Statistical Analysis Plan

NCT Number: NCT03997760

Title: A Phase 1 randomized, double-blind, placebo-controlled, multicenter, ascending dose, safety and PK/PD study of SHP655 (rADAMTS13) in sickle cell disease at baseline health

Study Number: SHP655-101

Document Version and Date: Version 1.0, 04 JUL 2022

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STATISTICAL ANALYSIS PLAN

PRODUCT: Recombinant ADAMTS13

A Phase 1 randomized, double-blind, placebo-controlled, multicenter, ascending dose, safety and PK/PD study of SHP655 (rADAMTS13) in sickle cell disease at baseline health

PROTOCOL IDENTIFIER: SHP655-101

Study Sponsor(s): **Takeda Development Center Americas, Inc**.
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REVISION HISTORY

Version	Issue Date	Summary of Changes
0	2020 Mar 25	First draft document
1.0	2022 Jul 04	Update according to Protocol Amendment 2.0

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ABBREVIATIONS

ADAMTS13	A Disintegrin and Metalloproteinase with Thrombospondin Type 1 Motif, Member 13
ADAMTS13ag	ADAMTS13 Antigen
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
AUC	Area Under the Concentration-Time Curve
$AUC_{(0-72)}$	AUC from Zero (predose) to 72 hours Postdose
$AUC_{(0-inf)}$	AUC from Zero (predose) Extrapolated to Infinite Time
$AUC_{(0-last)}$	AUC from Zero (predose) to Time of Last Quantifiable Concentration
AUMC	Area Under the Moment Curve
$AUMC_{(0-72)}$	AUMC from Zero (predose) to 72 hours Postdose
$AUMC_{(0-inf)}$	AUMC from Zero (predose) Extrapolated to Infinite Time
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
BPI	Brief Pain Inventory
CBC	Complete Blood Count
CL	Systemic Clearance
cm	Centimeter
C_{max}	Observed Maximum Concentration
CRA	Clinical Research Associate
[redacted]	[redacted]
DEC	Dose Escalation Committee
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
HBc	Anti-Hepatitis B-core Total
HBsAg	Hepatitis B Surface Antigen
HCV	Anti-Hepatitis C Virus
HEOR	Health Economics and Outcomes Research
Hgb	Hemoglobin
HIV	Anti-Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
IP	Investigational Product
IR	Incremental Recovery
IRT	Interactive Response Technology

IU	International Units
IV	Intravenous
kg	Kilogram
[redacted]	[redacted]
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantitation
ml	Milliliter
mmHg	Millimeters of Mercury
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
$MRT_{(0-72)}$	MRT from Zero (Predose) to 72 Hours Postdose
$MRT_{(0-inf)}$	MRT from Zero (Predose) Extrapolated to Infinite Time
n	Number
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
rADAMTS13	Recombinant ADAMTS13
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCD	Sickle Cell Disease
SI	Système International
SOC	System Organ Class
$t_{1/2}$	Terminal Half-Life
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TFL	Table/Figure/Listing
t_{max}	Time to Reach Cmax
TSP1	Thrombospondin 1
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
V_{ss}	Volume of Distribution at Steady State
VWF	Von Willebrand Factor

VWF:Ag	VWF:Antigen
VWF:RCo	VWF:Ristocetin Cofactor Activity
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This study will assess safety (including immunogenicity), tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ascending doses of SHP655 in sickle cell disease (SCD). It is expected that SHP655 (recombinant - a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 [rADAMTS13]) activity will be inhibited by plasma free hemoglobin and thrombospondin-1 to variable degrees across subjects. Additionally, dosing of SHP655 to supraphysiologic levels has not been characterized clinically. Understanding the relationships among PK, PD, biomarkers, and their clinical correlates can guide the design of the adaptive Phase 2/3 study.

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of exploratory and safety data. PK/PD data analyses will be provided in the Clinical Pharmacology Analysis Plan (CPAP). Specifications for tables, figures, and listings are contained in a separate document.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Assess safety, tolerability, and immunogenicity of SHP655 in subjects with SCD at baseline health.

2.1.2 Secondary Objective(s)

Pharmacokinetic Objective:

- Assess the single dose PK of SHP655 at 3 dose levels in subjects with SCD.

Pharmacodynamic Objectives:

- Assess the effect of SHP655 on von Willebrand factor (VWF) and platelets.
- Study the correlation of plasma free hemoglobin and thrombospondin on SHP655 activity and VWF.

2.1.3 Exploratory Objective

- Assess additional exploratory biomarkers, [redacted].

2.2 Endpoints

2.2.1 Primary Endpoint(s)

Serious adverse events (SAEs)/adverse events (AEs), adverse changes in vital signs and laboratory parameters, and incidence of binding and inhibitory antibodies to SHP655 occurring up to 28±3 days after SHP655 infusion, are the primary endpoints on this study.

2.2.2 Secondary Endpoint(s)

Pharmacokinetic

Area under the concentration-time curve (AUC) from zero (predose) to 72 hours postdose ($AUC_{(0-72)}$), AUC from zero (predose) extrapolated to infinite time ($AUC_{(0-inf)}$), AUC from zero (predose) to time of last quantifiable concentration ($AUC_{(0-last)}$), terminal half-life ($t_{1/2}$), systemic clearance (CL), mean residence time (MRT) from zero (predose) to 72 hours postdose ($MRT_{(0-72)}$), MRT from zero (predose) extrapolated to infinite time ($MRT_{(0-inf)}$), volume of distribution at steady state (V_{ss}), observed maximum concentration (C_{max}), time to reach C_{max} (t_{max}), and incremental recovery (IR) will be estimated for ADAMTS13 activity and ADAMTS13 antigen (ADAMTS13Ag). This will be further discussed in the CPAP.

Pharmacodynamic

- VWF:antigen (VWF:Ag), VWF:Ristocetin cofactor activity (VWF:RCo) and platelet count.
- Plasma free hemoglobin and plasma thrombospondin levels.

2.2.3 Exploratory Endpoint(s)

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

3. STUDY DESIGN

3.1 General Description

This is a Phase 1 randomized, double-blind, placebo-controlled, multicenter ascending dose study evaluating the safety, tolerability, and immunogenicity of SHP655 (rADAMTS13) in 18 to 65-year-old subjects with SCD. This study will also characterize the PK and assess the PD of SHP655 and its effect on biomarkers.

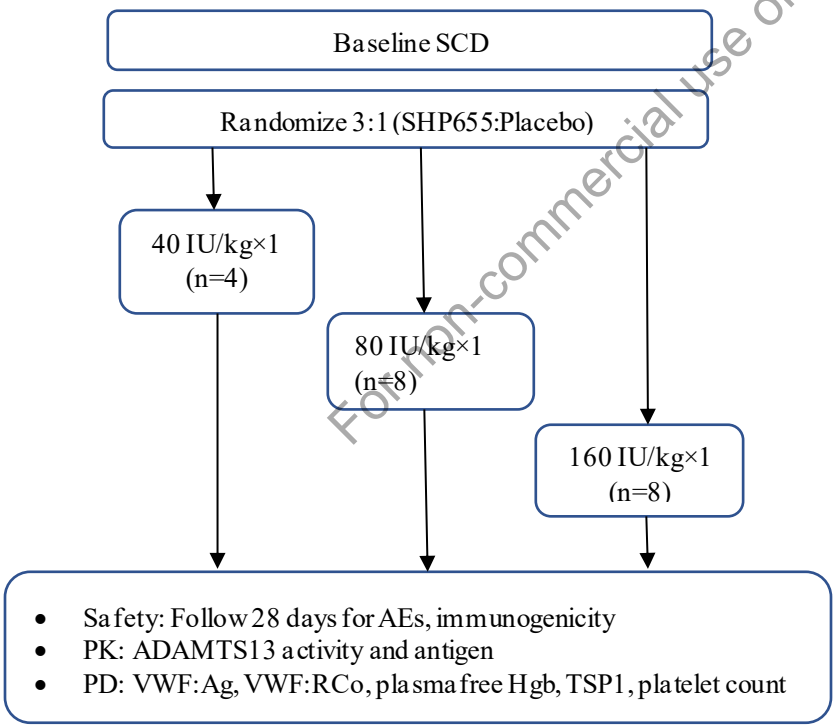
Dose escalation

Approximately 20 subjects with baseline SCD will be randomized in a 3:1 ratio to receive either SHP655 or placebo as single IV infusion at 3 dose levels: 40 IU/kg (n=4), 80 IU/kg (n=8), or 160 IU/kg (n=8). The dose cohorts will be opened sequentially, after safety data up to the Day 13 visit of the last subject in the previous dose cohort has been reviewed by the Dose Escalation Committee. The number of subjects will be increased to 8 subjects per dose cohort (6 active:2 placebo) in the 80 IU/kg and 160 IU/kg dose cohorts for more robust PK, PD, clinical, and biomarker assessments.

The study schematic diagram from the protocol is presented below in

Figure **1**.

Figure 1: Study Schematic



Abbreviations: ADAMTS13=A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; AEs=Adverse events; PD=Pharmacodynamics; PK=Pharmacokinetics; SCD=Sickle cell disease; TSP1=Thrombospondin 1; VVF:Ag=von Willebrand factor antigen; VWF:RCo=von Willebrand factor:Ristocetin cofactor.

3.2 Randomization

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

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to IP allocated to the subject, once eligibility has been determined.

Individual subject treatment is automatically assigned by the interactive response technology (IRT) following a 3:1 ratio between SHP655 vs. placebo within each dose cohort.

Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same IP packing identification number may not be assigned to more than one subject.

3.3 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. SHP655 and placebo will be prepared by an unblinded pharmacist and will be provided to the investigator or designee in a blinded manner after reconstitution. Investigators do not have access to the randomization (treatment) code except under circumstances described in Section 6.2.4 of the protocol.

3.4 Sample Size and Power Considerations

Four evaluable subjects (3 active:1 placebo) will be the first to be enrolled at the 40 IU/kg dose cohort in baseline health in order to obtain initial safety and PK data. The number of subjects will be increased to 8 evaluable per dose cohort (6 active:2 placebo) in the 80 and 160 IU/kg dose cohorts for more robust PK, PD, clinical and biomarker assessments.

Sample size:

40 IU/kg (n=3)	80 IU/kg (n=6)	160 IU/kg (n=6)	Placebo (n=5)

Sample size is not selected by a power calculation. It is chosen to provide descriptive statistics for safety, tolerability, immunogenicity and PK data following administration of SHP655.

Subjects may be replaced at the same dose cohort for drop out prior to the Day 13 immunogenicity sampling.

4. STATISTICAL ANALYSIS SETS

Classification into all Analysis Sets, except for PK and PD Analysis Sets, will be conducted prior to database lock. The PK and PD Analysis Sets will be concluded after database lock using final data from the database and final concentrations in accordance to the criteria specified below. The placebo group will be pooled for the presentations. Where applicable, the total column will pool only the SHP655 treatment groups.

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent.

4.2 Enrolled Set

Enrolled Set consists of all subjects who have signed informed consent and also passed inclusion/exclusion criteria.

4.3 Safety Analysis Set

The Safety Analysis Set will consist of all subjects randomized and who received any dose of IP. Analysis will be performed according to the treatment regimen actually received regardless of the randomized treatment regimen.

4.4 Completers Set

The Completers Set will consist of all subjects in the Safety Analysis Set who have completed the study completion/termination visit.

4.5 Pharmacokinetic Analysis Set

The PK Analysis Set will consist of all subjects who receive at least 1 complete dose of SHP655 or placebo and provide at least 1 concentration measured at a scheduled time post start of infusion for at least 1 of the PK analytes and have no major protocol deviations or events that may affect the integrity of the PK data. Subjects in this population will be included for all PK summaries. See CPAP for further details.

4.6 Pharmacodynamic Analysis Set

The PD Analysis Set will consist of all subjects who receive at least 1 complete dose of SHP655 or placebo and provide at least 1 valid data point postdose of the respective infusion for at least 1 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. Subjects in this population will be included for all PD summaries. See CPAP for further details.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all Screen Failures (i.e., subjects who were screened but not randomized) will be presented along with reasons for screen fail and details of any AEs.

The number and percentage of subjects who were included in each defined analysis set in section 4 will be summarized by treatment group and overall.

The number and percentage of subjects who completed and prematurely discontinued will be presented for each treatment group and overall. Reasons for premature discontinuation as recorded on the study completion / early termination page of the electronic case report form (eCRF) will be summarized (number and percentage) by treatment group and overall. All subjects who prematurely discontinued will be listed.

The number of subjects enrolled, 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).

A listing for subject disposition, subjects randomized, deviations from inclusion/exclusion criteria, study analysis set classification, subjects who terminated from the study, as well as study lot numbers, will be presented.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Safety Analysis Set.

The following demographic characteristics will be summarized, in the following order in the table, age (years), sex, ethnicity, and race, at screening. A baseline characteristics table

summarizing weight (kg) & height (cm), body mass index (BMI) (kg/m^2) will be presented. Listings will be presented.

5.3 Medical History

Medical history will be collected at the Screening Visit (Day -28 to 0) and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

The medical history will be summarized, presenting frequency counts, by system organ class (SOC) and preferred term (PT), for each treatment group and overall, for the Safety Analysis Set. A listing will also be presented.

5.4 Prior Medications, Therapies and Procedures

Prior medications/therapies will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). Prior procedures will be coded using the latest version of MedDRA.

Prior medications (therapies/procedures) are defined as any medications, therapies or procedures with an end date within 30 days prior to the date of treatment (IP infusion). Prior blood transfusion history will be collected for 90 days prior to screening. Prior treatment information must be recorded in the subject's source document including use of oral opioids.

The prior therapies, procedures and medication usage will be summarized by the number and proportion of subjects in each treatment group and in overall subjects within each therapeutic class / system organ class, and preferred term, for the Safety Analysis Set. Multiple medications (therapies/procedures) used by a subject in the same category will be counted only once.

All prior therapies, procedures and medications will be listed for the Safety Analysis Set.

5.5 Concomitant Medications, Therapies, and Procedures

Concomitant medications/therapies will be coded using the latest version of WHO-DD. Concomitant procedures will be coded using the latest version of MedDRA.

Concomitant medication (therapy) is defined as any medication (therapy) with a start date prior to the date of IP infusion and continuing after IP infusion or with a start date between the dates of IP infusion and completion/termination visit, inclusive. Concomitant procedure is defined as any procedure with a start date between the dates of IP infusion and completion/termination visit, inclusive. Any medication (therapy/procedure) with a start

date after the completion/termination visit date will not be considered a concomitant medication (therapy/procedure).

The concomitant therapies, procedures and medications used will be summarized by the number and proportion of subjects in each treatment group and in overall subjects within each therapeutic class / system organ class, and preferred term, for the Safety Analysis Set. Multiple medications (therapies/procedures) used by a subject in the same category will be counted only once.

All concomitant therapies, procedures and medications will be listed for the Safety Analysis Set.

5.6 Exposure to Investigational Product

A listing will be created by subject number presenting all the IP infusion data collected, for the Safety Analysis Set.

5.7 IP Infusion

Infusion duration (min), planned dose volume (mL), given dose volume (mL), and the difference between planned and given dose volume (mL), as well as the location, saline flush, and if the infusion was interrupted or not, duration of interruption (min), will be summarized by treatment group and overall, and listed, for the Safety Analysis Set.

5.8 Protocol Deviations

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

Protocol deviations will be presented in a listing.

6. EFFICACY ANALYSIS

There are no efficacy endpoints for this study. This study is focused on safety; thus, the primary safety analysis and exploratory analyses are defined below. The primary and exploratory analyses will be performed on the Safety Analysis Set.

6.1 Analyses of Primary Safety Endpoint(s)

The primary safety endpoints will include SAEs and AEs, adverse changes in vital signs and laboratory parameters, and incidence of binding and inhibitory antibodies to SHP655 occurring up to 28±3 days after SHP655 infusion.

Analyses of these parameters are described in section 7.

6.2 Analyses Secondary Endpoint(s)

The secondary endpoints for this study are related to PK/PD, and PK analysis will be further discussed in the CPAP.

6.3 Analyses of Exploratory Endpoint(s)

The exploratory variables, include but are not limited to [redacted] plasma free hemoglobin.

The exploratory endpoints will be listed and summarized by treatment group, dose level and overall, by visit. Summaries will include descriptive statistics for exploratory variables and changes from baseline at each assessment time point. Change from baseline will only be presented if both baseline and post baseline assessments exist.

7. SAFETY ANALYSIS

All safety analyses (including the primary analysis) will be performed on the Safety Analysis Set.

Safety variables include AEs, clinical laboratory variables, vital signs, and immunogenicity data and will be assessed using descriptive summaries by treatment group, dose level and overall, by visit. The placebo group will be pooled for the presentations. The total column will pool the SHP655 treatment groups.

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

7.1 Adverse Events

Adverse events will be coded using the latest version of MedDRA.

An AE that starts or worsens in severity on or after the infusion of IP will be considered a treatment emergent adverse event (TEAE).

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, by treatment group, dose level and overall, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to IP, TEAEs leading to study termination, and TEAEs leading to deaths.

The number and percentage of subjects reporting TEAEs, as well as the number of events, in each treatment group, dose level and overall will be tabulated by system organ class (SOC) and preferred term. A summary will also be presented 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. Serious TEAEs related to IP will be summarized. TEAEs related to IP will be summarized by maximum severity.

Presentation by SOC and preferred term will display SOC by descending incidence and preferred term within SOC by descending incidence of study drug events (across all treatment groups), and then alphabetically for equal frequencies.

TEAEs leading to study termination, TEAEs leading to death, TEAEs related to IP, serious TEAEs, and non-serious TEAEs will be summarized similarly, by SOC, preferred term and treatment group.

The following will also be summarized, frequently occurring (≥10%) serious TEAEs and frequently occurring (≥10%) non-serious TEAEs, by preferred term and treatment group.

Listings of all AEs, AEs related to IP, SAEs, AEs leading to death, and AEs leading to discontinuation, will be presented. TEAEs will be flagged.

AEs that occur at the time of IP infusion are of particular interest. Two additional listings will be presented which subset on AEs that occur on the same day as the IP infusion, displaying related and unrelated TEAEs. The same data will be summarized with the number and percentage of subjects, as well as the number of events in each treatment group, dose level and overall by preferred term.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) 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 group and overall, for the following clinical laboratory variables.

Chemistry Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Albumin, [redacted], Total bilirubin (TBL), [redacted], Blood Urea Nitrogen, Creatinine, Glucose, Sodium, Potassium, Chloride, Bicarbonate

Hematology Platelets, Hemoglobin, Hematocrit, Erythrocytes (Red Blood Cell [RBC]), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), [redacted], Leukocytes (White Blood Cell [WBC]), WBC Differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)

Local and central clinical laboratory data will be flagged for out-of-range values and will be listed for the Safety Analysis Set. A list of clinically significant abnormal values will also be presented. Results for blood group typing, [redacted], viral serology [Anti-Human immunodeficiency virus (HIV) 1/2, Anti-Hepatitis C virus (HCV), Hepatitis B surface antigen (HBsAg), Anti-Hepatitis B-core total (HBc), Anti- Hepatitis B surface antigen], and pregnancy testing at screening and baseline will only be presented in a listing.

7.3 Vital Signs

Descriptive statistics for vital signs, systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation, and their changes from baseline at each post-baseline visit and at the end of study will be presented by treatment group, dose level and overall.

Vital sign values will be considered PCS if they meet both the observed value criteria and the change from baseline criteria listed in Table 1. The number and percentage of subjects with PCS post-baseline values will be tabulated by treatment group and overall. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline vital sign value. A supportive listing of subjects with post-baseline PCS

values will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 1: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	**Change from Baseline**
Systolic blood pressure (mmHg)	High	*≥180*	*Increase of ≥20*
	Low	*≤90*	*Decrease of ≥20*
Diastolic blood pressure (mmHg)	High	*≥105*	*Increase of ≥15*
	Low	*≤50*	*Decrease of ≥15*
Pulse rate (beats per minute)	High	*≥120*	*Increase of ≥15*
	Low	*≤50*	*Decrease of ≥15*

[a] A post-baseline value is considered as a PCS value if its meets both criteria for observed value and change from baseline.

All vital signs data will be listed for the Safety Analysis Set. Descriptive statistics and listing will be presented for oxygen use.

7.4 Other Safety Data

Based on the availability of immunogenicity data, as applicable, the number and proportion of subjects with pre-existing (baseline), treatment-induced, treatment-boosted and overall incidences of ADA in serum, as well as titers will be summarized by treatment group and overall for subjects with a non-missing baseline sample. Similar summary will be provided for serum neutralizing antibodies.

- Pre-existing ADA positive is defined as a subject with positive ADA response in baseline sample.
- Treatment-induced ADA positive is defined as a subject who has negative ADA in baseline sample **and** has positive ADA response in any postbaseline assessment.
- Treatment-boosted ADA positive is defined as a subject who has positive ADA response in both baseline and postbaseline samples, **and** the maximum titer/value of the postbaseline ADA is ≥4 times that of the baseline titer value.

Individual results for binding and neutralizing antibodies to SHP655 will be presented in listings, including results for subjects with missing baseline sample. Data allowing, the relationship of immunogenicity with PK/PD may be evaluated as outlined in Sections 8.1 and 9.2.

8. PHARMACOKINETIC ANALYSIS

The non-compartmental PK analysis will be conducted at IQVIA and details are provided in the CPAP.

8.1 Pharmacokinetic Analyses in Support of Data Review by the Dose Escalation Committee

PK analysis using NCA method will be performed by the IQVIA Pharmacokineticist to support the Dose Escalation Committee (DEC). Analyses and data presentations will follow the conventions described in CPAP. The PK analyses in support of the DEC will be performed using unblinded data at the treatment/subject level and will only be shared according to the unblinding plan.

8.2 Relationships of Immunogenicity Results with Pharmacokinetics

Data allowing, observed and baseline-adjusted concentrations, as well as available PK parameters (C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ and CL) of ADAMTS13 activity and ADAMTS13:Ag in the placebo group and at each SHP655 dose level will be summarized by binding antibody status (positive vs. negative) and immunogenicity type (treatment-induced vs. treatment-boosted). Similarly, summaries of above ADAMTS13 activity and ADAMTS13:Ag PK concentraions and parameters will be provided by neutralizing antibody status and immunogenicity type.

Data allowing, for each SHP655 dose level, figures of arithmetic mean (SD) observed concentration-time data will be overlaid by binding antibody status (positive vs. negative) and immunogenicity type (treatment-induced vs. treatment-boosted) for each anti-ADAMTS13 antibody category (binding and neutralizing) and presented on linear scale plot. Individual and geometric mean PK exposure parameters (C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ and CL) will be plotted by binding antibody status (positive vs. negative) and immunogenicity type (treatment-induced vs. treatment-boosted) for each anti ADAMTS13 antibody category (binding and neutralizing).

9. PHARMACODYNAMIC ANALYSIS

9.1 Pharmacodynamic Data

9.1.1 Primary Pharmacodynamic Endpoint and Analysis

There is no primary PD analysis due to be performed on the study.

9.1.2 Secondary Pharmacodynamic Endpoints and Analysis

Summaries, using the following descriptive statistics: n, mean, median, standard deviation, CV%, minimum, and maximum, for [redacted], VWF:Ag, VWF:RCo levels over time, as well as for [redacted], plasma free hemoglobin, and plasma thrombospondin level, will be provided by treatment group and overall for all SHP655 dose levels. Observed value, change from baseline and percent change from baseline will be summarized. Listings including all the above PD parameters will be presented.

9.1.3 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

For each SHP655 dose level and each PD analyte, arithmetic mean (SD) observed ADAMTS13 activity data will be overlaid with PD responses over time on a figure with two linear y-axes. PD responses will include median and arithmetic mean (SD) observed value and change from baseline.

Scatter plots of individual PK exposure parameters (C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ and CL) and individual PD responses will be presented for graphical assessments of exposure-response. PD responses will include maximimum or minimum observed value and change from baseline, as applicable for each PD analyte.

9.2 Relationships of Immunogenicity Results with Pharmacodynamics

Data allowing, figures of arithmetic mean (SD) observed value and change from baseline PD data over time will be overlaid by antibody status (positive vs. negative) and immunogenicity type (treatment-induced vs. treatment-boosted) for each anti-ADAMTS13 antibody category (binding and neutralizing) and provided by treatment group.

10. HEALTH ECONOMICS AND OUTCOMES RESEARCH (HEOR) ENDPOINTS

The Health Economics and Outcomes Research (HEOR) outcome measures were collected for cohort 1 and 2, prior to Protocol Amendment 2. HEOR measures include:

- Rate of acute VOC complications
- Time interval between the initiation of IP infusion and discontinuation of IV narcotics
- Treatment satisfaction (TSMQ-9)
- Health-related quality of life assessments:
  - Brief Pain Inventory (BPI)
  - Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue

    - Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me)
- Pain score - Visual Analog Score (VAS)
- Days of hospitalization
- Type of transfusion

The HEOR outcome measures with available data will be listed for the Safety Analysis Set.

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

Although no formal data monitoring committee (DMC) will be involved in the management of this study, safety will be monitored by a Takeda Dose Escalation Committee. See Section 6.2.3.3 of the protocol for more details.

12. DATA HANDLING CONVENTIONS

12.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum, 1st and 3rd quartiles. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

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

- Minimum and maximum: N decimals
- Mean, median, and quartiles: N + 1 decimals
- Standard deviation: N + 2 decimals

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 with data available as described in the latest version of the Output Templates.

All values will be rounded using the SAS® function ROUND. All computed percentages will be presented using 1 decimal place, except for 100% which will be presented with no decimals.

12.2 Definition of Baseline

For each measure, safety and exploratory data, baseline will be defined as the last non-missing measurement obtained prior to the first dose date and time.

The last post-baseline assessment will be used as the end of study assessment.
For quantitative measurements where change from baseline (CFB) is presented, CFB will be derived as:

$$CFB = (Value\ at\ Timepoint\ X) - (Value\ at\ Baseline).$$

12.3 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, 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.

In the case of retests or repeated assessments, the last available measurement for that visit will be used for by-visit summaries.

Unscheduled results will not be included in summaries. All results (scheduled and unscheduled; original and repeated) will be presented in the listings.

12.4 Handling of Missing, Unused, and Spurious Data

12.4.1 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures/Opioids/Transfusions)

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.

12.4.1.1 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.

12.4.1.1.1 Missing Day and Month

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

12.4.1.1.2 Missing Month Only

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

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

12.4.1.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the study completion/termination visit is missing, then replace it with the Day 13 follow-up 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.

12.4.1.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the study completion/termination visit, then the day and month of the date of the study

completion/termination visit will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of the study completion/termination visit, 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 study completion/termination visit, then 01 January will be assigned to the missing fields.

12.4.1.2.2 Missing Month Only

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

12.4.1.2.3 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 study completion/termination visit, then the day of the date of the study completion/termination visit will be assigned to the missing day
- If either the year is before the year of the date of the study completion/termination visit or if both years are the same, but the month is before the month of the date of the study completion/termination visit, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the study completion/termination visit or if both years are the same, but the month is after the month of the date of the study completion/termination visit, then the first day of the month will be assigned to the missing day.

12.4.2 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g., AE start year and month are the same as the year and month of the dose of investigational product, then the AE will be classified as treatment emergent. To facilitate categorization of AEs as treatment emergent, imputation of dates can be used.

For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

12.4.2.1 Incomplete Start Date

Follow the same rules as in Section 11.4.1.1.

12.4.2.2 Incomplete Stop Date

Follow the same rules as in Section 11.4.1.2.

12.4.3 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the 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 dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries.

12.4.4 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the 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.

12.4.5 Character Values of Clinical Laboratory Variables

For the quantitative laboratory measurements reported as "<X", i.e., below the limit of quantification (BLQ), or ">X", i.e., above the upper limit of quantification (ALQ), these are to be presented in listings as "<X" or ">X" and summarized as "X" for "<X" or ">X".

13. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 of SAS® on a suitably qualified environment.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

15. REFERENCES

None