STATISTICAL ANALYSIS PLAN

NCT Number: NCT03922308

Study Title: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-blind Study in Patients With Acquired Thrombotic Thrombocytopenic Purpura (aTTP) to Evaluate the Pharmacokinetics,Safety and Efficacy of rADAMTS-13 (SHP655) Administered in Addition to Standard Of Care (SoC) Treatment

Study Number: SHP655-201

SAP Version and Date:

Version Final : 06-JAN-2022

STATISTICAL ANALYSIS PLAN

SHP655-201 (rADAMTS-13)
PHASE 2

A Phase 2, multicenter, randomized, placebo-controlled, double blind study in patients with acquired thrombotic thrombocytopenic purpura (aTTP) to evaluate the pharmacokinetics, safety, and efficacy of rADAMTS-13 (SHP655) administered in addition to standard of care (SoC) treatment

PROTOCOL IDENTIFIER: SHP655-201

Study Sponsor(s): Takeda Development Center Americas, Inc. (TDC Americas)
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STATISTICAL ANALYSIS PLAN - SIGNATURE PAGE

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[redacted] January 14, 2022

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REVISION HISTORY

Version	Issue Date	Summary of Changes	Author
0.1	07 Feb 2020	New Document	[redacted]
0.2	19 Apr 2020	Development version	
0.3	14Oct2020	Final version *Note: This is the first filed version as considered approved for first use to handle analysis.*	
0.4	05 Oct 2021	• Updated as per the latest protocol amendment 4.0.	
1.0	06 Jan 2022	Added rescue medication Updated ADA and NDA classification in Section 7.2.1 Update censoring rules for "time to" variables	

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ABBREVIATIONS

AE	Adverse Event
ALQ	Above Limit of Quantitation
SHP655	rADAMTS-13
BMI	Body Mass Index
BLQ	Below Limit of Quantitation
CI	Confidence Interval
CTMS	Clinical Trials Management System
aTTP	Acquired Thrombotic Thrombocytopenic Purpura
DMC	Data Monitoring Committee
ENR	All Subjects Enrolled Set
[redacted]	[redacted]
GH	General Health
H	upper limit of the normal range
[redacted]	[redacted]
IA	Interim Analysis
IP	Investigational Product
IRT	Interactive Response Technology
IU	International Units
L	Lower limit of the normal range
LDH	Lactate dehydrogenase
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MOCA	Montreal Cognitive Assessment
[redacted]	[redacted]
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
[redacted]	[redacted]
PEX	Plasma Exchange
[redacted]	[redacted]
PK	Pharmacokinetic
[redacted]	[redacted]
RASS	Richmond Agitation Sedation Scale
[redacted]	[redacted]
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SD	Standard Deviation (Specify This Spelling, To Use "SD" Consistently Instead Of "STD")
SOC	Standard of Care
TEAE	Treatment Emergent Adverse Event
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper Limit of Normal
[redacted]	[redacted]
WHO-DD	World Health Organization-Drug Dictionary
[redacted]	[redacted]
VWF	Von Willebrand factor

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the planned presentation and analysis of efficacy, pharmacokinetic (PK)/ pharmacodynamic (PD), laboratory and other safety data for the final study protocols version 4.0, dated 2020 SEP17 (Global). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. While this SAP defines the outlines the PK analysis, the specifics of PK analysis are detailed in the Clinical Pharmacology Analysis Plan (CPAP).

All analysis and summaries as well as health economics and outcome research data, will be prepared and reported according to this SAP document except the population PK/PD modeling. The population PK/PD modeling will be conducted outside the SAP, a modeling report will be generated and provided with clinical study report.

The overall goal of this study is to assess ADAMTS-13 activity in aTTP subjects in the context of plasma exchange (PEX) treatment, supplementation with rADAMTS-13 and the presence of anti-ADAMTS-13 autoantibodies, all of which will acutely change plasma ADAMTS-13 activity. The relationship between recovery of ADAMTS-13 activity and improvement in clinical outcomes will be explored.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

2.1.1 Co-Primary Objectives

- Assess the PK of ADAMTS-13 in aTTP subjects treated for an acute episode by daily PEX, immunosuppressant therapy, with or without SHP655 supplementation
- Study the PK/PD relationship between ADAMTS-13 activity levels on pathophysiological biomarkers as well as clinical efficacy parameters

2.1.2 Secondary Objectives

2.1.2.1 PK/PD Objectives

- Evaluate changes in levels of ADAMTS-13 binding and inhibitory autoantibodies in response to daily PEX, with or without SHP655 supplementation, during the acute episode and up to 30 days after the resolution of the TTP episode
- Evaluate ADAMTS-13 activity levels in subjects up to 30 days after TTP episode remission

- Specify dose(s) of SHP655 needed to achieve and maintain adequate plasma levels of rADAMTS-13 in order to support induction of remission and to reduce the number of PEX procedures needed for the treatment of acute aTTP episodes

2.1.2.2 Safety/Efficacy Objectives

- Assess the safety and immunogenicity of two regimens of SHP655 supplementation administered during an acute TTP episode in subjects undergoing PEX treatment and immunosuppressant therapy as measured by AEs, changes in vital signs and laboratory parameters
- Evaluate the occurrences of aTTP related complications, (including death, stroke, MI, and organ failure) aTTP relapses*, exacerbations** and end-organ function improvement
- Evaluate the time to aTTP related complications (including death, stroke, MI, and organ failure), aTTP relapses*, exacerbations** and end-organ function improvement
- Evaluate the occurrence of procedure (e.g. PEX, SHP655 infusions) related adverse events

*Defined as >30 days after achieving remission

**Defined as ≤30 days after achieving remission

2.1.3 Exploratory Objectives

[redacted]

2.2 Estimands

There is no primary estimand relating to PK/PD or safety for this study due to the type of data being collected to support the primary objective.

The primary efficacy estimand, based on the secondary efficacy endpoint, that is likely to support regulatory decisions, is described in Table 1.

Table 1 List of Select Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary Efficacy	The primary efficacy estimand is based on the secondary efficacy endpoint, time to remission.	Adults (18-75 years old) with aTTP as defined through inclusion and exclusion criteria as stated in the protocol, who are experiencing an acute TTP event.	Time to remission, defined as platelet count ≥150,000/μL, confirmed by a second platelet count ≥150,000/μL and LDH <2 ULN 48 hours following initial normalization.	Subjects who drop out will be censored at their last visit date at which normalization assessments could not be determined. Subjects who complete the study will be censored at their study completion date at which normalization assessments could not be determined. Subjects receiving rescue medicine will be included as failure (no event) and will be right censored for the purpose of the KM survival curve estimate *.	KM survival curve and log rank test to compare the SoC to each IP arm.

* When developing estimands for the study, it was decided that using the intention to treat principal with focus on time to resolution of an acute event, regardless of use of rescue medication as an intercurrent event was not appropriate for analysis of this study due to the purpose of a subject needing this type of intercurrent event. It was decided that due to the need of administering rescue medication to resolve the event it would provide an unbiased estimate of the efficacy endpoint and therefore not used.

2.3 Endpoints

2.3.1 Primary Endpoints

1. PK: ADAMTS-13 activity levels
2. PD: Platelet count and LDH levels

2.3.2 Secondary Endpoints

2.3.2.1 Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) Endpoints

1. The PK/PD temporal relationship of safety and efficacy parameters (e.g., platelet count, LDH levels), as a function of ADAMTS-13 activity
2. The ADAMTS-13 binding and inhibitory autoantibody levels in response to daily PEX, with or without SHP655 supplementation, during the acute TTP episode and up to 30 days after resolution
3. ADAMTS-13 activity levels in subjects receiving additional SHP655 for up to 30 days after the resolution of the TTP episode
4. The relationship between ADAMTS-13 activity and end-organ disease status (e.g., renal, neurologic, and cardiac)
5. PK parameters such as incremental recovery, area under the curve, systemic and antibody induced clearance, maximum ADAMTS-13 activity between PEX or SHP 655 infusions, and trough levels prior PEX
6. Occurrence of ADAMTS-13 activity trough levels >10%

2.3.2.2 Safety and efficacy

1. Time to normalization of platelet count, defined as platelet count ≥ 150,000/μL, which must be confirmed by a second normal platelet count ≥ 150,000/μL and LDH <2 ULN48 hours following initial normalization
2. Occurrence of remission, defined as a normal platelet count and LDH <2 ULN for at least 48 hours following initial normalization of platelet count (acute episode period)
3. Time to first exacerbation (aTTP episode ≤30days following remission)
4. Time to relapse (aTTP episode >30 days following remission)
5. Occurrence of exacerbation
6. Occurrence of relapse
7. Occurrence of major clinical events related to TTP including:

a. Death
b. Stroke
c. MI
d. Organ dysfunction not normalized within the 90-day observation period
   i. Chronic renal insufficiency
   ii. Neurologic impairment
   iii. Neurocognitive deficits

8. Incidence of major clinical events related to PEX, including clinically relevant bleeding (modified ITP score) or thrombosis at the site of line insertion, adverse reactions to plasma, including citrate reactions, allergic reactions, and TRALI
9. Changes in the titer of binding and inhibitory antibodies to ADAMTS-13 relative to baseline.
10. Occurrence of antibodies to SHP655
11. Occurrence of AEs and SAEs, and specifically product-related AEs and SAEs
12. Clinically relevant changes in vital signs, clinical chemistry, and hematology
13. Occurrence of subjects receiving rescue therapy
14. Occurrence of subjects meeting rescue criteria

2.3.2.3 Exploratory outcomes

[redacted]

2.3.2.4 [redacted]

[redacted]

3. STUDY DESIGN

3.1 General Description

This is a randomized, parallel, placebo-controlled, double-blind Phase 2 study. Approximately 30 evaluable subjects between the ages of 18 to 75 years experiencing an acute TTP episode will receive a single PEX and be randomized 1:1:1 into one of three treatment arms:

- Arm 1 – SoC plus placebo (n=10) Subjects will receive daily PEX and placebo immediately after PEX and 12±1 hour after completion of PEX.
- Arm 2 – SoC with SHP655 once daily (n=10) Subjects will receive daily PEX and 40 IU/kg ±4 IU/kg SHP655 once daily immediately after PEX and placebo 12±1 hour after completion of PEX.
- Arm 3 – SoC with SHP655 twice daily (n=10) Subjects will receive daily plasma exchange and 40 IU/kg ±4 IU/kg SHP655 twice daily immediately after PEX and 12±1 hour after completion of PEX.

The first PEX and IP may be administered in three scenarios:

- First PEX completed >4 hours prior to study enrollment: the first dose of IP should be administered immediately after the second PEX (first PEX completed on study)
- First PEX completed ⩽4 hours prior to study enrollment: the first dose of IP should be administered as soon as possible, but no more than 4 hours after the initial PEX

- First PEX delayed and randomization into study is complete: subject may receive a dose of IP prior to initiation of PEX, provided post-infusion PK samples according to Table 2 in Protocol are anticipated to be drawn. PEX initiation should never be delayed in order to complete study enrollment or study procedures.

An immunosuppressive regimen consists of methylprednisolone and rituximab: 1 g methylprednisolone iv once daily for 3 consecutive days, followed by 2.5 mg/kg/day; and 375 mg/m2 rituximab administered weekly for 4 weeks will be initiated within 2 days of enrollment for all subjects. Steroid tapering is permitted at the discretion of the investigator. Additional or modified immunosuppressive therapy can be considered in exceptional circumstances after consultation with the sponsor.

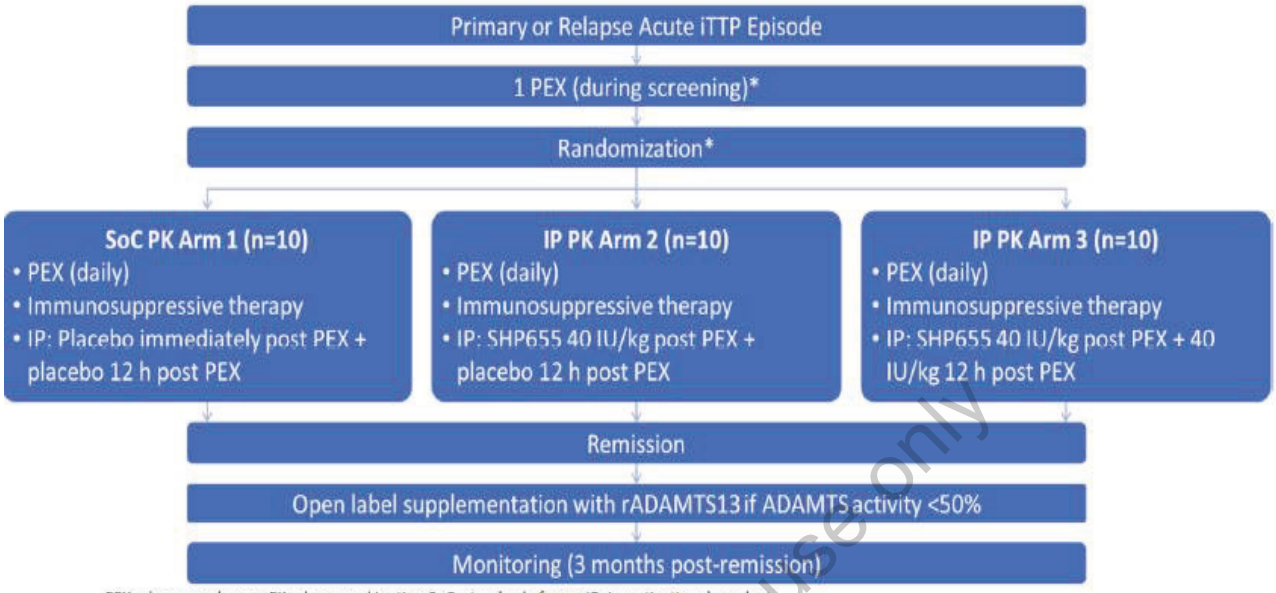
In all study Arms, the second daily IP dose (12 hours after PEX) will be terminated if the most recently resulted pre-PEX ADAMTS-13 activity level is >150% or above the limit of quantification (local lab). After the second dose has been suspended, the first daily IP dose (immediately after PEX) will be terminated if the most recently resulted pre-PEX ADAMTS-13 activity level is>150% or above the limit of quantification (local lab).

In all study Arms, planned modifications to the plasma volume treated with each PEX (e.g. 1.5 or 2 plasma volumes) or the frequency of PEX (e.g. BID or every other day) require sponsor approval. Changes in PEX treatment due to logistical or emergent issues (e.g. venous access problems, AEs leading to PEX discontinuation) do not require sponsor approval but must be documented.

Prior to protocol amendment 4, after resolution of the TTP episode, IP (placebo in Arm 1; SHP655 40 IU/kg ±4 IU/kg Arms 2 and 3) will be administered once weekly (maximum of 4 weekly doses of 40 IU/kg) if ADAMTS-13activity at the local lab is <50%. Activity must be measured at least once weekly and >72h after the last IP dose.

Post protocol amendment 4, after confirmed remission of the TTP episode, subjects will be given additional open-label IP (SHP655 40 IU/kg ±4 IU/kg) if ADAMTS-13 activity at the local lab is <50%. ADAMTS13 activity should be monitored Q3 Day ±1 days for 2 weeks and Q1Week ±3 days for 2 additional weeks. The overall study design is illustrated in Figure1.

Figure 1 Study Design



PEX, plasma exchange; PK, pharmacokinetics; SoC, standard of care; IP, investigational product.

*IP dosing (placebo [Arm 1] or SHP655 40 IU/kg [Arms 2 and 3]) may occur prior to the first PEX if enrollment and randomization are complete prior to the first PEX.
Shire Data on File.

3.2 Randomization

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

After screening, individual subject treatment is automatically assigned by the interactive response technology (IRT) to 1 of 3 arms. In the event enrollment in an arm is full, subjects will be randomly assigned to the remaining arm(s).

Subjects will independently be randomized to PK sampling schedule A or B, which differ in the sampling days starting with PEX#4 and thereafter.

Subjects with platelet count >50,000/µL will not be eligible for randomization to an arm already having 3 evaluable subjects with screening platelet count >50,000/µL.

3.3 Blinding

This is a double blinded study.

Double blind administration of placebo or SHP655 is given twice daily in all arms until remission is achieved. Prior to protocol amendment 4, the supplementation with placebo or SHP655 after remission was blinded. After the amendment, the supplementation after remission is open label.

3.4 Sample Size and Power Considerations

The sample size for this study is not based on a power calculation. It is a Phase 2 study with PK modeling as one of the primary objectives and is being conducted in aTTP subjects which is a rare condition.

The sample size of 10 subjects per treatment arm is selected to provide sufficient PK/PD data to develop the two models outlined in the co-primary objectives.

4. STATISTICAL ANALYSIS SETS

Analysis set identification will be established and approved ahead of database lock or any intermediate interim analyses that are planned for submission.

4.1 Screened Set (SCR)

The screened set will consist of all subjects who have signed an informed consent document.

4.2 Randomized Set (RAND)

The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.

For analysis, information on randomization, such as date of randomization will be pulled from the eCRF and treatment assignment will be pulled directly from the IRT randomization file. Handling of unblinded data is discussed in the Biostatistics unblinding plan.

4.3 Safety Analysis Set

4.3.1 Safety Analysis Set (SAS)

The safety analysis set will consist of all subjects randomized, who receive any dose of investigational product.

All safety analyses will be performed according to the treatment regimen actually received regardless of the randomized treatment regimen.

4.3.2 aTTP Safety Analysis Set (aTTP-SAS)

The aTTP safety analysis set will consist of all subjects in the safety analysis set with a confirmed aTTP diagnosis. Subjects provisionally randomized, and subsequently diagnosed with a condition different from aTTP, will not be included in this analysis set.

No supplemental analyses are planned for this analysis set.

4.4 Full Analysis Set (FAS)

The full analysis set will include all enrolled subjects with confirmed aTTP diagnosis who are treated with a study product and have an ADAMTS-13 activity reading from at least one post infusion sample. Analysis will be performed according to allocated treatment regimen regardless of the treatment regimen actually received.

4.5 Per-protocol Analysis Set (PP)

The per-protocol set will consist of all subjects in the full analysis set who do not have protocol deviations that may affect the efficacy endpoints. 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. Potential protocol deviations will be identified to be included into the CTMS upon team agreement.

Prior to study unblinding, a meeting will be held to assess the impact on efficacy outcomes of the protocol deviations identified throughout the conduct of the study. A major/important/critical deviation from CTMS will not necessarily influence the study results and will therefore not necessarily lead to exclusion from the Per Protocol analysis set. At this meeting the decision will be made on whether a subject will be excluded from the Per Protocol analysis set or not. The meeting will be attended by participants from Data Management,

Biostatistics Clinical Development (including medical monitors/advisors). Team members from both IQVIA and the sponsor will attend.

As part of blind data review prior to database lock, study medics may identify further events that exclude subjects from analysis. Such events will either be documented in the CTMS tracker if appropriate to conduct of the study or flagged through programming. As discussed above, assessment will be made to their impact on leading to exclusion from the analysis set or not.

Analysis will be performed according to the treatment regimen received.

4.5.1 COVID-19 Impact Assessment

In reaction to the COVID-19 pandemic, deviations listed in the CTMS tracker with prefix "COVID-19" will be considered separately as part of the subject selection for exclusion from the per-protocol analysis set. The impact to this study is likely minimal since the study was not put on enrollment hold. The acute event the enrolled subjects are experiencing requires hospitalization which assures that protocol procedures will be followed for the duration. No additional measures are anticipated to compensate for missing data. Supportive analyses are detailed in section 5.10. Additionally, during the blind data review meeting, if the rate of protocol deviations recorded as an impact of COVID-19 is higher than anticipated, analyses described in section 6, may be repeated and an additional COVID-19 per-protocol analysis set may be developed as part of a sensitivity analysis.

4.6 Pharmacokinetic Set (PK)

The Pharmacokinetic set will consist of all enrolled subjects with confirmed aTTP diagnosis who have received at least 1 dose of investigational product and who have at least 1 evaluable post-dose PK value (ADAMTS-13 antigen and ADAMTS-13 activity). The PK data may be excluded from the summaries on the affected days 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, rescue treatment).

Samples from subjects receiving rescue medicine will be excluded from the primary and secondary endpoint analysis after the rescue medicine is initiated. For pharmacokinetic modeling, all available PK data may be considered. For further details, refer to the separate Modeling and Simulation Plan.

4.7 Pharmacodynamic Analysis Set (PD)

The pharmacodynamic (PD) set will consist of all enrolled subjects with confirmed aTTP diagnosis who have received at least 1dose of investigational product and who have at least 1 evaluable post-dose PD value; this includes LDH and platelets results. Samples from subjects receiving rescue medicine will be excluded from the primary and secondary endpoint analysis

after the rescue medicine is initiated. For PK/PD modeling, all available PD data may be considered.

Subjects in this population will be included for all PD summaries. All PD analyses will be performed according to the treatment received regardless of the randomized treatment regimen.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Disposition of subjects will be presented for the Screened analysis set in the planned listings and the table summaries.

The number of subjects included in each analysis set (i.e., Randomized, Safety, aTTP safety, Full, PK, PD and Per Protocol Set) will be summarized by treatment arm and overall. The Screened Set will be summarized only overall.

Additionally, the number and percentage of subjects who completed or prematurely discontinued during the study will be presented for treatment arm. Reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment as a subset of the subjects who prematurely discontinued the study. Percentages for withdrawal are based on the number of subjects who prematurely withdraw from the study.

The number of subjects screened, randomized and completed will be tabulated by site and country. 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).

Additionally, the presentation of planned listings will include the following:

- Screen Failures (i.e., subjects who were screened but not randomized) including reasons for screen fail and details of any AEs.
- Subject disposition.
- Prior subject participation.
- Inclusion/Exclusion criterion exceptions.
- Assignment to analysis sets.
- All subjects who prematurely discontinued during the study.

5.2 Demographic and Other Baseline Characteristics

Demographic data and other Baseline characteristics will be presented by treatment arm and overall for the Safety Analysis Set and the Full Analysis Set.

No statistical testing will be performed for demographic or other Baseline characteristics.

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

The following demographic characteristics will be summarized in the following order in the tables: age (years), sex, ethnicity, race, weight (kg), height (cm), and BMI (kg/m^2). In addition, baseline creatinine clearance will be summarized for the purpose of capturing kidney manifestations.

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

Subjects may fall under multiple race categories, if this occurs i.e. more than one race is selected on the eCRF, they will be counted in each.

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:

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

Creatinine Clearance derivations are described in section 6.5.2.1.

5.3 Medical History

Medical history will be collected at the screening/ enrollment visit and will be coded using MedDRA Version 24.0, as documented by Data Management in the *Data Coding guideline* at the time of performing the analysis. They will be listed for the Safety Analysis Set.

The medical history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment arm and overall for the Safety Analysis Set.

5.4 Prior Medications, Therapies, Procedures and Non-Drug Therapies

Prior medications will be coded using 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. Prior therapies and procedures will be coded using MedDRA Version 24.0.

Prior medications, therapies or procedures are defined as any medication, therapy or procedure with both a start date and a stop date prior to the date of the first dose of investigational product. Missing and partial dates will be handled as described in section 12.5.4.

The prior therapies, procedures and medication usage will be summarized by the number and proportion of subjects in each treatment arm and in overall subjects within each preferred term for the Safety Analysis Set. Multiple medication usage by a subject in the same category will be counted only once.

All prior therapies, procedures and medication will be listed for the Safety Set. Listings will report the data as captured in the database and not make use of imputations as set out in section 12.5.4.

5.5 Concomitant Medications, Therapies, Procedures and Non-Drug Therapies

Concomitant medications will be coded using 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.

Concomitant medication/Non-Drug Therapy/procedure is defined as any medication/ Non-Drug Therapy/procedure 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 (including follow up treatment), inclusive.

Any medication/ Non-Drug Therapy/procedure with a start date after the date of the last dose of investigational product (including follow up treatment) is not be considered a concomitant medication/ Non-Drug Therapy/procedure.

The concomitant therapies, procedure and medication usage will be summarized by the number and proportion of subjects in each treatment arm receiving each medication and in overall subjects within each preferred term for the Safety Analysis Set. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant therapies, procedures and medication will be listed for the Safety Analysis Set. Listings will report the data as captured in the database and not make use of imputations as set out in section 12.5.4.

Immunosuppressive daily treatments will not be captured within the concomitant medications eCRF page. Presence of Methylprednisolone, Prednisone, Prednisolone, Rituximab or other approved treatment for this purpose will not be programmatically checked but as part of data review will be monitored.

5.6 Immunosuppressive Therapies

An immunosuppressive regimen consists of methylprednisolone and rituximab:1 g methylprednisolone iv once daily for 3 consecutive days, followed by 2.5 mg/kg/day; and 375 mg/m2 rituximab administered weekly for 4 weeks will be initiated within 2 days of enrollment for all subjects. Steroid tapering is permitted at the discretion of the investigator. Additional or modified immunosuppressive therapy can be considered in exceptional circumstances after consultation with the sponsor.

Corticosteroids will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

All Immunosuppressive therapies will be summarized by the number and proportion of subjects in each treatment arm and in overall subjects within each category and preferred term (for Corticosteroids) for the Safety Analysis Set, separating by daily treatment period (collected on Immunosuppression Daily Treatment Period eCRF page), follow up (collected on Immunosuppression Follow Up Visits eCRF page) and overall. Multiple treatment usage by a subject in the same category will be counted only once.

All Immunosuppressive therapies will be listed for the Safety Analysis Set.

5.7 Exposure to Investigational Product

Exposure to investigational product will be summarized for the Safety Analysis Set by treatment arm and a listing will be presented by subject number giving administration details. Dose modifications made as a result of a TTP episode will be captured within this listing.

Potency of ADAMTS13 activity in the SHP655 dosing solution will be used to derive the actual dose as follows:

$$\text{Actual dose (IU/kg)} = [\text{FRETS (IU/mL)} \times \text{actual dose volume (mL)}] / \text{Baseline body weight (kg)}$$

Exposure to investigational product will be summarized by quantity, total number of doses and duration on treatment, defined as the sum of durations (stop date/time minus start date/time, in minutes) of all the infusions administered, accounting for interruptions, for Safety Analysis Set by treatment arm and by acute period (with reason for administration as "Acute treatment" as collected on eCRF page), post-remission period (with reason for administration as "Post-remission supplementation" as collected on eCRF page), and overall study. Actual dose will be listed and summarized.

The number and percentage of subjects having an incidence of dose modifications (their second daily IP dose terminated) prompted by a TTP event, including a 95% confidence interval for

each of the proportions, will be summarized by treatment arm. The 95% confidence interval will be obtained from an exact Clopper-Pearson test in SAS®.

5.8 Exposure to PEX

[redacted]. PEX will be assigned to the period using the following logic:

- For subjects who experience exacerbation, PEX with start date before exacerbation date will be considered as acute period; PEX with start date on or after exacerbation date will be considered as follow up period.
- For subject without exacerbation, all PEX will be considered as acute period.

A listing will be created by subject number and visit giving the date and time of PEX administration details, anticoagulant details, as well as volumes and types of replacement fluid(s) exchanged and blood losses.

5.9 Measurements of Treatment Compliance

Treatment compliance is not applicable for this protocol.

A listing will be produced to display a subject planned treatment and actual treatment what they have received.

5.10 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database. It will be obtained from the CTMS. The CRO/ sponsor will classify major and minor protocol deviations per the agreed protocol deviation management plan. The Takeda study team will review the protocol deviations and their classification throughout the study and before treatment unblinding and database lock.

Decisions of the review will include accuracy of major and minor protocol deviations categorization.

Confirmed major and minor protocol deviations will be documented in the Protocol Deviation tracker for the study. Major/minor protocol deviations will be summarized by category and site for each treatment arm (SHP655 and Placebo) and overall. Major/minor protocol deviations will be listed. Reporting of protocol deviations will be based on the randomized Set.

COVID-19 related deviations will be summarized and listed in the same handling as described above.

5.11 COVID-19 Vaccination Follow Up

A listing will be created by subject number for COVID-19 vaccination follow up, as well as date of contact and method of contact.

6. EFFICACY ANALYSES

All efficacy analyses will be presented by treatment arm for the Full Analysis Set and then repeated on the Per-Protocol Analysis Set. Listings will be presented only on the Full Analysis Set.

Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product (IP) (SHP655 or placebo) (based on dates or date/times), regardless of PEX administration timing. When time is not available, assessment occurring on the same day as the first dose are assumed to be pre-dose. It should be noted that due to the study design and entry of patients into the emergency room, Screening/ Enrollment visit may occur on the same day as the start of the treatment period, meaning scheduled assessments will not need to be duplicated. Any assessments taken on the day of treatment period start can be assumed to be prior to administration of IP.

No formal statistical testing is planned for this study. and no significant tests are planned. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

6.1 Analyses of Primary Efficacy Endpoint

Details of the primary endpoints, platelet counts and LDH levels, are discussed in the PK (section 8) and PD (section 9) analysis sections for both assessment of PK profiles of ADAMTS-13 and PK/PD relationships between ADAMTS-13 activity levels and pathophysiological biomarkers as well as clinical efficacy parameters.

6.2 Analyses of Secondary Efficacy Endpoints

All time to event efficacy endpoints will be analyzed by the non-parametric Kaplan Meier (KM) estimator of the survival curve and by use of hazard ratios for SHP655 against Placebo arms. Estimates of the median time to event as well as proportions of subjects with event will be derived, together with two-sided, 95% confidence intervals. Graphical presentations of Kaplan-Meier plot will be presented. Details on censoring is discussed in subsequent sections.

Occurrence endpoints will be assessed as proportions and two-sided 95% CI for the proportions will be derived by exact Clopper-Pearson test in SAS®.

Occurrence rates will include a Poisson CI using a normal approximation (estimate lambda from event proportion, using follow-up days as a time unit)

$$\lambda = \#\text{events/person-days}$$

95% CI :

$$[\lambda - 1.96 * \sqrt{(\frac{\lambda}{\text{persondays}})}, \quad \lambda + 1.96 * \sqrt{\left(\frac{\lambda}{\text{persondays}}\right)}]$$

6.2.1 Assessment of Remission

Time to normalization of platelet count is defined as platelet count ≥ 150,000/μL, which must be confirmed by a second normal platelet count ≥ 150,000/μL and LDH <2 ULN 48 hours following initial normalization. An event of this type is identified by the investigator and captured in the eCRF as date of remission. A subject's time to normalization of platelet counts will be censored at the day they take rescue therapy for those who do not adequately respond to treatment and take rescue medication or for those who respond to treatment after they receive rescue medication. Subjects who do not adequately respond to treatment and do not complete the study will be censored at the last available visit date. And subjects who do not adequately respond to treatment and complete the study will be censored at the date of study completion.

Occurrence of remission is defined as a normal platelet count and LDH <2 ULN for at least 48 hours following initial normalization of platelet count (acute episode period). An event of this type is identified as the date of visit to which remission is recorded.

6.2.1.1 Platelet and LDH Recovery

Additional to *assessment of remission,* which is analyzed based on the site entered response to remission on platelet counts and LDH. Time to platelet recovery and time to LDH recovery will be individually analyzed based on post IP administration laboratory reported results. Platelet recovery is defined as the first recovery of platelet count ≥ 150,000/μL. LDH recovery is defined as the first recovery of LDH <2 ULN. A subject's time to platelet recovery and time to LDH recovery will be censored at the day they take rescue therapy for those who do not experience the event and take rescue medication or for those who experience the event after they receive rescue medication. Subjects who do not experience the event and do not complete the study will be censored at the last available visit date. And subjects who do not experience the event and complete the study will be censored at the date of study completion.

6.2.1.2 Clinically Relevant Bleeding

Modified Immune Thrombocytopenic Purpura (ITP) scores, per body system, are collected until remission of the acute event is achieved. Occurrence of ITP bleeding scores will be summarized over time by body system and treatment group. Individual scoring will be listed.

6.2.1.3 PEX administration

Time to the stopping of PEX administration will be analyzed to gain an understanding of how consistently PEX use is being stopped compared to that of remission. An event of this type is

identified by the last known administration date of PEX. Subjects who do not experience the event and do not complete the study will be censored at the last available visit date. And subjects who do not experience the event and complete the study will be censored at the date of study completion**.**

Incidence of PEX related events, including thrombosis at the site of line insertion, adverse reactions to plasma, including citrate reactions, allergic reactions, and TRALI will be summarized during the acute period, during the follow up period and for the study overall. Refer to Section 5.8 for the derivation of period for PEX administration

6.2.2 Exacerbation and Relapse

Time to first exacerbation (aTTP episode ≤30 days following remission) and time to first relapse (aTTP episode >30 days following remission) endpoints will be counted from the date of remission. If a subject experiences multiple exacerbations/relapses during their time on the study, for the purposes of this analysis they will only be considered at their earliest exacerbation/ relapse, i.e. if a subject relapse's having already experienced an exacerbation, they will only be counted in their earliest (first) exacerbation. Subjects who do not experience the event and do not complete the study will be censored at the last available visit date. And subjects who do not experience the event and complete the study will be censored at the date of study completion.

The occurrence of relapse/exacerbations and the time to relapse/exacerbation will be summarized separately by subjects enrolled before or after Protocol Amendment 4.0.

6.2.3 aTTP related complications

The occurrence of an aTTP related complications including death, stroke, myocardial infarction (MI) and organ dysfunction will be assessed from the time a subject is first administered treatment.

Death in the context of an aTTP related complication will be determined as any AE where 'Serious Reason(s)' is captured as 'Death'.

All AEs will be coded, as discussed in section 7.1 and prior to database lock/ any interim reporting, a review of the adverse event form will occur at which point identification of AEs will be assessed by the study medics to classify terminology associated with stroke and MI.

6.2.4 End-Organ Function Improvement

Organ dysfunction definitions are described in section 6.5.2. Individually, chronic renal insufficiency, neurologic impairment and neurocognitive deficits will be assessed as the number of subjects not reaching normalization within the 90-day observation period.

6.2.5 Rescue Medication

The number and percentage of subjects who met rescue medication criteria will be tabulated by treatment arm and reason for initiating rescue medication.

The number and percentage of subjects who received rescue medication will be tabulated by treatment arm and preferred term.

Rescue medications will be listed.

6.2.6 Sensitivity Analyses of Secondary Efficacy Endpoint(s)

As part of a sensitivity analysis on the secondary efficacy endpoints, reporting of time to remission will be repeated, accounting for the use of rescue medication, where applicable. For subjects where rescue therapy is initiated and the administration of IP (SHP655 or placebo) is suspended, subjects will not be censored and instead followed to remission for the purpose of analysis. Subjects who do not adequately respond to treatment and do not complete the study will be censored at the last available visit date. And subjects who do not adequately respond to treatment and complete the study will be censored at the date of study completion.

6.3 Multiplicity Adjustment

Not applicable.

6.4 Control of Type I Error

Not applicable

6.5 Analyses of Exploratory Endpoints

[redacted]

6.5.1 [redacted]

[redacted]

6.5.2 [redacted]

6.5.2.1 [redacted]

[redacted]

[redacted]

6.5.2.2 [redacted]

[redacted]

6.5.2.3 [redacted]

[redacted]

6.5.2.4 [redacted]

[redacted]

6.5.2.5 [redacted]

[redacted]

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Set. Listings will be presented only on the Safety Analysis Set. Safety variables include AEs, clinical laboratory variables, and vital signs. 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. Listings will be presented only on the Safety Analysis Set.

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

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 24.0.

An AE (classified by preferred term) that occurs during the Double-blind Evaluation Phase will be considered a TEAE if it has a start date on or after the first dose of double-blind investigational product or if it has a start date before the date of the first dose of double-blind investigational product but increases in severity on or after the date of the first dose of double-blind investigational product. If more than 1 AE with the same preferred term is reported before the date of the first dose of double-blind investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the Double-blind Evaluation Phase under the preferred term. All AEs reported in the database will be used for analysis.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs within each of the following categories will be presented:

- All TEAEs.
- Severe TEAEs.
- TEAEs related to IP.
- TEAEs not related to IP.
- TEAEs related to study procedure.

- Serious TEAEs.
- TEAEs leading to discontinuation of study.
- TEAEs leading to discontinuation/interruption of IP.
- TEAEs leading to death.
- Serious TEAEs related to IP.

The overall summary will include the number and percentage of subjects having an TEAE by category.

The number and percentage of subjects reporting TEAEs, as well as the number of events, in each treatment arm and overall will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and maximum severity. TEAEs considered related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

TEAEs and related TEAEs will be summarized by preferred term by descending frequency. Serious TEAEs, TEAEs leading to discontinuation of investigational product and serious TEAEs leading to death, will be summarized by SOC, preferred term and treatment arm.

All AEs for each subject, including "was this AE a COVID-19 vaccination related complication?" information, will be listed for the Safety Analysis Set.

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

- Handling of unknown causality and unknown severity grades are described in Section 12.5.
- 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

Descriptive statistics for clinical laboratory values (in SI units or conventional units depending on the study) and changes from baseline at each assessment time point as well as shift tables

from baseline to each visit for quantitative variables will be presented by treatment arm and overall for clinical laboratory variables. All laboratory results will be summarized by treatment arm. Serum pregnancy tests will only be listed.

Results from the central laboratory, bioanalytical specialty laboratories and local laboratories will be included in the reporting for this study. Results will be presented using CDISC compliant terms and standard international (SI) units. Conversion factors to standardize results to SI units will be developed and maintained for sign off prior to database lock.

The hematology panel is performed locally and consists of complete blood count [hemoglobin, hematocrit, erythrocytes (i.e., red blood cell count), and leukocytes (i.e., white blood cell count)] with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.

The clinical chemistry panel is performed locally and consists of ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose. LDH samples are collected separately to chemistry testing, tested locally.

Other laboratory assessments include, ADAMTS-13 Gene mutation (central), blood type testing is (local), HIV1/2, HBV, HCV (central). ADAMTS-13 Activity is performed locally prior to IP, confirmed by the bioanalytical lab alongside the ADAMTS-13 Antigen testing. Anti-rADAMTS-13 binding and inhibitory antibodies, including Anti-rADAMTS-13 binding total Ig, Anti-ADAMTS-13 inhibitory Ab, Anti-rADAMTS-13 inhibitory Ab are analyzed at the bioanalytical lab. VWF antigen and multimers (central) and pregnancy test: serum (local).

[redacted]

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.

Central and local laboratory results for all parameters (planned or unplanned) will be listed for the Safety Analysis Set, including separate listings for abnormal and clinically significant results.

7.2.1 Immunogenicity

Summaries of both anti-drug antibodies (ADA) including rADAMTS-13 binding total Ig (Evaluation and Titers) and neutralizing antibodies (NAb), endogenous (Anti-ADAMTS13 inhibitory antibody) and exogenous (Anti-rADAMTS13 inhibitory antibody) will be presented as a count based on detection of each antibody type by subject at both baseline and post baseline. These will be also assessed by acute period and a follow up period. Acute period and follow up period for ADA and Nab summary as classified as below:

- Acute period: assessment occurred from the first to last doses of investigational product for acute treatment, inclusive.
- Follow up period: assessments occurred from the date of last dose of investigational product for acute treatment, exclusive, to date of last dose of investigational product (including follow up treatment), inclusive.

Where multiple assessments are collected at any given timepoint, if there is at least one positive identification this will be used for analyses.

Each subjects ADA and NAb endogenous profiles will be categorized and summary counts will be presented by the following terms: persistent positive and transient positive.

A subject's profile on ADA or Nab endogenous results is thought to be transient positive if the subject is seen to have positive detection of the given antibody post administration of IP that later becomes negative by the time of study completion, regardless of the baseline assessment result and any in-between assessment results.

A subject's profile on ADA or Nab endogenous is thought to be persistent positive if the subject is seen to have a positive detection of the given antibody post administration of IP that is maintained through to the time of study completion, regardless of the baseline assessment result and any in-between assessment results. If the only positive detection is their end of study visit assessment this is also deemed persistent positive.

For Nab exogenous, the following categories are defined based on Baseline (Screening) and post-dose (End of Study [EOS]) values:

Persistent negative: negative at both Baseline/Screening and post-dose/EOS

Persistent positive: positive at both Baseline/Screening and post-dose/EOS

Baseline positive only: positive at Baseline/Screening and negative post-dose/EOS

Missing: missing at Baseline/Screening, or post-dose/EOS, or both.

Additionally, in order to assess the effect of ADA and NAb on primary efficacy endpoints, summary counts on ADA and NAb status at the time of remission, exacerbation and relapse will be presented. As well as summary counts of ADA and NAb titer values over time.

Since some patients might have unscheduled plasma exchange before their screening assay, all of the aforementioned summaries will be repeated on a subset of subjects that did not administer PEX prior to their screening assessment in order to see if there is an immediate change in antibody detection as a result of taking PEX.

Multiple figures will be produced, these include:

- Subject profile plot of ADAMTS-13 activity over time, by ADA status at baseline.
- Subject profile plot of ADAMTS-13 antigen results over time, by ADA status at baseline.
- Subject profile plot of ADAMTS-13 activity over time, by NAb status at baseline.
- Subject profile plot of ADAMTS-13 antigen results over time, by NAb status at baseline
- Subject profile plot of ADA titer results over time.
- Subject profile plot of NAb titer results over time.

Separate to the listing produced as part of the laboratory reporting as described in section 7.2 ADA evaluations and titers and NAb concentrations will be listed with identification of is the ADA and NAb profiles are treatment induced and or treatment boosted.

7.3 Vital Signs

Descriptive Summary statistics for vital sign (e.g., systolic and diastolic blood pressure, pulse rate and body weight) and their changes from baseline at each post-baseline visit and at the end of study will be presented by treatment arm and overall.

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:

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

Weight and height will be converted as specified in Section 5.2.

All vital signs data will be listed for the Safety Analysis Set.

8. PHARMACOKINETIC ANALYSIS

The pharmacokinetic analysis will be conducted by the pharmacokinetics CRO (IQVIA Pharmacokineticist) for Clinical Pharmacology and Pharmacokinetics Department of Takeda.

The methodology for the PK analysis is described in the Clinical Pharmacology Analysis Plan (CPAP).

8.1 Statistical Analysis of Pharmacokinetic Data

Only descriptive statistical analysis will be done as detailed in the CPAP.

Drug Concentration

A listing of PK blood sample collection times, derived sampling time deviations, and levels of ADAMTS-13 activity and ADAMTS-13:Ag in original units reported by the bio-analytical laboratory and converted units, and change-from-baseline concentrations will be provided.

Individual PK observed levels of ADAMTS-13 activity and ADAMTS-13:Ag in converted units and change-from-baseline values will be summarized and presented graphically.

Pharmacokinetic Parameters

Individual PK parameters of ADAMTS-13 activity and ADAMTS-13:Ag will be listed and summarized, and presented graphically.

The categories for PK parameters summarized by status for ADA (binding total Ig) and for NAb (endogenous [Anti-ADAMTS13 inhibitory antibody] and exogenous [Anti-rADAMTS13 inhibitory antibody]) are defined as follows.

For ADA and Nab endogenous, the status will be considered as positive if at least one result measured on the corresponding study day is positive; otherwise, the status will be considered as negative for that study day.

9. PHARMACODYNAMIC ANALYSIS

9.1 Pharmacodynamic Data

9.1.1 Primary Pharmacodynamic Endpoint and Analysis

9.1.1.1 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

PK/PD relationships between ADAMTS-13 activity levels and pathophysiological biomarkers as well as clinical efficacy parameters will be explored through graphical displays. By use of scatter plots, individual subject ADAMTS-13 activity levels will be plotted against Platelet count and LDH levels over time differentiated by treatment group.

Additionally, further analysis of PD data including modelling and relationships will be performed as set out in the Modelling and Simulation Plan. Secondary Pharmacodynamic Endpoints and Analysis

The relationship between ADAMTS-13 activity and end-organ disease status (e.g., renal, neurologic, and cardiac) will be assessed graphically. By use of scatter plots and trend lines,

individual subject and central tendencies (mean, median) of ADAMTS-13 activity levels will be plotted against Creatinine Clearance levels, RASS scores and MoCA scores over time differentiated by treatment group. All three endpoints derivations are to be calculated as described in section 6.5.2**.**

10. OTHER ANALYSES

10.1 [redacted]

[redacted]

10.1.1 [redacted])

10.1.1.1 [redacted]

[redacted]

[redacted]

10.1.1.2 [redacted]

[redacted]

10.1.1.3 [redacted]

[redacted]

10.1.1.4 [redacted]

[redacted]

[redacted]

10.1.1.5 [redacted]

[redacted]

10.1.1.6 [redacted]

[redacted]

[redacted]

10.1.1.7 [redacted]

[redacted]

10.1.1.8 [redacted]

[redacted]

10.1.1.9 [redacted]

[redacted]

10.2 [redacted]

[redacted]

[redacted]

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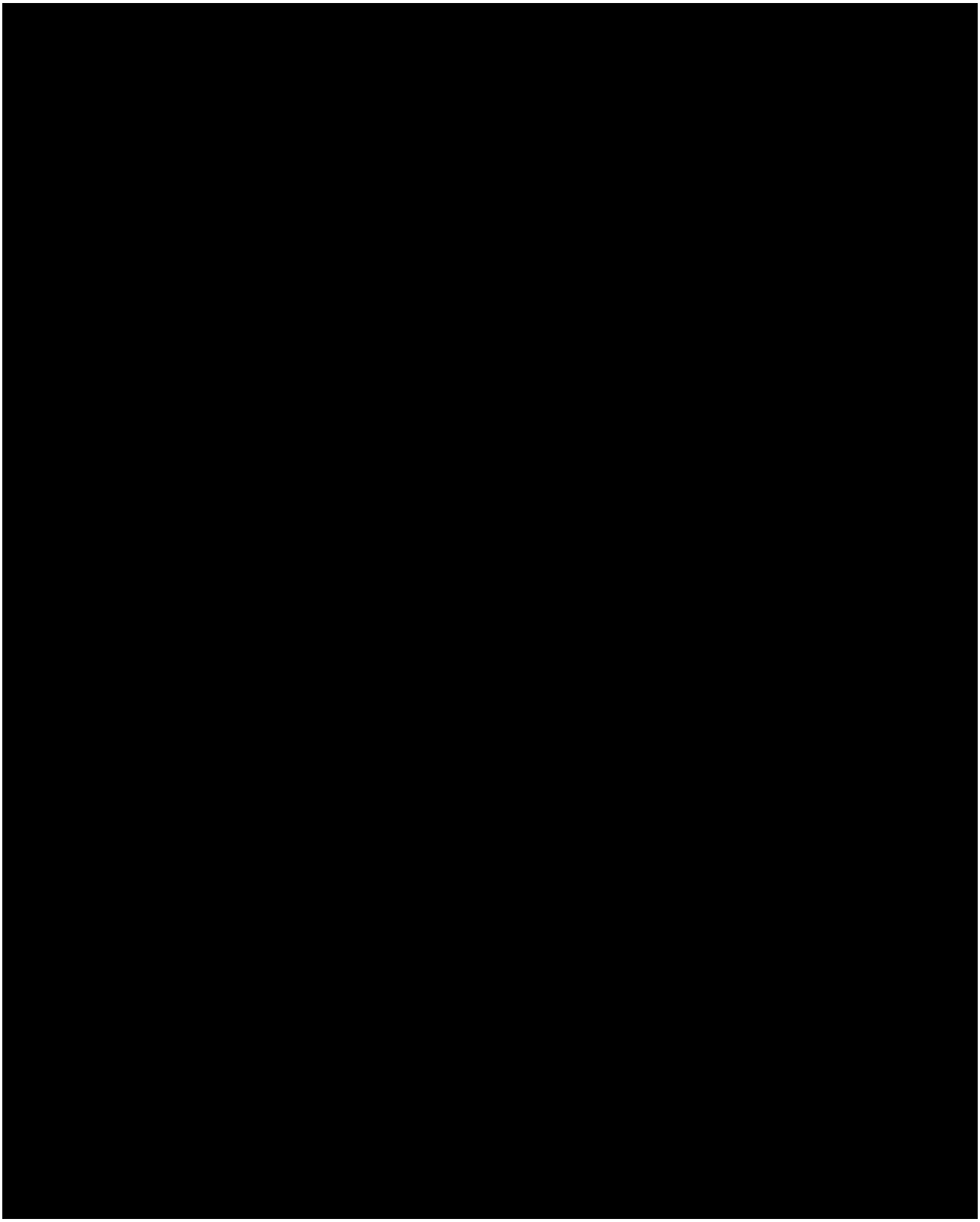
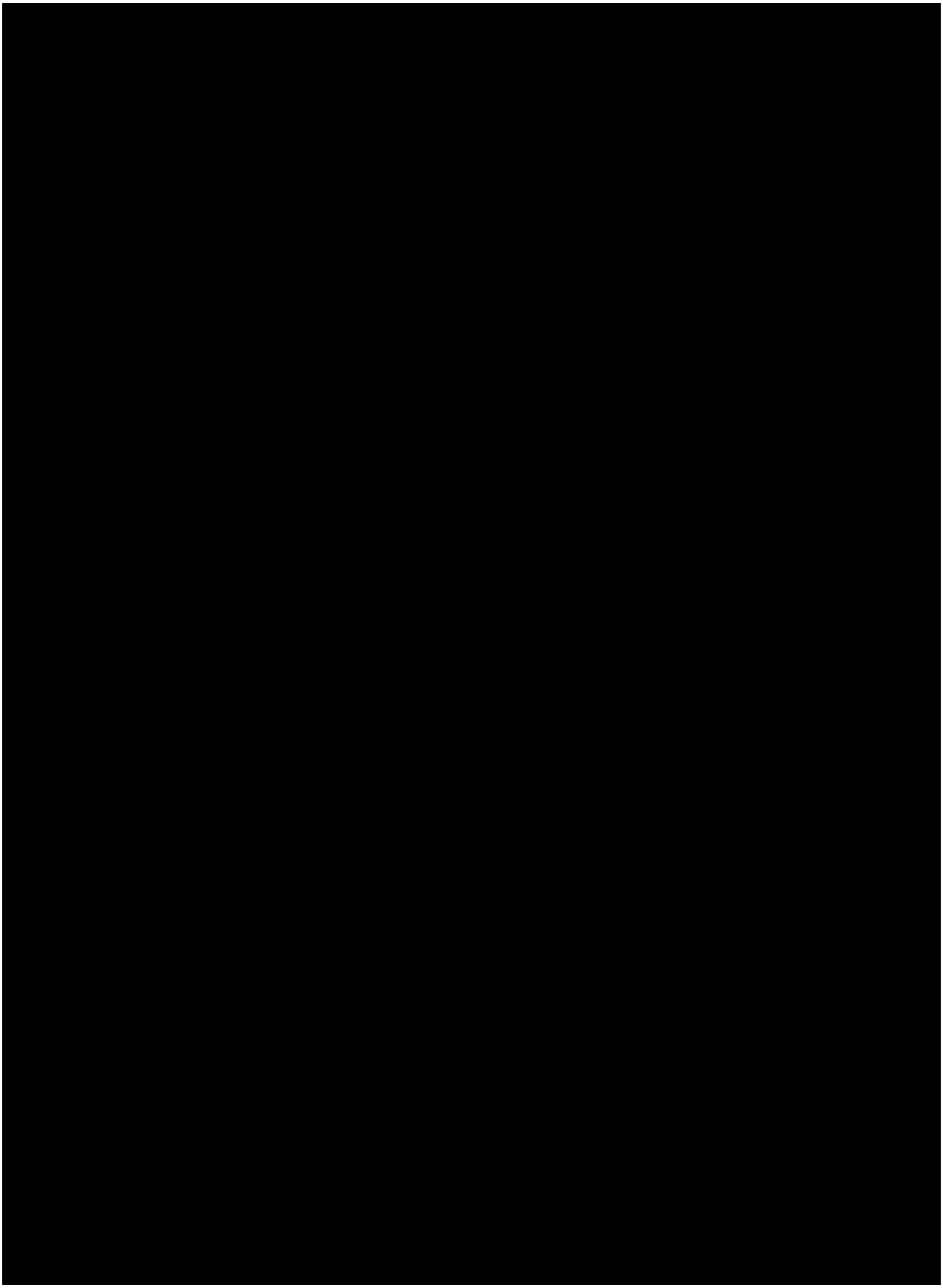
[redacted]





[redacted]

10.3 [redacted]

10.4 [redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

11. INTERIM ANALYSIS/ DATA MONITORING COMMITTEE

11.1 Data Monitoring Committee (DMC)

The DMC will be responsible for the ongoing monitoring of safety of subjects enrolled in the study according to the DMC charter. Recommendations made by the DMC to alter the conduct of the study or to amend the protocol will be forwarded to Takeda for review and for a final decision. Takeda or its designee will notify investigative sites and regulatory authorities as appropriate, of DMC recommendations (which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints). The DMC will be consulted if the study is discontinued.

Analyses of the data for DMC review will be conducted according to the DMC charter. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not applicable.

11.2 Interim Analyses

An interim analysis (IA) will be performed after 18 subjects have achieved remission and when approximately 50% of the planned sample size has been enrolled and treated in the three arms.

The IA will include all data, collected by this time point, for all subjects enrolled in the study. IA results will be used to evaluate a preliminary treatment effect, assess initial PK/PD parameters, and inform the phase 3 clinical development planning.

Analyses will cover the co-primary objectives, both secondary PK/PD and safety/ efficacy objectives and a subset of exploratory objectives. [redacted]

Access to results from the IA will be restricted to a small group of Takeda personnel designated as unblinded who thereafter will be removed from participation in oversight of

daily conduct of this study. The interim analysis data and results may be used in regulatory interactions but will not be made public or used in scientific manuscripts.

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.

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.

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

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

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.

12.2 Definition of Baseline

Unless otherwise stated, Baseline is defined as the last non-missing (scheduled or unscheduled) measurement obtained prior to the date and time of the first dose of investigational product. When time is not available, assessment occurring on the same date as the first dose are assumed to be pre dose.

Because of the need for urgent treatment, there is no baseline visit. Rather, baseline measurements are to be collected as part of the screening procedures. Screening and baseline assessments should be completed prior the initial SoC PEX, but the initial SoC PEX must not be delayed in order to accommodate screening procedures.

12.3 Definition of Visit Windows

All data 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. For summaries, only scheduled visits will be considered. All visits including unscheduled visits will be listed.

Study day will be calculated as follows (if the first dosing day is Study Day 1. If it is Day 0, the formula needs to be adjusted):

- If the assessment date is on or after the date of first dose of IP:

  Study day = assessment date – first dosing date + 1

- If the assessment date is before the date of first dose of IP:

  Study day = assessment date – first dosing date

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 is repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, 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 Severity Assessment for Adverse Events

- If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of “Mild” will be assigned.
- If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of “Severe” will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and the imputed values will be used in data listings.

12.5.2 Missing Causality assessment for Adverse Events

Handling of unknown causality assessment:

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

12.5.3 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" for "<X" and "X" for ">X".

12.5.4 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

12.5.4.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

12.5.4.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

12.5.4.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

12.5.4.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of

investigational product, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

12.5.4.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date. If the stop date of any event is missing and the corresponding status indication of "ongoing" is missing, all attempts to capture the information should be made but should this not be possible, the same approach should be taken as described above for last dose of investigational product.

12.5.4.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

12.5.4.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

12.5.4.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

12.5.5 Missing Relationship to Investigational Product or Study Procedure for Adverse Events

If the relationship to investigational product or study procedure is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

13. ANALYSIS SOFTWARE

All data processing, summarization, and analyses are to utilize SAS® software package, Version 9.4 or later. If the use of other software is warranted the final clinical study report (CSR) is to detail what software was used.

All derivations, statistical analyses, summaries, and listings for PK data will be generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.0 or higher (Certara, L.P., Princeton, New Jersey). The PK figures may be prepared using the same versions of SAS.

14. REFERENCES

All questionnaires are filed in eTMF in English on Study level, folder *02.02.02 Subject* Questionnaire. The local language ones are filed on Country level.

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15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Updated sponsor from Shire to Takeda

16. APPENDICES

None