Statistical Analysis Plan

NCT Number: NCT03393975

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 BAX 930 (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 Number: TAK-755-281102

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TAKEDA PHARMACEUTICALS

STATISTICAL ANALYSIS PLAN

BAX 930 / SHP655 / rADAMTS13
PHASE 3

A phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of BAX 930 (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])

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Study Sponsor(s):

Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, MA 02421, USA

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, AUSTRIA

Author: [redacted], IQVIA
[redacted], IQVIA (Final)
[redacted] (Version 2.0)
[redacted], IQVIA (Version 3.0)
[redacted], Takeda (Version 4.0)

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STATISTICAL ANALYSIS PLAN - SIGNATURE PAGE

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Prepared by:

[redacted], Statistics, Takeda

DocuSigned by:
[redacted]
Signature

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Date

[redacted], Statistics, Takeda

DocuSigned by:
[redacted]
Signature

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0.1, 0.2	08 Aug 2019	New Document	[redacted]
0.3	14 Oct 2019	Development version	[redacted]
0.4	18 Aug 2020	Final version *Note: This is the first filed version as considered approved for first use to handle analysis.*	[redacted]
0.5	31 Jan 2021	PA secondary endpoints	[redacted]
1.0	27 Jan 2022	Updated for consistency with PA 15	[redacted]
2.0	12 May 2022	Updated for consistency with PA 15 and 3002 study SAP	[redacted]
3.0	7 Sep 2022	Updates include, • Add details of using protocol deviation file to derive PPAS, PKFAS and PDAS • Add sensitivity analyses of secondary and exploratory efficacy endpoints based on MFAS, SAF and PPAS. • Add details for the derivation of isolated TTP manifestations. • Add AE by severity analysis. • Add rules to handle lab and vital sign data for analysis. • Add rules to handle rescreened subjects that passed screening and entered the study more than once.	[redacted]

4.0	13 May 2024	• Add baseline/efficacy/safety subgroup analysis by age (>=12 years and < 12 years) • Add ANCOVA analysis of CHG/PCHG of platelet count data for adult and adolescent. • Summarize lab/vital sign data by study week instead of study visit. • Add the categories of "critical" into analysis of protocol deviation. • Add site level protocol deviation analysis. • Add COVID-19 related analysis. • Remove qualitative lab summary table of hematology, clinical chemistry and biomarker of organ damage because of sparse data. _ • For lab/vital sign shifting analysis, it was considered from baseline to each post baseline visit, now updated as change from baseline to the average of each prophylactic period (period 1, period 2 and period 3) because of data sparseness. • Update analysis of health utilization data by incorporating the data source from AE data, adding non-annualized analytical result and removing annualizing result for OD cohort. • Update the population for the two estimands from "Adult and pediatric subjects" to "Adult, adolescent and pediatric subjects" • Update the primary analysis set from FAS to MFAS for	[redacted]

		secondary and exploratory efficacy outcome measures	

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ABBREVIATIONS

AE	Adverse Event
ALQ	Above Limit of Quantitation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the plasma Curve
BAX 930	rADAMTS13
BAX 930 ORT	rADAMTS13 manufactured in Orth
BAX 930 SIN	rADAMTS13 manufactured in Singapore
BMI	Body Mass Index
BLQ	Below Limit of Quantitation
BP	Bodily Pain
BUN	Blood urea nitrogen
ºC	Celsius scale
CI	Confidence Interval
CK-MB	Creatinine Kinase Myocardial Band
CL	Clearance
cm	centimeter
C_{max}	Maximum concentration (following infusion)
CK-MB	Creatinine Kinase Myocardial Band
CSR	Clinical Study Report
CTMS	Clinical Trials Management System
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
cTTP	congenital Thrombotic Thrombocytopenic Purpura
CV%	Coefficient of Variation
DHR	Data Handling Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	All Subjects Enrolled Set
EQ-5D-3L	EuroQol 5 Dimensions Questionnaire 3-Level
EQ-5D-Y	EuroQol 5 Dimensions Questionnaire Youth version
ºF	Fahrenheit scale
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
GLMM	generalized linear mixed-effects model
GH	General Health
H	upper limit of the normal range
HAV	Hepatitis A virus

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
HRU	Healthcare Resource Utilization
hTTP	hereditary Thrombotic Thrombocytopenic purpura
IA	Interim Analysis
IgG	Immunoglobulin G
IgM	Immunoglobulin M
in	Inch
IP	Investigational Product
IR	Incremental Recovery
IU	International Units
kg	Kilogram
L	Lower limit of the normal range
lb	Pound
LDH	Lactate dehydrogenase
LLOQ	Lower Limit Of Quantitation
LOV	Last Observed Value
LVOT	Last Value On Treatment
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary For Regulatory Activities
MFAS	Modified Full Analysis Set
MH	Mental Health
mL	Milliliter
n	number
NSE	Neuron-Specific Enolase
OPE	Observation Period for Efficacy
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
Ped QL	Pediatric Quality of Life Inventory
PF	Physical Functioning
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PPAS	Per-Protocol Analysis Set
PRO	cTTP-specific patient reported outcomes
Q1W	as once every week
Q2W	as once every 2 weeks
RBC	Red Blood Cell

RCo	Ristocetin Cofactor activity
RE	Role-Emotional
RND	Randomized analysis set
RP	Role-Physical
S100B	S100 calcium-binding protein B
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAF	Safety Analysis Set
SD	Standard Deviation (Specify This Spelling, To Use "SD" Consistently Instead Of "STD")
SF	Social Functioning
SF-36	36-Item Short Form Health Survey
SI	International System of Units
SoC	Standard of Care
$t_{1/2}$	Terminal half-life
TEAE	Treatment Emergent Adverse Event
TSQM-9	Abbreviated 9-item Treatment Satisfaction Questionnaire for Medication
TTP	Thrombotic Thrombocytopenic Purpura
UK	United Kingdom
ULN	Upper Limit Of Normal
USS	Upshaw-Schulman Syndrome
VAS	Visual Analogue Scale
VT	Vitality
Vss	Volume of distribution at steady state
WHO-DD	World Health Organization-Drug Dictionary
VWF	Von Willebrand factor
VWF:Ag	von Willebrand factor: antigen
VWF:Rco	von Willebrand factor: ristocetin cofactor activity

1. INTRODUCTION

This document describes the rules and conventions to be used in the planned presentation and analysis of efficacy, safety, pharmacokinetic (PK) and pharmacodynamics (PD) data for Protocol 281102. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

The purpose of this phase 3 study is to assess safety and efficacy of BAX 930 in the prevention and treatment of acute episodes of thrombotic thrombocytopenic purpura (TTP) in subjects with severe congenital deficiency of ADAMTS13 (cTTP; defined as plasma ADAMTS13 <10%, as measured by the fluorescent resonance energy transfer-VWF73 [FRETS] assay).

Throughout this document the terms TAK-755 and BAX 930 are used interchangeably to refer to the test agent under investigation.

2. OBJECTIVES, ESTIMAND(S), AND OUTCOME MEASURES

2.1 Objectives

2.1.1 Primary Objective

To determine the incidence of acute TTP events in subjects with severe cTTP receiving either standard of care (SoC) or BAX 930 as a prophylactic treatment

2.1.2 Secondary Objective(s)

2.1.2.1 Efficacy

1. To evaluate the efficacy of BAX 930 in the treatment of acute TTP events as measured by the 1) number of acute TTP events responding to treatment and 2) time to resolution in both the prophylactic and the on-demand cohorts
2. To evaluate the incidence of isolated TTP manifestations including thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurologic signs and symptoms, and abdominal pain in the prophylactic cohort
3. To evaluate the incidence rate of dose modification and supplemental dose for each treatment in the prophylactic cohort

2.1.2.2 Safety

1. To evaluate the safety and tolerability of BAX 930 in terms of related AEs and SAEs in both the prophylactic and the on-demand cohorts
2. To assess the immunogenicity of BAX 930 as measured by the incidence of binding and inhibitory antibodies to ADAMTS13 in both the prophylactic and the on-demand cohorts

2.1.2.3 Pharmacokinetics and Pharmacodynamics

1. For both adult and pediatric subjects two crossover PK evaluations and an end-of-study ADAMTS13 PK evaluation (PK-III) may be performed for up to 288 hours post-infusion in the prophylactic cohort
   - PK-I: To characterize the baseline PK of ADAMTS13 activity after administration of BAX 930 ORT or BAX 930 SIN and SoC prior to Period 1
   - PK-II: To assess the PK comparability between BAX 930 SIN and BAX 930 ORT, in subjects who received BAX 930 ORT in PK-I.
   - PK -III: To assess if any time dependent PK changes occur due to long-term exposure to BAX 930 SIN at the end of Period 3.
2. To assess VWF:antigen (VWF:Ag), and VWF:ristocetin cofactor activity (Rco) at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment in the prophylactic cohort.
3. To assess ADAMTS13 activity (pre-infusion ADAMTS13 levels) and select VWF parameters prior to each PK infusion of SoC or BAX 930 in the prophylactic cohort
4. To evaluate the effect of immunogenicity on the PK profile of ADAMTS13

2.1.3 Health Related Quality of Life and Resource Utilization

1. To evaluate Health Related Quality of Life (HRQoL), treatment satisfaction, and health resources utilization in each of the treatment periods in both the prophylactic and the on-demand cohorts

2.1.4 Exploratory Objectives

1. To evaluate the incidence of subacute TTP events in subjects receiving the respective prophylactic treatment
2. To assess the relationship between ADAMTS13 activity levels (measured and/or estimated from PK parameters) and time of occurrence of acute TTP events, subacute TTP events, and a composite of TTP manifestations in the prophylactic group
3. To assess shifts in biomarkers of organ damage, including troponin T (cTnT) and I (cTnI) (cardiac), creatine kinase myocardial band (CK-MB) fraction (cardiac), neuron-specific enolase (NSE) (brain), S100B (brain), and serum creatinine (kidney), during routine prophylaxis with the SoC treatment and BAX 930 as well as during acute TTP events in the prophylactic cohort
4. To characterize the PK profile of ADAMTS13 activity at the end of the study
5. To evaluate additional exploratory PD biomarkers, including but not limited to VWF multimer patterns, ADAMTS13 mediated VWF cleavage products and coagulation readouts, at baseline and following infusion of the SoC agent and BAX 930.

2.2 Estimands

The primary, and secondary estimands are described in Table 1.

Table 1 List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or outcome measure)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	The primary estimand is the annualized acute TTP event rate of subjects with severe cTTP while treated prophylactically.	Adult, adolescent and pediatric subjects with severe cTTP, receiving prophylactic treatment who comply with the inclusion/exclusion criteria in the protocol and are in MFAS.	Annualized incidence rate of acute TTP events. Calculated as the number of acute TTP events during the on-treatment observation period multiplied by 12*28 divided by the duration of observation period in days.	Changes in dosing will not be considered. Subjects who discontinue treatment will be included for the duration of their prophylactic treatment (while on treatment strategy). Subjects will be included in the treatment group they are assigned to receive.	The mean model-based annual rate of acute TTP events and corresponding 95% CI will be presented for each treatment group for the prophylactic cohort.
Secondary	The secondary estimand is the proportion of acute TTP events responding to BAX 930 in subjects with severe cTTP in the on-demand and the prophylactic cohort	Adult, adolescent, and pediatric subjects with confirmed severe cTTP who comply with inclusion/exclusion criteria in the protocol and who receive BAX 930 as treatment for the acute TTP event.	The proportion of acute TTP events treated with BAX 930 who achieve resolution. The proportion is calculated as the number of acute TTP events treated with BAX 930 and achieving resolution, divided by the total number of acute TTP events occurring in the study and are treated with BAX 930.	Subjects who discontinue treatment before resolution will be considered as failures (composite strategy).	The proportion of acute TTP events responding to BAX 930 will be presented together with a 95% CI interval.

2.3 Outcome Measures

2.3.1 Primary Outcome Measure

1. Incidence of acute TTP events among subjects receiving either BAX 930 or SoC prophylactically during the corresponding treatment periods

2.3.2 Secondary Outcome Measures

2.3.2.1 Efficacy

1. Proportion of acute TTP events responding to BAX 930, defined as not requiring the use of another ADAMTS13-containing agent
2. Time to resolution of acute TTP events following initiation of treatment (for the acute TTP event) with BAX 930 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 microangiopathic hemolytic anemia defined as an elevation of LDH >1.5× of baseline or >1.5×ULN
5. Incidence of neurological symptoms (e.g., 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
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

2.3.2.2 Safety/Immunogenicity

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

2.3.2.3 Pharmacokinetics/Pharmacodynamics

1. Assessment of the PK parameters (incremental recovery [IR], area under the plasma curve [AUC], terminal half-life [t1/2], mean residence time [MRT], systemic clearance [CL], steady state volume of distribution [Vss], and maximum concentration following infusion [Cmax]) for ADAMTS13 activity and ADAMTS13 antigen for both the SoC agent and BAX 930

2. Assessment of PD markers, such as VWF:Ag and VWF: Rco, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment
3. Assessment of ADAMTS13 activity (pre-infusion ADAMTS13 levels) and select VWF parameters prior to each PK infusion of SoC or BAX 930
4. Assessment of the impact of immunogenicity (immunogenicity status, time of onset) on ADAMTS13 antigen and activity

2.3.2.4 Health Related Quality of Life and Resource Utilization

1. Assessment of HRQoL including chronic TTP-related symptoms and disabilities, including cognitive function, using the following instruments:
   - cTTP-specific patient reported outcomes (PROs)
   - 36-Item Short Form Health Survey (SF-36)
   - Abbreviated 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9)
   - EuroQol 5 Dimensions Questionnaire 3-Level (EQ-5D-3L) and EQ-5D-youth (EQ-5D-Y)
   - Pediatric Quality of Life Inventory (Ped QL)
2. Assessment of health care resource utilization, including hospital length of stay for acute TTP events, resource utilization during prophylaxis, and days missed from school/work due to TTP-related illness

2.3.2.5 Exploratory Outcome Measures

1. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), while receiving prophylactic treatment with BAX 930 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 BAX 930 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 subacute TTP events in subjects receiving prophylactic treatment
5. Assessment of additional exploratory PD biomarkers including but not limited to VWF multimer patterns, ADAMTS13 mediated VWF cleavage products, and coagulation readouts, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment.

Note: [a] composite of the secondary outcome measure is defined as the occurrence of at least one of the secondary outcome measures (3 to 7).

3. STUDY DESIGN

3.1 General Description

This is a Phase 3, prospective, randomized, controlled, open-label, multicenter, 2-period crossover study with a single arm continuation evaluating the safety and efficacy of BAX 930 in the prophylactic and on-demand treatment of subjects with severe cTTP.

Detailed information on study design can be found in the Clinical Study Protocol Section 9.2, Overall Study Design. A brief summary is provided in the following sections.

3.1.1 Prophylaxis Treatment Cohort

The principal part of the study involves the prophylactic treatment of cTTP. There are 3 periods, 2 crossover PK and one end-of-study PK assessment. Adult, adolescent, and pediatric subjects, who are screened prior to 01 October 2021, will initiate the study with BAX 930 ORT. Following the first randomized crossover PK evaluation (PK-I) of both the subject's SoC product and BAX 930 ORT, subjects will receive 6 months of prophylaxis treatment with SoC product and 6 months of prophylaxis treatment with BAX 930 ORT. Once Period 2 is completed, subjects will enter Period 3. Subjects will receive treatment with BAX 930 ORT in Period 3 until BAX 930 SIN is available at their site. Once BAX 930 SIN is available, subjects who received BAX 930 ORT in PK-I will initiate a randomized crossover PK evaluation between BAX 930 ORT and BAX 930 SIN, which is PK-II and then initiate an additional 6 months of prophylaxis treatment with BAX 930 SIN in Period 3. After the last IP infusion of Period 3, a subset of total subjects from the prophylactic cohort may undergo another PK assessment i.e., PK-III, following which they will be enrolled and followed in the continuation study. Table 2 provides the schematic of the study design for Subjects Entering Study with BAX 930 ORT.

Subjects who are screened for Study 281102 after 30 September 2021, will follow the same design principles as with BAX 930 ORT with two exceptions: 1) that subjects will initiate the study with BAX 930 SIN instead of BAX 930 ORT and 2) an end-of-study PK-III may be conducted in lieu of the aforementioned PK-II assessment. These subjects will first undergo PK-I as a randomized crossover between BAX 930 SIN and SoC. After completing Period 1 with either BAX 930 SIN or SoC, subjects will enter Period 2 and crossover to the alternative treatment (BAX 930 SIN for subjects who start on the SoC and SoC for subjects who start on BAX 930 SIN) and remain on that treatment for another 6 months during Period 2. Once Period 2 is completed, subjects will enter Period 3 with BAX 930 SIN. Subjects may then undergo an end-of-study, PK-III assessment. Table 3 provides the schematic of the study design for Subjects Entering Study with BAX 930 SIN.

Table 2: Prophylactic Cohort Randomization (For BAX930 ORT)

Randomization Sequence	PK I		Period 1 (6 months)	Period 2 (6 months)	Randomization	PK II		Period 3 (6 months)	PK III Infusion 5
	Infusion 1	Infusion 2				Infusion 3	Infusion 4		
1 (BAX 930 – SoC)	SoC	BAX 930 ORT	BAX 930 ORT	SoC	1	BAX 930 ORT	BAX 930 SIN	BAX 930 SIN	BAX 930 SIN
					2	BAX 930 SIN	BAX 930 ORT		
2 (SoC – BAX 930)	BAX 930 ORT	SoC	SoC	BAX 930 ORT	1	BAX 930 ORT	BAX 930 SIN		
					2	BAX 930 SIN	BAX 930 ORT		

PK: Pharmacokinetic. SoC: Standard of care.

Table 3: Prophylactic Cohort Randomization (For BAX930 SIN)

Randomization Sequence	PK I		Period 1 (6 months)	Period 2 (6 months)	Period 3 (6 months)	PK III
	Infusion 1	Infusion 2				
1 (BAX 930 – SoC)	SoC	BAX 930 SIN	BAX 930 SIN	SoC	BAX 930 SIN	BAX 930 SIN
2 (SoC – BAX 930)	BAX 930 SIN	SoC	SoC	BAX 930 SIN		

The SoC regimen will be determined by the investigator for each subject and will be defined by the subject's treatment product and dosing regimen at the time of entry into the study.

It is anticipated that TTP-related events will occur during the study. These events will be classified as acute TTP events, isolated TTP manifestations, or subacute TTP events according to the classifications provided in Table 4.

Table 4: 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 the 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 x of baseline or >2 x ULN	Elevation of LDH >1.5 x of baseline or > 1.5 x ULN	Elevation of LDH >1.5 x of baseline or > 1.5 x 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 (e.g., 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 (e.g., 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

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

Acute TTP events will be managed by the same treatment agent (SoC or BAX 930) as employed for the prophylactic treatment the subject is receiving at that time.

3.1.2 On-Demand Treatment Cohort

Subjects experiencing an acute TTP event, meeting all other inclusion criteria, and entering and consenting to treatment in the study through the on-demand cohort will be randomized to receive urgent treatment with either the SoC or BAX 930. Upon resolution of the acute TTP event, subjects may choose to move to the prophylaxis treatment cohort of the study or discontinue entirely. Subjects electing to move to the prophylaxis treatment cohort will

move directly to Period 1 and will not receive PK-I infusions. Subjects switching from on-demand treatment cohort to prophylaxis cohort will receive the same treatment in Period 1 as the randomized on-demand treatment, and the alternative treatment in Period 2.

3.2 Randomization

This is a randomized, open-label, active-controlled clinical study. Subjects in the prophylaxis cohort will 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 will 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, will 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 will have to randomized evenly between the two sequences: ORT-SIN, SIN-ORT.

3.3 Blinding

This is an open-label study.

3.4 Sample Size and Power Considerations

In total, approximately 42 adult (≥18 years old) subjects and 15 adolescent (>12-≤17 years old) or pediatric (<12 years old) subjects will be enrolled in this study, including approximately 36 adult subjects and 12 adolescent or pediatric subjects starting in the prophylaxis cohort, and approximately 6 adult subjects and 3 adolescent or pediatric subjects, in the on-demand cohort.

The sample size is limited by the extremely low prevalence of the disease (0.5 to 4 per million) (Mansouri Taleghani et al., 2013). The updated approximate number of subjects reflects the current, observed enrollment patterns and accounts for a 10% dropout rate. The number of subjects starting enrollment in the prophylactic cohort should allow an overall assessment of efficacy and safety of BAX 930, including immunogenicity, and PK following infusion.

The sample size of approximately 36 adult (≥18 years old) subjects and 12 adolescent (4 subjects age >12-≤17) or pediatric subjects (4 subjects age >6-<12, and 4 subjects age 0-<6) in the prophylaxis cohort, will also provide an estimate of the safety and efficacy of the IP. If 15 of the 30 enrolled adult prophylaxis subjects receive FFP and each subject receiving FFP will have at least 14 infusions per treatment period, there will be 210 total FFP infusions. With 210 FFP infusions, there is a >99% probability that at least 1 SAE will be observed, if as reported in the literature, the rate of serious adverse reactions (SARs) is 6% (Huisman et al., 2014).

The sample size for the on-demand cohort will be approximately 6 adult subjects, if enrollment allows, and 3 pediatric or adolescent subjects.

The sample size is not selected as a result of a power calculation and the primary outcome measure will not be assessed by a formal significance test.

4. STATISTICAL ANALYSIS SETS

4.1 All Subjects Enrolled Set (ENR)

The all subjects enrolled set (ENR) will comprise all subjects for whom informed consent has been obtained.

4.2 Randomized Analysis Set (RND)

The randomized analysis set (RND) will include all subjects that were randomized into one of the treatment sequences for the prophylactic cohort or one of the treatment arms for the on-demand cohort.

4.3 Safety Analysis Set (SAF)

The safety analysis set (SAF) will include all subjects treated with at least 1 dose of TAK-755 or SoC treatment after randomization. All safety analyses will be performed on the safety analysis set and subjects will be analyzed by the treatment received.

Efficacy analyses will also be conducted over the SAF to provide estimate based on actual treatments received. Only patients with confirmed cTTP diagnosis will be included in such analyses.

4.4 Full Analysis Set (FAS)

The full analysis set (FAS) will include all subjects with a confirmed cTTP diagnosis receiving at least 1 dose of TAK-755 or SoC treatment after randomization. Subjects will be included in the data group to which they are randomized, regardless of the treatment received.

4.5 Modified FAS (MFAS)

The modified full analysis (MFAS) is based on 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 will 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 will be used in the MFAS-based efficacy analysis. The period over which the outcome will be evaluated is between the first dose date and the date of the Month 6 visit for period 1. Data in period 2 and beyond will be also included for MFAS-based efficacy analysis.

4.6 Per-protocol Analysis Set (PPAS)

The per-protocol analysis set (PPAS) will include all subjects in the MFAS who have no major protocol deviations from the protocol affecting the efficacy outcome or treatment of the subject. Protocol deviations documented during the conduct of the study in the Clinical Trials Management System (CTMS) will be taken into consideration during the review.

During the study, protocol deviations review meetings will be held on a regular basis. During these meetings any potential protocol deviations will be identified and to be included into the CTMS upon team agreement.

Prior to performing any analysis as set out in this SAP, a meeting will be held discussing the impact of any major protocol deviation on the analysis. Protocol deviations are defined as major if they have an influence on the efficacy outcome, PK outcome, or the treatment of the subject. A major/important/critical deviation from CTMS will not necessarily influence the study results and will therefore not necessarily lead to exclusion from the PPAS. At this meeting the decision will be made on whether a subject will be excluded from the PPAS or not. The meeting will be attended by participants from Data Management, Biostatistics Clinical Development (including medical monitors/advisors). Teams from both IQVIA and the sponsor will attend.

4.7 Pharmacokinetic Full Analysis Set (PKFAS)

The pharmacokinetic full analysis set (PKFAS) will be a subset of the FAS and will contain all subjects who receive at least one dose of investigational product and provide adequate post-dose PK measurements at a scheduled PK timepoint for at least one of the PK analytes without major protocol deviations or events that may affect the integrity of the PK data. If a subject has a major protocol deviation or events that may affect the integrity of the PK data, then the subject will be flagged as exclusion from the analysis set. Subjects in this population will be used for all respective PK concentration summaries.

The serial profiles or sparse samples (pre-infusion and post-infusion ADAMTS13) may be excluded from the corresponding PK infusion or visit if not valid due to protocol violations/deviations or events with potential to significantly affect the concentration data (examples include, but may not be limited to: incomplete or missed corresponding dose, sample processing errors that lead to inaccurate bioanalytical results, washout for FFP or any other ADAMTS13 containing products interfering with ADAMTS13 PK being shorter than the protocol required time windows).

Subjects with evaluable PK parameters will be a subset of the PKFAS and will consist of all evaluable subjects in PK-I or PK-II evaluations with sufficient data to calculate at least 1 PK parameter. Subjects in this subset of PKFAS will be used for all applicable PK parameter summaries.

The Pharmacokinetic (PK) analysis set and Pharmacokinetic full analysis set are used interchangeably. The PK analysis set will be the primary set for PK analyses based on the treatment received. For more information on non-compartmental PK analysis, refer to CPAP.

4.8 Pharmacodynamic Analysis Set

The pharmacodynamics analysis set (PDAS) will be a subset of FAS and contain all subjects who receive at least one dose of investigational product and provide at least one valid data point post-dose of the respective infusion for at least one PD measurement for any of the PD outcome measures and have no major protocol deviations or events that may affect the integrity of the PD data. If a subject has a major protocol deviation or events that may affect the integrity of the PD data, then the subject will be flagged as exclusion from the analysis set. Subjects in this population will be used for all respective PD concentration summaries.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study.

Disposition of subjects will be presented for the ENR analysis set in the planned listings and the table summaries. Subjects who switch from the on-demand to the prophylaxis cohort upon resolution of the acute TTP event, and go through the crossover of Period 1 and 2 as randomized, will be summarized as specified in Section 12.1 General Data Reporting Conventions.

The presentation of planned listings will include the following:

- Screen Failures (i.e., subjects who were screened but not randomized) including reasons for screening failure.
- Subject disposition.
- Visit dates.
- Assignment of subjects to analysis sets.

The following summary tables are planned for presentation:

Subject disposition will be performed over the number of subjects who are enrolled, screening failed or randomized and entered each period of the study, complete the study and prematurely discontinue the study, including the reason for study discontinuation.

Subject disposition will be displayed as follows:

- by cohort: Prophylactic (TAK-755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755 , SoC and Total),
- by country and site, and
- by age group, race group, and sex as defined in Section 6.5.

Reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) in cohort Prophylactic (TAK-

755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755, SoC and Total) for the Enrolled Set.

The number and percentage of subjects included in each analysis set by cohort, Prophylactic (TAK-755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755, SoC and Total), except for Enrolled Set where only an overall summary will be provided.

The number of subjects enrolled, randomized and completed will be tabulated by cohort: Prophylactic (TAK-755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755, SoC and Total). In addition, the duration of enrollment, in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site – the first date of informed consent for any subject at that site + 1). Screening failure subjects and Subjects that passed screening but prematurely discontinued from study without randomization will be also presented in separate categories.

A subject will be considered completed if the reason for completion/termination indicates the subject completed the study. Otherwise, the subject will be considered discontinued.

5.2 Demographic and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the SAF, FAS, MFAS, and PPAS if different, by cohort: Prophylactic (TAK-755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755, SoC and Total).

No statistical testing will be performed for demographic or other baseline characteristics. Subjects who switch from the on-demand to the prophylaxis cohort upon resolution of the acute TTP event, and go through the crossover of Period 1 and 2 as randomized, will be summarized as specified in Section 12.1 General Data Reporting Conventions.

The following tables and listings are planned for presentation:

- Demographic and baseline characteristics.
- cTTP history
- Listings for History of Acute TTP events in the past 12 months, History of Subacute TTP events in the past 12 months, cTTP pre-study treatment

Quantitative and qualitative assessments will be summarized as specified in Section 12.1 General Data Reporting Conventions.

The following information will be obtained from the eCRF:

- Age, sex, race, ethnicity and whether the subject is of childbearing potential are to be obtained from the *Demography* eCRF.
- Weight will be obtained from the *Weight* eCRF at Screening.
- Height will be obtained from the *Height* eCRF at Screening.
- Study participation in another Baxter/Baxalta study will be obtained from the *Subject Participation* eCRF.
- Age at diagnosis, Karnofsky or Lansky score, blood group, rhesus factor, genetic mutation confirmed before or on screening, ADAMTS13 activity levels prior to treatment and presence of Acute and Subacute TTP events in the past 12 months will be obtained from the *cTTP, USS, hTTP Disease History* eCRF.
- History of Acute TTP events in the past 12 months: duration of the event, platelet count, LDH, other organ specific signs and symptoms and treatment for Acute TTP Event will be obtained from the *Acute Event History Entry* eCRF.
- History of Subacute TTP events in the past 12 months: duration of the event, platelet count, LDH, other organ specific signs and symptoms and treatment for Subacute TTP Event will be obtained from the *Sub-Acute Event History Entry* eCRF.
- cTTP pre-study treatment will be obtained from the *cTTP pre-study treatment* eCRF.
- The following derivations based on eCRF reported results will be performed:
- Race will be presented as "Multiple" in summaries if more than 1 race is selected on the eCRF.
- Height will be converted from inches (in) to centimeter (cm) as follows:

$$Height\ (cm) = Height\ (in)\ \times 2.54$$

- Weight will be converted from pounds (lb) to kilograms (kg) as follows:

$$Weight\ (kg)\ = Weight\ (lb) \times 0.453592$$

- Body mass index (BMI) will be derived as:

$$BMI\ (kg/m^2) = \frac{Weight(kg)}{[Height(cm)/100]^2}$$

- Event duration (days) = end date of event – start date of event +1
- Subgroup analyses on demographic and baseline characteristics, as well as cTTP history, will be performed for SAF and MFAS subjects by age group, race group, sex, and geographic region as defined in Section 6.5.

5.3 Medical History and Surgeries

Information on medical history and surgery will be obtained from the *Medical History* eCRF. Medical histories and surgeries will be listed and summarized for the SAF.

Medical history and surgery will be coded and summarized using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) as documented by Data Management in the *Data Coding guideline* at the time of performing the analysis and presented by system organ classes (SOC) and preferred terms (PT).

Medical history and surgery summaries will be presented by cohort, Prophylactic (TAK-755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755, SoC and Total).

5.4 Prior Medications and Non-Drug Therapies

Information on prior medications and non-drug therapies will be obtained from the *Concomitant Medication/Non-Drug Therapy* eCRF. Information on AEs and medical histories for which the medication or non-drug therapies has been given, will be obtained from the *Adverse Events* and *Medical History* eCRFs.

Prior medication is defined as any medication with the start date prior to the first dose administration date of TAK-755 or SoC, whichever happens first, and it's not continued to be taken after the first dose of study treatment.

Prior medication and non-drug therapies will be listed for the SAF. No summaries will be presented on prior medications or non-drug therapies.

Medications will be coded using the latest version of the World Health Organization-Drug Dictionary (WHO-DD) as documented by Data Management in the *Data Coding guideline* at the time of performing the analysis.

The following derivations based on eCRF reported results are to be performed:

- Assignment to Prior: A medication or non-drug therapy will be assigned as "Prior" if the medication or non-drug therapy started and stopped prior to first TAK-755 or SoC administration in the current study.
- Based on the reason for medication or therapy, the actual AE or medical history term will be obtained linking the information from the particular eCRF.

5.5 Concomitant Medications and Non-Drug Therapies

Information on concomitant medications and non-drug therapies will be obtained from the *Concomitant Medication/Non-Drug Therapy* eCRF. Information on AEs and medical histories for which the medication or non-drug therapies has been given, will be obtained from the *Adverse Events* and *Medical History* eCRFs.

Concomitant medication/non-drug therapy is defined as any medication/non-drug therapy with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusive.

Medication and non-drug therapies will be listed for the SAF. Summary tables for SAF will be presented on concomitant medications or non-drug therapies by cohort: Prophylactic (TAK-755 – SoC, SoC – TAK-755and Total) and On Demand (TAK-755, SoC and Total), as well.

Medications will be coded using the latest version of the WHO-DD as documented by Data Management in the *Data Coding guideline* at the time of performing the analysis.

The following derivations based on eCRF reported results are to be performed:

- Assignment to Concomitant: A medication or non-drug therapy will be assigned as 'Concomitant' if the medication or non-drug therapy: i) Started on or after the first TAK-755or SoC administration in the current study or ii) were ongoing or ended, on or after the date of first TAK-755 or SoC administration.
- Based on the reason for medication or therapy, the actual AE or medical history term will be obtained linking the information from the particular eCRF.

5.6 Exposure to Investigational Product

Throughout this document, 'treatment' refers to TAK-755 or SoC unless otherwise specified, i.e., with specific SoCs treatments pooled in presentation.

Dosing will be derived using actual potency of ADAMTS13 for TAK-755 and also using FRETS-VWF73 potency of ADAMTS13 activity for SoC.

The following information will be obtained from the eCRF:

- Information on study infusions from the *Exposure* eCRF.
- Body weight from the *Weight* eCRF.
- Any modifications on study infusions from the *Dose Modifications* eCRF.
- Dosing frequency as captured on the *Date of Visit* eCRF.

The following derivations based on eCRF reported results will be performed:

- Total Dose: Total dose is defined as total dose received in given time period. E.g. Total dose received in Period 1, for prophylactic treatment is Sum of all doses received in Period 1 for prophylactic treatment.
- Body weight adjusted dose will be determined as the actual dose (in IU for both actual potency and FRETS-VWF73 potency of ADAMTS13) received divided by the latest available body weight (kg) at the time of infusion.
- Total weight adjusted dose would be the sum of the weight adjusted doses for a subject.
- Average weight adjusted dose would be the average of the weight adjusted doses for a subject.
- Actual/Planned Ratio = [Actual dose/Planned dose].

  Actual dose and planned dose will be captured with either of the following units IU, mg, mg/m², mg/kg or other as specified in the eCRF. The actual/planned ratio will only be calculated when the actual dose and planned dose were captured with the same unit or when either of the planned or actual dose can be converted to the same unit.

- Duration of infusion (minutes) = end date/time of treatment administration – start date/time of treatment administration.
- Time since previous infusion (days) = start date/time of current treatment administration – end date/time of previous treatment administration.
- The observation period for efficacy for each study period x (OPEx, where $x \in [1,2,3]$ represents the period) in days will be determined as:

  $$OPEx(Days) = (Stop\ Date - Start\ Date) + 1$$

  where "Start Date" refers to the first infusion within the period and "Stop Date" refers to 1 day prior to the first infusion of the next period (Period $x + 1$). If it is the last period, then "Stop Date" refers to the study completion or study discontinuation date.

  The OPEx in months will be determined from the OPEx in days as:

  $$OPEx(Months) = \frac{OPEx(Days)}{28}$$

  Note: The protocol defines 1 month as 28 days (see Protocol Section 9.3).

  The OPEx in years will be determined from the OPEx in days as:

  $$OPEx(\text{Years}) = \frac{OPEx(Days)}{12 \text{ x } 28}$$

  The overall OPEx in days will be determined from the OPEx in days as:

  $$OPE(\text{days}) = (\text{Stop Date} - \text{Start Date}) + 1$$

  where "Start Date" refers to the first infusion on the study and "Stop Date" refers to the study completion or study discontinuation date.
- Total number of infusions per period are determined as the count of the number of infusions, regardless of date and time, the subject had per period. Number of infusions will be determined overall and by reason for infusion per period.

Exposure to TAK-755 and SoC will be summarized as follows:

Extent of exposure will be summarized for the SAF, FAS, MFAS and PPAS, and listed for the SAF.

The summary table of extent of exposure will be presented by treatment cohort (prophylactic and on-demand), period (PK-I infusion 1, PK-I infusion 2, Period 1, Period

2, PK-II infusion 3, PK-II Infusion 4, Period 3, PK-III infusion 5 for prophylactic cohort, while OD treatment period for on-demand cohort) and treatment arm (TAK-755 and SoC).

For SAF, the summary table of extent of exposure will be also presented by treatment cohort (prophylactic and on-demand) and treatment arm (TAK-755 and SoC).

- Duration of exposure will be summarized by treatment group (i.e. TAK-755 and SoC) for prophylactic cohort based on SAF, FAS, MFAS and PPAS.
- Extent of exposure and duration of exposure to TAK-755 by TAK-755 ORT, TAK-755 SIN, and Total will be summarized for SAF, FAS, MFAS and PPAS. The listing will specify ORT or SIN of each TAK-755 infusion.
- The summary table of extent of exposure to TAK-755 SIN and TAK-755 ORT will be done for prophylactic subjects by period (PK-II infusion 3, PK-II infusion 4, period 3, PK-III infusion 5), while the summary table of duration of exposure to TAK-755 SIN and TAK-755 ORT will be presented by treatment cohort (prophylactic and on-demand).
- Based on subjects with at least one acute TTP event on study, and subjects with at least one subacute TTP event on study separately, for extent of exposure based on SAF.
- By age group, race group, sex and geographic region as defined in Section 6.5 for SAF and MFAS.

Dose Modifications will be listed for SAF with the reason for the dose modification reported.

5.7 Measurements of Treatment Compliance

Treatment compliance will be derived using results and derivations obtained from study exposure as described in Section 5.6 Exposure to Investigational Product.

Treatment compliance will be based on adherence to the infusion schedule and adherence to recommended prophylactic dose.

Subjects on the prophylactic cohort will be considered in adherence to the prophylactic infusion schedule if all of the following conditions are met as applicable:

The second PK dose in PK 1 and PK 2 took place 14 to 21 days after the first PK dose and the last PK dose (PK 3 infusion 5), when applicable, took place 14 ± 2 days after the last TAK-755 dose in Period 3.

- If prophylaxis dosing frequency is indicated as once every week (Q1W) in the *Date of Visit* eCRF, the current infusion is 7 ± 2 days from previous infusion.
- If prophylaxis dosing frequency is indicated as once every 2 weeks (Q2W) in the *Date of Visit* eCRF, the current infusion is 14 ± 2 days from previous infusion.
- Subjects that completed the study were exposed to both TAK-755 for 6 ± 1 months and SoC for 6 ± 1 months during Period 1 and Period 2 depending on randomization

and no less than 6 ± 1 months on TAK-755 SIN during Period 3. Where, 1 month = 28 days per protocol definition.

- Subjects that discontinued the study early followed the above dosing frequency until discontinuation. If the subject completed any periods before discontinuation, the subject was exposed to TAK-755 or SoC for 6 ± 1 months during the applicable periods. Where, 1 month = 28 days per protocol definition.
- For subjects experiencing an acute TTP event, the subject continues prophylaxis treatment 7 ± 1 days after their last acute treatment dose.

Subjects experiencing an acute TTP event regardless of study cohort will be considered in adherence to the acute TTP event infusion schedule if:

- Subjects randomized to SoC follows the investigator-recommended frequency during the acute TTP event.
- Subjects randomized to TAK-755 receive a daily dose of BAX 930 until 2 days after the acute TTP event is resolved.

An infusion of TAK-755or SoC will be considered in adherence to the recommended prophylactic dose if the actual amount of ADAMTS13 infused (IU/kg, mg, mg/m² or mg/kg, whichever is applicable) is between 90% and 110% of the planned dose (IU/kg, mg, mg/m² or mg/kg, whichever is applicable) to be infused. Infusions with actual amount infused not recorded in the eCRF will be excluded from the compliance calculations.

The number and percentage of TAK-755 infusions in adherence to the recommended prophylactic dose will be determined for each subject per period using the overall number of infusions per period for that subject as denominator.

Treatment compliance will be summarized for the SAF, FAS, MFAS and PPAS, and listed for the SAF. Summaries will be presented as follow:

- by treatment cohort (prophylactic and on-demand) for SAF
- by treatment cohort (prophylactic and on-demand), treatment period (PK-I infusion 1, PK-I infusion 2, period 1, period 2, PK-II infusion 3, PK-II infusion 4, period 3, PK-III infusion 5, and OD treatment period)and treatment arm (TAK-755 and SOC)
- by treatment period (PK-II infusion 3, PK-II infusion 4, period 3, PK-III infusion 5) and treatment arm (TAK-755 and TAK-755 ORT) for prophylactic subjects.
- by age group, race group, sex, and geographic region as defined in Section 6.5 for SAF and MFAS.

5.8 Protocol Deviations

Protocol deviations will be obtained from the CTMS.

Subject level protocol deviations will be summarized by classification (critical or major or minor) presenting the number of deviations and the number of subjects having the particular deviation. Subject level protocol deviations are to be summarized for the RND Set:

- by cohort: Prophylactic (TAK-755 – SoC, SoC –TAK-755 and Total) and On Demand (TAK-755, SoC and Total).
- by age group, race group, sex, and geographic region as defined in Section 6.5.

All subject level protocol deviations are to be listed for the RND Set. Furthermore, site level protocol deviations will be listed by site ID.

The pandemic of COVID-19 broke out while the study is still ongoing, for the integrity of data, COVID-19 related PDs will be entered into CTMS database, and COVID-19 related AEs and COVID-19 vaccine related data will be collected by AE page and SC/FA pages of eCRF separately. COVID-19 related PDs will be listed for the RND set, COVID-19 vaccination status will be listed for the ENR set, and the other COVID-19 relevant data will be listed for the SAF set.

6. EFFICACY ANALYSES

Analyses of the efficacy outcomes will be based on the MFAS, with sensitivity analysis performed over the FAS, PPAS, and SAF.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. No control of study-wide Type I error is implemented. (Section 6.3).

Only data from period 1 and period 2 will be used for model-based analysis. Also, estimates of 95% confidence intervals will be reported only when model-based analysis is conducted.

As an overview, the key elements of the efficacy analysis are summarized by endpoint in Table 5. Details will be covered by the following subsections in section 5.

Table 5 Analysis of different efficacy endpoints

Endpoint	Cohort	Analysis Period	Primary Analysis Set	Sensitivity Analysis Sets
Annualized acute TTP event rate (primary efficacy endpoint)	Prophylactic cohort including on-demand cohort subjects that enter the prophylactic cohort	Prophylactic period 1, 2, 3 and total of period 1 and 2 Note: Inferential analyses are based on periods 1 and 2 only	MFAS	1. Repeat in FAS, SAF and PPAS 2. Exclude data after re-enrolment from Subject [redacted] based on MFAS
Acute TTP event responding to TAK-755	Prophylactic and on-demand cohorts	On-demand TAK-755 period and prophy TAK-755 period (including prophy period 3)	MFAS	1. Repeat in FAS, SAF and PPAS 2. Repeat for MFAS with all events regardless of central lab confirmation.

Time to resolution of acute TTP events	Prophylactic and on-demand cohorts	First acute TTP event with central lab confirmation during the entire study	MFAS	1. Repeat in FAS, SAF and PPAS 2. Repeat for first acute TTP event per subject regardless of central lab confirmation
Annualized incidence rate of all other events	Prophylactic cohort including on-demand cohort subjects that enter the prophylactic cohort	Prophylactic period 1, 2, 3 and total of period 1 and 2 Note: Inferential analyses are based on periods 1 and 2 only	MFAS	1. Repeat in FAS, SAF and PPAS 2. Exclude the data collected during the first 14 days of each study period 3 Exclude data after re-enrolment from Subject [redacted] based on MFAS

6.1 Analyses of Primary Efficacy Outcome Measure

6.1.1 Acute TTP events

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

Acute TTP events are defined in Table 4. For this analysis, a unique acute TTP event can be considered as each event recorded by the investigator on the Thrombotic Thrombocytopenic Purpura Events eCRF.

The number of acute TTP events per subject by treatment and period will be determined as the count of acute TTP events a subject had experienced during each targeted period under the treatment of interest. The annualized acute TTP event rate will be derived as:

$$annualized\ acute\ TTP\ event\ rate = Number\ of\ acute\ TTP\ events / OPEx(Years)$$

Summary statistics related to acute TTP events will be presented by period and treatment for the following endpoints:

1) Number (percentage) of subjects with acute TTP events,
2) total number of acute TTP events,
3) duration of the observation period for efficacy (OPE*x* in years), to calculate the annualized acute TTP event rate,
4) annualized acute TTP event rate

In addition, the above summaries will be done by age group, race group, sex, and geographic region as defined in Section 6.5 for MFAS subjects.

Information on acute TTP events and management of the event will be listed for all subjects, as well as platelet counts and LDH results that are collected during the occurrence of each event.

The primary estimation method for the annualized acute TTP event rate will be model based. The acute TTP event rate will be assumed to have a negative binomial distribution, and the mean acute TTP rate will be estimated using a generalized linear mixed-effects

model (GLMM) with a negative binomial distribution as a family and a logarithmic link function (the default) 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) will be included in the model as categorical variables. The SAS® code for the GLMM) is provided in APPENDIX 16.1. If the model fails to converge, simplified models, e.g., by removing the sequence effect, may be explored, or descriptive statistics on event rates may be reported without a statistical model.

The model-based estimate of mean annual rate and corresponding standard error will be presented for each treatment for the prophylactic cohort, as well as the ratio of the two treatment incidence rates, accompanied by a two-sided, 95% CI and p-value. Point estimates and confidence intervals obtained from the generalized linear model will be exponentiated prior to presentation. In addition, model-based estimates, two-sided 95% CI and p-value for period and sequence effects will be presented.

If no events are experienced within a treatment arm, a GLMM will not be fitted, the ratio of rates will not be calculated. Descriptive statistics on event rates will be reported without a statistical model.

Additionally, within-subject difference of the annualized acute TTP event rates between the two study treatments SoC and TAK-755 will be summarized for all subjects and the adolescent and adult subjects (≥12 years).

6.1.2 Acute TTP Event Figures

For each subject in the prophylactic cohort, a stacked figure containing 4 plots will be produced. The 4 stacked plots will present:

- ADAMTS13 activity vs time,
- Platelet counts vs time,
- LDH vs time, and
- Creatinine levels vs time.

Each of the stacked plots will use the same time axis and each will have markers showing the timing of acute TTP events, and subacute TTP events relative to first prophylactic infusion. The relevant treatment arm will be indicated as well.

6.1.3 Sensitivity Analyses of Primary Efficacy Outcome Measure

A sensitivity analysis will be done based on the FAS, SAF, and PPAS for the primary efficacy analysis. Another sensitivity analysis based on MFAS by excluding data after re-enrolment from subject [redacted] will be conducted.

6.2 Analyses of Secondary Efficacy Outcome Measures

Consistency checks will be conducted between reported dates and dates derived based on the meeting of the defined criteria for subacute events or TTP manifestations where both are available. Unless otherwise stated, analysis of the secondary efficacy outcomes will be based on MFAS, with sensitivity analyses based on the FAS, SAF and PPAS.

6.2.1 Acute TTP events Responding to TAK-755

An acute TTP event responding to TAK-755 is defined as a resolved event not requiring the use of another ADAMTS13-containing agent for its resolution. Acute TTP events are considered resolved when: (a) Platelet count is ≥150,000/μL or drop of platelet count is within 25% of baseline, whichever occurs first, and (b) Elevation of LDH ≤1.5 x baseline or ≤1.5 x ULN. Note that the date/time of the acute TTP event resolution will be reported in the *Thrombotic Thrombocytopenic Purpura Events* eCRF. Medications given as treatments for acute TTP events will be linked to the acute TTP event on the *Concomitant Medications* eCRF. A medical review of the concomitant medications given for each acute TTP event will be performed to determine which qualify as ADAMTS13-containing agents. This information will be incorporated into the analysis to determine response toTAK-755.

For this analysis, only acute TTP events treated with TAK-755 treatment will be considered. The number and proportion of acute TTP events which responded to TAK-755 will be reported for both the prophylactic and on-demand cohorts in total and separately. A subject will be considered as responded to TAK-755 if the acute TTP event has resolved (as defined above) and the acute TTP event did not require use of another ADAMTS13-containing agent prior to its resolution. Furthermore, a sensitivity analysis will be conducted for MFAS using all eligible events regardless of central lab confirmation.

6.2.2 Time to resolution of acute TTP events

Kaplan-Meier analysis will be performed for the time from initial treatment on or after randomization of the acute TTP event to resolution of the acute TTP event. Acute TPP events are considered resolved when: (a) Platelet count is ≥150,000/ μL or drop of platelet count is within 25% of baseline, whichever occurs first, and (b) Elevation of LDH ≤1.5 x baseline or ≤1.5 x ULN. The SAS® code for Kaplan-Meier is provided in APPENDIX 16.11.

The following derivations will be performed:

- Time to resolution (Hours) of event (censoring = 1) will be derived as:

$$Time\ to\ resolution\ (Hours) = Date/Time\ of\ event\ resolution - Date/Time\ of\ initial\ treatment\ of\ event$$

  where "Date/Time to resolution" will be the date/time where the acute TTP event was resolved as reported in the Thrombotic Thrombocytopenic Purpura Events eCRF.

  If the acute TTP event was not resolved, the time to resolution is censored (censoring = 0) and calculated as follows:

$$Censored\ time\ to\ resolution\ (Hours) = Date/Time\ of\ last\ timepoint - Date/Time\ of\ initial\ treatment\ of\ event$$

where "Date/Time of last timepoint" is defined as either of the following whichever is available:

- The last date and time the subject received the applicable treatment (SoC orTAK-755), according to randomization, for the event.
- Date and time of study discontinuation.

- Time to resolution (Days) of event will be determined using Time to resolution in hours as:

$$Time\ to\ resolution\ (Days) = Time\ to\ resolution\ (Hours)/24$$

- Censored time to resolution (Days) of event will be determined using Censored time to resolution in hours as:

$$Censored\ time\ to\ resolution\ (Days) = Time\ to\ resolution\ (Hours)/24$$

For subjects experiencing an acute TTP event, a Kaplan-Meier curve for each treatment group will be drawn based on each subject's time to resolution of the acute TTP event pooled prophylactic and on-demand cohort data, and separately. Only the first central lab confirmed acute TTP event for each subject for each treatment group will be included in the analysis. Kaplan-Meier estimates of the median time to resolution will be presented for each treatment, along with the corresponding 95% CI. The Kaplan-Meier estimate of the 25th and 75th percentiles as well as corresponding 95% CI will also be displayed. Furthermore, a sensitivity analysis will be performed using first acute TTP events regardless of central lab confirmation.

6.2.3 Incidence of Thrombocytopenia, Microangiopathic hemolytic Anemia and Renal Dysfunction

Results for platelet count, LDH and serum creatinine will be obtained from both central and local laboratory.

Thrombocytopenia is defined as a drop in platelet count ≥ 25% of baseline or a platelet count < 150,000/µL. A drop in platelet count ≥ 25% of baseline will be determined as follows:

$$(Change\ from\ baseline/baseline) * 100\ \leq\ -25$$

Microangiopathic hemolytic anemia is defined as an elevation of LDH > 1.5 × baseline or >1.5 x ULN.

Renal dysfunction is defined as an increase in serum creatinine > 1.5 × baseline.

For each of the outcomes, similar analysis and summaries will be performed as described for acute TTP events in Section 6.1.1. For each subject, if multiple lab assessments meet the criteria of a particular isolated TTP manifestation occur on the same date within the same period, then only one such isolation will be counted (i.e., if a subject has two platelet count values meeting the definition for thrombocytopenia on the same day within the same period, only one will be counted for analysis). The baseline will be defined as the last non-missing value obtained prior to study drug administration for central and local lab data

separately, and only the same laboratory type (central with central baseline, or local with local baseline) will be considered in the comparison with baseline for the determination of isolated TTP manifestation.

6.2.4 Incidence of Neurological Symptoms, Abdominal Pain and Other TTP Manifestations

Neurological symptoms, abdominal pain and other TTP manifestations will be obtained from the *Adverse Events* eCRF. Only TTP-related and possibly related events will be included in the analysis.

Neurological symptoms include events of multiple coded terms, eg headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures.

Adverse events that are neither "Neurological Symptoms" nor "Abdominal Pain" are classified into the "Other" category.

For each subject, if multiple AEs meet the criteria of a particular isolated TTP manifestation occur on the same date in the same period, only a single manifestation will be counted (i.e., if a subject has both headache and confusion reported on the same date in the same period, only one will be counted for analysis).

For each of the outcomes, similar analysis and summaries will be performed as described for acute TTP events in Section 6.1.1.

6.2.5 Incidence of acute TTP episodes while subjects are on their final dose and dosing regimen for the study

Final dose/dosing regimen is derived as last dose regimen that doesn't change over time in terms of treatment name or dosing frequency. In this analysis, TAK-755 SIN and TAK-755 ORT are considered the same treatment. The number of acute TTP events while subjects on their final dose and dosing regimen per subject will be determined as the count of acute TTP events a subject experiences while on their final dose/dosing regimen. The annualized acute TTP event rate while subjects on their final dose and dosing regimen will be derived as:

*Annualized acute TTP event rate while subjects on their final dose and dosing regimen = Number of acute TTP events a subject experience while on final dose/dosing regimen/ [(Date/Time of last study timepoint - Date of first dose on final dose/dose regimen +1)/(12*28)]*

Where "Date/Time of last timepoint" is defined as the earliest date of study discontinuation or death date. If these two dates are not available, use the study completion date.

Similar analysis and summaries will be performed as described for acute TTP events in Section 6.1.1

6.2.6 Other Incidence Outcome Measures

The incidence of supplemental doses prompted by subacute TTP events will be summarized by treatment for the prophylactic cohort. A dose is a supplemental dose

prompted by a subacute TTP event if it's administrated at an acute event visit and falls into the window of the subacute event start date (inclusive) and one day after the subacute event end date (inclusive).

The incidence of dose modifications not prompted by an acute TTP event will be summarized by treatment for the prophylactic cohort. Dose modifications not prompted by an acute TTP event will be based on the information reported on the Dose Modification eCRF. Dose modifications not prompted by an acute TTP event is when dose modification based on clinical response is "Yes" but the reason is not "One acute TTP event".

For each of the outcomes, similar analyses and summaries will be performed as described for acute TTP events in Section 6.1.1.

6.2.7 Sensitivity analysis for secondary efficacy outcome measures

Additionally, sensitivity analyses will be done for all secondary outcome measures after excluding data collected during the first 14 days of each study period. For the event-based outcome measures, only events with a start date during the study period included in the analysis, will be considered.

6.3 Multiplicity Adjustment

No multiplicity adjustment to control Type I error is planned in the study.

6.4 Analyses of Exploratory Outcome Measures

Unless otherwise stated, analysis of the exploratory efficacy outcomes will be based on MFAS with sensitivity analyses based on FAS, SAF and PPAS.

6.4.1 Incidence of TTP Manifestations

Incidence of TTP manifestations, defined as a composite of the secondary outcome measures (secondary efficacy outcome measures 3 to 7 specified in Section 2.3.2.1), while receiving prophylactic treatment with TAK-755 or SoC during the 6 months of the corresponding treatment.

Incidence of TTP manifestations, defined as a composite of the secondary outcome measures (secondary efficacy outcome measures 3 to 7 specified in Section 2.3.2.1), while receiving the final prophylactic treatment regimen with TAK-755 or SoC. The final dose and dosing regimen is defined in Section 6.2.5.

The incidence rate of the two composite endpoints above, will be analyzed and summarized as described for the primary efficacy outcome in Section 6.1.1. Tabular summaries will be presented:

- by study period and treatment: Prophylactic (Period 1, Period 2, Period 1 and 2, and Period 3).
- by age group, race group, sex, and geographic region (based on MFAS) as defined in Section 6.5.

6.4.2 Incidence rate of Subacute TTP Events

Subacute TTP events are defined in Table 4. For this analysis, a unique subacute TTP event can be considered as each event recorded by the investigator on the Thrombotic Thrombocytopenic Purpura Events eCRF and identified as subacute TTP event.

Information on subacute TTP events and management of the events will be listed for the FAS.

Similar analysis and summaries will be performed as described for acute TTP events in Section 6.1.1.

Tabular summaries will be presented:

- by study period and treatment: Prophylactic (Period 1, Period 2, Period 1 and 2, and Period 3).
- by age group, race group, sex, and geographic region (based on MFAS) as defined in Section 6.5.

6.4.3 Biomarkers of Organ Damage

The shifts in biomarkers of organ damage will be assessed as discussed in Section 7.2, Clinical Laboratory Evaluations.

6.5 Subgroup Analyses

Analysis of efficacy, AE and immunogenicity data will be presented the following subgroups:

Age group 1:

- ≥ 12 years
- < 12 years

Age group 2:

- ≥ 18 years
- 12 to <18 years
- 6 to <12 years
- < 6 years

Race group:

- White
- Japanese
- Other (neither White nor Japanese)

Sex:

- Male
- Female

Geographic Region:

- US
- Europe
- Japan

Table 6: Subgroup Analyses by Data Type

Data Type	Age Group 1	Age Group 2	Race Group	Sex	Geographic Region
Disposition	x	x	x	x	
Demographics	x	x	x	x	x
Medical History and Surgeries					
Prior Medications and Non-drug Therapies					
Concomitant Medications and Non-drug Therapies					
Exposure	x	x	x	x	x
Treatment Compliance		x	x	x	x
Protocol Deviations		x	x	x	x
Primary Efficacy Measure	x	x	x	x	x
Secondary Efficacy Measures	x	x	x	x	x
Exploratory Efficacy Measures	x	x	x	x	x
Adverse Events	x	x	x	x	x
Clinical Laboratory Data		x	x		
Immunogenicity		x	x	x	x
Vital Signs		x		x	x
ECG		x	x		

7. SAFETY ANALYSIS

The safety analysis will be performed using the SAF. Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables. For each safety variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that safety variable. Last Value on Treatment (LVOT) will be defined as the last valid assessment obtained after Baseline and whilst on investigational product. Last Observed Value (LOV) will be defined as the last valid assessment obtained after Baseline.

All safety analyses will be conducted according to the treatment the subject received.

7.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment phase will be considered a Treatment Emergent Adverse Event (TEAE) if it has a start date-time on or after the start date-time of the first dose of the treatment the subject is taking on that assessment or period or if it has a start date-time before the start date-time of the first dose of the treatment the subject is taking on that assessment or period but increases in severity on or after the start date-time of the first dose of the treatment the subject is taking on that assessment or period.

The following information will be obtained from the eCRF:

- AEs from the *Adverse Events* eCRF.
- Date and time of TAK-755 or SoC administration from the *Exposure* eCRF.
- Reason for not completing the study from the *Completion/Termination* eCRF.

Summary tables will be based on TEAEs, referred to AEs for brevity. An overall summary of number of subjects within each of the following categories will be presented:

- All AEs.
- AEs excluding cTTP related or possibly related events.
- AEs related or possibly related to cTTP.
- AEs related to IP.
- AEs not related to IP.
- AEs related to study procedure.
- Mild AEs
- Moderate AEs
- Severe AEs.
- Severe AEs excluding cTTP related or possibly related events.
- Severe AEs related or possibly related to cTTP.
- Severe AEs related to IP.
- Severe AEs related to study procedure.
- SAEs.
- SAEs excluding cTTP related or possibly related events.
- SAEs related or possibly related to cTTP.
- SAEs related to IP.
- SAEs related to study procedure.
- AEs leading to discontinuation of study.
- AEs leading to discontinuation of IP
- AEs leading to interruption of IP.
- AEs leading to death.

The overall summary will include the number and percentage of subjects having an AE by category as well as the number of events.

AEs will be summarized by treatment cohort, treatment period and treatment arm within cohort. In addition to the overall summary table, summary tables will be prepared according to system organ class (sorted alphabetically) and preferred term (sorted in order of descending frequency). Summary tables are to indicate the number (and percentage) of subjects who experienced AEs as well as the number of AEs. These summary tables will be done for some of the categories above as requested. AEs will be also summarized by maximum severity, SOC and PT, in which only the number (and percentage) of subjects will be presented.

AE summaries, overall and by system organ class and preferred term, will be prepared by age group, race group, sex, and geographic region as defined in Section 6.5.

All AEs, including non-TEAEs, for each subject, will be listed for the SAF.

AEs will be coded using the latest version of the MedDRA as documented by Data Management in the *Data Coding guideline* at the time of performing the analysis.

AEs are considered to have occurred during or after SoC administration if:

- The last infusion received prior to the start of the AE (used the imputed date if AE start date is partial) was SoC.
- The known start date and/or time of the AE (used the imputed date if AE start date is partial) is equal to or after the date and/or time of last SoC infusion.

AEs are considered to have occurred during or after TAK-755 administration if:

- The last infusion received prior to the start of the AE (used the imputed date if AE start date is partial) was TAK-755.
- The known start date and/or time of the AE (used the imputed date if AE start date is partial) is equal to or after the date and/or time of last TAK-755 infusion, prior to the AE.

Handling Partial AE Start Date

- If year and month are known, and it is the month and year of the first study drug dose date, use the first study drug dose date.
- If year and month are known, and the year/month is not the year/month of the first study drug dose date, use the first day of the month.
- Should any of the previous start dates created be after a complete stop date provided, use the stop date instead of the date that would otherwise be created.

Time since last TAK-755 or SoC infusion will be determined as:

$$Time = [Start\ Date/Time\ of\ AE] - [Date/Time\ of\ Last\ \text{TAK} - 755\ or\ SoC\ Exposure]$$

where the date/time of last TAK-755 or SoC exposure are the last possible TAK-755 or SoC administration, regardless of reason, prior to the start of the AE. Time since last TAK-755 or SoC infusion will be determined if the full start date (regardless of whether time is

known or not) of the AE is known. Time since last TAK-755 or SoC infusion will be presented in either hours or days, based on the following criteria:

- Presented in hours if start time of AE is known and time since last TAK-755 or SoC infusion is < 24 hours.
- Presented in days if start time of AE is known and time since last TAK-755 or SoC infusion is ≥ 24 hours.
- Presented in days if start time of AE is not known.
- Duration of AE will be determined as:

  $$Duration = [End\ Date/Time\ of\ AE] - [Start\ Date/Time\ of\ AE]$$

  The duration of an AE will be presented in either hours or days, based on the following criteria:

  - Presented in hours if both start time and end time of the AE is known and the duration is < 24 hours.
  - Presented in days if both start time and end time of the AE is known and the duration is ≥ 24 hours.
  - Presented in days if either start time or end time or both are unknown.
- An AE relevant to TAK-755 or SoC is considered related as assessed by the Investigator if the AE is indicated as "Possibly related" or "Probably related" in the eCRF. An AE relevant to TAK-755 or SoC is considered unrelated as assessed by the Investigator if the AE is indicated as "Not related" or "Unlikely related" in the eCRF. An AE relevant to cTTP is indicated as "Related" or "Possibly related" and "Not related" in the eCRF.
- Handling of unknown causality and unknown severity grades are described in Section 5.5, Handling of Missing, Unused, and Spurious Data.
- An AE is considered leading to discontinuation of study medication if indicated as "Drug withdrawn" in the eCRF.
- An AE is considered leading to discontinuation of study if the AE is indicated as the primary reason why the subject did not complete the study from the Study Completion/Termination eCRF panel.
  - An AE is considered as leading to death if the question "Did the serious event result in death?" is indicated as "Yes" or if the outcome in the eCRF is indicated as "Fatal".

7.2 Clinical Laboratory Data

Results from the central and local laboratory will be included in the reporting for this study. Results will be presented using CDISC compliant terms and standard international (SI) units.

Information from the Investigator on abnormal results will be obtained from the following eCRFs:

- Central Lab Collection – Hematology Sample eCRF.
- Central Lab Collection – Chemistry Sample eCRF.
- Central Lab Collection – Urine Sample eCRF.
- Local Laboratory Hematology – Adult & Adolescent eCRF.
- Local Laboratory Hematology – Pediatric eCRF.
- Local Laboratory Chemistry – Adult & Adolescent eCRF.
- Local Laboratory Chemistry – Pediatric eCRF.

The following laboratory parameters from central laboratory will be included in all summaries:

- Hematology: Red blood cell (RBC) count, hemoglobin, hematocrit, haptoglobin, reticulocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e., white blood cell count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.
- Clinical chemistry: Sodium, potassium, chloride, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), LDH, bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine and glucose.
- Urinalysis: Erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite and pH.
- Viral Serology: Human Immunodeficiency Virus (HIV) (i.e., anti-HIV 1, HIV 2), hepatitis A virus (HAV) (i.e., anti-HAV [Immunoglobulin G (IgG) and M (IgM)]), hepatitis B virus (HBV) (i.e., hepatitis B surface antigen, anti-Hepatitis B core, anti-hepatitis B surface antibody), hepatitis C virus (HCV) (i.e., anti-HCV ELISA), Parvovirus B19 (i.e., anti-B19V [IgG and IgM]), CD4 levels (at screening in HIV-positive subjects).
- Pregnancy test: Urine and serum.

The following summaries will be provided for central laboratory data alone:

- Quantitative laboratory assessments on observed and change from baseline results.
- Qualitative laboratory assessments (except hematology, clinical chemistry and biomarker of organ damage).

Shift from baseline to each period (period 1, period 2 and period 3) with Baseline defined as in Section 12.2. For each parameter within each period, if there is at least 1 abnormally low or high value for a subject, the subject will be classified as low or high, respectively, for that period. If the subject has both low and high values for a specific parameter within the period, the subject will be classified both low and high for the period. The shifts will

be created for all laboratory categories and include the following categories as reported on the eCRF:

- Low
- Normal
- High

Low, normal and high will be derived from comparison of lab results to references ranges allowing allocation to one of these three categories. The count and percent of the SAF will be presented as well as a comparison to baseline.

Only central laboratory results will be summarized for the SAF by period, treatment cohort and treatment arm. Analyses will be summarized by study week derived using the study visit and dosing regimen. If a subject has multiple values on one date during the on-demand period, then the mean value will be used. Central and local laboratory results for all parameters (planned or unplanned) will be listed for the SAF, including separate listings for abnormal and clinically significant results. Descriptive statistics for central laboratory results (by study week for prophylactic periods or by study visit otherwise) will be presented in a box-plot for the SAF. In the boxplot, only data from scheduled visits will be used. Individual and summary figures for platelets, LDH, serum creatinine and all biomarker tests will be presented.

Central laboratory result summaries, for chemistry and hematology labs, will be prepared by age group and race group as defined in Section 6.5.

If both central lab results and local lab results are available for the same subject at same date/time, then the central lab results will be used for the summary. Both sets of results will be listed.

The following derivations will be performed based on results obtained from the central laboratory and eCRF:

- A result will be considered out of range if the observed result is less than the lower limit of the normal range (indicated as "L") or larger than the upper limit of the normal range (indicated as "H"). The normal range will be provided by the central laboratory.
- A result will be considered clinically significant if indicated as such by the Investigator on the eCRF.
- Quantitative laboratory measurements reported as "<X", i.e., BLQ, or ">X", i.e., ALQ are to be presented in listings as "<X" or ">X" and summarized in summaries as "X" in both cases.

7.3 Vital Signs

Information for Vital Signs will be obtained from the *Vital Signs*, *Height* and *Weight* eCRFs.

Summary statistics on observed and change from baseline vital sign data will be presented for the SAF by period, treatment cohort and treatment arm. Analyses will be summarized by study week derived using the study visit and dosing regimen. For Q1W subjects, the summary results will be also presented every other week. The mean value will be used for analysis if a subject has multiple data on the same date during the on-demand period. A summary figure on body temperature will be presented. All vital signs results will be listed for the SAF Set. Descriptive statistics for vital sign results (by study week for prophylactic periods or by study visit otherwise) will be presented in a box-plot for the SAF. In the boxplot, only pre-dose data from scheduled visits will be used.

Vital sign summaries will be prepared by age group, sex, and geographic region as defined in Section 6.5.

The following derivations based on eCRF reported results will be performed:

- Body Temperature will be converted from Fahrenheit scale (ºF) to Celsius scale (ºC) as follows:

$$Body\ Temperature\ (^{\circ}\mathrm{C}) = \frac{5}{9}(Body\ Temperature\ [^{\circ}\mathrm{F}] - 32)$$

- Weight and height will be converted as specified in Section 6.2, Demographic and Baseline Characteristics.
- A result will be considered clinically significant if indicated as such by the Investigator on the eCRF.
- Shift from baseline to each period (period 1, period 2 and period 3) with Baseline defined as in Section 12.2. For each subject, the value of each period is determined using the same logic as specified for lab shift table. The shifts will be created for vital signs and include the following categories as reported on the eCRF:
  - Normal.
  - Abnormal, not clinically significant.
  - Abnormal, clinically significant.

7.4 Electrocardiogram (ECG)

Information on ECG evaluations will be obtained from the *12-Lead Electrocardiogram* eCRF.

ECG evaluations will be listed and summarized for the SAF Set. ECG interpretation (normal, abnormal not clinically significant and abnormal clinically significant) will be summarized by treatment sequence. Shift from baseline to each period (period 1, period 2 and period 3) with baseline defined as in Section 12.2 will also be tabulated by treatment sequence. For each subject, the value of each period is determined using the same rule as specified for lab shift table.

ECG summaries will be prepared by age group and race group as defined in Section 6.5.

The following derivations based on eCRF reported results will be performed:

Adverse events and medical history forms will be merged with the applicable number provided as part of the "Reason for abnormality" to obtain the specific term for presentation in the listings.

7.5 Other Safety Data

7.5.1 Inhibitor/Antibody Development

The following immunogenicity results as presented in the planned output templates will be analyzed by a central laboratory and presented using the SAF by treatment cohort and treatment arm:

- Anti-rADAMTS13 binding antibodies.
- Anti-ADAMTS13 neutralizing antibodies (Results ≥ 0.6 BU considered positive).
- Anti-rADAMTS13 neutralizing antibodies (Results >= 0.6 considered positive)
- Anti-CHO protein antibodies.

As part of the AE follow-up, any sample testing positive will need to be confirmed after 2 – 4 weeks. Only confirmed neutralizing anti-ADAMTS13 antibodies will be considered inhibitors.

Results for above mentioned assays will be listed and summarized descriptively.

The number and percentage of subjects with an incidence (defined as a positive testing result for each antibody above) will be displayed by treatment cohort, treatment period (pre-dose, PK-assessment, period 1 and period 2, period 3) and treatment arm.

Immunogenicity summaries will be prepared by age group, race group, sex, and geographic region as defined in Section 6.5.

- The following derivations will be performed based on results obtained from the central laboratory:
- For anti-ADAMTS13 neutralizing antibodies measured using Bethesda based assays, the result will be considered positive when the obtained result is ≥ 0.6 BU.
- For categorical results, results reported as "positive" or "detectable" by the laboratories will be considered as positive.
- For the analyses on the number of subjects and percentage a subject will be counted as having a positive result if the subject had a positive result at any time point. Only subjects that had no positive results throughout the whole study will be counted toward negative for this analysis.

7.5.2 Physical Examination

Information for physical examination will be obtained from the *Physical Examination* eCRF.

Physical examination results will be listed for the SAF. No summaries of physical examination will be presented.

8. PHARMACOKINETIC ANALYSIS

For the details of the pharmacokinetic analysis please refer to the Clinical Pharmacology Analysis Plan (CPAP). Evaluations of ADAMTS13 activity (measured using FRETS assay, and a different assay in the case such assay, that is insensitive to hemolysis, can be validated) and ADAMTS13:Ag are described below.

The summaries of the PK concentration and PK parameters (listed below) for PK-I, PK-II and PK-III will be presented as follows:

- Serial PK-I samples for the prophylactic cohort and treatment, SoC or BAX 930 ORT; also split by age group and overall.
- Serial PK-II samples for the prophylactic cohort and rADAMTS13 material, BAX 930 ORT or BAX 930 SIN; also split by age group and overall.
- Serial PK-III samples for a subset of the prophylactic cohort and BAX 930 SIN; also split by age group and overall.

The PK concentration summaries for sparse sample collection will be presented as follows:

- Sparse samples for the prophylactic and on-demand cohorts, for SoC or BAX 930 ORT and BAX 930 SIN, dosing regimen and visit; also split by age group and overall.

For all sparse observed PK concentration (ADAMTS13 activity and ADAMTS13 Ag) time data analysis (tables and or figures), baseline adjustment or correction will not be performed.

8.1 Drug Concentration

A listing of PK blood sample collection times, derived sampling time deviations, and concentrations of ADAMTS13 activity and ADAMTS13:Ag will be provided.

Serial PK samples collected for PK-I, PK-II and for PK-III, and sparse PK samples collected pre-infusion and post-infusion at prophylaxis dosing, interval study visit, and during acute TTP events will be listed and summarized for each analyte by scheduled time. For the purpose of calculating descriptive statistics, concentrations that are below the limit of quantitation (BLQ) will be treated as zero.

Figures of concentration-time data for each individual profile for BAX 930 and SoC will be presented on linear and semi-logarithmic scales.

8.2 Handling Below Limit of Quantitation (BLQ) Values

The data handling conventions for ADAMTS13 concentration and activity are provided in the CPAP.

8.3 Pharmacokinetic Parameters

For PK-I, PK-II and PK-III, single-dose PK parameters for ADAMTS13 activity (measured using FRETS assay, and a different assay in the case that an assay that is insensitive to hemolysis can be validated) and ADAMTS13:Ag will be estimated by noncompartmental methods using actual elapsed time from the start of infusion. Details of the parameters and their calculations are provided in the CPAP.

For the non-compartmental PK analysis (ADAMTS13 activity and ADAMTS13 Ag) baseline adjustment or correction will be performed as described per study CPAP.

8.4 Statistical Analysis of Pharmacokinetic Data

Pharmacokinetic parameters for pediatric subjects (Age ≥ 6 to < 12 , Age ≥ 12 to <18, and Age < 6) will be assessed separately from adults (those with Age ≥18). An attempt will be made to determine PK parameters using a non-compartmental method described in this SAP for pediatric subjects based on the reduced sampling schedule and may include C_{max}, t_{max}, and appropriate estimates of AUC over the sampling period (e.g., $AUC_{(0\text{-}168h)}$). A population PK model may be developed for ADAMTS13 activity (as data allow). Details of the methodology for the population PK will be captured separately under a modeling analysis plan (separately from the SAP).

Within subject differences of pharmacokinetic parameters between PK-I and PK-II, PK-I and PK-III, and PK-II and PK-III will be summarized for the BAX 930 treatment group.

For graphical assessment of PK comparability between treatment product (BAX 930 ORT or BAX 930 SIN) in PK-II, individual and geometric mean values of C_{max}, AUC_{all}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ versus treatment product will be presented for each analyte in adults (Age ≥ 18) and adolescent subjects (Age ≥12 to <18), where sufficient data are available. Additional graphical presentations of PK data may be added at the discretion of the PK scientist, if further illustration of the PK results is deemed appropriate.

If sufficient data are available, comparisons between BAX 930 ORT and BAX 930 SIN will be assessed in PK-II using a linear mixed effects model, with terms for sequence, subject nested within sequence, period (from PK-II cross-over), and treatment, on the log-transformed values of C_{max} and AUCs (e.g., $AUC_{(0\text{-}last)}$, AUC_{all} and $AUC_{(0\text{-}inf)}$). Subject nested within sequence will be treated as a random effect and the other terms will be considered as fixed effects. The analyses will be performed for adult and adolescent subjects. From these analyses, least-squares (LS) means, LS treatment differences, and 90% CIs for the treatment differences on log-scale will be obtained. The results will be transformed back to the original scale by exponentiation to provide treatment geometric LS means, point estimates of the geometric test/reference (BAX 930 SIN/BAX 930 ORT) LS mean ratios and 90% CIs for these ratios.

9. PHARMACODYNAMIC ANALYSIS

9.1 Pharmacodynamic Data

A listing of blood sample collection times, derived sampling time deviations, and PD measurement of plasma VWF:RCo, VWF:Ag, VWF multimer structure analysis (quantitative and qualitative data, as available), and ADAMTS13 mediated VWF cleavage products will be provided.

Serial PD samples collected during PK-I, PK-II and PK-III, and sparse PD samples collected pre- and post-infusion at prophylaxis dosing, interval study visit, and during acute TTP events, will be listed and summarized for each analyte by scheduled time. The proportion of subjects (n [%]) with detectable ADAMTS13 cleavage products (from the evaluable total samples at the respective time point) will also be summarized by scheduled times. This summary will include only sample with N>3 per time point.

For the purpose of calculating descriptive statistics, concentrations that are BLQ will be treated as zero.

Figures of concentration-time data for each individual profile will be presented on linear and semi-logarithmic scales.

Change from baseline in PD measurements will be derived, as applicable.

9.1.1 Primary Pharmacodynamic Outcome and Analysis

The PD concentration summary will be presented as follows:

- Serial PK-I samples for the prophylactic cohort for SoC or BAX 930 ORT; also split by age group and overall.
- Serial PK-II samples for the prophylactic cohort for BAX 930 ORT or BAX 930 SIN; also split by age group and overall.
- Serial PK-III samples for a subset of the prophylactic cohort for BAX 930 SIN; also split by age group and overall.
- Sparse samples for the prophylactic and on-demand cohorts and for SoC, BAX 930 ORT and BAX 930 SIN, dosing regimen (for BAX 930 only) and visit; also split by age group and overall.

9.1.2 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

Exposure response analysis will be conducted to demonstrate a quantitative relationship of ADAMTS13 exposure to a) platelet and LDH levels, b) prevention of cTTP manifestations (by organ class and composite outcome defined as the occurrence of at least one of the isolated TTP manifestations irrespective of organ class). The specific intent of exposure response modeling is to use a time-to-event framework (i.e., not only if event occurred but when did it occur) to characterize the effect of the ADAMTS13 PK time profile and heterogeneity in prevention of isolated TTP manifestations by, organ class (secondary outcome), and composite outcome (exploratory outcome) using the pivotal trial data. Then clinical trial simulations (CTS) using the above model will be used to predict: the probability

of preventing these organ class manifestations, composite outcome, and events for different ADAMTS13 exposure metric ranges; and, demonstrate whether TAK-755 provides an improved opportunity to prevent these manifestations over SoC. Details of the methodology will be captured separately under a modeling analysis plan (separately from the SAP).

Additionally, the relationship between ADAMTS13 activity levels and change in VWF:RCo, VWF:Ag, platelets and incidence of acute and subacute TTP events will be explored.

For each prophylactic enrollment type and overall, for screening, first dose, interval visit and completion assessments, as applicable, mean stacked figures containing 4 plots will be produced. The 4 stacked plots will present:

- ADAMTS13 activity and VWF:RCo vs time,
- ADAMTS13 activity and VWF:Ag vs time
- ADAMTS13 activity and platelet count vs time, and
- ADAMTS13 activity and LDH vs time.

Each of the stacked plots will use the same time axis, with scale of ADAMTS13 activity always on the left-hand axis and the PD parameter on the right-hand axis, and each will have markers showing the timing of acute TTP events and subacute TTP events relative to first prophylactic infusion.

Details for PK/PD analyses will be described separately from the SAP in a modeling analysis plan.

10. OTHER ANALYSES

10.1 Health-related Quality of Life (HRQoL) Analyses

Further to reporting of summary statistics and listing of the HRQoL data, additional analysis will be performed as discussed in the PRO SAP.

Some PRO assessments are age restricted or age specific in the protocol. For such assessments, the age criteria refer to age at screening (i.e., subjects should be given the same questionnaire at follow-up that they were given at baseline, even if they move up an age range in the study). If a subject takes a different version (e.g. they take EQ-5D-3L instead of EQ-5D-Y) of the assessment than planned per protocol, or takes an assessment not planned per protocol (e.g. a 17 year old completes SF-36), then the results of that assessment will be listed but not summarized.

The scoring of the questionnaires will be performed by a qualified vendor and the final scores will be incorporated into the SDTM datasets for analysis and reporting in the clinical study report (CSR).

10.1.1 Short-Form 36 (SF-36) Questionnaire

The Short-Form 36 (SF-36) is a self-administered, validated questionnaire designed to measure general health related quality of life. The questionnaire is divided in 8 domains including: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. From this questionnaire 2 summary scores can be calculated, the physical component score and the mental component score.

Information on the SF-36 will be obtained from electronic patient diaries for participants age ≥18 years.

The SF-36 scores and changes from baseline will be summarized for the MFAS Set by treatment cohort, treatment arm, period and visit. SF-36 individual results and calculated scores will be listed for the SAF.

10.1.2 EuroQol 5 Dimension Questionnaire 3 Level (EQ-5D-3L or EQ-5D-Y)

The EuroQol 5-dimension questionnaire 3 level (EQ-5D-3L) is a generic measure of health, consisting of a descriptive system. It captures the following domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. The self-rated health is captured using a visual analog scale. The youth version (EQ-5D-Y) contains the same features but uses more child-friendly wording.

Individual results for each of the questions will be obtained from electronic patient diaries for the EQ-5D-3L for participants age ≥16 years and the EQ-5D-Y for participants age 8 to <16 years.

The EQ-5D-3L scores and changes from baseline will be summarized for the MFAS by treatment cohort and treatment arm for subjects aged ≥16 years. The EQ-5D-Y scores and changes from baseline will be summarized for the MFAS by treatment cohort and treatment arm for subjects aged 8 to <16 years. EQ-5D-3L and EQ-5D-Y individual results and calculated scores, including changes from baseline, will be listed for the SAF.

10.1.3 Pediatrics Quality of Life Questionnaire (PedsQL)

The pediatrics quality of life questionnaire (PedsQL) is a generic HRQoL instrument designed specifically for a pediatric population. The questionnaire consists of different questions based on the age of the subjects for ages 2-4, 5-7, 8-12 and 13-17. The PedsQL capture data for the following domains: physical functioning, emotional functioning, social functioning, school functioning, psychosocial functioning, physical health and a total score.

Information on the PedsQL will be obtained from electronic patient diaries using the child report (23 items) for participants age 13 to <18 years, child version (23 items) for participants age 8 to <13 years, parent proxy (23 items) for participants age 5 to <8 years, and parent proxy (21 items) for participants age 2 to <5 years.

The PedsQL scores and changes from baseline will be summarized for the MFAS Set by treatment cohort and treatment arm separately for subjects aged 2 to <5, 5 to <8, 8 to <13 and 13 to <18 years. PedsQL individual results and calculated scores will be listed for the SAF.

10.1.4 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The treatment satisfaction questionnaire for medication (TSQM-9) is a validated measure consisting of 3 domains (efficacy, convenience and overall satisfaction) and 9 questions.

Individual results for each of the questions will be obtained from electronic patient diaries. for participants age ≥18 years.

3 sub-scales domain scores range from 0 to 100 with higher scores representing higher satisfaction with the treatment on that domain. This questionnaire does not contain a total score.

The TSQM-9 scores and changes from baseline will be summarized for the MFAS by treatment cohort and treatment arm for subjects aged ≥18 years. TSQM-9 individual results and calculated scores will be listed for the SAF.

10.1.5 cTTP Patient Reported Outcome (PRO) Assessment

The cTTP patient reported outcome (PRO) assessment is focused on measuring the symptoms and impacts of the disease. It is a 26-item questionnaire assessing a number of concepts, including the following: fatigue, pain (joint, muscle, abdominal, chest), neuro-cognitive impairment, vision difficulties, headaches, bruising, emotional functioning and impact on daily activities.

Individual results for each of the questions will be obtained from electronic patient diaries. for participants age ≥12 years.

The cTTP PRO assessment individual and domain scores and changes from baseline will be summarized for the mFAS by treatment cohort and treatment arm for subjects aged ≥12 years and for subjects aged 12 to <18 years and ≥18 years. All information on the cTTP PRO assessment will be listed for the SAF.

10.2 Healthcare Resource Utilization (HRU) Analyses

Information on health resource utilization including number of hospitalizations and duration of hospitalization not due to SAE, as well as, number of acute care visits, number of emergency room visits, and duration of absence from school/work will be reported in the *Health Resource* eCRF. In addition, Information including number of hospitalizations and duration of hospitalization due to SAE will be collected by the *Adverse Events* eCRF.

For each item of hospitalization, acute care and emergency room, the data from the same subject will be considered as a duplicate if they have the same start date, and therefore, will be only counted once for the calculation of visit number. While for each item of hospitalization and absence from school/work, the duration will be calculated for each subject with the overlapping days between different entries excluded.

HRU data captured in the electronic diary was retired mid-way through the study to avoid duplicate data capture. It will not be used in analysis.

Information on health resource utilization will be summarized for MFAS by treatment cohort and treatment arm. Both annualized and non-annualized results will be considered, where annualized results are obtained via dividing the non-annualized values by OPE*x* (in

years) that is defined in Section 6.1.1. In addition, summaries by age group will be considered. All information on health resource utilization will be listed for SAF.

The following derivations based on eCRF reported results will be performed:

- Duration of hospitalization in days:

$$Duration(Days) = (End\ Date\ of\ Hospitalization - Start\ Date\ of\ Hospitalization) + 1$$

- Study days for the start and end dates of the health resource use as described in Section 5.3: Reference Start Date and Study Day.

11. INTERIM ANALYSIS/ DATA MONITORING COMMITTEE

11.1 Data Monitoring Committee (DMC)

The safety data for this study will be reviewed periodically by a DMC. A separate set of outputs will be provided for the DMC.

11.2 Interim Analyses

An interim analysis (IA) will be performed after 30 adult or adolescent subjects in the prophylactic cohort complete the study.

All analyses included in this SAP will be included in the IA.

All efficacy analyses will be done in all subjects included in IA as well as only in adolescent and adult subjects as applicable (aged ≥12 years).

In addition, analyses of disposition, demographics and baseline characteristics, extent of exposure, treatment compliance, protocol deviations, PK/PD and HRQoL as applicable will also be done in adolescent and adult subjects (aged ≥12 years).

The interim analysis will be performed on a database cleaned up to the data cut-off date for the interim analysis:

- All outstanding data issues and queries resolved.
- No missing visits or pages.
- All irresolvable data issues documented in the Data Handling Report (DHR) from Data Management.
- All coding of medications and AEs completed.
- SAE reconciliation completed.
- All reconciliation of vendor data with eCRF data completed successfully.
- Source data verification is completed and relevant records are frozen.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Unless otherwise specified, the default summary statistics for quantitative variables will be as follows:

- The number of subjects in each category (n).
- Mean.
- Standard deviation (SD).
- Median.
- Minimum.
- Maximum
- Q1
- Q3

When n ≥2, all summary statistics above will be calculated; When n=1 all summary statistics except SD will be reported; When n=0, only n will be presented.

The number of subjects (n) with missing or unavailable results for quantitative variables will be presented as "Not reported" where applicable. A "Not reported" category will only be presented should there be unavailable results. No distinction based on the reason for unavailable results will be made in any presentations.

If the original data has N decimal places (as derived from the raw data) (i.e., decimal precision [N]) then the summary statistics are to contain the following decimal places (with a maximum of 3 decimals):

- Minimum and maximum: N.
- Mean and median: N+1.
- Standard deviation: N+2.

For qualitative variables the number (n) and percentage (%) of subjects in each category will be the default summary presentation. Unless otherwise specified, percentages will be calculated relative to the total number of subjects in the relevant analysis set as described in the latest version of the Output Templates. In the event of unavailable assessments, a "Not reported" category will be presented. A "Not reported" category will only be presented if applicable. The "Not reported" category will be presented with a percentage so that the sum of the percentages of all categories, including the "Not reported" category, totals 100%. No distinction based on the reason for unavailable results will be made in any presentations.

The default significant level will be 5%; confidence intervals will be 95% and all tests will be 2-sided, unless otherwise specified in the description of the analyses.

P-values obtained from statistical inference tests will be presented using 4 decimal places. P-values smaller than 0.0001, will be presented as "<0.0001" and p-values larger than 0.9999, but less than 1, will be presented as ">0.9999". A p-value of exactly 1 will be presented as "1.0000".

All values will be rounded using the SAS® function ROUND. All computed percentages will be presented using 1 decimal place.

The final planned analysis identified in this SAP will be performed by IQVIA or Takeda Biostatistics following Baxalta, now part of Shire's authorization of this SAP and Database Lock.

The final analysis will be performed on a clean database, with characteristics similar to those set out for the interim analysis in Section 11.2, Interim Analysis.

It is to be noted that all verbatim text from the eCRF to be presented in any outputs are to be presented "as is" with no "manual hard coding" corrections for such data

All PK concentrations PD measurements will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory or clinical laboratory regardless of how many significant figures or decimals the data carry. Baseline adjusted concentrations will be reported and analyzed with the same precision as the unadjusted concentrations.

Derived PK parameters will be rounded for reporting purposes in by-subject listings. The unrounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, C_{max} and IR) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (eg, t_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data.

Summary statistics of PK concentrations and PD measurements will include: n, number and percentage of values <LLOQ, arithmetic mean, SD, coefficient of variation (CV%), median, minimum and maximum. Summary statistics for all PK parameters (except for t_{max}) include: n, geometric mean, geometric coefficient of variation (Geo CV%), arithmetic mean, SD, median, minimum, and maximum. The PK parameter t_{max} will be summarized using n, median, minimum and maximum. An $n \geq 3$ will be required for calculations of descriptive statistics. If n=2, only n, minimum and maximum will be reported. If n <2, no descriptive statistics will be calculated; only n will be presented.

For the reporting of descriptive statistics, the median and mean will be presented to one digit more precision than the source data. Standard deviation and standard error will be presented to two digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. Ratios of means for PK parameters

will be presented with two decimal places (as a percentage). P-values, if any, shall be reported to four decimal places or as <0.0001.

For subjects switch from On-demand cohort to prophylactic cohort, the subjects will be summarized under both cohorts. A separate listing with subject number, cohort, start date and stop date of each cohort will be provided for this group of subjects.

There are two rescreened subjects that passed screening and entered the study more than once ([redacted] and [redacted]), which are allowed by protocol. Each rescreened subject is treated as two different subjects for analysis, and all data as collected are included. Furthermore, subject [redacted] has two prophylactic enrollments while subject [redacted] only has one, sensitivity analyses are conducted for efficacy endpoints on MFAS by excluding the data after re-enrollment collected from subject [redacted].

12.2 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing (scheduled or unscheduled) value obtained prior to study drug administration. If the date of the last non-missing assessment and the reference start date coincide and the time of either is missing, the assessment will be considered baseline.

12.3 Definition of Visit Windows

All data (except lab and vital sign data from prophylactic periods) will be presented by nominal visit date as recorded on the eCRF. Visits will not be reassigned from the recorded nominal visit to any other visit based on dates.

12.4 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

12.5 Handling of Missing, Unused, and Spurious Data

Except for the below specified, missing data will not be imputed.

12.5.1 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

12.5.2 Missing or Partially-Missing Date for Medication

If missing or partial dates do not allow for assignment of a medication/non-drug therapy as prior or concomitant (based on the definitions given in Section 5.4 and Section 5.5), then the medication/non-drug therapy will be considered concomitant. This imputation reflects a "worst-case" scenario.

12.5.3 Missing Severity Assessment for Adverse Events

If severity is missing for an AE (i.e. severity "unknown" in database), then the severity of the AE will be considered as "severe" for reporting purposes. This imputation reflects a "worst-case" scenario.

12.5.4 Missing Causality assessment for Adverse Events

Handling of unknown causality assessment:

- If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as "related"

12.5.5 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. For the quantitative laboratory measurements reported as "<X", i.e., BLQ, or ">X", i.e., ALQ are to be presented in listings as "<X" or ">X" and summarized in summaries as "X" in both cases.

12.5.6 Missing Pharmacokinetic data

For PK data, if any concentration data are considered spurious (e.g., sample processing errors that lead to inaccurate bioanalytical results), they will be excluded from the analysis, and the reason for exclusion from the analysis will be documented. The PK data and whether it should be excluded will be discussed during the analysis assignment meeting together with the analysis sets.

13. ANALYSIS SOFTWARE

All data processing, summarization, and analyses are to utilize the most recent version of SAS® software package available for IQIVA and TAKEDA team. If the use of other software is warranted the final clinical study report (CSR) is to detail what software was used.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The changes to the analysis specified in protocol version Amendment 15, dated 18 Nov 2021, are summarized below:

- The third exploratory efficacy outcome measure listed in the protocol version referenced above, incidence of TTP manifestations requiring supplemental dose treatment, cannot be analyzed as data were not captured in the EDC on

supplemental doses given for a TTP manifestation. No analyses or data summaries will be performed.

- The age subgroup categories were updated to include subjects age 12 and subjects aged >17 but <18 years into a subgroup as follows:

Protocol Specified Subgroup	SAP Updated Subgroup
0 to <6 years	<6 years
≥6 to <12 years	6 to <12 years
>12 to ≤17 years	12 to <18 years
≥18 years	≥18 years

- "Other TTP manifestations" reported by the site will be summarized for efficacy analysis.
- Add efficacy analysis based on SAF by actual treatment with the subject without confirmed cTTP diagnosis excluded.
- Laboratory and vital signs results will be summarized by study week instead of study visit due to differences in visit schedule by dosing regimen. Even though a visit may be classified as nominal visit 1, these may occur at different study weeks due to different frequency of study visits (i.e., subjects receiving weekly dosing have more frequent visits compared to subjects receiving every-other-week dosing). To assess the change over time appropriately, for data from prophylactic periods, week is derived using visit and TAK-755 dosing regimen.
- Data collected for S100B and NSE will not be included in analysis due to issues with the stability of samples and inconsistency with the assay used for testing, respectively.
- Results from biomarkers of organ damage, including cardiac troponin T (cTnT), cardiac troponin I (cTnI), and creatinine kinase myocardial band (CK-MB) will be listed instead of summarized in tables.

15. REFERENCES

Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated treatment satisfaction questionnaire for medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;7:36.

Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014;51(1):17-24.

Mansouri Taleghani M, von Krogh AS, Fujimura Y, et al. Hereditary thrombotic thrombocytopenic purpura and the hereditary TTP registry. Hamostaseologie. 2013;33(2):138-143.

16. APPENDICES

16.1 Sample SAS code

Clopper Pearson

The following SAS® code will be used to perform the Clopper-Pearson test:

```
PROC FREQ DATA = <data>;
 BY <variable>;
 WEIGHT <count>;
 TABLES <result> / binomial (exact cp) alpha = 0.05 cl;
RUN;
```

where:

<data> refer to the input dataset.

<variable> refer to the parameter or event by which the results are needed.

<count> refer to the number of subjects with the particular result.

<result> refer to the actual result, i.e., “Yes”, “No”.

Generalized Linear Mixed-effects Model

The following SAS® code will be used to perform the generalized Linear Mixed-effects analysis:

```
PROC GLIMMIX DATA = <data>;
 CLASS <treatment> <subject> <period> <sequence>;
 MODEL <event> = <treatment> <period> <sequence> / DIST = <dist> OFFSET = <log_OPE>
   LINK = LOG;
 RANDOM <subject>;
 LSMEANS <treatment> / BYLEVEL OM CL;
 ODS OUTPUT LSMEANS = <outdata>;
RUN;
```

where:

<data> refers to the input dataset.

<treatment> the particular treatment at time of event.

<period> the specific period at time of event.

<event> the number of events during the observation period.

<dist> the applicable distribution for the model, i.e., “NEGBIN”, “ID”.

<log_OPE> the logarithm of the OPEx in years, specific to each treatment arm, only add OFFSET if applicable.

Only add the LINK if applicable.

Kaplan-Meier

The following SAS® code will be used to perform the Kaplan-Meier analysis:

```
PROC LIFETEST DATA = <data>;
 STRATA <cohort> <treatment>;
 TIME <time>*STATUS(0);
 ODS OUTPUT LSMEANS = <outdata>;
RUN;
```


where:

<data> refers to the input dataset.

<cohort> the particular treatment cohort.

<treatment> the particular treatment arm.

<time> is the time in hours to resolution.

ANCOVA model

The SAS sample code below will be used to perform ANCOVA analysis:

```
PROC GLM DATA = <data>;
CLASS <treatment> (ref=”SoC”);
MODEL <aval> = <base>  <treatment> /solution;
LSMEANS <treatment>/ DIFF PDIFF TDIFF CL STDERR;
ODS OUTPUT LSMeans=LSMeans LSMeanDiffCL=LSMeanDiffCL;
RUN;
```

where

<data> is the input dataset;

<treatment> is the (planned) treatment of the period;

<aval> is the change from baseline or percentage change from baseline;

<base> is the period baseline;