controlled comparison Periods 1 and 2, both lasting 6 months, a total of 276 TEAEs were reported in 39/47 (83.0%) subjects on TAK-755 prophylaxis vs 303 TEAEs in 44/48 (91.7%) subjects on SoC prophylaxis. The incidence of TEAEs was lower in the uncontrolled TAK-755 Period 3 (226 TEAEs in 32/46 [69.6%] subjects).

However, the incidence of TEAEs in the Phase 3b Study 3002 was similar to period 1 & 2 (124 TEAEs reported in 21 [84.0%] subjects).

In the controlled phase (period 1 and 2 in Study 281102), the most common TEAEs (reported in ≥10% subjects, regardless of treatment) were by updated data of the D120 responses headache, fatigue, thrombocytopenia, nasopharyngitis, abdominal pain, urticaria and vomiting. The most common TEAEs in period 3 were headache, nasopharyngitis, abdominal pain and nausea.

The applicant provided errata for the CSR of study TAK-755-281102 and corrections for the table of 'TEAEs in ≥5% of Subjects in the Prophylactic Cohort by Preferred Term, in Descending Order by Total Subject Number — Safety Analysis Set' as requested.

In Study 3002 (≥10% overall) most common TEAEs were headache, COVID-19, nasopharyngitis, cough, abdominal pain, dizziness, pyrexia, upper respiratory tract infection and viral infection regardless of relatedness to study drug.

Treatment emerging adverse events related to the drug

Treatment related TEAE was defined as all TEAEs considered by the investigator to be possibly or probably related to study drug.

In Study 281102 period 1 and 2, SoC-related TEAEs were reported for 22 [45.8%] subjects and for TAK-755-related TEAEs was 2 [4.3%] subjects. In period 3, 1 (2.2%) subject in the TAK-755 experienced a TEAE related to study drug.

TAK-755-related TEAEs occurring in 1 subject each in Periods 1, 2, included constipation, ADAMTS13 activity abnormal, headache, pruritus, hypertension in one patient each. The most common SoC-related TEAE SOCs were skin and subcutaneous tissue disorders (11 subjects [22.9%]); immune system disorders (4 subjects [8.3%]); and injury, poisoning and procedural complications (4 subjects [8.3%]), and nervous system disorders (3 subjects [6.3%]).

The **adverse drug reactions**, defined by the MAH as 'frequently occurring TEAEs (in >2% of subjects exposed to TAK-755) assessed by the investigator as having a plausible causal relationship to TAK-755' and proposed for inclusion in section 4.8 of the SmPC, are headache (28.6%), nausea (14.3%), feeling hot (5.4%), hypertension (5.4%), pruritus (3.6%) and somnolence (3.6%).

Rate of TEAEs in site

While Study 281102 enrolled cTTP subjects across 22 clinical trial sites in 9 countries with all sites contributing at least one patient to the study, a high proportion of subjects were enrolled at a single site, under the supervision of a single PI. Over half of all TEAE were reported by this site, both for TAK-755 and SoC, resulting in an EAER for site of a factor 2 compared to the overall study. However, there was a substantially lower rate of related TEAE, mainly for TAK-755 (no related AE, compared to around 13 in the overall cohort). A high number of the SAE were reported by this site (8/10 SAE) and also the one SoC treatment discontinuation was from this site. Although this limitation was evaluated with sensitivity analyses of study outcome measures in which Site was excluded from the primary efficacy and safety analyses.

Overall, the most common TEAEs in the prophylactic cohort of pooled studies 281102 and 3002 belong to the SOCs (system organ classes) "Infections and infestations", "Nervous system disorders", "gastrointestinal disorders" and "general disorders and administration site conditions".

Considering TEAEs by EAER (exposure-adjusted event rate) and PT, 14 TEAE PTs had an EAER of ≥10 events/100SY, during TAK-755 prophylaxis. Those were, in descending order by EAER: headache, migraine, abdominal pain, COVID-19, dizziness, nasopharyngitis, lethargy, nausea, diarrhea, cystitis, oropharyngeal pain, fatigue, upper respiratory tract infection, and platelet count decreased. In contrast, during SoC prophylaxis, 24 TEAE PTs had an EAER of ≥10 events/100SY. Those were, in descending order by EAER: headache, nasopharyngitis, thrombocytopenia, fatigue, urticaria, platelet count decreased, vomiting, lethargy, oropharyngeal pain, epistaxis, migraine, abdominal pain, pruritus, rash, drug hypersensitivity, nausea, cystitis, arthralgia, paranesthesia, cough, pyrexia, iron deficiency, tachycardia and myalgia.

7/54 (13.0%) subjects experienced 22 TEAEs considered related to TAK-755. 22/48 (45.8%) subjects experienced 40 TEAEs related to SoC. This corresponds to 32.2 TAK-755-related events/100SY vs. 145.1 SoC-related events/100SY.

The most frequently reported treatment-related TEAEs during SoC prophylaxis were hypersensitivity reactions and infusion reactions (urticaria, drug hypersensitivity, rash, pruritus, allergic transfusion reaction, infusion related hypersensitivity reaction, infusion related reaction). The only treatment-related TEAE of comparable of such kind to occur during TAK-755 prophylaxis was 1 event of pruritus.

Table 38: Treatment related TEAEs during prophylactic treatment in pooled studies 281102 and 31002 – in descending order by EAER during SoC prophylaxis

	TAK-755 (N=54)		**SoC** (N=48)	
Preferred Term	**n (%) E**	**E/100SY**	**n (%) E**	**E/100SY**
Average exposure time (days)	*425.0*		*192.9*	
Any related TEAEs	7 (13.0) 22	32.2	22 (45.8) 40	145.1
Urticaria	0	0	7 (14.6) 9	32.7
Drug hypersensitivity	0	0	5 (10.4) 5	18.1
Rash	0	0	4 (8.3) 5	18.1
Pruritus	1 (1.9) 1	1.5	3 (6.3) 3	10.9
Headache	1 (1.9) 10	14.6	2 (4.2) 2	7.3
Allergic transfusion reaction	0	0	2 (4.2) 2	7.3
Fatigue	0	0	2 (4.2) 2	7.3
Infusion related hypersensitivity reaction	0	0	2 (4.2) 2	7.3
Tachycardia	0	0	2 (4.2) 2	7.3
Paraesthesia	0	0	1 (2.1) 2	7.3
Somnolence	1 (1.9) 1	1.5	1 (2.1) 1	3.6
Agitation	0	0	1 (2.1) 1	3.6
Cough	0	0	1 (2.1) 1	3.6
Infusion related reaction	0	0	1 (2.1) 1	3.6
Pyrexia	0	0	1 (2.1) 1	3.6
Vomiting	0	0	1 (2.1) 1	3.6
Feeling hot	2 (3.7) 2	2.9	0	0
Nausea	2 (3.7) 2	2.9	0	0
Constipation	1 (1.9) 2	2.9	0	0
ADAMTS13 activity abnormal	1 (1.9) 1	1.5	0	0
Abdominal distension	1 (1.9) 1	1.5	0	0
Hypertension	1 (1.9) 1	1.5	0	0
Thrombocytosis	1 (1.9) 1	1.5	0	0

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; E=number of events; E/100SY=events per 100 subject-years; EAER=exposure-adjusted event rate; ISE=integrated summary of efficacy; ISS=integrated summary of safety; n=number of subjects; SoC=standard of care; TEAE=treatment-emergent adverse event

Source: ISS/ISE Table 14.3.1.13

Severe TEAEs occurred with slightly greater frequency during SoC prophylaxis (50.8 severe events/100SY) than during TAK-755 prophylaxis (42.5 severe events/100SY) based on EAER and in a comparable proportion of subjects in both groups. Headache and abdominal pain were the only severe TEAEs to occur in >1 subject during either treatment; both occurred more frequently during SoC than during TAK-755 treatment, based on EAER. All other severe TEAEs occurred in 1 subject each. The only severe TEAE considered related to study treatment was an event of urticaria in a subject on SoC. No severe treatment-related TEAEs were reported for the prophylactic cohort treated with TAK-755.

The applicant states that 50% of subjects at site received weekly TAK-755 dosing, compared to only 4.8% of subjects not at Site. It was speculated that subjects at the site may have had more symptomatic cTTP requiring more frequent treatment prior to study enrollment. Furthermore, the majority of headache that contributed to the overall high number of TEAEs reported for site were reported by only four subjects, all of whom were enrolled at Site. Also, despite the higher EAER for TEAEs, Site -had a lower rate of related TEAEs than the combined rate at other sites for both TAK-755 and SoC, in particular reporting no TEAEs related to TAK-755. However, this comparison is limited by the small number of TEAEs that were related to TAK-755 (22 events in 7 subjects) on the studies overall. Of note, only 5 sites (out of 30 total active sites) reported any TEAEs considered related to TAK-755. Therefore, although Site did not report any TAK-755-related TEAEs, this was consistent with the majority of sites on the studies. Furthermore, when data from one site are removed from the overall summary of TEAEs during prophylactic treatment in pooled Studies 281102 and 3002, the conclusions remain generally consistent with those for the overall study:

Table 39: Overall Summary of TEAEs During Prophylactic Treatment in Pooled Studies 281102 and 3002 – by Site

Parameter	Overall Study		Site		Not Site	
	TAK-755 (N=54)	SoC (N=48)	TAK-755 (N=8)	SoC (N=9)	TAK-755 (N=46)	SoC (N=39)
Average Exposure Time, days	425.0	192.9	817.8	269.9	356.7	175.2
Any TEAEs						
n (%)	39 (72.2)	37 (77.1)	8 (100)	9 (100)	31 (67.4)	28 (71.8)
E	638	306	374	171	264	135
E/100SY	934.1	1110.2	1920.9	2365.4	540.7	663.9
TEAEs related to study drug						
n (%)	7 (13.0)	22 (45.8)	0	4 (44.4)	7 (15.2)	18 (46.2)
E	22	40	0	7	22	33
E/100SY	32.2	145.1	0	96.8	45.1	162.3
Any TEAEs by maximum severity, n (%)						
Mild	12 (22.2)	13 (27.1)	1 (12.5)	1 (11.1)	11 (23.9)	12 (30.8)
Moderate	19 (35.2)	17 (35.4)	0	3 (33.3)	19 (41.3)	14 (35.9)
Severe	8 (14.8)	7 (14.6)	7 (87.5)	5 (55.6)	1 (2.2)	2 (5.1)
TEAEs leading to death						
n (%) E	0	0	0	0	0	0
Serious TEAEs						
n (%)	8 (14.8)	8 (16.7)	6 (75.0)	3 (33.3)	2 (4.3)	5 (12.8)
E	10	9	8	3	2	6
E/100SY	14.6	32.7	41.1	41.5	4.1	29.5
Serious TEAEs related to study drug						
n (%) E	0	1 (2.1) 1	0	0	0	1 (2.6) 1

E/100SY	0	3.6	0	0	0	4.9
TEAEs leading to study drug discontinuation						
n (%) E	0	1 (2.1) 1	0	1 (11.1) 1	0	0
E/100SY	0	3.6	0	13.8	0	0
TEAEs leading to study withdrawal						
n (%) E	0	0	0	0	0	0

E=number of events; E/100SY=events per 100 subject-years; ISE=integrated summary of efficacy; ISS=integrated summary of safety; n=number of subjects with the event; SoC=standard of care; TEAE=treatment-emergent adverse event

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths have been reported in any clinical studies of TAK-755.

No serious TEAEs were reported for study 281101. In the pooled studies 281102 and 3002 a total of 16 (22.2%) subjects of the prophylactic cohort experienced 24 serious TEAEs. In comparison, 11/71 (15.5%) subjects experienced 13 serious TEAEs under TAK-755 treatment and 9/48 (16.7%) subjects experienced 9 serious TEAEs under SoC. Serious TEAEs occurred about a third as frequently under TAK-755 (EAER of 10.4 events/100SY) than under SoC (EAER of 30.1 events/100SY). During the controlled comparison treatment periods (Periods 1 and 2) in Study 281102, serious TEAEs were reported for 1 subject (2.1%) during TAK-755 and 7 subjects (14.6%) during SoC. No serious TEAEs were considered related to TAK-755. The following serious TEAEs occurred during SoC prophylaxis: thrombocytopenia, pyrexia, seasonal allergy, road traffic accident, shoulder fracture, platelet count decreased, headache, and sinus disorder. The following serious TEAEs occurred during TAK-755 prophylaxis: thrombocytopenia, TTP, tachycardia, hyperthyroidism, abdominal pain, COVID-19, Campylobacter gastroenteritis, gastroenteritis clostridial, pilonidal disease, pneumonia, headache, adrenal torsion, and ovarian cyst.

Only one serious TEAE of pyrexia in 1/48 (2.1%) subject of the prophylactic cohort under SoC treatment was considered treatment-related.

2.6.8.4. Laboratory findings

Across all cTTP clinical studies, there were no clinically meaningful trends in clinical laboratory parameters other than in the cTTP-related parameters of platelet count, LDH, and creatinine and no clinically meaningful abnormalities in clinical laboratory parameters considered related to TAK-755. There were no clinically meaningful trends in vital signs in any cTTP clinical study. No clinically meaningful physical examination results were observed in any cTTP clinical study. There were no clinically meaningful trends in ECG measurements in any cTTP clinical study.

Study 281101

No trends over time or between the three dose cohorts were observed in any of the laboratory variables, except platelet count and LDH which showed dose-dependent variations. Platelet count tended to be lower in TTP patients compared to the general population and LDH levels tended to be unusually high in these patients. After BAX930 infusion, platelet counts increased and LDH levels decreased before returning to baseline levels, consistent with ADAMTS13 activity. The remaining biomarkers (cTNT, cTNI, D-dimer, NSE, S-100 B and creatinine kinase) observed overall showed only marginal variations from baseline. Considering individual clinically significant abnormalities, one subject of Cohort 2 (20 IU/kg BW) showed a decrease in haemoglobin of mild severity on day 1 of the study that was considered as related to blood sampling. The event resolved on day 10 without

medication. No specific trends over time or between the 3 dose cohorts were observed for the ECG measurements, in the physical and neurologic examination or vital signs.

Study 281102

Also, with updated data of the D120 responses there were no clinically meaningful trends over time in laboratory parameters (other than cTTP-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. There were no trends over time in vital signs and no obvious differences in vital signs between the prophylactic TAK-755 and SoC groups in crossover periods 1 and 2, nor any obvious trends in vital signs with longer duration of prophylactic TAK-755 treatment in Period 3. No abnormal findings were reported regarding physical examinations. Six subjects had abnormal ECG screening results, 5 of them were assessed as not clinically significant by PI. No abnormal ECG results were reported for any post-screening visit.

The applicant provided errata for the CSR of study TAK-755-281102 as requested.

With the Addendum of 15 Apr 2024, Figure 14.2.1.1. 'Subject Level Acute and Sub-acute TTP Event Figures' was updated. The intended purpose of this figure, as stipulated in the statistical analysis plan (SAP), was to provide figures of 4 laboratory parameters (ADAMTS13 activity, lactate dehydrogenase levels, platelet count, and serum creatinine concentration) over time for any subject who had an acute thrombotic thrombocytopenic purpura (TTP) event while receiving prophylactic treatment.

The following adjustments were made: i) Correction of subject ID, ii)The figures of the 4 key laboratory parameters over time for this subject were accidently repeated multiple times in the original version and iii) the statement that this patient did not have an acute TTP event while receiving prophylactic treatment (or at any time) was corrected, this subject was the only subject who had an acute TTP event while receiving prophylactic treatment with standard of care'.

Study TAK-755-3002

No clinically meaningful adverse trends or shifts from baseline were observed in laboratory parameters. Platelet counts and LDH levels on study were generally within normal ranges except for individual clinically significant abnormalities (low platelet counts, low mean corpuscular haemoglobin concentration (MCHC), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), haemoglobin, and erythrocyte counts). In some patients; high bilirubin and LDH was measured during study visits. High LDH was correlated with subacute or acute TTP events. No trends in vital signs were observed in the actual values or changes from baseline. No clinically significant physical examination results were observed. No clinically significant changes from baseline in ECG were observed.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not Applicable.

2.6.8.6. Safety in special populations

Table 40: Treatment-emergent Adverse Events in Subjects by Age Groups >65 Years (Safety Analysis Set)

MedDRA Terms	Age <65 (N=55) n (%) m	Age 65-74 (N=1) n (%) m	Age 75-84 (N=0) n (%) m	Age 85+ (N=0)[a] n (%) m
Total AEs	38 (69.1) 629	1 (100) 9	0	0
Total serious AEs	8 (14.5) 10	0	0	0
Fatal	0	0	0	0
Hospitalization	8 (14.5) 9	0	0	0
Life-threatening	1 (1.8) 1	0	0	0
Disability/incapacity	0	0	0	0
Other (medically significant)	2 (3.6) 2	0	0	0
AE leading to drop-out	0	0	0	0
Psychiatric disorders	5 (9.1) 7	0	0	0
Nervous system disorders	22 (40.0) 254	1 (100) 1	0	0
Accidents and injuries	7 (12.7) 10	0	0	0
Cardiac disorders	1 (1.8) 2	0	0	0
Vascular disorders	8 (14.5) 11	0	0	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	30 (54.5) 105	0	0	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Loss or lack of balance[a]	11 (20.0) 22	0	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects experiencing the event
[a] A subject is counted once if AE from Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, or Upper limb fracture
Percentages are based on Safety Analysis Set within each column
Adverse events were classified into system organ class and preferred term using version 25.0 of MedDRA

2.6.8.6.1. Adverse events by age group

Study 281101

No stratification by special populations were implemented by the Applicant.

Pooled studies 281102 and TAK-755-3002

Regarding the data presented with the D120 responses, the 72 subjects who received prophylactic treatment in Studies 281102 and 3002 were comprised of 52 adult subjects (72.2%), 1 subject ≥65 years old (1.8%) and 20 paediatric subjects (27.8%) (6 subjects [8.3%] in the age group of <6 years, and 7 subjects [9.7%] each in the age groups of 6 to <12 years and 12 to <18 years).

In the group with the most subjects of ≥18 years, the overall tendency for TEAEs was lower in the TAK-755 treated group compared to SoC (869.1 E/100SY vs. 1311.2 E/100SY). This was also reported for TEAEs related to study drug (23.2 E/100SY upon treatment with TAK-755 vs. 143.3 E/100SY upon treatment with SoC). The number of subjects experiencing severe TEAEs was similar for both groups (10/51 (19.6%) subjects treated with TAK-755 vs. 7/36 (19.4%) subjects treated with SoC). However, the EAER for serious TEAEs was lower in TAK-755 treated subjects compared to SoC (11.6 E/100SY

upon treatment with TAK-755 vs. 26.0 E/100SY upon treatment with SoC). None of them were related to study drug.

Subjects at the age of 12 to <18 years, overall experienced more TEAEs under TAK-755 compared to SoC (50 TEAEs under treatment with TAK-755 vs. 9 TEAEs under treatment with SoC). However, no events related to TAK-755 have been reported. Whereas 4 TEAEs related to SoC did occur. No severe TEAEs have been reported. One subject experienced 1 serious TEAE in each treatment group. However, it was not related to study drug.

Subjects at the age of 6 to <12 years, overall experienced more TEAEs under TAK-755 compared to SoC (60 TEAEs under treatment with TAK-755 vs. 9 TEAEs under treatment with SoC). However, no events related to TAK-755 have been reported. Whereas 2 TEAEs related to SoC did occur. No severe TEAEs have been reported. No serious TEAE has been reported in the TAK-755 group. One subject experienced 1 serious TEAE in the SoC cohort.

In the group of subjects with <6 years incidence between treatment groups was comparable.

4 prophylactic subjects have discontinued prematurely from the 2 studies. All 4 subjects were adults aged ≥18 years, including 1 subject aged ≥65 years.The safety profile in paediatric subjects is consistent with the safety profile in adult and adolescent subjects, and no safety concerns were identified in paediatric subjects. The frequency of TEAEs overall was comparable between paediatric groups and adult subjects based on percentage of subjects. Regarding EAER, incidence was comparable or lower for paediatric groups.

The following tables were provided by the Applicant at the request of the CHMP:

Table 41: Overall Summary of TEAEs During Prophylactic Treatment in Pooled Studies 281102 and 3002 – by Age Group

Parameter	≥18 years		12 to <18 years		6 to <12 years		<6 years	
	TAK-755 (N=51)	SoC (N=36)	TAK-755 (N=7)	SoC (N=4)	TAK-755 (N=7)	SoC (N=4)	TAK-755 (N=6)	SoC (N=4)
Average Exposure Time, days	682.3	215.0	498.9	196.3	335.7	200.8	194.8	183.5
Any TEAEs								
n (%) E	48 (94.1) 900	34 (94.4) 302	6 (85.7) 50	3 (75.0) 9	7 (100.0) 60	3 (75.0) 9	5 (83.3) 18	4 (100.0) 12
E/100SY	869.1	1311.2	481.1	385.2	857.9	376.6	517.4	549.3
TEAEs related to study drug								
n (%) E	6 (11.8) 24	18 (50.0) 22	0	3 (75.0) 4	0	1 (25.0) 2	0	1 (25.0) 1
E/100SY	23.2	143.3	0	171.2	0	83.7	0	45.8
Any TEAEs by maximum severity, n (%)								
Mild	17 (33.3)	11 (30.6)	2 (28.6)	2 (50.0)	3 (42.9)	2 (50.0)	2 (33.3)	2 (50.0)
Moderate	21 (41.2)	16 (44.4)	4 (57.1)	1 (25.0)	4 (57.1)	1 (25.0)	3 (50.0)	2 (50.0)
Severe	10 (19.6)	7 (19.4)	0	0	0	0	0	0
TEAEs leading to death								
n (%) E	0	0	0	0	0	0	0	0
Serious TEAEs								
n (%) E	10 (19.6) 12	5 (13.9) 6	1 (14.3) 1	1 (25.0) 1	0	1 (25.0) 1	0	1 (25.0) 1
E/100SY	11.6	26.0	9.6	42.8	0	41.8	0	45.8
Serious TEAEs related to study drug								

Table 41: Overall Summary of TEAEs During Prophylactic Treatment in Pooled Studies 281102 and 3002 – by Age Group

Parameter	≥18 years		12 to <18 years		6 to <12 years		<6 years	
	TAK-755 (N=51)	SoC (N=36)	TAK-755 (N=7)	SoC (N=4)	TAK-755 (N=7)	SoC (N=4)	TAK-755 (N=6)	SoC (N=4)
n (%) E	0	0	0	0	0	1 (25.0) 1	0	0
E/100SY	0	0	0	0	0	41.8	0	0
TEAEs leading to study drug discontinuation								
n (%) E	0	1 (2.8) 1	0	0	0	0	0	0
E/100SY	0	4.3	0	0	0	0	0	0
TEAEs leading to study discontinuation								
n (%) E	0	0	0	0	0	0	0	0

E=number of events; E/100SY=events per 100 subject-years; ISE=integrated summary of efficacy; ISS=integrated summary of safety; n=number of subjects with the event; SoC=standard of care; TEAE=treatment-emergent adverse event

Table 42: Treatment-emergent Adverse Events by System Organ class, Preferred Term, and Treatment Cohort in Pooled Studies 281102 and 3002 – by Age Group

System Organ Class	Prophylactic Cohort		On-Demand Cohort	
	n (%) m	n (%) m	n (%) m	n (%) m
<6 years	TAK-755 (N=6)	SoC (N=4)	TAK-755 (N=0)	SoC (N=1)
Infections and Infestations	4 (66.7) 5	2 (50.0) 3	0	0
Gastrointestinal Disorders	4 (66.7) 6	1 (25.0) 2	0	0
General Disorders and Administration Site	2 (33.3) 3	1 (25.0) 3	0	0
Blood and Lymphatic System Disorders	1 (16.7) 1	2 (50.0) 3	0	0
Investigations	1 (16.7) 1	0	0	0
Metabolism and Nutrition Disorders	1 (16.7) 1	0	0	0
Vascular Disorders	1 (16.7) 1	0	0	0
Injury, Poisoning, and Procedural Complications	0	1 (25.0) 1	0	0
6 to <12 years	TAK-755 (N=7)	SoC (N=4)	TAK-755 (N=1)	SoC (N=0)
Infections and Infestations	6 (85.7) 24	3 (75.0) 4	0	0
Respiratory, Thoracic and Mediastinal Disorders	4 (57.1) 11	1 (25.0) 1	0	0
General Disorders and Administration Site	4 (57.1) 5	1 (25.0) 1	0	0
Investigations	4 (57.1) 6	0	0	0
Gastrointestinal Disorders	2 (28.6) 3	2 (50.0) 2	0	0
Blood and Lymphatic System Disorders	2 (28.6) 3	0	1 (100) 1	0
Injury, Poisoning, and Procedural Complications	2 (28.6) 3	0	0	0
Nervous System Disorders	1 (14.3) 2	0	0	0
Immune System Disorders	1 (14.3) 1	0	0	0
Musculoskeletal and Connective Tissue Disorders	1 (14.3) 1	0	0	0
Skin and Subcutaneous Tissue Disorders	1 (14.3) 1	0	0	0
Cardiac Disorders	0	1 (25.0) 1	0	0
12 to <18 years	TAK-755 (N=7)	SoC (N=4)	TAK-755 (N=0)	SoC (N=0)

Table 42: Treatment-emergent Adverse Events by System Organ class, Preferred Term, and Treatment Cohort in Pooled Studies 281102 and 3002 – by Age Group

System Organ Class	Prophylactic Cohort		On-Demand Cohort	
	n (%) m	n (%) m	n (%) m	n (%) m
Injury, Poisoning, and Procedural Complications	3 (42.9) 3	2 (50.0) 2	0	0
Infections and Infestations	3 (42.9) 11	1 (25.0) 1	0	0
Investigations	3 (42.9) 3	0	0	0
Skin and Subcutaneous Tissue Disorders	2 (28.6) 2	1 (25.0) 1	0	0
Gastrointestinal Disorders	2 (28.6) 9	0	0	0
Immune System Disorders	1 (14.3) 2	1 (25.0) 3	0	0
Nervous System Disorders	1 (14.3) 10	1 (25.0) 1	0	0
Musculoskeletal and Connective Tissue Disorders	1 (14.3) 2	0	0	0
Reproductive System and Breast Disorders	1 (14.3) 2	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (14.3) 2	0	0	0
Vascular Disorders	1 (14.3) 2	0	0	0
Blood and Lymphatic System Disorders	1 (14.3) 1	0	0	0
Ear and Labyrinth Disorders	1 (14.3) 1	0	0	0
Endocrine Disorders	0	1 (25.0) 1	0	0
≥18 years	TAK-755 (N=51)	SoC (N=36)	TAK-755 (N=2)	SoC (N=3)
Infections and Infestations	39 (76.5) 168	15 (41.7) 31	0	1 (33.3) 1
Nervous System Disorders	32 (62.7) 318	13 (36.1) 100	0	1 (33.3) 3
Gastrointestinal Disorders	24 (47.1) 98	12 (33.3) 28	0	1 (33.3) 1
General Disorders and Administration Site	23 (45.1) 47	13 (36.1) 19	0	0
Respiratory, Thoracic and Mediastinal Disorders	23 (45.1) 54	8 (22.2) 19	0	0
Injury, Poisoning, and Procedural Complications	18 (35.3) 27	8 (22.2) 11	0	0
Skin and Subcutaneous Tissue Disorders	13 (25.5) 21	10 (27.8) 20	0	2 (66.7) 2
Musculoskeletal and Connective Tissue Disorders	12 (23.5) 24	10 (27.8) 11	0	0
Metabolism and Nutrition Disorders	12 (23.5) 26	4 (11.1) 4	0	0
Blood and Lymphatic System Disorders	11 (21.6) 16	9 (25.0) 17	0	1 (33.3) 2
Vascular Disorders	10 (19.6) 13	4 (11.1) 5	0	0
Investigations	10 (19.6) 18	5 (13.9) 10	0	1 (33.3) 2
Eye Disorders	7 (13.7) 14	3 (8.3) 6	0	0
Psychiatric Disorders	7 (13.7) 14	3 (8.3) 5	0	0
Reproductive System and Breast Disorders	7 (13.7) 16	2 (5.6) 6	0	0
Ear and Labyrinth Disorders	5 (9.8) 7	0	0	0
Cardiac Disorders	3 (5.9) 6	2 (5.6) 2	0	0
Renal and Urinary Disorders	3 (5.9) 6	2 (5.6) 2	0	0
Endocrine Disorders	2 (3.9) 2	0	0	0
Immune System Disorders	2 (3.9) 4	4 (11.1) 5	0	0
Hepatobiliary Disorders	1 (2.0) 2	0		
Neoplasms Benign, Malignant and Unspecified	0	1 (2.8) 1		

m=Number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects experiencing an event.
Percentages are based on Safety Analysis Set within each column

Table 42: Treatment-emergent Adverse Events by System Organ class, Preferred Term, and Treatment Cohort in Pooled Studies 281102 and 3002 – by Age Group

System Organ Class	Prophylactic Cohort		On-Demand Cohort	
	n (%) m	n (%) m	n (%) m	n (%) m

Adverse events were classified into system organ class and preferred term using version 25.0 of MedDRA
Subjects were counted once per system organ class and once per preferred term

2.6.8.6.2. Adverse events by ethnicity

The 72 subjects who received prophylactic treatment in Studies 281102 and 3002 were composed of 40 white subjects (55.6%); 17 Asian subjects (23.6%), including 6 Japanese subjects (8.3%) and 11 Chinese subjects (15.3%); 2 black or African American subjects (2.8%), 1 subject of multiple races (1.4%), and 12 subjects for whom race was not reported (16.7%). The white subjects experienced more TEAEs under TAK-755 compared to SoC. However, considering treatment duration, the EAER was higher for the SoC group. TEAEs considered related to IP occurred with a higher prevalence in the SoC group. The tendency for severe TEAEs was nearly equal for TAK-755 and SoC. Also, the number of serious TEAEs was comparable for both groups. The EAER showed a higher prevalence of serious TEAEs for the SoC group. No serious TEAEs were considered related to IP. No TEAE led to study discontinuation, 1/36 (2.8%) subject under SoC experienced 1 TEAE that led to discontinuation of SoC treatment.

Considering the overall occurrence of TEAEs the reported values for Japanese and other Asian subjects resembled the white subjects. None of the Chinese subjects were treated with SoC, therefore results cannot be compared with the TAK-755 group. Also, the results for subjects of other ethnicity resembled the white subjects. However, no TEAEs were considered related to TAK-755, more serious TEAEs occurred in the SoC group. One serious TEAE was considered related to SoC.

2.6.8.6.3. Adverse events by sex

No detailed discussion of TEAEs considering sex in study reports of studies 281101, 281102 or 3002 or in the summary for pooled studies 281102 and 3002 was available. No tables listing TEAEs by sex and SOC and/or PT have been provided for studies 281101 or 3002. For study 281102, tables showing TEAEs by SOC/PT and sex have been provided. However, presented data were shown for separate study periods, separate PK infusions or summarized for periods 1 – 3 only, including the study phases separately or a summary for phases 1, 2 and 3 without the PK-phases.

The 55 subjects who received prophylactic treatment in Studies 281102 and 3002 until the initial cut-off date of 12 Aug 2022 were comprised of 22 males (40.0%) and 33 females (60.0%).

Table 43 (ISS/ISE Tables) modified by the assessor

		Male			Female		
		TAK-755	SoC	Total	TAK-755	SoC	Total
N		21	20	22	33	28	33
Any TEAEs	Number (%) of Subjects	16 (76.2%)	14 (70.0%)	18 (81.8%)	23 (69.7%)	23 (82.1%)	26 (78.8%)
	Number of Events	95	61	156	543	245	788
	Events per 100SY	394.4	549.2	-	1228.3	1488.9	
TEAEs considered related to IP	Number (%) of Subjects	3 (14.3%)	8 (40.0%)	9 (40.9%)	4 (12.1%)	14 (50.0%)	16 (48.5%)
	Number of Events	3	14	17	19	26	45
	Events per 100SY	12.5	126.0	-	43.0	158.0	-
Severe TEAEs	Number (%) of Subjects	1 (4.8%)	2 (10.0%)	-	7 (21.2%)	5 (17.9%)	-

Serious TEAEs	Number (%) of Subjects	1 (4.8%)	2 (10.0%)	2 (9.1%)	7 (21.2%)	6 (21.4%)	11 (33.3%)
	Number of Events	1	2	3	9	7	16
	Events per 100SY	4.2	18.0	-	20.4	42.5	-
Serious TEAEs related to IP	Number (%) of Subjects	0	0	0	0	1 (3.6%)	1 (3.0%)
	Number of Events	0	0	0	0	1	1
	Events per 100SY	0	0	-	0	6.1	-
TEAEs leading to study discontinuation	Number (%) of Subjects	0	0	0	0	0	0
	Number of Events	0	0	0	0	0	0
	Events per 100SY	0	0	-	0	0	-
TEAEs leading to IP discontinuation	Number (%) of Subjects	0	1 (5.0%)	1 (4.5%)	0	0	0
	Number of Events	0	1	1	0	0	0
	Events per 100SY	0	9.0	-	0	0	-

At the request of the CHMP, the Applicant provided two tables listing TEAEs by SOC, PT, and gender for the prophylactic subjects, as well as for the OD subjects. Frequency of any TEAEs was comparable in male vs. female subjects receiving TAK-755. However, for some SOCs, notable imbalances have been observed between male vs. female subjects. The most frequent TEAEs for subjects receiving TAK-755 have been reported in the SOCs gastrointestinal disorders; general disorders and administration site conditions; and respiratory, thoracic, and mediastinal disorders. The most frequent TEAEs for subjects receiving SoC have been reported in the SOCs general disorders and administration site conditions; gastrointestinal disorders; and injury, poisoning and procedural complications. Imbalance in the incidence rate of study drug related TEAEs were considered due to the small number of subjects. Also, most of the related events have been experienced by a single female subject. This argumentation can be followed for the related TEAEs. In general, TEAEs for which imbalances have been observed between male and female patients were considered not related to treatment. Also, these imbalances have been observed in general for TAK-755 and standard of care in similar rates. Therefore, the lack of relation of these TEAEs to treatment is considered reasonable. However, regarding observed imbalances between TAK-755 and SoC groups in male and female patients, frequencies are comparable to overall numbers as already presented in the original dossier. Imbalances for some SOCs have been observed between male vs. female patients. However, as mentioned above, concerned TEAEs were not related to treatment.

2.6.8.6.4. Use in pregnancy and lactation

Drugs with a molecular weight of >1,000 Da cross the placenta very poorly (Syme *et al.* 2004). As a large protein with a molecular weight of 172 kDa, TAK-755 is expected to have only limited, if any, access to a conceptus and interaction with intracellular organelles, including DNA. In rat studies, there was no biologically relevant placental transfer, no reproductive or developmental toxicity at doses up to 400 IU/kg, and no effects on fertility at up to 400 IU/kg.

Study 281101

No subject has been reported pregnant during this study.

Study 281102

No subject has been reported pregnant during this study.

Study 3002 and CPU

There have been 4 patients with cTTP who have been exposed to TAK-755 during pregnancy, 2 subjects in Study 3002 and 2 patients who received TAK-755 through CPU.

A young rollover subject in Study 3002 was found to be pregnant 1 week after her last dose of TAK-755. She was discontinued from the study due to protocol requirements. Her scheduled dose of TAK-755 that was due two days after the pregnancy was found was withheld. The subject was intolerant to plasma infusion, as she had developed a severe allergy to plasma (including angioedema, tachycardia, and shortness of breath with throat swelling). With repeated exposure to plasma, despite premedication with steroids, acetaminophen, and antihistamine, urticaria and tachycardia recurred. The investigator therefore planned to manage the patient on an intermediate-purity Factor VIII product on withdrawal from the study (previously, on Study 281102, the subject had been treated with a Factor VIII product at a dose frequency of every week during the SoC treatment period). Approximately 2 months after study discontinuation, the subject had a first-trimester miscarriage that was considered unrelated to TAK-755.

A rollover subject in Study 3002 was found to be pregnant and discontinued to comply with protocol requirements. The subject resumed treatment with TAK-755 under a CPU program and delivered a healthy full-term baby with no safety concerns reported by the investigator.

A female diagnosed with cTTP in the third trimester of a pregnancy that had been complicated by ischemic stroke and thrombocytopenia. A previous pregnancy resulted in intrauterine foetal death at 20 weeks gestation, followed a stroke 2 weeks later. She received TAK-755 40 IU/kg Q1W through CPU starting at 33 weeks gestation. She delivered a healthy baby by caesarean section at 37 weeks gestation. The baby had a low birth weight for the gestational age of 33 weeks of **1865 g**.

A female experienced her first acute TTP event and suffered a stroke during her second trimester of pregnancy. She achieved remission but shortly afterwards had a second acute exacerbation of TTP. She received TAK-755 Q1W through CPU. The patient has since delivered a healthy baby but **according to the treating physician there were no adverse events due to TAK-755**.

No studies of the effect of TAK-755 on lactation have been conducted. It is unknown whether TAK-755 would be excreted in milk.

2.6.8.6.5. Adverse events pre and post production transfer (Orth vs. Singapore)

Regarding the transfer of the production of TAK-755 from Orth to Singapore, it was shown that the overall AE profile of TAK-755 ORT to TAK-755 SIN was comparable. Thirty-three adult subjects were exposed to TAK-755 ORT during Study 281102 Periods 1, 2, and 3 for an average exposure time of 229.8 days. Fifty adult subjects were exposed to TAK-755 SIN, predominantly during Study 281102 Period 3 and Study 3002, for an average exposure time of 524.7 days. With the initial MAA, the EAER in the TAK-755 ORT group, was higher (1260.1 E/100SY) compared to the TAK-755 SIN (797.1 E/SY). This difference of about 40% was also observed for the treatment-related TEAE between ORT and SIN, 44.4 events/100SY for ORT vs 30.2 events/100SY for SIN. No updated numbers for events per 100 study years have been presented with data provided upon D120 responses for TAK-755 ORT vs. TAK-755 SIN.

Table 44: Overall summary of adverse events by TAK-755 product for subjects ≥ 18 years (safety analysis set)

		Prophylactic Cohort	
		TAK-755 ORT (pivotal prophy P1/P2/P3)	TAK-755 SIN (pivotal prophy P1/P2/P3 and 3002)
Category	Statistic	(N=33)	(N=41)
Average Exposure Time (Days)		229.5	298.1
Any TEAEs	Number(%) of Subjects	27 (81.8)	30 (73.2)
	Number of Events	284	290
	Events per 100SY	1260.1	797.1
TEAEs considered related to IP	Number(%) of Subjects	4 (12.1)	3 (7.3)
	Number of Events	10	11
	Events per 100SY	44.4	30.2
TEAEs by Strongest Relationship to IP			
Not Related	Number(%) of Subjects	16 (48.5)	20 (48.8)
Unlikely Related	Number(%) of Subjects	7 (21.2)	7 (17.1)
Possibly Related	Number(%) of Subjects	1 (3.0)	0
Probably Related	Number(%) of Subjects	3 (9.1)	3 (7.3)
TEAEs by Maximum Severity			
Mild	Number(%) of Subjects	11 (33.3)	11 (26.8)
Moderate	Number(%) of Subjects	11 (33.3)	12 (29.3)
Severe	Number(%) of Subjects	5 (15.2)	7 (17.1)
Any TEAEs Leading to Death	Number(%) of Subjects	0	0
	Number of Events	0	0
	Events per 100SY	0	0
Serious TEAEs	Number(%) of Subjects	2 (6.1)	6 (14.6)
	Number of Events	3	6
	Events per 100SY	13.3	16.5
Study Drug Related-Serious TEAEs	Number(%) of Subjects	0	0
	Number of Events	0	0
	Events per 100SY	0	0
Any TEAEs Leading to Study Discontinuation	Number(%) of Subjects	0	0
	Number of Events	0	0
	Events per 100SY	0	0
Any TEAEs Leading to Discontinuation of IP	Number(%) of Subjects	0	0
	Number of Events	0	0
	Events per 100SY	0	0

P1 = period 1, P2 = period 2, P3 = period 3; IP = Investigational Product.
Percentages are based on safety analysis set within each column.
Subjects were counted by the treatment most recently taken when the event occurred. Subjects were counted once per category.

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The majority of TEAE PTs were experienced by comparable percentages of adult subjects during treatment with TAK-755 ORT vs TAK-755 SIN. None of these TEAEs were considered related to TAK-755 except 1 event of hypertension.

Overall, the percentage of concerned subjects was comparable regarding the TEAEs by SOCs experienced in both groups. However, concerning PTs, diarrhoea, migraine, nasopharyngitis, lethargy, epistaxis, anaemia, hypertension, pain and vision blurred had a higher occurrence under treatment with TAK-755 ORT. COVID-19, pyrexia, fatigue and hypoesthesia were reported in higher numbers in TAK-755 SIN treated subjects.

No subjects with cTTP developed neutralising antibodies to ADAMTS13 during treatment with either TAK-755 ORT or TAK-755 SIN. One subject with iTTP had binding and neutralising antibodies during treatment with TAK-755 ORT, while 5 subjects had binding antibodies during treatment with TAK-755 SIN.

2.6.8.6.6. Compassionate use

Of the 9 subjects included in the compassionate use report, one teenager (40 IU/kg Q1W TAK-755) had an AE of moderate flatulence.

Of the 9 CPU patients, 5 were adults and 4 were paediatric patients. The ages of the paediatric patients at the start of TAK-755 treatment were 36 hours (a neonate), 10 years (n=2), and 13 years. The neonate, now aged 2 years, has not developed any detectable ADAMTS13 antibodies after 83 infusions of TAK-755 and repeated antibody testing. There have been no reports of ADAMTS13 antibodies being detected in the remaining CPU patients either. Of note, this patient had 2 previous siblings who were both born with severe neonatal thrombotic microangiopathy, and both died within 2 weeks after birth. At 2 years of age, the patient had reached all developmental milestones, with no acute episodes of cTTP and no treatment-related AEs. Limited safety information available for the other CPU patients are presented in the Compassionate Use Report.

Table 45: Demographics and baseline characteristics of patients with cTTP treated with TAK-755 on compassionate grounds

Characteristic	Patients Treated with TAK-755 Total (N=9)
Age at the start of treatment (years, unless specified otherwise)	
Min, Max	36 hours – 72 years
0 to <6 years old	1
6 to <12 years old	2
12 to <18 years old	1
18 to <65 years old	4
≥65 years old	1
Sex	
Male	0
Female	9
Country	
Switzerland	2
England	3
United States	3
Singapore	1

2.6.8.6.7. OD Cohort

The 7 subjects who received on-demand treatment in Study 281102 were comprised of 4 males (57.1%) and 3 females (42.9%), (<65 years). Among the 3 subjects who received on-demand TAK-755, no TEAEs were reported. Among the 4 subjects who received on-demand SoC, 3 subjects experienced a total of 11 TEAEs. There were no serious AEs, TEAEs leading to study drug discontinuation or study withdrawal in the on-demand cohort. The only TEAE reported by >1 on-demand subject was pruritus (2 subjects who received SoC) Other TEAEs reported by 1 subject each were headache, nausea, hypoesthesia, blood LDH increased, thrombocytopenia, paraesthesia, and tooth abscess. One event of nausea and 1 event of pruritus were considered related to SoC; all other TEAEs were considered not related to study drug.

2.6.8.7. Immunological events

2.6.8.7.1. ADA assessment approach

An ELISA using a tiered approach was developed by the Applicant to semi-quantitatively screen, confirm and titer apadamtase specific "anti-ADAMTS13" or "anti-rADAMTS13" binding antibodies in human citrated plasma matrix. Samples are incubated in microtiter plates coated with rADAMTS13. rADAMTS13-bound antibodies were detected using an HRP-conjugated goat anti-human Ig antibody. Quantification of bound secondary antibody is accomplished by an enzyme-dependent colour-change reaction, which is directly proportional to the amount of bound antibody. A human plasma pool from untreated donors (negative control) was spiked with monoclonal human anti-ADAMTS13-IgG1 antibody (Charité: 0.5 µg/mL; Krems: 0.1/0.25/1.0 µg/mL) to serve as positive control. The assay was performed at Charite/CheckImmune for Studies 281101 and 281102, and the method was transferred to KREMS and LabCorp SHA for Study TAK-755-3002.

Table 46: Method validation information-detection of anti-rA13

Analyte	anti-rA13 Ab (Ig)	anti-rA13 Ab (Ig)	anti-rA13 Ab (Ig)
Test facility	Charite/CheckImmune[a]	KREMS	LabCorp SHA
Document ID	VR-281101-01-01	FHSOP-31-0002-TI044-04-VR.01, FHSOP-31-0002-TI044-02-DR.01	8471-024
Assay platform	ELISA	ELISA	ELISA
Matrix	Citrated plasma	Citrated plasma	Citrated plasma
Coating reagent	rA13	rA13	rA13
Detection Ab	Goat anti-human Ig HRP	Goat anti-human Ig HRP	Goat anti-human Ig HRP
Positive control	Anti-rA13 mAb	Anti-rA13 mAb	Anti-rA13 mAb
MRD	1:20 (screening)	1:20	1:20
Assay cut point	OD cutoff: 0.304; confirm: >2 step titer reduction	CP factor: daily NC mean-0.086; confirmatory 59% inhibition	CP factor: daily NC mean*2.02; confirmatory 38.78% inhibition
Precision	Mode titer 5±1 step dilution	PC mode titer ±1 step dilution (HPC mode titer 6)	≤20% CV
Sensitivity	31.25 ng/mL	84 ng/mL (based on LPC mean)	≤31.25 ng/mL (estimated)
Selectivity	Passed	Passed, all spiked samples (250 ng/mL PC) tested positive	Selectivity: passed for normal matrix, hemolysis, lipemic plasma
Linearity/hook effort	1:20 to 1:2560	Passed, no hook effect	Passed, no hook effect
Freeze/thaw stability	5	5	5
Ambient stability	ND	18 hours	24 hours 14 minutes
4°C stability	24 hours	ND	72 hours 14 minutes
Studies supported	281101, 281102	TAK-755-3002	TAK-755-3002 (China)

For Studies 281101 and 281102, the minimal reportable anti-ADAMTS13 binding antibody titer is 1:80 since the confirmatory assay cut off is defined as a signal reduction >2 steps of dilution with ligand competition versus without ligand competition. For Study TAK-755-3002, the minimal reportable titer is 1:20 since the confirmatory assay cut point is determined by percent inhibition with ligand competition at the minimum required sample dilution (1:20) during the validation.

2.6.8.7.2. Detection of Anti-ADAMTS13 and Anti-rADAMTS13 Neutralising Antibodies

The applicant presents a modified Nijmegen-Bethesda coagulation assay for the qualitative detection of neutralising ADAs in human citrated plasma samples. In brief, (endogenous) ADAMTS13 heat inactivated samples are mixed, at a ratio of 1:2 (1+1) with either normal human plasma or rADAMTS13 spiked in heat inactivated normal human plasma pool and incubated. As 100% control normal human plasma or rADAMTS13 spiked into heat inactivated normal human plasma pool mixed with HEPES-NaCI-BSA buffer at a ratio of 1:2 (1+1) is used. The presence of an anti-ADAMTS 13 or anti-BAX930 inhibitor in the test sample results in a decreased residual ADAMTS13 activity compared to the 100% control. Residual ADAMTSS13 activity is determined using the semi-quantitative FRETS-VWF73 activity assay from which the anti-ADAMTS13/BAX930 inhibitor concentration is calculated and expressed in IU/mL Inhibitor titer are calculated with the Bethesda calibration curve and expressed as BU/mL, where 1 BU is equivalent to 50% loss in ADAMTS13 activity in the sample versus an inhibitor-free control mixture. The assay cut point (0.6 BU/mL) recommended for coagulation factor inhibitory assays is determined by the assay sensitivity, precision, and accuracy during validation. Samples are considered NAb negative if the result is <0.6 BU/mL and NAb positive if the result is ≥0.6 BU/mL. Note that since TAK-755 is a composition of protein with identical amino acid sequence as endogenous ADAMTS13 and Q/R variant with a single amino acid difference, thus the Nab's detected by the 2 assays could be cross reactive.

Table 47: Method validation summary -detection of anti-ADAMTS13/rADAMTS13 Nab

Analyte	rADAMTS13 NAb	rADAMTS13 NAb	rADAMTS13 NAb	ADAMTS13 NAb	ADAMTS13 NAb
Test facility	Baxter	KREMS	LabCorp SHA	KREMS	LabCorp SHA
Document ID	OR-13-00588-02-VB.01	S01-101-02-VR, A1 to S01-101-02-VR, A2 to S01-101-02-VR, FHSOP-31-0025-TI001-03-VR-01	8471-019	S01-101-04-VR, FHSOP-31-0025-TI002-02-VR.01	8471-012
Assay platform	Bethesda-Nijmegen modification of FRETS-VWF73 Activity	Bethesda-Nijmegen modification of FRETS-VWF73 Activity	Bethesda-Nijmegen modification of FRETS-VWF73 Activity	Bethesda-Nijmegen modification of FRETS-VWF73 Activity	Bethesda-Nijmegen modification of FRETS-VWF73 Activity
Matrix	Citrated plasma	Citrated plasma	Citrated plasma	Citrated plasma	Citrated plasma
100% control substrate	rADAMTS13	rADAMTS13	rADAMTS13	NHP	NHP
Positive control	Anti-ADAMTS13 mAb	Anti-ADAMTS13 mAb	Anti-ADAMTS13 mAb	Anti-ADAMTS13 mAb	Anti-ADAMTS13 mAb
MRD	1:12.5 predilution	1:12.5 predilution	1:12.5 predilution	1:12.5 predilution	1:12.5 predilution
Activity range for assessment	30% to 70% residual activity	25% to 75% residual activity	30% to 75% residual activity	25% to 75% residual activity	30% to 75% residual activity
Assay cut point	0.6 BU/mL	0.6 BU/mL	0.6 BU/mL	0.6 BU/mL	0.6 BU/mL
ULOQ	1:6 predilution	8 BU/mL	26.7 BU/mL (1:32)	4 U/mL	26.6 BU/mL(1:32)
Accuracy (A13 activity curve, %Bias)	Within ±20%, ±25% at LLOQ and ULOQ	Within ±20%, ±25% at LLOQ and ULOQ	Within ±20%, ±25% at LLOQ and ULOQ	Within ±20%, ±25% at LLOQ and ULOQ	Within ±20%, ±25% at LLOQ and ULOQ
Precision (A13 activity curve, %CV)	≤20%, ≤25% LLOQ and ULOQ	≤20%, ≤25% LLOQ and ULOQ	≤20%, ≤25% LLOQ and ULOQ	≤20%, ≤25% LLOQ and ULOQ	≤20%, ≤25% LLOQ and ULOQ
NAb PC accuracy (%Bias)	Within ±25%, ±30% at LLOQ and ULOQ	Within ±30%	Within ±30%	Within ±30%	Within ±30%
NAb PC precision (%CV)	≤25%, ≤30% LLOQ and ULOQ	CV ≤30%	CV ≤30%	CV ≤30%	CV ≤30%
Dilutional linearity	Up to 1:6 predilution (4.33 BU/mL)	Up to 8 BU/mL	Up to 1:32 predilution (26.7 BU/mL)	Up to 4 BU/mL	Up to 1:48 predilution (26.6 BU/mL)
Freeze/thaw stability	2	5	5	5	5
Ambient stability	60 minutes	1 hour	25 hours 15 minutes	1 hour	25 hours
4°C stability	ND	ND	74 hours 15 minutes	ND	73 hours
-70°C stability	6 months	2 years (US Pharmacopoeia)	24 months (US Pharmacopoeia)	2 years (US Pharmacopoeia)	24 months (US Pharmacopoeia)
Studies supported	281101	281102, TAK-755-3002	TAK-755-3002 (China)	281102, TAK-755-3002	TAK-755-3002 (China)

A13=ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13); CV=coefficient of variation; ID=identification; FRETS-VWF73=fluorescence resonance energy transfer substrate composed of 73 amino acids from the A2 domain of von Willebrand factor; LLOQ=lower limit of quantification; mAb=monoclonal antibody; MRD=minimum required dilution; NAb=neutralizing antibody; ND=not determined; NHP=normal human plasma; PC=positive control; rADAMTS13=recombinant ADAMTS13; SHA=Shanghai; ULOQ=upper limit of quantification; US=United States

2.6.8.7.3. Immunogenicity in clinical studies

In study 281101, all 15 subjects consistently tested negative for ADAMTS13/TAK-755 binding and neutralising antibodies and anti–CHO protein antibodies. There was no evidence of immunogenicity after a single infusion of up to 40 IU/kg TAK-755.

In study 281102, no neutralizing antibodies were detected in any subject with confirmed cTTP, also at the updated data cut-off. Subject was positive for low-titer binding antibodies at baseline (on Day -197, before exposure to TAK-755) and then intermittently during the study (on Days 1, 15, 41, 209, and 420) without increasing in titer. Subject was positive for binding and neutralizing antibodies against TAK-755 on Day 309. This subject was initially enrolled as a cTTP patient but was later confirmed by the investigator to have iTTP based on updated medical history, genetic analysis, and clinical course and was consequently withdrawn from the study as not meeting eligibility criteria. The antibodies detected in this subject were considered to be driven by iTTP disease etiology and not induced by TAK-755. Transient anti–CHO protein antibodies were detected at low titers at a single time point in each of 2 subjects, with subsequent negative tests and no temporally associated TEAEs.

In study 3002, no neutralising antibodies were detected also at the updated data cut-off. Low-titer binding antibodies against TAK-755 that did not increase over time were detected in 12 subjects in Study 3002. Detection of these binding antibodies was not temporally associated with any TTP events or any AEs consistent with symptoms of a hypersensitivity reaction.

Studies 281102 and 3002 used different laboratories to perform the binding antibody assay. The study 281102 laboratory had a minimum reportable titer of 1:80. The Study 3002 laboratories used a different method of confirming binding antibodies that allowed confirmation at a minimum reportable titer of 1:20. The apparent increase in the percentage of subjects with binding antibodies in those treated with TAK-755 prophylaxis for ≥18 months is considered a function of the lower assay threshold used in Study 3002 the smaller sample sizes of subjects treated for longer durations.

Table 48: ADAMTS13-bidning antibodies detected in pooled studies 281102 and 3002, n (%)

Treatment Interval	TAK-755 (N=71)	SoC (N=48)
Overall	14 (20.0% of 70 subjects)[a]	1 (2.1% of 48 subjects)
0 to <6 months	5 (7.1% of 70 subjects)[a]	1 (2.1% of 48 subjects)
6 to <12 months	4 (6.2% of 65 subjects)	1 (2.6% of 38 subjects)
12 to <18 months	4 (9.1% of 44 subjects)	0 of 2 subjects
18 to <24 months	5 (14.7% of 34 subjects)	N/A
24 to <30 months	4 (14.3% of 28 subjects)	N/A
30 to <36 months	3 (15.8% of 19 subjects)	N/A
36 to <42 months	1 (12.5% of 8 subjects)	N/A

ADAMTS13=a disintegrin and metalloproteinase with thrombospondin motifs 13; ISE=integrated summary of efficacy; ISS=integrated summary of safety; iTTP=immune-mediated thrombotic thrombocytopenic purpura; n=number of subjects; N/A=not applicable; SoC=standard of care

[a] Includes the subject who had iTTP.

Note: Percentages are based on the number of subjects who test positive at any timepoint during the indicated study interval out of the total number of subjects with non-missing results at any timepoint during the indicated study interval.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No other clinical pharmacology studies, such as studies of drug-drug interactions, food effects or thorough QT, have been conducted. Since TAK-755 is a recombinant protein with a molecular weight of 172 kDa, such studies are not necessary or relevant according to the Applicant.

2.6.8.9. Discontinuation due to adverse events

There have been no TEAEs leading to discontinuation of TAK-755 or withdrawal from any of the clinical studies assessing TAK-755 in cTTP.

One of the four subjects originally enrolled for Cohort 2 (20 IU/kg BW) in study 281101 discontinued from the study before receiving the investigational product, per Sponsor's decision.

In Study 281102, the only TEAE leading to discontinuation of study drug occurred in a subject on SoC, who had a hypersensitivity reaction to fresh frozen plasma. One subject was withdrawn for not meeting eligibility criteria. No subjects receiving TAK-755 had any TEAEs that led to an interruption in study drug infusion. Whereas 7 subjects receiving SoC experienced 8 TEAEs (7 events of hypersensitivity, 1 event of tachycardia) leading to an interruption in study drug infusion.

In Study 3002, 2 rollover subject became pregnant and were withdrawn from the study, as required by protocol.

2.6.8.10. Post marketing experience

There are no post marketing data available since TAK-755 has not been marketed in any region as of the Day 120 data cut date, 12 Aug 2023.

2.6.9. Discussion on clinical safety

The safety and tolerability of TAK-755 treatment against cTTP was investigated in three clinical studies (281101 (phase 1 single dose), 281102 (phase 3 study) and 3002 (single arm continuation study). In addition, supportive data from 9 subjects with cTTP who received TAK-755 through compassionate use was provided.

In total, 71 unique participants, including 20 paediatric subjects, were exposed to at least one dose of TAK-755 in the 3 cTTP clinical studies. Considering the orphan nature of cTTP, the size of the safety database is acceptable, although not considered sufficient to evaluate less common adverse events. In the cTTP clinical trials, 33 subjects have been exposed to TAK-755 for at least 1 year allowing conclusions on the intended long-term use in the prophylactic setting. However, only 2 individuals received TAK-755 in the on-demand setting, limiting possible conclusions for this dosing schedule.

In the pooled studies 281102 and 3002 the overall exposure duration for SoC was lower than for TAK-755 (209.6 days vs. 588.8 days), necessitating the implementation of exposure-adjusted event rate (EAER) for long-term comparisons outside the controlled periods 1 and 2 of study 281102. However, the number and nature of TEAEs for TAK-755 and SoC were overall consistent in study 2801102 Period 3 and Study 3002 (long-term TAK-755 data) with Period 1 and 2 of study 281102 (direct comparison of TAK-755 and SoC; no difference in the duration of exposure). Hence, it can be assumed that the provided data allows also meaningful conclusions on the safety of TAK-755 compared to SoC in the long-term prophylactic treatment of cTTP.

No deaths occurred during the studies. No TEAEs leading to discontinuation of TAK-755 or study withdrawal after TAK-755 were reported in the clinical studies. The only TEAE leading to discontinuation of study drug occurred during SoC prophylaxis. In addition, TEAEs that led to interruption of study drug infusion occurred exclusively during SoC prophylaxis (8 subjects). Only one serious TEAE was considered treatment-related (SoC group). In addition, TAK-755 showed an advantageous safety profile in comparison with SoC regarding the frequency of serious TEAEs (TAK-755: EAER of 10.4 events/100SY; SoC: EAER of 30.1 events/100SY). The events were rather

unspecific and may be related to cTTP. No concerning patterns, linking TAK-755 or SoC treatment to a specific serious safety signal, can be deduced.

In pooled studies 281102 and 3002, 35 severe TEAEs have been reported under TAK-755 treatment (10/74 (14.1%%) subjects; 28.1 events/100SY) of which none were considered related to treatment. Under SoC treatment, 14 severe TEAEs have been reported (7/48 (14.6%) subjects, 46.8 events/100SY) of which one severe TEAE of urticaria was suggested to be treatment-related. Of note, in periods 1 and 2 of study 281102 (direct comparison TAK-755/SoC treatment), the incidence for severe TEAEs was lower for TAK-755 compared to SoC (6.4% vs 12.5%).

In the pooled studies, reported TEAEs after TAK-755 were mostly mild or moderate and not considered related to treatment. According to EAER, a numerically higher incidence for TEAEs was reported for SoC compared to TAK-755 (1108.8 events/100SY vs. 826.2 events/100SY). The difference was more pronounced in the numbers of TEAEs considered related to IP: 133.6 events/100SY under SoC treatment vs. 19.3 events/100SY for TAK-755.

It needs to be emphasised that the clinical significance of the differences observed between TAK-755 and SoC is uncertain due to the limited size of the safety database und the divergent exposure duration. However, based on the available data, some potentially causative safety patterns were discernible.

Overall, headache was the most frequent TEAE present after TAK-755 and SoC in the pooled studies 281101 and 3002 with similar incidence. Other TEAEs such as migraine, abdominal pain, COVID-19, dizziness and diarrhoea (EAER E/100SY TAK-755 vs SoC: 31.3 vs 13.4, 29.7 vs 23.4, 24.9 vs 10.0, 18.5 vs 0.0 and 15.3 vs 10.0) occurred more frequently after TAK-755. According to SOC (PT; Safety Analysis Set), gastrointestinal disorders, infections and infestations, nervous system disorders, and respiratory disorders, thoracic and mediastinal disorders were more frequently after TAK-755 compared to SoC (45.1% vs 31.3%, 73.2% vs 43.8%, 47.9% vs 29.2 %, 39.4% vs 18.8%). Likewise, the incidence for upper respiratory infections was elevated after TAK-755 compared to SoC in the direct periods of study 281102 (12.8% vs 6.3%). Therefore, upper respiratory tract infections will be added to section 4.8 of the SmPC. On the other hand, TEAEs such as thrombocytopenia, urticaria and myalgia occurred more frequently after SoC compared to TAK-755 (EAER E/100SY SoC vs TAK-755: 50.1 vs 7.2, 30.1 vs 1.6 and 10.0 vs 1.6). When considering SOC (PT; Safety Analysis Set), immune system disorders (mainly drug hypersensitivity) occurred almost twice as often after SoC compared to TAK-755 (10.4% vs 5.6%). Also, the incidence in TEAEs such as urticaria (SoC 14.6%; TAK-755 2.8%) or drug hypersensitivity (SoC 8.3%; TAK-755 0.0%) were consistent between the direct comparison phase (P1/P2) of study 281102 and the pooled data at data cut-off.

The applicant provided errata for the CSR of study TAK-755-281102 as requested. These changes have no significant impact on the safety assessment of TAK-755. Therefore, no additional safety concerns arise from this updated information.

Together, the available data indicate an increased risk for immune system disorders such as hypersensitivity after SoC and an increased risk for gastrointestinal disorders and infections after TAK-755. As stated in section 4.4 of the SmPC, if signs and symptoms of severe allergic reactions occur, the administration of this medicinal product should be discontinued immediately and appropriate supportive care should be provided.

An increased risk for infections could be explained by the assigned anti-inflammatory effect (Kaili Lu, J Neuroinflammation, 2020) of ADAMTS13 which is delivered at a higher effective dose after TAK-755 compared to SoC (e.g: study 281102: TAK-755: mean (SD) weight-adjusted dose of 39.95 (1.249) IU/kg; fresh frozen plasma (FFP) SoC 9.09 (5.475) IU/kg). However, a higher rate of infections does not necessarily imply an increased risk of infection severity or TTP related outcomes, as case reports of

COVID-19 suggest. Despite the greater frequency of COVID-19 infections during TAK-755 prophylaxis, there was no corresponding increase in TTP events and no discernible impact of COVID-19 on subject safety. In fact, COVID-19 is associated with an increased risk for thrombosis and anti-inflammatory therapy is common in COVID-10 therapy. Hence, the ADAMTS13 mechanism of action could in theory even diminish severe outcomes of COVID-19, however the presented dataset does not allow for such a conclusion. COVID-19 was reported more frequently during TAK-755 prophylaxis than during SoC prophylaxis, as measured by both EAER and percentage of subjects (EAER E/100SY TAK-755 vs SoC: 24.9 vs 10.0). The applicant assumes that the difference may result from the fact that the SoC TEAE observation period (limited primarily to Periods 1 and 2 in Study 281102) occurred earlier for the bulk of subjects than the TAK-755 observation period. The SoC AE observation period occurred more toward the beginning of the COVID-19 pandemic, when there were lockdowns, greater cautiousness about contact with others, and less available testing for COVID-19. The later successive waves of COVID-19 infections may have been captured more fully during the much longer TAK-755 AE observation period than during the generally earlier and more limited SoC AE observation period. In addition, the applicant provided an analysis of the reported COVID-19 Treatment-emergent Adverse Events (Safety Analysis Set) evaluating the COVID-19 activity at the time of subject infection. The country-wide infection rates were generally higher during the TAK-755 treatment periods as compared to the SoC periods. Therefore, the provided data is overall in line with the applicant´s hypothesis that the higher incidence of COVID-19 in the TAK-755 group compared to SoC might derive from different sample time points.

Dizziness was reported in 2 subjects (13.3% of 15 subjects) in Study 281101 after a single dose of TAK-755 and in 12 subjects (16.9% of 71 subjects) during TAK-755 prophylaxis in pooled Studies 281102 and 3002. The EAER for dizziness during TAK-755 prophylaxis in pooled Studies 281102 and 3002 was even 18.5 events/100SY. No subjects reported dizziness during SoC prophylaxis in the pooled studies. Therefore, SoC -> TAK-755 switch-patients, used to the TEAE profile of SoC, might not expect this AE after cTTP treatment. Somnolence was reported in 2.8% of 71 subjects in pooled Studies 281102 and 3002, with one severe case (EAER 0.8 events/100SY) during TAK-755 prophylaxis and comparable in frequency to SoC. Dizziness and somnolence are therefore included in section 4.7 and 4.8 of the SmPC.

Also, TEAEs considered treatment-related showed some distinct patterns after TAK-755 or SoC. As already emphasized above, related TEAEs occurred generally more frequently after SoC compared to TAK-755. In the safety dataset, any related TEAE according to SOC (PT) occurred in 8.5% (TAK-755) vs 47.9% (SoC) of subjects. However, gastrointestinal disorders were more frequent after TAK-755 compared to SoC (4.2% vs 2.1%). On the other hand, immune system disorders, nervous system disorders (mainly drug HS), and skin and subcutaneous tissues disorders occurred more frequently after SoC compared to TAK-755 (10.4% vs 0.0%, 8.3% vs 4.2%, 22.9% vs 0.0%). Considering EAER (E/100SY), urticaria, drug hypersensitivity, rash, pruritus and allergic transfusion reactions occurred more frequently after SoC compared to TAK-755 (30.1 vs 0.0, 13.4 vs 0.0, 16.7 vs 0.0, 10.0 vs 0.0 and 10.0 vs 0.0). Together, TEAEs considered related to treatment corroborate especially the increased risk for hypersensitivity after SoC.

Of note, TEAEs considered related to TAK-755 treatment were rather unspecific and comparable with some of the symptoms of cTTP (e.g., headaches, lethargy and abdominal discomfort). This hampers identification of the TEAEs' cause, which might partially explain the low number of events considered to be treatment related. In addition, better knowledge of TEAEs related to SoC in comparison to the yet unknown side effects following the novel TAK-755 treatment might yield a relatively higher incidence of related TEAEs for SoC.

Such considerations also imply a possible lack of efficacy. However, the more specific and severe cTTP-related events (Study 281102 P1/P2 all cTTP-related TEAEs: TAK-755 27.7% vs SoC 41.7%; severe

TEAEs: TAK-755 6.4% vs SoC 12.5%; serious TEAEs: TAK-755 2.1% vs SoC 14.6%) occurred with higher incidence after SoC. Hence, this finding infers further suggests an increased efficacy of TAK-755 over SoC regarding the most relevant cTTP outcomes, despite the uncertainties regarding the cause of the overall observed TEAEs in general.

The rate of TEAE (EAER) reported by the site was two times higher compared to the rest of the study sites, both for TAK-755 and SoC. However, there was a substantially lower rate of treatment related TEAE, mainly for TAK-755 reported in this site compared to the rest of the study sites. Also, a high number of the SAE were reported by this site (8/10 SAE). In the responses to the D120 LoQ, the Applicant states that **weekly dosing** was received by 50% of patients at site vs. 4.8% of patients not at site. It is speculated, that patients at site may have had a more symptomatic cTTP requiring more frequent treatment prior to study enrolment. The high number of TEAEs at site is explained by a high number of headaches reported mostly by 4/10 patients. The imbalance in related TEAEs is explained via the overall **low number of related TEAEs** reported by only 5/30 active sites. Finally, the Applicant states that removing data from site, conclusions regarding TEAEs during prophylactic treatment in pooled studies 281102 and 3002 overall remain consistent. The argumentation of the Applicant seems reasonable and can be followed. Based on above arguments it can be agreed that several difference could have contributed to the deviating outcome on adverse events. However, these differences do not seem to impact general safety conclusions. This is considered acceptable.

For prophylactic treatment of cTTP, the presented safety database is considered sufficiently representative for the main target population. However, the available safety data stratified by age is limited (pooled studies 281102 and 3002). Especially for the groups of paediatric subjects, the data is constrained by sample size and exposure duration. For instance, only 4 subjects were included in each paediatric subgroup and no subject <12 years of age was treated >12 months.

Overall, the frequency for TEAEs was about two times lower in the paediatric compared to the adult cohort according to EAER (E/100SY). In addition, TEAEs related to study drug did not occur after TAK-755 treatment in paediatric patients (0.0 E/100SY) but at 23.2 E/100SY in adult cTTP patients. Importantly, TEAEs related to study drug occurred much more frequently after treatment with SoC across all age groups (e.g. adult patients 11.8% vs 50.0%). Data from 4 paediatric CPU patients support the overall good safety in paediatric and adult patients as observed in the clinical studies. Taken together, the limited safety dataset stratified by age suggests that the safety profile in paediatric patients is consistent with the safety profile in adult patients.

The applicant provided an overview of TEAEs by SOC/PT and age group (<6 years, 6 to <12 years, 12 to <18 years, ≥18 years) for pooled studies 281102 and 3002. Regarding TEAEs by **SOC** for pooled studies 281102 and 3002, most frequently reported TEAE categories in adult patients were also reported for the paediatric groups although frequencies differed: infections and infestations; nervous system disorders; gastrointestinal disorders; respiratory, and thoracic and mediastinal disorders. Overall, incidence for the respective SOC seemed to follow the rate of events per 100 study years (E/100SY). Also, the low number of paediatric patients, by group complicates interpretation. Based on the data available to date, there are currently no further concerns.

The applicant provided two tables listing TEAEs by SOC, PT, and gender for the prophylactic subjects, as well as for the OD subjects. Frequency of any TEAEs was comparable in male vs. female subjects receiving TAK-755. However, for some SOCs, notable imbalances have been observed between male vs. female subjects. E.g., regarding treatment with TAK-755, noteable imbalances for the SOCs respiratory, thoracic, and mediastinal disorders (male vs. female: 9 (33.3%) vs. 19 (43.2%) patients); injury, poisoning and procedural complications (12 (44.4%) vs. 11 (25.0%) patients); or gastrointestinal disorders (9 (33.3%) vs. 23 (52.3%) patients) have been shown. Also, comparing treatment with standard of care, imbalances between male and female patients have been shown, e.g.

for SOCs as nervous system disorders (male vs. female: 4 (20.0%) vs. 10 (35.7%) patients); respiratory, thoracic and mediastinal disorders (2 (10.0%) vs. 7 (25.0%) patients); injury, poisoning and procedural complications (2 (10.0%) vs. 9 (32.1%) patients). The most frequent TEAEs for subjects receiving TAK-755 have been reported in the SOCs gastrointestinal disorders; general disorders and administration site conditions; and respiratory, thoracic, and mediastinal disorders. The most frequent TEAEs for subjects receiving SoC have been reported in the SOCs general disorders and administration site conditions; gastrointestinal disorders; and injury, poisoning and procedural complications. Imbalance in the incidence rate of study drug related TEAEs were considered due to the small number of subjects. Also, most of the related events have been experienced by a single female subject. This argumentation can be followed for the related TEAEs. In general, TEAEs for which imbalances have been observed between male and female patients were considered not related to treatment. Also, these imbalances have been observed in general for TAK-755 and standard of care in similar rates. Therefore, the lack of relation of these TEAEs to treatment is considered reasonable. However, regarding observed imbalances between TAK-755 and SoC groups in male and female patients, frequencies are comparable to overall numbers as already presented in the original dossier. Imbalances for some SOCs have been observed between male vs. female patients. However, as mentioned above, concerned TEAEs were not related to treatment.

Only limited data on 4 pregnant patients under TAK-755 treatment were provided. The patient found pregnant in study 3002 had a first-trimester miscarriage approximately 2 months after study discontinuation not considered related to TAK-755. The applicant provided information about the detection of the pregnancy in relation to scheduled dose of the study drug (TAK-755) for this patient, discontinuation of the study and planned follow-up medication, as requested. Information on disease activity after the patient was discontinued from the study is not available. Provided data is considered sufficient. The two CPU patients already had a history of cTTP events during pregnancy and received TAK-755 after further cTTP exacerbation (medical emergency). In both cases, TAK-755 treatment was followed by remission of disease, and a healthy baby was delivered. No safety concerns due to TAK-755 were reported. Taken together, these case reports suggest that the increased risk for developing a blood clot that comes along with pregnancy together with cTTP are a greater safety risk for mother and fetus than TAK-755 treatment of the mother.

An at least theoretical concern regarding use of TAK-755 in pregnancy is however derived from preclinical data: Studies 8234215 and 8243420 describe symptoms of thrombotic thrombocytopenic purpura (TTP) in female cynomolgus monkeys upon repeated administration of 200 U/kg (1 of 5 females; study 8243420); 400 U/kg (2 of 5 females; study 8243420) and 800 U/kg (2 of 2 females; study 8234215) of TAK-755. Such symptoms comprise thrombocytopenia, haemolytic anemia, LDH enzyme release, increased reticulocytes, bilirubinaemia, generalised macroscopic skin haematoma and red foci in kidneys and the stomach, haemorrhage or congestion/haemorrhage in the heart, adrenals, stomach and skin. The findings correlated with high titres of neutralizing anti-TAK-755 antibodies, supporting the interpretation that cross-reaction between formed antibodies and endogenous ADAMTS13 caused the observed TTP-like events. (See also non-clinical aspects)

Neutralising antibodies could in theory lead to a TTP like phenotype in newborns of TAK-755 treated women following placental transfer of such antibodies during pregnancy. In the responses to the D120 LoQ, the Applicant agrees to monitor any related reports and states that the risk management plan has been updated accordingly. It is agreed, that the RMP has been updated regarding missing information on „Risks in case of pregnancy and lactation". The theoretical risk of NAb-formation during treatment with TAK-755 in pregnant women, the possibility of NAbs crossing the placenta and development of an immune-mediated TTP-like phenotype in the newborn is of concern and, therefore, needs to be adequately monitored after marketing authorisation.

Furthermore, as pregnant women are considered a target population for treatment with TAK-755 (pregnancy is a main trigger for TTP symptoms) and currently available data regarding safety (including the foetus/new-born) are extremely limited, further data collection in the post-marketing is considered necessary (please see RMP).

No studies of the effect of TAK-755 on lactation have been conducted. It is unknown whether TAK-755 would be excreted in milk. This is acknowledged and reflected in the SmPC.

No neutralising antibodies against ADAMTS13 were detected in any subject with confirmed cTTP in the clinical studies. Twelve rollover subjects were positive for binding antibodies in study 3002. The detection of the binding antibodies was not temporally associated with any TTP events or any AEs consistent with symptoms of a hypersensitivity reaction.

In summary, reported TEAEs after TAK-755 were mostly mild or moderate and not considered related to treatment. In addition, fewer TEAEs and related TEAEs were reported after TAK-755 compared to SoC. Also, serious cTTP-related events occurred exclusively after SoC. Hence, the safety profile of TAK-755 is acceptable for prophylactic treatment of cTTP as described in the clinical studies.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a MA under exceptional circumstances

The applicant investigated the feasibility of conducting a PASS in collaboration with the International hTTP Registry. Several shortcomings of the registry were identified, which would hinder the provision of meaningful data in a timely manner. The applicant proposed a global chart review study designed to estimate the risk of neutralising (inhibitory) antibodies to rADAMTS13, hypersensitivity reactions, risks in case of pregnancy, and long-term safety following TAK-755 administration. In view of the limitations of data acquisition foreseen with the International hTTP Registry this new proposal is considered acceptable.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.

2.6.10. Conclusions on the clinical safety

Overall, the sample size of the safety database is considered too small to detect less frequent adverse events but is considered acceptable in the light of the rarity of the disease (cTTP). The limited available safety data suggest an acceptable safety profile of TAK-755 for the prophylactic treatment of cTTP. Most importantly, overall data show trends of an overall advantageous safety profile of TAK-755 in comparison with SoC.

Concerning on-demand exposure, data on clinical safety is limited to the treatment of two acute events in two unique subjects. Although safety of TAK-755 in these two cases is reassuring, no meaningful conclusions can be drawn. However, it is understood that such patients, who had to be not on prophylaxis and having an acute event, are difficult to recruit, and therefore, from a safety point of view, this limited number is considered acceptable but further underlines the non-comprehensiveness of the overall data package.

The CHMP considers the following measures necessary to address the missing safety data in the

context of a MA under exceptional circumstances:

- In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.
- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the final results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.
- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.
- In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant identified the following safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neutralising (inhibitory) antibodies to rADAMTS13 • Hypersensitivity reactions
Missing information	• Risks in case of pregnancy and lactation • Long-term safety

2.7.2. Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
I. Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
II. **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
TAK-755 PASS study Planned	To evaluate specific safety concerns potentially related to TAK-755 in patients with cTTP, including the important potential risks and missing information delineated in the EU RMP, including neutralizing	• Neutralizing (inhibitory) antibodies to rADAMTS13 • Hypersensitivity reactions • Risks in case of	Protocol submission Final Report	Estimated: Q4 2024* Estimated: Q4 2030*

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	(inhibitory) antibodies to rADAMTS13, hypersensitivity reactions, risks in case of pregnancy, and long-term safety following TAK-755 administration	pregnancy and lactation • Long-term safety		
III. **Category 3** - Required additional pharmacovigilance activities				
None				

2.7.3. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Neutralising (inhibitory) antibodies to rADAMTS13	**Routine risk communication**: Sections 4.4 in the Summary of Product Characteristics (SmPC) Sections 2 of the Package Leaflet (PL) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 recommends that as with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies were not reported in patients treated with Adzynma in the cTTP clinical trials. Patients may develop antibodies to rADAMTS13 following treatment with Adzynma which could potentially result in a decreased response to rADAMTS13. **Other routine risk minimisation measures beyond the Product Information**: None proposed.
Hypersensitivity reactions	**Routine risk communication:** Sections 4.4 in the SmPC Sections 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 recommends that allergic-type hypersensitivity including anaphylactic reactions may occur. Patients should be informed of the early signs of hypersensitivity reactions including but not limited to tachycardia, tightness of the chest, wheezing and/or acute respiratory distress, hypotension, generalised urticaria, pruritus, rhinoconjunctivitis, angioedema, lethargy, nausea, vomiting, paresthesia, restlessness, and may progress to anaphylactic shock. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of Adzynma and provide appropriate supportive care. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Risk in pregnancy or lactation	**Routine risk communication:** Sections 4.6 in the SmPC Sections 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.6 recommends that the use of Adzynma if necessary, may only be considered after a thorough individual risk benefit analysis by the treating physician before and during treatment.

	Other routine risk minimisation measures beyond the Product Information: None proposed.
Long-term safety	**Routine risk communication:** Sections 4.4 and 4.6 in the SmPC Sections 2 of the Package Leaflet (PL) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None proposed.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Adzynma (rADAMTS13) is included in the additional monitoring list as it contains a new active substance and is approved under a MA under exceptional circumstances.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Adzynma is intended for prophylactic replacement of the missing enzyme activity as well as for on demand treatment of acute TTP events.

The agreed indication is the following: Adzynma is an enzyme replacement therapy (ERT) indicated for the treatment of ADAMTS13 deficiency in children and adult patients with congenital thrombotic thrombocytopenic purpura (cTTP). Adzynma can be used for all age groups.

Congenital thrombotic thrombocytopenic purpura is an ultra-rare, life-threatening, chronic, and debilitating blood clotting disorder with an estimated prevalence of 0.5 to 4 cases/million, and which is caused by severe ADAMTS13 deficiency, generally considered to be <10% of mean normal activity, due to mutations in the ADAMTS13 gene (Kremer Hovinga JA *et al,* Hereditary Thrombotic Thrombocytopenic Purpura. N Engl J Med 2019).

Often, conditions that are associated with increases in VWF activity, such as infections, trauma and pregnancy, are triggers for acute TTP events and consistent with the two peaks in initial presentation of cTTP: in newborns/childhood and during pregnancy. Symptoms may develop soon after birth, and childhood is a recognised vulnerable period for patients with cTTP. First presentation during pregnancy is also common, specifically during the second and third trimesters, where a remarkable increase in plasma VWF is thought to explain the increased risk for initial presentation, acute episodes, and intrauterine foetal growth restriction. Additional recognised risk factors for aggravation of cTTP and precipitation of an acute event are infections, trauma, and excessive alcohol intake.

The clinical presentation of cTTP lies on a spectrum of severity ranging from severe acute TTP episodes to chronic, recurring TTP manifestations which include thrombocytopenia, haemolytic activity, headache, abdominal pain, fatigue or lethargy, bruising, joint pain, muscular pain, forgetfulness and confusion. While the disease presentation is multifactorial, the root cause of cTTP disease activity is driven by severe ADAMTS13 deficiency, defined as <10% ADAMTS13 activity.

3.1.2. Available therapies and unmet medical need

There are no medications approved for routine prophylactic treatment of cTTP.

Current SoC treatment centres around the principle of replacing the missing ADAMTS13 enzyme through on-demand or regular prophylactic infusions of available plasma-based therapies.

Apart from FFP and S/D plasma, two plasma-derived concentrates containing factor VIII and VWF have been used: antihaemophilic factor (Koate-DVI) and intermediate purity factor VIII (BPL 8Y). Furthermore, plasma exchange therapy may be used for severe manifestations, e.g. in pregnancy.

Though shown to be effective for the treatment of cTTP, plasma-based therapies are reliant on donor plasma and have well-recognised drawbacks regarding non standardised amounts of ADAMTS13 activity, high infusion volume and tolerability issues, hence there remains a strong unmet need for alternative options.

3.1.3. Main clinical studies

The clinical study programme consists of three studies. The **phase 1 study 281101** administered single infusions at doses of 5, 20, and 40 U/kg body weight to three consecutive cohorts of patients with severe hereditary ADAMTS13 deficiency, confirmed by genetic testing and ADAMTS13 activity < 6% of normal and provided initial evidence of PK, PD and safety.

The **pivotal trial 281102** enrolled generally healthy subjects with confirmed hereditary TTP and ADAMTS13 activity <10%. Subjects entering the prophylactic cohort were randomised to 6 months of treatment either with standard of care or TAK-755 followed by 6 months of treatment with the other treatment modality and subsequently moving into the single-arm continuation phase of another 6 months of TAK-755 treatment. The prophylactic treatment consisted of 40 IU/kg rADAMTS13 Q1W or Q2W (depending on the subjects' pretrial SoC regimen). The prophylactic SoC dose and treatment regimen was to be determined by the investigator and could be any of the following: FFP; Pooled S/D treated plasma; FVIII:VWF concentrates. If an acute TTP event occurred during prophylaxis, subjects were to receive an initial dose of 40 IU/kg TAK-755, a subsequent dose of 20 IU/kg TAK-755 on Day 2 and additional daily doses of 15 IU/kg TAK-755 until 2 days after the acute TTP event was resolved (acute TTP event resolution defined as platelet count $\geq$150,000/μL or platelet count within 25% of baseline OR elevation of LDH $\leq$1.5$\times$ baseline or $\leq$1.5$\times$ULN).

Patients experiencing an acute TTP event could enter the trial via the on-demand cohort for a randomised treatment of the acute event with either SoC or TAK-755. Subjects could then proceed to the prophylactic cohort, re-enroll for another acute event or leave the trial. Subjects in the on-demand treatment cohort received the same dosing regimen for the treatment of their acute TTP event.

The trial is ongoing and data from a planned interim analysis were submitted to support this MAA. The data cut-off was on 12 Aug 2022, and data from 47 subjects are available in the FAS of the prophylactic cohort. For the on-demand cohort, data from 5 subjects are included in the FAS.

A total of 32 adult subjects, 4 adolescents (12 to <18 years) and 8 total paediatric subjects (4 aged <6 years and 4 aged 6 to <12 years) were included to the prophylactic cohort. The number of paediatric patients aged < 12 years included in the pivotal study is in agreement with the PIP. One adolescent and all paediatric subjects are still on study. All 5 subjects enrolled in the OD Cohort were adults.

The applicant submitted updated efficacy and safety data from Study 281102, based on the efficacy dataset with 34 adult and 4 adolescent subjects who all completed the study, and all 8 paediatric subjects (4 subjects aged <6 years; 4 subjects aged 6 to <12 years) who have all completed the controlled comparison Periods 1 and 2. A total of 3 paediatric subjects (aged 6 to <12 years) have completed the study and 5 paediatric subjects have completed at least 4 weeks of Period 3. For the on-demand (OD) cohort, there was 1 paediatric subject (aged <6 years) enrolled after the MAA data cutoff date (12 Aug 2022) who discontinued from the OD cohort after resolution of the acute event due to physician decision. As of 11 Aug 2023, in total data on all 6 subjects who completed the OD treatment in the OD cohort are provided.

The **phase 3b trial TAK-755-3002** is a single arm, open label continuation study investigating the efficacy and safety of prophylactic and on demand treatment with rADAMTS13 treatment up to 3 years. Subjects completing pivotal trial 28102 were eligible to roll over into the continuation trial, and non-rollover subjects fulfilling the in- and exclusion criteria could also enter this trial. The primary objective of this study is safety, and the key secondary efficacy outcome is the number and incidence rate of acute TTP events in subjects with cTTP undergoing prophylactic treatment with TAK-755. In addition, time to resolution of a treated acute TTP event as well as incidence of isolated TTP manifestations and the incidence of dose modifications were defined as secondary endpoints. Prophylactic and on demand doses of TAK-755 were identical to those employed in the pivotal trial.

Supportive efficacy data are available from a planned interim analysis. Data from 36 new and rollover subjects were included in the FAS of the prophylactic cohort and zero subjects were enrolled in the on-demand cohort at the data cut-off.

With the responses to D120 CHMP list of questions, data is extended to 49 adults, 10 adolescents, and 6 paediatric subjects who have received TAK-755 for up to 26 additional months of exposure to TAK-755 in the 3002 study.

Further supportive data derive from the experience of patients receiving apadamtase through **compassionate use**. Nine female patients were treated with TAK-755, ranging in age from 36 hours to 72 years.

3.2. Favourable effects

In the PD study, the overall exposure, including the meantime above 10% ADAMTS13 activity (>0.1 IU/ml) was considerably higher during TAK-755 treatment compared to SoC (5.2 vs 1.7 days) after a 40 IU/kg single dose. The mean duration above 10% ADAMTS13 activity was predicted to be longer at steady state (up to 9 days). Transient trends for decreasing large VWF multimers (including ultra-large multimers) and increasing levels of the intermediate form were observed over the first 24 hours post-dose in individual profiles at higher doses. More subjects receiving TAK-755 showed detectable ADAMTS13 mediated VWF cleavage products, compared to SoC administration, for the first approximately 5 days after infusion. The relative change of platelet counts over time suggests higher platelet counts in patients treated with TAK-755 during both treatment periods, confirming results from the QSP model. In the E-R model, the entire range of steady-state ADAMTS13 activity C_{ave} exposures for Q2W and Q1W dosing interval for TAK-755 was associated with ≥70% probability of being thrombocytopenia event-free. Similarly, the entire range of predicted Cave ADAMTS13 activity resulting from TAK-755 Q2W or Q1W dosing intervals was also associated with >80% probability of being MAHA event-free.

The primary endpoint of pivotal trial **281102**, i.e. the incidence of acute TTP events among subjects receiving either TAK-755 or standard of care (SoC) **prophylactically** during the corresponding treatment periods showed zero episodes in subjects while on TAK-755 treatment versus one episode in subjects receiving SoC treatment.

The overall annualised incidence of isolated TTP events, i.e. thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), renal dysfunction, neurological symptoms and abdominal pain during **prophylactic treatment** was 2.51 for rADAMTS13 and 3.58 for SoC. Similar numerical results were seen for each investigated sign or symptom except for renal dysfunction. The annualised event rates (SE) for the most common manifestation of TPP thrombocytopenia were 0.92 (0.262) and 1.72 (0.457) in the TAK-755 and SoC cohorts respectively and for MAHA these were 0.37 (0.136) and 0.59 (0.194) in the TAK-755 and SoC cohorts respectively.

The annualised event rate of subacute events was 0.04 (0.275) for rADAMTS13 and 0.30 (0.809) for SoC. The number of dose modifications not prompted by an acute TTP event was low and evenly distributed across treatments. One acute TTP event occurred in a subject being treated with SoC on the final dose and dosing frequency after any dose and/or schedule modifications occurred.

The efficacy endpoints investigating the effect of TAK-755 in the **on demand treatment** of acute TTP events were 1) the proportion of acute TTP events responding to TAK-755 treatment and 2) the time to resolution of acute TTP events following initiation of treatment with TAK-755 or SoC, in both the Prophylactic and the OD Cohorts throughout the duration of the study. One acute TTP event which met the protocol definition in the on-demand cohort was treated with rADAMTS13, did respond to

treatment and was resolved after a treatment duration of 3 days. The one acute event treated with SoC in the prophylactic cohort appears to have been resolved after 3 days as there were no further study visits. An additional SoC-treated acute event in the OD cohort was reported resolved after 1.5 days. Time to resolution of acute events in the OD cohort that did not meet the protocol-defined criteria for an acute event was 5 days in the TAK-755 cohort (1 event) and 2, 4, 5 and 5 days in the SoC cohort (4 events). In conclusion, time to resolution of acute events appeared to be comparable for TAK-755 and SoC.

Supportive efficacy data are available from a planned interim analysis of ongoing continuation trial **3002**. The primary outcome of study 3002 is safety, and the secondary efficacy endpoints investigate the effect of apadamtase for both prophylaxis and treatment of cTTP. No acute TTP events occurred while subjects received TAK-755 prophylaxis for a mean exposure of 11.8 months and up to 26 months. One acute TTP event occurred during screening in a non-rollover subject, prior to initiating dosing with TAK-755. The acute event was resolved by treatment with TAK-755 in 6 days. Another acute event occurred in a paediatric subject in context of COVID-19 infection. More than half of the subjects (58.3%) did not experience any of the protocol defined TTP manifestations (thrombocytopenia, microangiopathic haemolytic anaemia [MAHA], neurological symptoms, renal dysfunction, or abdominal pain) while receiving TAK-755 prophylaxis. Overall, the annualised incidence of isolated TTP manifestations was 1.74. Three subjects experienced 6 subacute TTP events during the study, resulting in an annualised incidence of 0.08. These outcomes are comparable to those from the pivotal trial 281102 and provide supportive evidence of the continued efficacy of rADAMTS13 in the prophylactic setting.

Paediatric patients

All paediatric (8) subjects < 12 years of age completed the main comparative cross-over part (ie, Periods 1 and 2). One paediatric subject (age <6 years old) completed the OD cohort. Study **3002** contributes to the paediatric dataset with 6 paediatric non-rollover patients <12 years old, and 7 rollover and 3 non-rollover patients 12 to <18 years of age.

In total, the paediatric population in Studies 281102 and 3002 include over 27% of the total subject population (20/72 subjects in ISS are <18 years of age). In addition to the clinical trial data, one neonate aged 36 hours old was treated with TAK-755 in a compassionate use program. At age 2 years, the child reached all developmental milestones for age, with no acute episodes. In general, the efficacy data in paediatric patients provided are consistent with the adolescent and adult data.

Both clinical trials excluded pregnant women, however data from the compassionate use programme provide reassuring supportive evidence of the beneficial effects of treatment during pregnancy whereas other measures (plasma derived treatments, plasma exchange) were insufficient. Importantly, outcomes from two pregnant patients are available. One pregnant female experienced thrombocytopenia that was unresponsive to plasmapheresis and had suffered an ischaemic stroke during the current pregnancy. The patient delivered a healthy infant and continues on Q2W rADAMTS13 prophylaxis. The second female patient suffered a stroke during the second trimester of her pregnancy and was managed with plasma exchanges but soon relapsed into another acute TTP event. With Q1W rADAMTS13 treatment, the patient achieved remission with an intact pregnancy.

3.3. Uncertainties and limitations about favourable effects

With regards to the non-clinical data, results showed that prophylactic as well as therapeutic administrations of rADAMTS13 in the rVWF-induced TTP model in ADAMTS13 KO mice do have effects on the chosen endpoints. Efficacy of TAK-755 was defined as the degree of prevention of decrease in platelet count and prevention of increase in lactate dehydrogenase (LDH), both parameters being

markers of TTP. However, in all animal groups in the therapeutic treatment, where ADAMTS13 KO mice received an intravenous injection of a high dose of rVWF and 15, 30 or 180 minutes later animals were treated with one dose of BAX 930 or buffer for BAX 930, the mean haematocrit and haemoglobin levels were lower than in the untreated ADAMTS13 KO mice, indicating no immediate beneficial effect of BAX 930 on these variables.

From a PK/PD perspective, the expected (and observed) low event rate may lead to overestimation of event-free range in the E-R model. The popPK model tends to underpredict high ADAMTS13 activity concentrations (>1 IU/mL). Measuring VWF parameters has limitations, as generally the reference range is wide and no cTTP-specific thresholds are defined. Furthermore, available assays for VWF multimer analysis are semi-quantitative and lack standardization, hampering a reliable interpretation. Platelet aggregation tests have not been performed.

Due to the very low number of acute TTP events in both Tak-755 and SoC (0 versus 1), no inferential statistical analysis but only descriptive statistics are presented for the primary endpoint of the pivotal trial 281102 pertaining to the **prophylactic treatment** with TAK-755. Before study start, the expected low number of observable acute events was repeatedly addressed by CHMP in the EMA SA procedures in 2016 and 2018 and a longer observation period than 6 months, at least 12 months, was strongly advised. However, even if the treatment periods of TAK-755 ORT and TAK-755 SIN are taken together for a full 12 months of prophylactic ERT, no acute event could be observed. In the SoC cohort, during 6 months of prophylactic treatment, one acute TTP could be observed. Even after doubling this observation period, incidence of acute TTP events would likely remain very low and no relevant gain in precision in the estimates of the treatment effect on primary endpoint could be expected. At the end, the outcome of 0 events can either be seen as a direct consequence of satisfactory efficacy of ERT using rADAMTS13, or as a result of the unpredictable natural disease course of hereditary TTP featuring discontinuous event incidence, or (most likely) a mixture of both. Thus, no firm conclusions regarding the efficacy of TAK-755 in the prophylactic setting can be drawn from the primary outcome of the pivotal study.

As the analysis of the primary endpoint renders no unequivocal result supporting the efficacy of rADAMTS13 in the prophylactic setting, the incidence of objective markers that are also hallmarks of the disease, i.e., thrombocytopenia and MAHA, gain a greater importance. These events were captured as secondary endpoints and their incidence was lower while being on TAK-755 prophylaxis compared to being on SoC prophylaxis.

With regard to the efficacy of TAK-755 in the **on demand treatment** of acute TTP episodes, only few events were captured during the clinical trials 281102 and 3002, which limits the proper assessment of data in this group. Difficulties in finding on-demand patients lie likely on the fact that patients with TTP who suffer from acute TTPs usually are on prophylaxis, as also evident from the registry data. Patients with a milder presentation are less likely to develop acute TTP. So, in general on-demand use of TAK-755 is expected to be limited.

Due to the exclusion of **pregnant women** from the clinical trial population, the external validity of the observed results is negatively impacted, as pregnancy is a relevant trigger for acute TTP events and the use of TAK-755 in pregnant women is highly likely after the granting of a MA.

Twelve **paediatric patients** are enrolled in pivotal trial 281102, 4 subjects each are in the age cohort <6, 6-<12 and 12-<18, respectively and 6 additional paediatric patients in study 3002, which is a limited number, but expected due to the rarity of the disease.

Considering all the above aspects, a MA under exceptional circumstances has been agreed with the following specific obligations:

- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the final results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.
- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.
- In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.
- In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.

3.4. Unfavourable effects

Adverse Events

In studies 281101, 281102 and 3002 most frequently reported TAEs were nervous system disorders, such as headache. Additionally, TEAEs such as migraine, abdominal pain, COVID-19, dizziness, and diarrhoea (EAER E/100SY TAK-755 vs SoC: 31.3 vs 13.4, 29.7 vs 23.4, 24.9 vs 10.0, 18.5 vs 0.0 and 15.3 vs 10.0) occurred more frequently after treatment with TAK-755.

In pooled studies 281102 and TAK-755-3002 a higher incidence for TEAEs was reported for SoC compared to TAK-755 (1108.8 events/100SY vs. 826.2 events/100SY).

Only few subjects experienced TEAEs considered treatment-related (6/71 (8.5%) subjects under TAK-755 vs. 23/45 (47.9%) subjects under SoC). TAK-755-related TEAEs were mostly gastrointestinal disorders (flatulence, nausea), nervous system disorders (headache) or investigations ("Von Willebrand's Factor Activity Decreased" and "Von Willebrand's Factor Antigen Decreased").

Most of the reported TEAEs were mild or moderate in severity. No severe TEAE under TAK-755 treatment was considered related to IP.

Serious Adverse Events, deaths, other significant events

No deaths have been reported in any clinical studies of TAK-755.

Only one serious TEAE of pyrexia in 1/48 (2.1%) subject of the prophylactic cohort under SoC treatment in pooled studies 281102 and 3002 was considered treatment-related. The SAE of pyrexia was considered resolved after 2 days of hospitalization and medication with saline and paracetamol.

Adverse events by sex

The 72 subjects who received prophylactic treatment in Studies 281102 and 3002 were comprised of 28 males (38.9%) and 44 females (61.1%). It was shown that TEAEs considered related to TAK-755 had a higher incidence in females than in males in pooled studies 281102 and 3002 (26.2 events/100SY in female subjects vs. 6.6 events/100SY in male subjects). With submission of the responses to the D120 LoQ, the Applicant provided two tables listing TEAEs by SOC, PT, and gender for the prophylactic subjects, as well as for the OD subjects. For the updated assessment, the 72 patients who received prophylactic treatment in pooled studies 281102 and 3002 were comprised of 28 males

(38.9%) and 44 females (61.1%). Frequency of any TEAEs was comparable in male vs. female subjects receiving TAK-755. However, for some SOCs of TEAEs considered not related to treatment, notable imbalances have been observed between male vs. female subjects.

Upper respiratory tract infections

The incidence for upper respiratory infections was elevated after TAK-755 compared to SoC (e.g. 15.5% vs 6.3%). in the direct comparison periods of study 281102). This has been reflected in section 4.8 of the SmPC.

Immunogenicity

No neutralising antibodies against plasma-derived or recombinant ADAMTS13 (TAK-755) were detected in any subject with confirmed cTTP across all clinical studies. In study 281102, low-titre binding antibodies against TAK-755 were detected in 1 subject with cTTP at baseline. In study 3002, low-titre binding antibodies against TAK-755 that did not increase over time were detected in 12 subjects in Study 3002. Additional analyses using an alternative assay and equal thresholds for both studies suggest that the increase is a function of the lower assay threshold used in Study 3002. Using different reporting thresholds for binding antibodies hampers continuity and interpretability of presented data.

Section 4.4 and 4.8 of the SmPC reflects that patients may develop antibodies to rADAMTS13 following treatment with Adzynma which could potentially result in a decreased response to rADAMTS13. "Neutralising (inhibitory) antibodies to rADAMTS13" and "Hypersensitivity reactions" have been added as an important potential risk in the RMP. In addition, additional risk minimisation measures have been agreed such as HCPs educational materials and patient card to highlight these risks.

3.5. Uncertainties and limitations about unfavourable effects

AEs vs. cTTP-symptoms

TEAEs considered related to TAK-755 treatment were rather unspecific and comparable with some of the symptoms of cTTP (e.g., headaches, lethargy and abdominal discomfort). This hampers causality assessment, which might also partially explain the low number of events considered to be treatment related.

Pregnancy, lactation, impaired renal or hepatic function

An at least theoretical concern regarding use of TAK-755 is derived from preclinical data: Studies 8234215 and 8243420 describe symptoms of thrombotic thrombocytopenic purpura (TTP) in healthy female *Cynomolgus* monkeys upon repeated administration of 200 U/kg (1 of 5 females; study 8243420); 400 U/kg (2 of 5 females; study 8243420) and 800 U/kg (2 of 2 females; study 8234215) of TAK-755. The findings correlated with high titers of neutralizing anti-TAK-755 antibodies, supporting the interpretation that cross-reaction between formed antibodies and endogenous ADAMTS13 caused the observed TTP-like events.

Potential development of neutralising antibodies (although not detected in the clinical development programme so far) during pregnancy could theoretically lead to TTP like phenotype in newborns of TAK-755 treated women following placental antibody transfer during pregnancy. The theoretical risk of NAb-formation during treatment with TAK-755 in pregnant women, the possibility of NAbs crossing the placenta and development of an immune-mediated TTP-like phenotype in the newborn is of concern and, therefore, needs to be adequately monitored after marketing authorisation (reflected in the updated RMP).

Furthermore, even though pregnant women are considered a target population for treatment with TAK-755 (pregnancy is a main trigger for TTP symptoms), currently available data regarding safety (including the foetus/newborn) are very limited.

No studies of the effect of TAK-755 on lactation have been conducted. It is unknown whether TAK-755 would be excreted in milk. Also, no data are available for patients with renal or hepatic function impairment.

Small Safety Database

Due to the ultra-rarity of cTTP the resulting safety databases for presented studies is accordingly small. In study 281101 15 subjects receiving treatment with TAK-755. In the prophylactic cohort of pooled studies 281102 and 3002 72 subjects, in the OD Cohort: 2 subjects were treated with the study drug. Additionally, 9 subjects received TAK-755 under CPU. Although, the size of the safety database may be sufficient to evaluate the occurrence of more common AEs, it may hinder capturing AEs of lower frequency (e.g., uncommon, or rare AEs). The sample sizes and exposure durations are very limited, which makes the assessment of the medicine effects in the paediatric population challenging. Only limited data on 4 pregnant subjects under TAK-755 treatment were provided.

Considering all the above uncertainties on the safety aspects, a MA under exceptional circumstances has been agreed and specific obligations have been requested to provide additional information. In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.

3.6. Effects Table

Table 49: Effects Table for Adzynma, all subjects (adult, adolescent, paediatric)

Effect	Short Description	Unit	Treatment TAK-755	Control SoC	Uncertainties/ Strength of evidence
Favourable Effects [1]					
Incidence of acute TTP events (primary endpoint)	Δ Plt ≥ 50% of baseline OR Plt < 100,000/µL AND Δ LDH > 2×of baseline OR LDH > 2×ULN	Number of events/number of patients	0/45	1/46	**Unc**: Due to low number of events no inferential statistical analysis presented, result not informative **SoE**: 1 subacute event was reported during TAK-755 and 7 events in 6 subjects during SoC prophylaxis.
Incidence of Thrombocytopenia	Δ Plt ≥ 25% of baseline OR Plt < 150,000/µL	Annualized Event Rate, LSM (SE)	0.92 (0.262)	1.72 (0.457)	**SoE**: objective endpoint, Unc: descriptive statistics only
Incidence of MAHA	Δ LDH > 1.5× baseline OR LDH > 1.5×ULN	Annualized Event Rate, LSM (SE)	0.37 (0.136)	0.59 (0.194)	**SoE**: objective endpoint Unc: small number of events, mean and SE overlaps between both treatments.

Incidence of Neurological symptoms	AEs in the SOC of **nervous system disorders**, AEs in the HLGT of **vision disorders**, and AEs with PT of **irritability** related or possibly related to cTTP	Annualized Event Rate, LSM (SE)*	0.13 (0.068)	0.23 (0.109)	**Unc**: small number of events, mean and SE overlaps between both treatments.
Abdominal pain	AEs of abdominal pain related or possibly related to cTTP	Annualized Event Rate, LSM (SE)*	0.09 (0.055)	0.17 (0.086)	**Unc**: small number of events, mean and SE overlaps between both treatments.
Number of Acute TTP Events Responding to TAK-755 Treatment (for on demand indication)		Events responding/total number of events	1/1	N/A	**Unc**: small number of events SoE: on demand treatment further supported by PopPK modelling data and data from the literature showing ability of TAK-755 to restore ADAMTS13 levels to normal and resolve an acute event.
Time to Resolution of Acute TTP Events		days	3 (1 event)	1.5 (1 event)	**Unc**: Reporting by investigator inconsistent. Small number of events. **SoE**: Time to resolution of acute events in the OD cohort that did not meet the protocol-defined criteria for an acute event were 5 days in the TAK-755 cohort (1 event) and 2, 4 and 5 days in the SoC cohort (4 events).
Unfavourable Effects [2]					
Treatment related TEAEs	Incidence for treatment related TEAEs in the prophylactic cohort of pooled studies 281102 and 3002	Events/100 subject years (EAER)	19.3	133.6	Unc: The small sample set impairs the significance of the difference between TAK-755 and SoC.

Abbreviations: SOC = System organ class; EAER= EAER=exposure-adjusted event rate; LSM= least squares mean ; MAHA = microangiopathic haemolytic anaemia SE= standard error; HLGT = high-level group term; PT = preferred term;
Plt = platelet count; Δ = Drop (for platelets) or Increase (for LDH); TEAE= treatment emergent adverse event; ULN = Upper limit of normal.
Notes: [1] iCSR of trial 281102 [2] ISS/ISE Tables of pooled studies 281102 & 3002

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is a strong pharmacological rationale for treating (severe) ADMATS13 deficiency by replacement therapy with a recombinant version of the missing enzyme in both a prophylactic and on-demand setting.

Efficacy of TAK-755 was demonstrated in the ADAMTS13 KO mouse model which appropriately mimics, and closely reflects, the condition in patients with hereditary ADAMTS13 deficiency, hence strongly supporting the strong biological rationale of treating ADAMTS13 deficiency by replacement of the missing enzyme. Specifically, ADAMTS13 KO mice do not produce the murine ADAMTS13 enzyme and

therefore can be challenged to develop TTP-like symptoms by administration of recombinant VWF (rVWF) containing ultra-large multimers. These TTP-like symptoms include thrombocytopenia, decreased haematocrit and increased serum lactate dehydrogenase with platelet aggregation in the heart ventricles and myocardial necrosis. Administration of TAK-755 to ADAMTS13 KO mice in a prophylactic fashion before rVWF challenge led to clinically relevant protection from TTP-like symptoms (protection from alterations in haematocrit or haemoglobin levels and from developing schistocytosis). Therapeutic administration of TAK-755 shortly after rVWF challenge also led to a reduction of TTP-like symptoms (decreased severity of TTP-related pathohistological findings).

Due to the very low number of observed acute TTP events in the pivotal trial, no inferential statistical analyses were planned or presented for the primary endpoint and no firm conclusions regarding the efficacy of TAK-755 in preventing the acute events in the prophylactic setting can be drawn from the primary outcome. Secondary endpoints comprise clinically relevant outcomes and in general the incidence of disease-related signs and symptoms as captured by secondary endpoints were for most endpoints numerically lower for TAK-755 than for SoC. Of special relevance are the objective and frequent signs of thrombocytopenia and MAHA, for which less events accrued during prophylaxis with TAK-755 than during prophylaxis with SoC. Furthermore, the overall high exposure, including extended time above 10% ADAMTS13 activity (>0.1 IU/ml), indicates activity of TAK-755 and especially supports the pharmacological rationale of this treatment concept which essentially is replacement therapy. Decreasing large VWF multimers over the first 24 hours post-dose and the presence of VWF cleavage products for approximately 5 days after infusion, along with increasing platelet counts over an extended period of time, further indicate the effectiveness of TAK-755 on pharmacodynamic parameters.

No acute events were treated with TAK-755 while on prophylaxis and only two acute events were treated in the on-demand cohort. However, the data available from these two cases, popPK modelling data and data from the literature support on-demand treatment rationale and ability of TAK-755 to restore ADAMTS13 levels to normal and resolve an acute event.

The number of paediatric patients < 12 years is in line with the key elements of the PIP. Efficacy and safety of TAK-755 in this group appears in line with the efficacy and safety observed in adults.

The poor tolerability of treatment with human plasma, the frequent incidence of hypersensitivity reactions leading to the need for premedication as well as a necessary high infusion volume is well known and compounds the burden of disease for cTTP patients. Data derived from the three submitted clinical trials show an overall acceptable and rather benign safety profile of TAK-755. Inherent safety concerns for SoC (most frequently FFP) were not observed in the same degree for TAK-755. None of the patients receiving rADAMTS13 had to discontinue from a clinical trial due to an adverse event in contrast to one subject receiving SoC who developed a hypersensitivity reaction. In addition, no subject needed an interruption of the infusion when receiving rADAMTS13, while 7 subjects receiving SoC experienced 8 such adverse events. No deaths or serious adverse events were reported under TAK-755 treatment.

It is acknowledged that the safety database is limited with regards to its size and ability to detect rare adverse events, however, this is a direct consequence of the ultra-rare prevalence of this orphan disease. Therefore, the importance of these results in the light of the current unmet medical need should be considered in the framework of a MA under Exceptional Circumstances.

3.7.2. Balance of benefits and risks

The beneficial effects with regards to prophylactic and on demand treatment of TTP manifestations indicated by the totality of the submitted clinical and preclinical PK/PD and efficacy data together with

the strong pharmacological rationale to treat ADAMTS13 deficiency by replacement with recombinant ADAMTS13 outweigh the observed unfavourable effects of rADAMTS13. However, the data are not considered comprehensive and therefore a MAA under Exceptional Circumstances is agreed.

3.7.3. Additional considerations on the benefit-risk balance

cTTP is an ultra-rare orphan disease with an unpredictable nature featuring discontinuous event incidence, which renders the provision of firm and comprehensive clinical evidence for efficacy unfeasible. Due to the extremely low patient numbers and the rare and unpredictable incidence of TTP events it is not considered reasonable to expect sufficient data that could inform a non-inferiority or superiority approach versus standard of care. Data from the Hereditary TTP Registry in 123 patients with confirmed cTTP resulted in an estimate of a median rate of 0.10 (range: 0.02-8.91) acute episodes per year (van Dorland, 2019). Therefore, the totality of data has to be taken into account for the benefit risk consideration for Adzynma, and the Applicant was asked to provide a justification for a marketing authorisation under exceptional circumstances according to Article 14(8) of Regulation (EC) 726/2004, as already discussed in the scientific advice procedure EMEA/H/SAH/068/1/2016/PA/III and propose a meaningful SOB supporting this MA modality.

The submitted dossier shows the following limitations with regards to the submitted evidence:

Quality of evidence

Even though the pivotal trial randomises eligible patients to treatment with rADMAST13 or SoC, the methodological options for the comparative assessment of prophylactic treatment benefit of TAK-755 vs SoC remain vague from the planning perspective. In this context, it needs to be noted that in former EMA-SA interaction, the Applicant was strongly advised to prospectively explore relevant effect sizes and precision of the effect estimates for treatment differences. In the advice letter from 2016 CHMP acknowledged that a strict test for superiority might not be feasible in a situation with such few patients. However, it was pointed out that the study nonetheless needed to provide compelling evidence of the clinical benefit. Now, in retrospect, the main issue in this context is the lack of a thorough suitability-check of 'acute TTP event incidence' as primary efficacy endpoint, in particular in light of the chosen (primary) 6 months observation periods. During SA interaction, substantial heterogeneity among patients for acute event incidences was discussed as potential limiting factor, which led to recommendations to either implement longer (than 6 months) observation periods or to enrich the study population to target expectedly higher incidences.

As neither of these recommendations was followed, the primary trial objective to go for a side-by-side incidence estimation appears as cautious consequence. The lack of an attempt to formalise the primary objective following a non-inferiority approach is seen as missed opportunity to better inform regulatory assessment and decision making. The primary endpoint was defined in accordance with the primary objective of this study, and the critical comments above regarding the methodological weaknesses of this "side-by-side investigation" of TAK-755 and SoC instead of a more direct comparative analysis are valid for both primary objective and primary endpoint in a similar fashion. The secondary and exploratory efficacy endpoints are considered meaningful and clinically relevant.

Efficacy: precision of the effect size

Due to the very low number of acute TTP events, no inferential statistical analyses but only descriptive statistics were planned or presented for the primary endpoint. Before study start, the expected low number of observable acute events was repeatedly addressed by CHMP in the EMA SA procedures in

2016 and 2018 and a longer observation period than 6 months, at least 12 months, was strongly advised.

However, even if the treatment periods of TAK-755 ORT and TAK-755 SIN are taken together for a full 12 months of prophylactic ERT, no acute event could be observed. In the SoC cohort, during 6 months of prophylactic treatment, one acute TTP could be observed. Even after doubling this observation period, incidence of acute TTP events would likely remain very low and no relevant gain in precision in the estimates of the treatment effect could be expected. At the end, the outcome of 0 events can either be seen as a direct consequence of satisfactory efficacy of ERT using rADAMTS13, or as a result of the unpredictable natural disease course of hereditary TTP featuring discontinuous event incidence, or (most likely) a mixture of both. Thus, no firm conclusions regarding the efficacy of TAK-755 in the prophylactic setting can be drawn from the primary outcome of the pivotal study. Nevertheless, in non-clinical animal studies, efficacy of TAK-755 has been demonstrated in the ADAMTS13 KO mouse model, which is considered to sufficiently reflect the TTP disease condition in patients with hereditary ADAMTS13 deficiency.

Efficacy: clinical meaningfulness of the endpoint

The primary efficacy endpoint, incidence of acute TTP events among subjects receiving either TAK-755 or SoC prophylactically during the corresponding treatment periods, covers in principle a clinically relevant and meaningful outcome, however, the side-by-side evaluation instead of a more comparative approach and the limited number of events observed distracts from the usefulness of the selected outcome measure, therefore outcomes from additional secondary endpoints were considered.

Safety: exposure, length of follow-up

In total, 82 unique subjects were exposed to TAK-755. Main safety data come from 71 subjects with a mean exposure of 14.01 months (maximum 22.6 months) in Study 281102 and an additional 11.8 months (maximum 26 months) in continuation study 3002. Therefore, the clinical safety database is considered very small and not able to identify rare or uncommon adverse events. For a treatment foreseen to be chronic and life-long, this is at the lower limit of acceptance but ultimately dictated through the ultra-rare prevalence of the disease.

Target population vs study population

Due to the exclusion of pregnant women from the clinical trial population, the external validity of the observed results is negatively impacted, as pregnancy is a relevant trigger for acute TTP events and the use of TAK-755 in pregnant women is highly likely after the granting of a MA. Data from the compassionate use programme provide reassuring supportive evidence of the beneficial effects of treatment during pregnancy whereas other measures (plasma derived treatments, plasma exchange) are insufficient.

The number of paediatric patients enrolled in pivotal trial 281102, 4 subjects each are <6, 6-<12 and 12-<18, respectively, is small. Study 3002 contributes to the paediatric dataset with 6 paediatric non-rollover patients <12 years old, and 7 rollover and 3 non-rollover patients 12 to <18 years of age. Reassuring supportive data are available from 4 paediatric patients (36 hours, 10 years, 10 years, 13 years) in the compassionate use programme.

Pharmacological rationale

TAK-755 is recombinant ADAMTS13. ADAMTS13 is a plasma zinc metalloprotease that binds and cleaves newly released ultra-large forms of von Willebrand factor (VWF). This site-specific cleavage reduces the VWF size and its platelet-binding properties. Thus, the biological role of plasma ADAMTS13

is to regulate 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 induce formation of platelet rich microthrombi. As a recombinant equivalent to endogenous ADAMTS13, with similar potency, pharmacokinetic and pharmacodynamic properties, the use of TAK-755 in cTTP patients replenishes plasma ADAMTS13 activity, which is expected to reduce or eliminate the spontaneous formation of VWF-platelet microthrombi and thus, the occurrence of TTP events, as well as TTP manifestations. In conclusion, the pharmacologic rationale of this enzyme replacement therapy is supported and was in addition to the clinical pharmacology data successfully demonstrated in non-clinical animal studies (in the ADAMTS13 KO mouse model).

Natural history/ course of the disease

The clinical presentation of cTTP lies on a spectrum of severity ranging from severe acute TTP episodes to chronic, recurring TTP manifestations which include thrombocytopenia, haemolytic activity, headache, abdominal pain, fatigue or lethargy, bruising, joint pain, muscular pain, forgetfulness, and confusion.

Due to the persistent severe ADAMTS13 deficiency, patients with cTTP are at constant risk for developing signs and/or symptoms associated with increased TTP disease activity, especially in the presence of triggering factors such as infections. These "TTP manifestations" can be severe, and may exist as single manifestations (eg, only thrombocytopenia) or in combination (eg, thrombocytopenia in combination with headache). Existing understanding of cTTP pathophysiology suggests that TTP manifestations are all due to spontaneous formation of VWF-platelet-rich microthrombi leading to varying degrees of organ ischemia, which in severe cases or over longer time, may lead to persistent organ damage associated with morbidity and premature mortality. Considerable clinical heterogeneity in disease onset and incidence of TTP manifestation is observable in cTTP patients, impeding comparative clinical evaluation approaches.

Based on the above, the clinical data are not considered comprehensive.

Marketing authorisation under exceptional circumstances

As it is not possible to generate comprehensive data on the product, a marketing authorisation under exceptional circumstances was proposed. The applicant agreed that a marketing authorisation under exceptional circumstances is the appropriate way forward for the Adzynma dossier and has submitted a justification for fulfilling the requirements laid down part II.6 of Annex I of Directive 2001/83/EC. The justification based on the ultra-rarity of the disease, the very limited data with regards to the natural history and the consequential non-comprehensiveness of the dossier is considered acceptable from a regulatory point of view.

In addition, the Applicant has agreed to commit to the following SOBs:

- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the final results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.
- In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.

- In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.
- In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.

With regards to the required PASS, the applicant explored the possibility of conducting the PASS in collaboration with the International hTTP Registry. Several shortcomings of the registry were identified, which would hinder the provision of meaningful data in a timely manner. Therefore, a global chart review study designed to estimate the risk of neutralising (inhibitory) antibodies to rADAMTS13, hypersensitivity reactions, risks in case of pregnancy, and long-term safety following TAK-755 administration was agreed.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence and in the present state of scientific knowledge, comprehensive information cannot be provided. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall benefit/risk balance of Adzynma is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Adzynma is not similar to Cablivi within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Adzynma is favourable in the following indication(s):

Adzynma is an enzyme replacement therapy (ERT) indicated for the treatment of ADAMTS13 deficiency in children and adult patients with congenital thrombotic thrombocytopenic purpura (cTTP). Adzynma can be used for all age groups.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of Adzynma in home/self-administration, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational materials for use of Adzynma in home/self-administration, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use are aimed at providing guidance on how to manage risks of hypersensitivity with home/self-administration.

The MAH shall ensure that in each Member State where Adzynma is marketed, all healthcare professionals who are expected to prescribe and patients/caregivers who are expected to use Adzynma have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Healthcare professionals (HCP) guide for hypersensitivity in home/self-administration for Adzynma
- Patient/caregiver alert card for hypersensitivity in home/self-administration for Adzynma

- **Guide for healthcare professionals:**

- The HCP will receive information on the risk of hypersensitivity associated with Adzynma
- Likelihood of hypersensitivity should be factored into the eligibility assessment for home/self-administration
- The HCP should communicate the signs and symptoms of hypersensitivity and action steps to advise the patient should take if hypersensitivity occur
- The HCP will be provided with the key points to counselling patients on risk and use of the Patient/caregiver alert card

- **Patient/caregiver alert card:**
  - Hypersensitivity reactions may occur while on Adzynma
  - Information on signs and symptoms related to hypersensitivity reactions and when to seek attention from healthcare professionals
  - Understand the action steps (i.e., seek immediate medical attention) should signs and symptoms occur
  - Contact details of Adzynma prescriber

The patient information pack:

- Patient information leaflet

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.	December 2024
In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.	September 2027
In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post-authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.	Final study report: December 2030

Description	Due date
In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.	Annually within the annual reassessment

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rADMATS13 is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0489/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.