Clinical Study Protocol

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: Protocol Amendment 2.0 (Global), 12 JUL 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

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PROTOCOL: SHP655-101

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.
SHORT TITLE:	A Phase 1 randomized study of SHP655 (rADAMTS13) in sickle cell disease
STUDY PHASE:	Phase 1
ACRONYM:	RAISE (**R**ecombinant **A**DAMTS13 **I**n **S**ickle cell diseas**E**)
DRUG:	recombinant ADAMTS13
IND NUMBER:	018839
SPONSOR:	Takeda Development Center Americas, Inc. 95 Hayden Avenue, Lexington, MA 02421, USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter
PROTOCOL HISTORY:	**Protocol Amendment 2.0 (Global): 12 JUL 2021** *Replaces:* Protocol Amendment 1.0 (Global) 17 MAY 2019 *Protocol History:* Original Protocol (Global) 28 MAR 2019

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PROTOCOL SIGNATURE PAGE

Sponsor's Approval

Si [redacted]	Date: [redacted]
[redacted], MD	

Investigator's Acknowledgement

I have read this protocol for Study SHP655-101.

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.

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

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I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____ _____ _____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

- Original Protocol (28 MAR 2019)
- Protocol Amendment 1.0 (17 MAY 2019)
- Protocol Amendment 2.0 (12 JUL 2021)

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **2.0**	**Amendment Date** **12 JUL 2021**	**Global/Region/ Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: The primary purpose of this amendment is to remove Part B of the study (enrollment of subjects with acute vaso occlusive crisis [VOC]).		
Description of Each Change and Rationale		**Section(s) Affected by Change**
1. The description of the study as a Phase 1/2 study was changed to Phase 1.	To reflect the investigative objective of this study.	Title Page Protocol signature page Section 1.1, Synopsis Section 2.2.2 Section 2.4 Section 4.1 Section 4.2
2. The Sponsor name and address was updated to the following; Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421	To reflect the recent legal entity name change and centralization of clinical trial development.	Title Page Throughout, where appropriate
3. Emergency contact information was updated.	To reflect current emergency personnel and contact information.	Emergency Contact Information
Remove Part B of the study that includes subjects with VOC.	To reflect the Sponsor decision to complete the Phase 1 safety study in subjects at baseline health (Part A) before designing the next trial in the clinical development program.	Title Page Protocol signature page Section 1.1, Synopsis Section 1.2 Section 1.3 Section 3.1 Section 3.2 Section 4.1 Section 4.2 Section 4.4 Section 5.1

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Description of Each Change and Rationale		**Section(s) Affected by Change**
		Section 5.2 Section 6.2.3, Dosing Section 6.2.3.3, Dose Escalation Committee Section 8.1, Study Schedule Section 8.1.1, Screening Visit Section 8.1.2, Treatment Period Section 8.1.4, Study Completion/Termination Visit Section 8.2.2.5, Pregnancy Test Section 8.2.3, Pharmacokinetics Section 8.2.4, Pharmacodynamics Section 8.2.5, Biomarkers Section 9.2, Planned Interim Analysis Section 9.3, Sample Size and Power Considerations Section 9.6.1, Pharmacokinetic Analysis Section 9.6.2, Pharmacodynamic Analysis Section 9.6.3, Pharmacokinetic-Pharmacodynamic Relationship Section 9.7, Efficacy Analysis
The product quality complaint email was updated to ctmcomplaint@takeda.com.	Updated for accuracy	Product Quality Complaints
Assessment of [redacted]	The assays involved with these biomarkers are investigative and under development.	Section 1.1, Synopsis Section 1.3 (Table 2) Section 3.1.2 Section 3.1.3 Section 3.2 Section 8.2.4 Section 8.2.5 Throughout the document

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Protocol Amendment Summary and Rationale: The primary purpose of this amendment is to remove Part B of the study (enrollment of subjects with acute vaso occlusive crisis [VOC]).		
Description of Each Change and Rationale		**Section(s) Affected by Change**
All Health Economics and Outcomes Research (HEOR) objectives, endpoints, and assessments were removed from the study.	To reflect removal of endpoints most relevant to Part B.	Section 1.1, Synopsis Section 1.2 Section 1.3 Section 3.1.3 Section 3.2 Section 8.2.1 Section 8.2.5 Section 9.8
Assessment of the effect of SHP655 on platelet count was added as a secondary, pharmacodynamic objective, and platelet count as a PD endpoint.	ADAMTS13 cleavage of VWF may directly result in dissolution or prevention of platelet aggregates, resulting in an increase in the platelet count.	Section 1.1, Synopsis Section 3.1.2 Section 3.2 Section 8.2.4 Section 9.6.2
The list of exploratory markers was updated.	To reflect changes to the [redacted], removal of Health Economics and Outcomes Research endpoints, and for consistency throughout the protocol	Section 1.1, Synopsis Section 3.2 Section 8.2.5 Section 9.7
The pain score by VAS and oxygen use were removed as exploratory endpoints.	To reflect removal of all exploratory efficacy endpoints due to the change to a Phase 1 study	Section 1.1, Synopsis Section 1.2 Section 1.3 (Table 1) Section 8.2.1 Section 8.2.5
Dose justification was updated and clarified regarding discussion of the PK/PD modeling and the relevant preclinical toxicology studies in rats and nonhuman primates.	Updated for completeness and clarity, and to harmonize with information presented in the IND.	Section 4.3
This study will be conducted in approximately 20 sites across the United States.	This Phase 1 study will not be conducted in Europe.	Section 1.1, Synopsis Section 4.4
The exclusion criteria were updated to indicate at which visit each criterion applies.	Updated for clarity	Section 1.1, Synopsis Section 5.2

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Description of Each Change and Rationale		**Section(s) Affected by Change**
Exclusion criteria 5 was updated to include exclusionary bilirubin levels at the Screening Visit, "…direct bilirubin level >2 mg/dL, or indirect bilirubin level >5 mg/dL."	Due to the nature of this phase 1 safety study, the exclusion criterion was clarified for elevated bilirubin levels. Exclusion criteria for indirect bilirubin ensures unconjugated bilirubin levels remain within the range validated for the ADAMTS13 activity assay. High direct bilirubin levels were excluded, which may indicate hepatic dysfunction.	Section 1.1, Synopsis Section 5.2
Exclusion criteria 11 and 12 were deleted.	Exclusion criteria 11 and 12 were designed for hospitalized subjects in Part B and are no longer applicable.	Section 1.1, Synopsis Section 5.2
The Note defining menopausal was removed from the exclusion criteria. Detailed definitions of acceptable methods of contraception for female and male subjects were removed.	To simplify the protocol and improve consistency with the change to a US-only study. The FDA does not require these detailed definitions within the protocol.	Section 1.1, Synopsis Section 5.2 Section 5.4 Appendix 4
Exclusion criteria 8 and 9 were simplified to exclude febrile subjects and those with infections requiring IV antibiotics.	Removal of subjects presenting with a VOC allows the criteria to be simplified to reduce confusion.	Section 1.1, Synopsis Section 5.2
Exclusion criteria 14 was updated to exclude use of anticoagulant or antiplatelet therapy within the past 3 weeks before dosing; crizanlizumab within the past 30 days before dosing; and voxelotor within the past 14 days before dosing.	To specify wash-out periods for 1.) anticoagulant and anti-platelet therapies, based on advice from the FDA that these should be restricted during the study; and 2.) recently approved protocol-restricted concomitant treatments for SCD.	Section 1.1, Synopsis Section 5.2

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Description of Each Change and Rationale		**Section(s) Affected by Change**
Exclusion criteria 23 was added to exclude subjects with active hepatitis B, hepatitis C, or HIV infections.	To clarify the exclusion criteria for the protocol-specified viral serology assessments.	Section 1.1, Synopsis Section 5.2
A statistical analysis description for PD measurements was added, and the statistical analysis of exploratory variables was updated.	To improve clarity and consistency throughout the protocol.	Section 1.1, Synopsis Section 1.2 (Figure 1) Section 9.6.2 Section 9.7
Details regarding exploratory biomarkers were removed in Figure 1.	To improve clarity by keeping focus on the most relevant information.	Section 1.2
The 9 h (±30 min) PK assessment timepoint was changed to 8 h (±30 min).	Subject burden may be reduced with an 8-hour PK sampling timepoint, as it limits the amount of time spent at the clinic.	Section 1.3 (Table 2)
Collection of daily opioid use data was removed from the Schedule of Activities and text regarding collection of oral opioid use as a Prior Treatment was updated.	To reflect the removal of Part B endpoints related to opioid use; data on oral opioid use will be collected in the same manner as other prior and concomitant treatments.	Section 1.3 (Table 1) Section 6.6.1
The introduction of this study was updated to reflect relevant background information for SCD subjects at baseline.	To reflect the removal of Part B, and to reduce excess information that may not pertain to the current study population.	Section 2
Following the review of unblinded data for a completed dose cohort by the DEC, and a recommendation by the DEC that it is safe to proceed with enrollment of the next dose cohort, the Sponsor study team will have access to the unblinded data for the completed dose cohort, with details to be specified in an unblinding plan.	Clarify the procedure for Sponsor review of unblinded data following completion of a dose cohort and review of safety data by the DEC. Unblinding the Sponsor study team is unlikely to introduce a bias as efficacy is not being evaluated and cohorts are independent from each other.	Section 6.2.4 Appendix 1.4

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Description of Each Change and Rationale		**Section(s) Affected by Change**
Figure 2 was removed.	Due to the removal of Part B of the study, Figure 2 no longer improves the clarity of the study design.	Section 1.3
Glutamine was replaced with glutamic acid in the introduction of the indication.	Updated for correction.	Section 2.1
In the benefit/risk assessment section, the description of the specific criteria for Dose Escalation Committee activities was removed and references were added to the relevant sub-sections of Section 6.2.3 for clarity.	For consistency with information provided in Section 6.2.3 Dosing.	Section 2.4
Stopping criteria for dose escalation was changed from 2 or more subjects receiving active drug who have a severe AE, to 2 or more subjects receiving active drug who have a related SAE.	Language was changed to ensure subjects remain on treatment unless an SAE occurs that is related to treatment.	Section 6.2.3
IV opioid use was removed as a permitted concomitant medication.	To reflect removal of hospitalized subjects experiencing an acute crisis.	Section 6.6.3
The following text was added, “The Sponsor recommends that subjects not be administered a vaccine against SARS-CoV2 during the Study Period. Should a subject receive such a vaccination during the Study Period, the Sponsor recommends study investigators to follow patients closely for vaccine-related adverse events for 14 days after vaccination, in collaboration with the study medical monitor."	Based on safety concerns following the recent pause of the Johnson & Johnson and AstraZeneca COVID-19 vaccines.	Section 6.6.3
The prohibited treatment list was updated to include L-glutamine, voxelotor, and crizanlizumab are restricted during the study period.	To specify that the recently approved therapies for sickle cell disease are restricted during the study period.	Section 1.1, Synopsis Section 5.2 Section 6.6.4

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Description of Each Change and Rationale		**Section(s) Affected by Change**
Lack of efficacy was removed from the list of reasons for discontinuation.	Efficacy is not a main objective of this study.	Section 7.2
The method for selecting subject identifiers was updated.	To reflect the current subject identifier format.	Section 8
Full analysis set was removed	All efficacy analyses have been removed.	Section 1.1, Synopsis Section 9.5 Section 9.7
PK Assessments, PD Assessments, and Immunogenicity Assessment sections were removed from Appendix 2 Clinical Laboratory Tests.	To clarify that these assessments are not part of 'clinical laboratory assessments' per the Schedule of Activities.	Appendix 2
ECG was removed as a safety assessment.	An ECG is not a planned safety assessment in this study.	Appendix 3
The definition IP was updated to, "Investigational Product (SHP655 and Placebo)".	For clarity	Appendix 4

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See Appendix 5 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol" within 24 hours to the Takeda Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Takeda medical monitor using the details below.

For protocol- or safety-related questions or concerns during normal business hours 9:00 AM through 5:00 PM EST (North America), the investigator must contact the IQVIA and Takeda medical monitors:

IQVIA medical monitor

[redacted], MD
Mobile: [redacted]
E-mail: [redacted]

Takeda Medical Monitor

[redacted], MD, ScD
Mobile: [redacted]
E-mail: [redacted]

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For protocol- or safety-related questions or concerns outside of normal business hours, the investigator must contact the 24-hour hotline:

For 24-hr urgent medical contact: contact on mobile phone, or at the following numbers:

US primary +1 512 652 0191
US alternate +1 512 652 0864
EU +33 186 990 019

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Takeda within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

This includes any instances wherein the quality or performance of a Takeda product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination); or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products); or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g., reconstitution difficulty

- Missing components
- Damage to the product or unit carton
- A mislabeled product (e.g., potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

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For instructions on reporting AEs related to product complaints, see Appendix 1, Appendix 3.4.

Please use the information below as applicable to report the Product Quality Complaint or Non-Medical Complaint:

Origin of Product Quality Complaint	**E-mail Address:** ctmcomplaint@takeda.com

Telephone number (provided for reference if needed):
Takeda, Cambridge, MA (USA)
1-800-828-2088

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: SHP655-101	**Drug:** recombinant ADAMTS13
Title of the study: 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	
Short title: A Phase 1 study of SHP655 (rADAMTS13) in sickle cell disease	
Study phase: Phase 1	
Number of subjects (total and per treatment arm): A total of approximately 20 subjects will be randomized to IP or placebo as follows: Four evaluable subjects (3 active:1 placebo) at the 40 IU/kg dose cohort to be increased to 8 evaluable subjects per dose cohort (6 active:2 placebo) in the 80 IU/kg and 160 IU/kg dose cohorts.	
Investigator(s): Multicenter study	
Site(s) and Region(s): The study will be conducted approximately at 20 sites in the United States	
Study period (planned): 2019-2022	**Clinical phase:** 1
Objectives: **Primary:** • Assess safety, tolerability, and immunogenicity of SHP655 in subjects with SCD at baseline health. **Secondary:** Pharmacokinetic • Assess the single dose pharmacokinetics (PK) of SHP655 at 3 dose levels in subjects with SCD. Pharmacodynamic • 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. **Exploratory:** • Assess additional exploratory biomarkers, [redacted].	
Rationale: This study will assess safety (including immunogenicity), tolerability, PK, and pharmacodynamics (PD) of ascending doses of SHP655 in SCD. It is expected that SHP655 (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.	
Investigational product, dose, and mode of administration: **Investigational product**: SHP655 (rADAMTS13)	

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Mode of Administration: Single intravenous (IV) infusion.

Dose:

SHP655 will be administered at 3 dose levels of 40, 80, and 160 IU/kg.

Placebo will be administered in an equivalent volume of the 3 dose levels of 40, 80, and 160 IU/kg as single IV infusion.

Methodology:

This is a Phase 1, randomized, double-blind, placebo-controlled, multicenter, ascending dose study evaluating safety, tolerability, and immunogenicity of SHP655 (rADAMTS13) in 12- to 65-year-old subjects with SCD. This study will characterize the PK and PD profile of SHP655.

Approximately 20 subjects with baseline SCD will be randomized in a 3:1 ratio to receive either SHP655 or placebo as a single IV infusion at one of the 3 dose levels of 40, 80, or 160 IU/kg. 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 first 3 subjects will be dosed a minimum of 14 days apart to observe and interpret reactions and adverse events in order to ensure that no SAE requiring a pause or stop of the clinical trial (see Section 6.2.3.1 and Section 6.2.3.2) has occurred in the most recently treated subject.

Enrollment and escalation to the next dose cohort will be paused for review if anaphylaxis, neutralizing antibody, or death is reported.

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Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Age 18 to 65 years at the time of signing the informed consent.
2. An understanding, ability, and willingness to fully comply with study procedures and requirements.
3. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.
4. Male or female with a documented history of HbSS or HbSβo thalassemia (based on clinical record of genetic, electrophoresis, or high-performance liquid chromatography testing).
5. Subject currently taking hydroxyurea must be on a stable dosing for 3 months at screening.

Exclusion Criteria:

1. The subject was diagnosed with acute VOC in the 21 days before dosing on Day 1.
2. The subject has undergone blood transfusion within the last 30 days or blood transfusion on ≥2 occasions in the last 90 days, at Screening Visit.
3. The subject has a history of acquired or congenital thrombotic thrombocytopenic purpura.
4. The subject has serum creatinine level >1.2 mg/dL at the Screening Visit
5. The subject has alanine transaminase >3×upper limit of normal (based on clinical laboratory normal range), direct bilirubin level >2 mg/dL, or indirect bilirubin level >5 mg/dL at the Screening Visit.
6. The subject has a hemoglobin level <5 g/dL at the Screening Visit.
7. The subject has a platelet count of <100 000/mm3 at the Screening Visit.
8. Signs or symptoms of infection requiring treatment with IV antibiotics during the Screening Period.

9. The subject has fever with body temperature of ≥38.5ºC (101.3ºF) at the Screening Visit or before dosing on Day 1.
10. The subject has acute chest syndrome (ACS), diagnosed or strongly suspected, as evidenced by a new infiltrate on chest radiograph, and one or more of the following criteria:
    - Fever with body temperature >39°C (102.2°F)
    - Hypoxia (confirmed by arterial blood gases with PaO2 <70 mmHg)
    - Chest pain
    - Suspicious findings on physical examination (tachypnea, intercostal retraction, wheezing, and/or rales).
11. The subject has recently (within the past 28 days, from Screening Visit) undergone major surgery, requires hospitalization, documented serious bacterial infection requiring antibiotic treatment, or significant bleeding.
12. The subject has had a recent (within the past 90 days, from Screening Visit) episode of stroke, transient ischemic attack, symptomatic pulmonary hypertension, or seizure.
13. Any history of hemorrhagic stroke or bleeding diathesis.
14. The subject has received any of the following protocol-restricted medicines: a) systemic steroid therapy within 48 hours before dosing, or there is the expectation that such therapy may be given during the study (inhaled or topical steroids are allowed); b) Anticoagulant or antiplatelet therapy within the past 3 weeks before dosing; c) crizanlizumab within the past 30 days before dosing; d) voxelotor within the past 14 days before dosing.
15. For subjects receiving chronic or long-acting opioids, a change in dose or pain requiring medical attention in the past 14 days before dosing.
16. The subject has a medical or psychiatric condition that, in the opinion of the investigator, may pose a risk to the subject for participation or interfere with the conduct or results of the study.
17. The subject has received or plans to receive any other investigational agent within the 4 weeks prior to the study Screening Visit or during the course of the study.
18. There is the expectation that the subject will not be able to be followed for the duration of the study.
19. The subject is i) pregnant, or ii) lactating, or iii) either a female of childbearing potential or a male who is unable or unwilling to comply with birth control methods or abstinence until the end of study visit.
20. The subject with active use of illicit drugs (excluding marijuana) and/or alcohol dependence, as determined by the investigator.
21. The subject has been administered SHP655 previously.
22. Known life-threatening hypersensitivity reaction, including anaphylaxis, to the parent molecule ADAMTS-13, hamster protein, or other constituents of SHP655.
23. The subject has a positive test result for hepatitis B surface antigen, or hepatitis C antibody, or HIV antigen/antibody, at the Screening Visit. However, a subject with a hepatitis C antibody and a negative hepatitis C virus RNA polymerase chain reaction test is not excluded.

Maximum duration of subject participation in the study:

The planned duration of participation is 2 months.

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Endpoints:

Primary:

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.

Secondary:

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).

Pharmacodynamic

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

Exploratory:

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

Statistical analysis:

Safety Analysis Set: all subjects randomized and who received any dose of IP.

PK Analysis Set: 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.

PD Analysis Set: 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.

Safety, including immunogenicity data, will be summarized descriptively by dose cohort.

Adverse events and SAEs will be tabulated and summarized according to the Medical Dictionary for Regulatory Activities, in total, by treatment and by dose level. Individual and summary vital signs and clinical laboratory data will be presented in tabular form with mean, standard deviation, quartiles, and range as appropriate.

For laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

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Pharmacokinetic parameters for ADAMTS13 activity and ADAMTS13:Ag following SHP655 or placebo infusion will be derived using non-compartmental methods, including but not limited to, where applicable and estimable: Incremental recovery, C_{max}, t_{max}, $t_{1/2}$, mean residence time from zero (predose) extrapolated to infinite time, mean residence time from zero (predose) to 72 hours postdose, area under the concentration-time curve from zero (predose) to time of last quantifiable concentration ($AUC_{0\text{-}last}$), area under the concentration-time curve from zero (predose) extrapolated to infinite time ($AUC_{0\text{-}inf}$), area under the concentration-time curve from zero (predose) to 72 hours postdose, CL, and V_{ss}.

PK concentrations and PK parameters will be listed and summarized by dose level (and by scheduled time as applicable). Figures of concentration-time profiles and exposure PK parameters versus dose level will be presented.

The observed PD measurements of plasma VWF:Ag, VWF:RCo, plasma free hemoglobin, plasma thrombospondin, and platelet count will be listed and summarized by treatment, dose level, and scheduled time. Ratio to baseline values will be calculated for VWF:Ag, VWF:RCo, and platelet count. Individual and mean PD profiles over time will be presented. The correlation of plasma free hemoglobin and thrombospondin with ADAMTS13 activity and VWF will be assessed.

The exploratory variables of [redacted] will be listed and summarized by treatment, dose level, and scheduled time.

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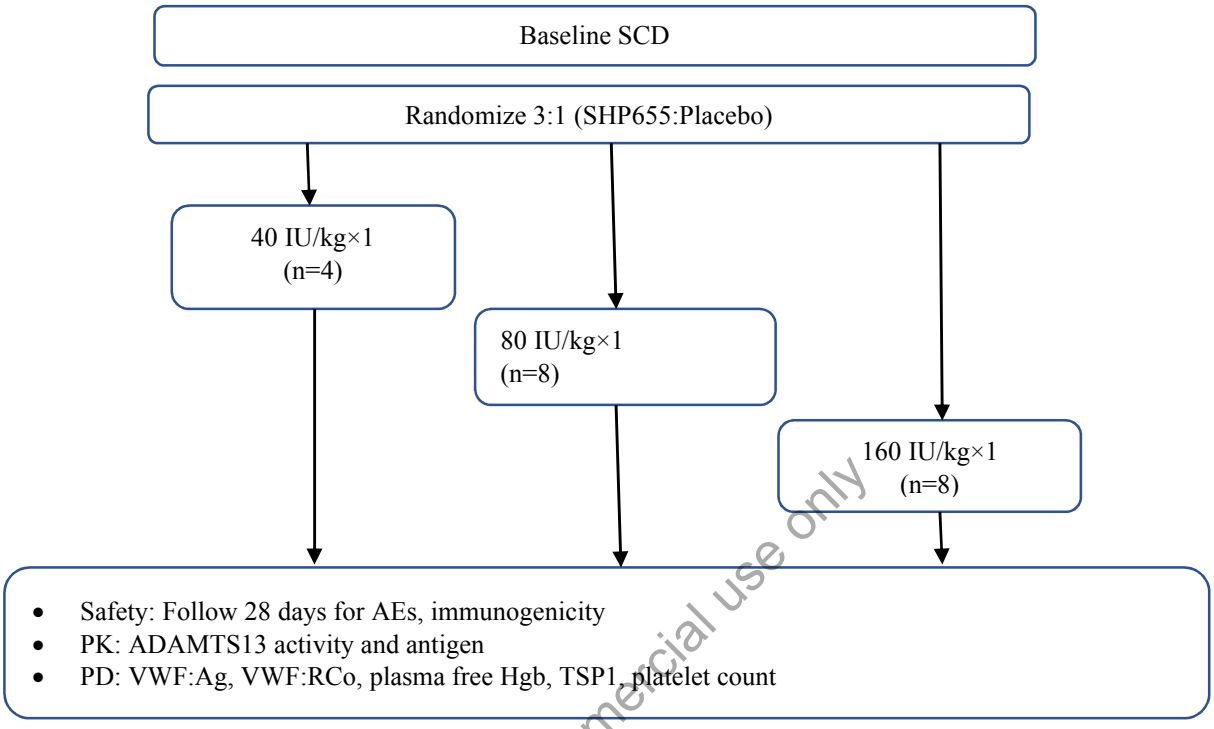
1.2 Schema

Figure 1. Study Schematic



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.

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1.3 Schedule of Activities

Table 1. Schedule of Study Procedures and Assessments

Procedures/Assessments	Screening	Randomization/ PK Baseline Visit	PK Assessments	Follow-Up	Study Completion/ Termination Visit[a]
	Day -28 to 0	Day 1	Day 1, 2, 4, 6, 8, and 10	Day 13 ±2 days	Day 28 ±3 days
Informed Consent[b]	X				
Eligibility Criteria	X	X			
Demographics and Medical History	X				
Prior and Concomitant Medications	X	X	X	X	X
Non-drug Therapies	X	X	X	X	X
Physical Examination	X	X		X	X
Adverse Events	X	X	X	X	X
Laboratory testing[c]	X	X	X	X	X
Vital Signs[d,e]	X	X[e]	X	X	X
Height/weight	X	X			
IP infusion		X			
Peripheral O_2 saturation[f]		X	X	X	X

IP=Investigational product; O_2=Oxygen; PK=Pharmacokinetic; SOP=Standard operating procedure; VAS=Visual analog scale

a. Including for subjects who withdraw or discontinue.
b. Occurs at enrollment (before screening and prior to any study-specific procedure).
c. Laboratory assessments are listed in Table 2.
d. Vital signs include: pulse rate, respiratory rate, body temperature, and blood pressure.
e. Vital signs should be recorded within 5 minutes before the 15 minutes and 1-hour PK samplings, and within 30 minutes before all other PK samplings.
f. Peripheral oxygen saturation will be assessed as per local nursing SOP.

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Table 2. Schedule of Laboratory Assessments

Assessment	Screening	PK Baseline Visit	PK Assessments	Follow-Up	Study Completion/ Termination Visit
	Day -28 to 0	**Within 1 hour prior to IP infusion**	**15 min (±5min), 1 h (±5 min), 3 h (±30 min), 8 h (±30 min), 24 h (±2 h), 72 h (±4 h), 120 h (±24 h), 168 h (±24 h), 216 h (±24 h), and 288 h (±24 h)**	**Day 13 ±2 days**	**Day 28 ±3 days**
PK/PD assessments[a]		C	C		C
Complete Blood Count[b]	L	L	L[f]	L	L
[redacted]					
Plasma free hemoglobin, [redacted][c]		C	C[f]	C	C
Thrombospondin[d]		C	C[f]	C	C
Clinical Chemistry[e]	L	L	L[f]	L	L
[redacted]					
Immunogenicity[g]		C		C	C
[redacted]					
Viral serology[h]	C				
Blood group[i]	L				
Urine pregnancy test[j]	L	L			

ADAMTS13=A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; anti-HBc=Hepatitis B-core total antibodies; C=Testing at central/specialty laboratory; HCV=Hepatitis C virus; HBsAg=Hepatitis B surface antigen; h=Hour; HIV=Human immunodeficiency virus; [redacted]; IP=Investigational product; L=Testing at local laboratory; min=Minute; PD=Pharmacodynamic; PK=Pharmacokinetic; VWF=von Willebrand factor; VWF:Ag=von Willebrand factor antigen; VWF:RCo=von Willebrand factor:Ristocetin cofactor activity.

a. ADAMTS13 activity, ADAMTS13 antigen, VWF:RCo, VWF:Ag, [redacted].
b. Complete blood count with platelets and leukocyte differential.
c. Plasma free hemoglobin requires separation of platelet-poor plasma within 2 hours of collection.
d. Requires special handling (See Laboratory Manual).
e. Clinical chemistry assessments: Sodium, potassium, chloride, bicarbonate, albumin, alanine aminotransferase, aspartate aminotransferase, [redacted], bilirubin (total, [redacted]), alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.
f. To be performed at the following time points only: 3 h, 9 h, 24 h, 72 h, 120 h, 168 h.
g. Immunogenicity assessments: Anti-ADAMTS13 antibody (binding and neutralizing).
h. Viral serology: Anti-HIV 1/2, HBsAg, anti-HBc, anti-HBsAg, anti-HCV.
i. Only if not available in subject's medical history.
j. For females of childbearing potential. To be performed if pregnancy is suspected during study period, or on withdrawal of the subject from the study.

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2. INTRODUCTION

2.1 Indication and Current Treatment Options

Sickle cell disease (SCD) is a common genetic disorder affecting millions of people globally and decreasing life expectancy by 25 to 30 years (U.S. Preventive Services Task Force, 1996). In 2006, the World Health Organization (WHO) recognized SCD as a global public health problem (World Health Organization., 2006). Sickle cell disease is caused by a single base substitution of valine for a glutamic acid at the sixth amino acid of the gene coding for the hemoglobin (Hgb) β chain. This leads to sickle beta globin, which when deoxygenated forms chains of hemoglobin polymers that cause rigid and deformed (sickle-shaped) red blood cells. These sickle red cells are adhesive to endothelium and often unable to traverse the microcirculation. Damaged endothelium promotes white blood cell and platelet activations and adhesion, which in conjunction with sickled red cells, form blockages (vaso-occlusion) that cause decreased oxygen supply to tissues. The resulting ischemic blockages in the microvasculature cause severe hypoxia in tissues throughout the body, which can cause excruciating pain - often in multiple sites simultaneously - and additional debilitating comorbidities. Protracted and repeated exposure to these hypoxic crises can cause broad-ranging tissue injury, potentially leading to organ failure and even death.

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Management of SCD has evolved slowly. Currently, the only curative therapy for SCD is bone marrow transplant but the use of this procedure is limited because of a lack of related or well-matched stem cell donors and risk for mortality and complications such as graft versus host disease (Bolaños-Meade and Brodsky, 2014). Chronic red cell transfusion therapy can reduce symptoms and complications of SCD but comes with a risk of infection, allo-immunization and significant iron overload. The primary pharmacotherapy approved for SCD is hydroxyurea. Hydroxyurea has been shown to reduce, but not eliminate VOCs requiring medical care and reduce the need for blood transfusions. Hydroxyurea continues to have a relatively low rate of use, especially in adults, partly because of its side effect profile, need for monitoring and concerns of toxicity. L-glutamine was recently approved by the food and drug administration for the reduction of VOCs as well, but there has yet to be widespread use of this agent partly because of a modest effect in clinical studies. Currently there are no agents approved for the amelioration of vaso-occlusive painful episodes once they occur (Kato et al., 2018). Despite these therapeutic options, patients with SCD continue to suffer significant morbidity and mortality, and there is an imperative to identify and evaluate new treatments.

There has been increasing evidence to suggest that an elevated level of von Willebrand factor (VWF) antigen and the accumulation of larger VWF multimers in circulation are associated with the development of vaso-occlusion and thrombotic complications in patients with SCD (Zhou et al., 2009).

The existence of hyper-adhesive ultralarge VWF (ULVWF) multimers in plasma and on vascular endothelium indicates that the activity of metalloprotease ADAMTS13, which cleaves ULVWF multimers to reduce their adhesiveness, is probably impaired in these patients with SCD. This impairment may come from biochemical inhibitors of ADAMTS13 (free hemoglobin and thrombospondin-1) and/or by the relative deficiency of ADAMTS13 that occurs as the concentrations of ULVWF increase without a concomitant increase in ADAMTS13 concentration (Bonnefoy et al., 2006; Novelli et al., 2013; Zhou et al., 2011).

Ultralarge VWF additionally promotes the aggregation of other processes that lead to vaso-occlusion in SCD (see Figure 2 in Zhou et al., 2011). As VWF binds endothelium and activated platelets, blood flow decreases. Decreased blood flow promotes white blood cell adherence to endothelium, decreases red cell transit time to promote increased deoxygenation and further sickling and hemolysis, which in turn releases free hemoglobin that impairs ADAMTS13 function.

The pathophysiologic role of VWF is thought to be common to all VOCs, and therefore treatment with rADAMTS13 may be relevant for all VOCs. As therapeutic concentrations of ADAMTS13 are achieved, ULVWF is cleaved into lower molecular weight forms that are less adhesive and less able to trap cells in low blood flow areas. Therapeutic levels of ADAMTS13 is hypothesized to increase blood flow and lead to faster resolution of VOC pain that is caused by ischemia.

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There may be multiple reasons for the acquired ADAMTS13 deficiency associated with SCD, all affecting the synthesis and activity of the metalloprotease. The proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-8 have been shown to stimulate the secretion of ULVWF from inflamed endothelial cells, and IL-6 has been shown to inhibit ADAMTS13. It was also observed that the VWF cleavage activity of plasma ADAMTS13 is about 35% lower in patients with SCD than in normal individuals, even though the antigen level of the metalloprotease was normal. Similarly, others have reported that the ADAMTS13 activity/VWF antigen ratio is lower in patients with SCD. These observations support the view that there is acquired ADAMTS13 deficiency associated with SCD.

2.2 Product Background and Clinical Information

Takeda has developed a recombinant ADAMTS13 (rADAMTS13) named SHP655 (previously known as BAX 930) which is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that expresses the human ADAMTS13 complementary DNA (cDNA). To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final product.

A plasma-protein-free method and 2 virus inactivation steps are used in this process. This process virtually eliminates any risk of transmission of human blood-borne viruses or other adventitious agents that could, in theory, be introduced by the use of animal- or human-derived raw materials. The only proteins present in the final product other than SHP655 are trace quantities of host cell (i.e., CHO) protein.

SHP655 is a composition of the fully glycosylated recombinant human ADAMTS13 protein and a fully glycosylated recombinant human ADAMTS13 protein variant. Testing of the SHP655 cell bank in 2017 revealed a single nucleotide exchange (A to G) in the catalytic domain resulting in amino acid change Glutamine "Q" to Arginine "R" at position 97 at the protein level (described as "Q97R variant"). Further investigation revealed that the Q97R variant was consistent throughout product development, was a rare naturally occurring variant in humans and did not appear to increase immunogenicity. No differences in the structure/function relationship of native and variant protein in the composition was observed and no safety concerns have been identified. Variant protein constitutes between 52%-72% of the product.

SHP655 is a lyophilized formulation for intravenous (IV) injection. SHP655 is a composition of the fully glycosylated recombinant human ADAMTS13 protein and a fully glycosylated recombinant human ADAMTS13 protein variant that appears to be benign in nature.

See Section 6.1 for further information on the investigational product (IP) and its usage in this study. A detailed description of SHP655 is also provided in the investigator's brochure (IB).

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2.2.1 Nonclinical studies

Nonclinical studies have been performed *in vitro* and *in vivo* to characterize the safety, efficacy, pharmacokinetic (PK), and toxicity of SHP655 (Denorme et al., 2016; Denorme et al., 2015; Höllriegl et al., 2013; Kopic et al., 2016; Plaimauer and Scheiflinger, 2004).

The SHP655 nonclinical development program to support the planned Phase 1 trial in patients with sickle cell disease is based on the nonclinical program conducted with SHP655 for the indication of congenital TTP (cTTP). It includes in vivo testing for efficacy, safety pharmacology, pharmacokinetics (PK), and toxicity in several rodent and nonrodent species, including non-human primates.

In addition to the nonclinical efficacy studies already submitted in support of TTP, which are considered supportive for the SCD indication, because the underlying proposed mechanism of action is the same, the sponsor completed specific in vitro and in vivo efficacy studies with SHP655 to support the use in the indication of SCD.

In an in vitro pharmacology proof-of-concept study, the inhibitory effect of hemoglobin on ADAMTS13-mediated VWF multimer cleavage and whether ADAMTS13 can prevent or override this inhibitory effect of hemoglobin were evaluated. Results confirmed the inhibitory effect of hemoglobin at concentrations approximating those in patients during acute VOC and showed that this effect can be prevented by appropriate concentrations of rADAMTS13.

In an in vivo pharmacology proof-of-concept study, a transgenic mouse model for human SCD (Tim Townes mouse), was used to assess the effects of SHP655 administration on hypoxia induced SCD-related acute VOC. Mice were studied under two forms of hypoxia, a severe form to study the survival and more mild version to study the effect on blood and tissue parameters. Under the severe hypoxic conditions, SS mice treated with SHP655 survived, while all vehicle-treated SS animals were sacrificed in extremis. Under the milder hypoxic conditions, SHP655 reduced the hypoxia-induced systemic inflammation and hemolysis, pulmonary vascular leakage, vaso-constriction, inflammatory vasculopathy, formation of cell inflammatory infiltrate, and thrombi in lung and kidney.

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General safety pharmacology evaluations did not find deleterious effects of SHP655 on cardiovascular and respiratory functions in cynomolgus monkeys. Pharmacokinetic evaluations demonstrated similar PK profiles for SHP655 in rats and cynomolgus monkeys.

Overall, the completed nonclinical toxicity studies with SHP655 support the following conclusions:

- SHP655 did not cause any adverse effects on respiratory and cardiovascular function in cynomolgus monkeys at a dose up to 400 IU/kg, which was the highest dose tested.
- In a 4-week repeat dose toxicity study in rats the no-observed-adverse-effect-level (NOAEL) was 1820 IU/kg/day, the highest dose tested in this study and the maximum feasible dose.
- In a long-term toxicity study in rats, there was no evidence of toxicity after IV injection of 400 IU/kg every 3 days for 26 weeks. Based on these results, the NOAEL was considered to be at 400 IU/kg, which was the highest dose tested.
- Administration of 80, 200, or 400 IU/kg SHP655 once a week for 29 days in cynomolgus monkeys did not cause any adverse clinical symptoms, target organ pathologies, or other adverse findings directly attributable to the test item. The NOAEL was the highest dose tested, 400 IU/kg.
- SHP655 was well tolerated after IV (intended clinical administration route) (5 mL), intra-arterial (5 mL), and paravenous (0.5 mL) administration in a local tolerance study in New Zealand white rabbits.

- In female fertility and embryo-fetal development and pre and postnatal development studies in rats, no reproductive toxicity was observed at doses up to 400 IU/kg, which was the highest dose tested. A human placenta transfer study demonstrated that there is no biologically relevant transfer of SHP655 from the maternal blood circulation to the embryo.

Please see Section 4 of the IB for further details on nonclinical studies of SHP655.

2.2.2 Clinical studies

The use of SHP655 has not yet been examined in patients with SCD. In the completed first in human Phase 1 Study 281101 in patients with congenital thrombotic thrombocytopenic purpura, SHP655 was active in vivo, including effects on VWF multimers and platelet counts.

Please refer to Section 5 of the IB for further details on effects of SHP655.

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2.3 Study Rationale

Sickle cell disease patients have a higher ratio of ULVWF:ADAMTS13 activity compared to that found in the healthy population. By increasing the concentration of plasma ADAMTS13 with SHP655, a more physiologic balance of ULVWF:ADAMTS13 ratio may be restored (Schnog et al., 2006; Sins et al., 2017). Dosing to achieve a meaningful increase over normal activity (i.e., supraphysiologic) levels is anticipated to be necessary to achieve a therapeutic effect in the presence of biochemical inhibitors (i.e., plasma free hemoglobin and thrombospondin-1) to ADAMTS13 and relatively high concentrations of ULVWF.

This study will assess safety (including immunogenicity), tolerability, PK and pharmacodynamics (PD) of SHP655 in SCD. Understanding the relationships among PK, PD, biomarkers, and their clinical correlates can guide the design of the subsequent studies.

2.4 Benefit/Risk Assessment

The benefit-risk relationship was carefully considered in the planning of this study. Based on the nonclinical data available from the IB to date, the conduct of this study is considered justifiable using the dose(s) and dosage regimen(s) of SHP655 as specified in this clinical study protocol. A direct benefit is considered unlikely for participants in this Phase 1 study. The sample size of the dose cohorts was chosen to provide descriptive statistics to further explore the safety, PK, PD, and immunogenicity of SHP655 in the specific indication. Participation in this study may help develop important scientific knowledge that should contribute to the development of better comprehensive treatment of subjects with SCD. A Dose Escalation Committee is planned for ongoing safety review during the study.

The Dose Escalation Committee may stop enrollment and/or escalation to the next dose cohort based on the criteria outlined in Section 6.2.3.1 and Section 6.2.3.2. A list of dose-limiting toxicities can be found in Section 6.2.3.2.

In summary, it needs to be determined that the benefits of conducting the study outweigh the potential risks of SHP655 administration at this stage of product development. The key societal benefit is a better understanding of treatment options for patients with SCD.

Currently, the highest dose planned for this study is 160 IU/kg, allowing a 2.5-fold safety margin from the lowest NOAEL in the 6-month toxicity study (400 IU/kg). Data from the most recent repeat dose toxicity study in rat, with daily administration of 800 and 1820 IU/kg/day for 30 days even allow 5-fold and 11-fold, based on exposure and dose respectively, safety margin for the highest dose planned for this study of 160 IU/kg.

Always refer to the latest version of the SHP655 IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of SHP655.

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2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Appendix 1.

3. OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

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 VWF and platelets
- Study the correlation of plasma free hemoglobin and thrombospondin on SHP655 activity and VWF.

3.1.3 Exploratory Objective

- Assess additional exploratory biomarkers [redacted].

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3.2 Study Endpoints

Table 3. Objectives and Endpoints

Objective	Endpoint(s)
Primary	
Assess safety, tolerability, and immunogenicity of SHP655 in subjects with SCD subjects at baseline health	• SAEs/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.
Secondary	
Assess the PK of SHP655 at 3 dose levels in subjects with SCD	• Including but not limited to: IR, C_{max}, t_{max}, $t_{1/2}$, $MRT_{0\text{-}inf}$, $MRT_{0\text{-}72}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}72}$, CL, and V_{ss} will be estimated for ADAMTS13 activity and ADAMTS13 antigen.
Assess the effect of SHP655 on von Willebrand factor (VWF) and platelet count.	• VWF:antigen (VWF:Ag), VWF:Ristocetin cofactor activity (VWF:RCo), and platelet count.
Study the correlation of plasma free hemoglobin and thrombospondin on SHP655 activity	Plasma free hemoglobin and plasma thrombospondin levels
Exploratory	
Assess additional exploratory biomarkers, [redacted].	[redacted]

ADAMTS13=A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; AE=Adverse event; $AUC_{0\text{-}72}$=Area under the concentration-time curve from zero (predose) to 72 hours postdose; $AUC_{0\text{-}inf}$=Area under the concentration-time curve from zero (predose) extrapolated to infinite time, $AUC_{0\text{-}last}$=Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration; CL=Systemic clearance; C_{max}=Observed maximum concentration; [redacted]; IR=Incremental recovery; [redacted]; $MRT_{0\text{-}72}$=Mean residence time from zero (predose) to 72 hours postdose; $MRT_{0\text{-}inf}$=Mean residence time from zero (predose) extrapolated to infinite time; PK=Pharmacokinetic; SAE=Serious adverse event; SCD=Sickle cell disease; $t_{1/2}$=Terminal half-life; t_{max}=Time to reach C_{max}; V_{ss}=Volume of distribution at steady state; VWF=von Willebrand factor.

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4. STUDY DESIGN

4.1 Overall Design

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.

There will be a 14-day interval between dosing for the first 3 subjects in any dose cohort. The higher dose cohorts will be opened only after safety data from up to Day 13 post-infusion from all subjects at the corresponding dose have been evaluated by the Dose Escalation Committee. Enrollment and escalation to next dose cohort will be paused for review if anaphylaxis, neutralizing antibody, or death is reported.

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4.2 Scientific Rationale for Study Design

The ratio of ULVWF:ADAMTS13 activity is higher in subjects with SCD than in healthy people. Hence, the study population selected for this study includes subjects with SCD. Additionally, dosing of SHP655 to supraphysiologic levels has not been characterized clinically. In this Phase 1, dose escalation study, SHP655 or placebo will be administered as single dose IV infusion at 3 dose levels (40, 80, and 160 IU/kg) to evaluate PK, PD, clinical, and biomarker assessments.

Using a placebo improves the integrity of the study in several ways. Placebo provides a comparison group for evaluation of safety in a study population that is anticipated to have comorbidities that are reported as AEs. Obtaining PK/PD assessments on subjects receiving placebo serves as a control group for PK/PD and biomarker assessments.

Blinding IP treatment removes bias from the study design. Knowledge of active versus placebo treatment can influence reporting of safety events, perception and reporting of pain, and affect clinical management decisions that can influence study outcomes. Similarly, randomization reduces bias by ensuring that a relationship between baseline characteristics and outcomes is due to chance, and not by confounding traits (e.g., disease severity).

A Dose Escalation Committee is included in the study design to provide ongoing monitoring of safety and study progress. At each dose level, a decision must be made about the safety of increasing to a higher dose level. The Dose Escalation Committee may recommend that the number of subjects at a dose level be changed to obtain additional safety information, cap enrollment at a dose level, or modify a dose at a subsequent dose level, taking into consideration data that are observed in other cohorts.

4.3 Justification for Dose

Dosing to achieve a meaningful increase over normal activity (i.e., supraphysiologic) levels is anticipated to be needed for a therapeutic effect in the presence of biochemical inhibitors to ADAMTS13 and relatively high concentrations of ULVWF. Doses are escalated to evaluate safety prior to higher dose exposure. Single dose exposure to 40 IU/kg has been found to be safe and well tolerated in subjects with congenital thrombotic thrombocytopenia purpura and was selected as the starting dose for this study.

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A mechanistic PK/PD modeling study guided dosing of SHP655 by providing a quantitative relationship between dose level and VWF activity. Based on the clinical goal of reducing the VWF activity level in SCD patients with a VOC to a normal level, the model indicates that this can be achieved with a single dose of approximately 120 U/kg. The low exposures of SHP655 in the monkey study were attributed to neutralizing antibodies and are not considered to be predictive of antibody formation in humans, therefore the rat data is more relevant for deriving safety margins. The NOAEL (1820 U/kg) observed in the 30-day daily administration study in rats represents a 10.8X safety margin to the starting dose (40 U/kg) and a 5.6X safety margin to the highest proposed clinical dose 160 U/kg in the initial Phase 1 clinical trial based upon predicted clinical exposure. Thus, the dose levels selected in this study were 40, 80, and 160 IU/kg.

4.4 Duration of Subject Participation and Study Completion Definition

The subject’s maximum duration of participation is expected to be approximately 2 months. The study will be completed in approximately 2 years.

The study completion date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the End of Study Visit or Termination Visit, whichever is later (refer to Section 8.1.3).

Sites and Regions

The study will be conducted at approximately 20 sites in the United States.

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5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. Age 18 to 65 years at the time of signing the informed consent.
2. An understanding, ability, and willingness to fully comply with study procedures and requirements.
3. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.
4. Male or female with a documented history of HbSS or HbSβo thalassemia (based on clinical record of genetic, electrophoresis, or high-performance liquid chromatography testing).
5. Subject currently taking hydroxyurea must be on a stable dosing for 3 months at screening.

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5.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. The subject was diagnosed with acute VOC in the 21 days before dosing on Day 1
2. The subject has undergone blood transfusion within the last 30 days or blood transfusion on ≥2 occasions in the last 90 days, at Screening Visit.
3. The subject has a history of acquired or congenital thrombotic thrombocytopenic purpura.
4. The subject has serum creatinine level >1.2 mg/dL at the Screening Visit
5. The subject has alanine transaminase >3×upper limit of normal (based on clinical laboratory normal range), direct bilirubin level > 2 mg/dL, or indirect bilirubin level >5 mg/dL at the Screening Visit.
6. The subject has a hemoglobin level <5 g/dL at the Screening Visit.
7. The subject has a platelet count of <100 000/mm3 at the Screening Visit.
8. Signs or symptoms of infection requiring treatment with IV antibiotics during the Screening Period.
9. The subject has fever with body temperature of ≥38.5ºC (101.3ºF) at the Screening Visit or before dosing on Day 1.

10. The subject has acute chest syndrome (ACS), diagnosed or strongly suspected, as evidenced by a new infiltrate on chest radiograph, and one or more of the following criteria:
    - Fever with body temperature >39°C (102.2°F)
    - Hypoxia (confirmed by arterial blood gases with PaO2 <70 mmHg)
    - Chest pain
    - Suspicious findings on physical examination (tachypnea, intercostal retraction, wheezing, and/or rales).
11. The subject has recently (within the past 28 days, from Screening Visit) undergone major surgery, requires hospitalization, documented serious bacterial infection requiring antibiotic treatment, or significant bleeding.
12. The subject has had a recent (within the past 90 days, from Screening Visit) episode of stroke, transient ischemic attack, symptomatic pulmonary hypertension, or seizure.
13. Any history of hemorrhagic stroke or bleeding diathesis.
14. The subject has received any of the following protocol-restricted medicines: a) systemic steroid therapy within 48 hours before dosing, or there is the expectation that such therapy may be given during the study (inhaled or topical steroids are allowed); b) Anticoagulant or antiplatelet therapy within the past 3 weeks before dosing; c) crizanlizumab within the past 30 days before dosing; d) voxelotor within the past 14 days before dosing.
15. For subjects receiving chronic or long-acting opioids, a change in dose or pain requiring medical attention in the past 14 days before dosing.
16. The subject has a medical or psychiatric condition that, in the opinion of the investigator, may pose a risk to the subject for participation or interfere with the conduct or results of the study.
17. The subject has received or plans to receive any other investigational agent within the 4 weeks prior to the study Screening Visit or during the course of the study.
18. There is the expectation that the subject will not be able to be followed for the duration of the study.
19. The subject is pregnant or lactating or a female of childbearing potential or male unable or unwilling to comply with birth control methods or abstinence until the end of study visit.
20. The subject with active use of illicit drugs (excluding marijuana) and/or alcohol dependence, as determined by the investigator.
21. The subject has been administered SHP655 previously.
22. Known life-threatening hypersensitivity reaction, including anaphylaxis, to the parent molecule ADAMTS-13, hamster protein, or other constituents of SHP655.

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23. The subject has a positive test result for hepatitis B surface antigen, or hepatitis C antibody, or HIV antigen/antibody, at the Screening Visit. However, a subject with a hepatitis C antibody and a negative hepatitis C virus RNA polymerase chain reaction test is not excluded.

5.3 Restrictions

No dietary or activity restrictions are associated with this study.

5.4 Reproductive Potential

5.4.1 Female Contraception

Sexually active females of childbearing potential should use a highly effective or acceptable method of contraception. Females of childbearing potential must be advised to use these contraceptive methods throughout the study period.

Female subjects should be either:

- Postmenopausal
- Surgically sterile, or
- Of childbearing potential with a negative urine and/or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at Screening Visit.

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5.4.2 Male Contraception

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent during the study period.
- Agree to use a male condom when having penile-vaginal intercourse with a partner of childbearing potential who is not currently pregnant during the study period.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

SHP655 and placebo (0.9% saline)

Dosage form:

Lyophilized formulation in capacity of 2 dosing solutions (100 and 300 IU/mL).

Dosage frequency:

One dose is administered per subject.

Mode of Administration:

Intravenous

SHP655 (rADAMTS13), a recombinant ADAMTS13, which is synthesized by a genetically engineered CHO cell line that expresses the human ADAMTS13 cDNA. It will be provided in lyophilized formulation together with sterile water for reconstitution for IV administration. Additional information is provided in the current SHP655 IB.

The reference/comparator product is placebo (0.9% saline).

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6.1.2 Blinding the Treatment Assignment

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.

6.2 Administration of Investigational Product

The reconstituted solution of SHP655 should be inspected for particulate matter and discoloration prior to administration. The solution should be clear and colorless in appearance. If not, do not administer the product. SHP655 should be administered at room temperature and within 3 hours of reconstitution. Prior to administration, ensure that venous access via an IV cannula is available. However, for IP infusion, the butterfly needle may be inserted immediately prior to the infusion.

6.2.1 Interactive Response Technology for Investigational Product Management

An IRT system will be used for screening and randomizing subjects, recording subject visits, IP supply dispensation and management, inventory management and supply ordering, IP expiration tracking and management, IP return, and emergency unblinding. Please refer to the Study Manual for additional details regarding the IRT system.

6.2.2 Allocation of Subjects to Treatment

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.

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Individual subject treatment is automatically assigned by the 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.

6.2.3 Dosing

The IP will be administered intravenously.

SHP655/placebo will be administered as a single IV infusion at 3 dose levels: 40 IU/kg (n=4), 80 IU/kg (n=8), and 160 IU/kg (n=8).

The IP will be infused at 4 mL/min, to achieve an infusion rate of 1200 IU/min with 300 IU/vial preparation.

Note: For 100 kg person at 160 IU/kg = 16 000 IU/1200 IU/min = 13 minutes.

The first 3 subjects in each dose cohort will be dosed a minimum of 14 days apart to observe and interpret reactions and adverse events in order to ensure that no related SAE requiring a pause or stop of the clinical trial (see Section 6.2.3.1 and Section 6.2.3.2) has occurred in the most recently treated subject.

In the event that DLT criteria are met (see Section 6.2.3.2), either revision of the dose to a lower, intermediate level or augmented enrollment of the previous dose level will be considered.

6.2.3.1 Stopping Criteria for Dose Escalation

1. If 2 or more subjects in a given cohort receiving active drug have a related SAE in any vital organ or body system, no further subjects will be enrolled or dosed until further evaluation of the available data is made by the medical monitor and investigator to determine whether to stop or proceed with the study. Following a safety review of the event, study enrollment or dosing of currently enrolled subjects may be restarted if the Dose Escalation Committee determines that it is safe to proceed with the study.
2. Any neutralizing antibody to SHP655 that develops after administration.
3. Any death that is possibly related to SHP655 administration.
4. If any other drug-related event occurs in subjects receiving active drug and is deemed to pose an unacceptable risk to subjects by the investigator or medical monitor after further evaluation, no further subjects will be enrolled or dosed until further evaluation of the available data is made by the Dose Escalation Committee to determine whether to proceed with the study. Following a safety review of the event, study enrollment or dosing of currently enrolled subjects may be restarted if the medical monitor and the investigator determine that it is safe to proceed with the study.

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6.2.3.2 Dose Limiting Toxicities

DLT are defined according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

DLT are defined as two events of any of the following AEs at least possibly related to SHP655 within a dose cohort:

- Purpura Grade 2
- Gastrointestinal hemorrhage Grade 1 (lower gastrointestinal, oral, esophageal, gastric, duodenal, ileal, cecal, or colonic hemorrhage)
- Epistaxis Grade 2

- Menorrhagia Grade 2
- Hematuria Grade 1

In the event that 2 DLTs are observed within a dose cohort, a Dose Escalation Committee meeting will be convened to review the treatment assignment of the subjects experiencing the toxicities to determine if DLT criteria have been met.

The following are DLTs if observed in one SHP655 treated subject:

- Purpura Grade 3 or higher
- Gastrointestinal hemorrhage Grade 2 or higher (lower gastrointestinal, oral, esophageal, gastric, duodenal, ileal, cecal, or colonic hemorrhage)
- Epistaxis Grade 3 or higher
- Menorrhagia Grade 3 or higher
- Hematuria Grade 2 or higher
- Stroke Grade 2 or higher
- Intracranial hemorrhage Grade 1 or higher
- Any Grade 4 AE at least possibly related to SHP655 exposure.

DLTs are not to be AEs assessed by the investigator as disease related.

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6.2.3.3 Dose Escalation Committee

Throughout the study, dose escalation meetings will commence at regular time points to review safety data and authorize progression into the next cohort. The Dose Escalation Committee may recommend continuing the study, stop dose escalation, expand a dose cohort to obtain more safety data, modify or add a dose escalation in between planned dose cohorts (e.g., 120 IU/kg after the 80 IU/kg dose cohort is evaluated), and add a dose to a treatment regimen within a dose cohort. The following arrangement is planned for the Dose Escalation Committee to help maintain study integrity.

The Dose Escalation Committee will convene at least after every dose cohort has been enrolled and completed up to the 2 week Follow-Up Visit.

If AEs are observed within a dose cohort that could meet DLT criteria, the Dose Escalation Committee will review treatment assignments to determine whether the DLT has been reached.

The Dose Escalation Committee will recommend whether:

1. It is safe to proceed to the next dose cohort

2. A dose level may be modified, reduced, or repeated, depending on the outcome of the safety data review
3. A dose level should be added or eliminated
4. Protocol modifications regarding dosing are needed

Dose escalation committee review meetings will be held after SAE and immunogenicity data are available up to Day 13 of the last subject in the dose cohort. This dose cohort will be opened for Dose Escalation Committee review. Enrollment will be paused for review for any case of anaphylaxis, neutralizing antibody, life-threatening condition, or death.

The Dose Escalation Committee will have a charter that defines roles, responsibilities, and procedures.

6.2.4 Unblinding the Treatment Assignment

The treatment assignment must not be unblinded to the investigator during the study except in emergency situations where identification of the IP is required for medical management of the subject. The investigator should contact the medical monitor as soon as possible after the treatment code has been broken and the investigator is unblinded.

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In the event that the treatment assignment code is broken, the date and the signature of the person who broke the code are recorded on the IRT and in the source documents, as applicable. The reason for breaking the code will be recorded in the source documents, as appropriate, based on safety or deviation reporting. Upon breaking the blind, the subject will be withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to IQVIA and Takeda. For blinded studies, there will be a provision for unblinding to ensure adequate management of the subject in the case of an emergency.

Following the review of unblinded data for a completed dose cohort by the DEC, and a recommendation by the DEC that it is safe to proceed with enrollment of the next dose cohort, the Sponsor study team will have access to the unblinded data for the completed dose cohort, with details to be specified in an unblinding plan.

6.2.5 Dose Modification

The decision to proceed to the next dose cohort will be made by the Dose Escalation Committee based on safety, tolerability, and preliminary PK and/or pharmacodynamic data. Enrollment will be paused for review for any case of anaphylaxis, neutralizing antibody, or death.

The Dose Escalation Committee will monitor the safety of the study and will have standing to stop dose escalation, expand a dose cohort to obtain more safety data, modify or add a dose escalation in between planned dose cohort, and add a dose to a treatment regimen within a dose cohort.

In the event that DLT criteria are met (see Section 6.2.3.2), either revision of the dose to a lower, intermediate level or augmented enrollment of the previous dose level will be considered.

The IP will be permanently discontinued or temporarily discontinued based on Dose Escalation Committee's decision or after discussion with sponsor.

6.3 Labeling, Packaging, Storage, and Handling of Investigational Product

6.3.1 Labeling

Labels containing study information and pack identification are applied to the IP (s) container.

All IP(s) is labeled with a minimum of the following: Protocol number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date, batch number and/or packaging reference, the statements "For clinical study use only" and/or "CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use".

Space is allocated on the label so that the site representative can record a unique subject identifier.

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Additional labels (e.g., those used when dispensing marketed product) may, on a case-by-case basis, be applied to the IP in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.
- Identify the study subject by name.
- Break the study blind

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Details are provided in Section 6.1.1.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are administered by qualified study personnel or designee. The pharmacist/nominated team member will enter the unique subject identifier on the IP bottle/carton labels as they are distributed. Unblinded pharmacists will have access to IP supplied by the sponsor. Other study staff should only have access to IP in blinded syringes with the appropriate label.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the IP is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

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Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the IP and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the IP that could affect the integrity of the product(s), e.g., fumigation of a storage room.

All controlled-substance IP for the sponsor's studies must be stored in a securely locked, substantially constructed room or cabinet according to all applicable local, state, and/or national laws. Limited, controlled access to these IP(s) must be maintained, as well as chain of custody, for all IP movement.

6.3.4 Special Handling

SHP655 must not be used beyond the expiration date printed on the vial. Freezing should be avoided at all times to prevent damage to the diluent vial. Before administration, the reconstituted product has to be brought to room temperature. Storage of SHP655 post-reconstitution should be limited to 3 hours at room temperature.

In case large volumes of SHP655 are required, it is possible to pool multiple vials of SHP655 together. The contents of each reconstituted product can be drawn in a single syringe. The recommended storage condition for SHP655 is 2 to 8°C. The expiration date for SHP655 is included on the IP label. The stability of the clinical lots will be monitored throughout the period of use in clinical studies.

For additional information please refer to the SHP655 IB and/or other specific instructions provided by the sponsor. Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the IP to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

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The investigator has overall responsibility for administering/dispensing IP. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the IP only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the IP carrying his/her treatment assignment. All administered medication will be documented in the subject's source and/or other IP record.

No IP stock or returned inventory from a Takeda-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, and empty/used IP packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO).

For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (i.e., IRT) do not require a shipment form. Returned IP (s)must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any IP prior to shipment. Shipment of all returned IP must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile IPs delivered with those used and returned. All IP(s) must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

The IP will be administered in the study center by the authorized study center staff. The investigator or designee will record the correct dose, date, and time of administration on the Drug Accountability Record.

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6.6 Prior and Concomitant Therapy

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, as appropriate) received within 30 days prior to the Screening Visit (Visit 1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol defined follow-up period) must be recorded in the subject's source document.

6.6.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days of the date of screening. 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.

6.6.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between screening and the study completion/termination visit, inclusive. Concomitant treatment information must be recorded in the subject's source document.

6.6.3 Permitted Treatment

Use of stable dose of hydroxyurea for 3 months prior to Screening Visit, and steroid for inhalation or topical application are permitted during the study. Females of childbearing potential are to continue using their hormonal contraceptives and postmenopausal women are allowed to use hormone replacement therapy.

The investigator must record the use of all concomitant medications, both prescribed and over-the-counter, into the electronic case report form (eCRF) and subject's medical records. This includes medications used on both a regular and an as needed basis.

Subjects should be discouraged from starting any new medication, both prescribed and over-the-counter, without consulting the investigator, unless the new medication is required for emergency use or has been prescribed for clinical need.

The Sponsor recommends that subjects not be administered a vaccine against SARS-CoV2 during the Study Period. Should a subject receive such a vaccination during the Study Period, the Sponsor recommends study investigators to follow patients closely for vaccine-related adverse events for 14 days after vaccination, in collaboration with the study medical monitor.

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6.6.4 Prohibited Treatment

- Systemic steroids within 48 hours prior to randomization
- L-glutamine, voxelotor, and crizanlizumab are restricted during the study period
- Anticoagulant or anti-platelet medications
- Illicit drugs are prohibited during the study treatment
- Coagulation factor concentrates
- Administration of another investigational drug or device

A subject who has taken any of these medications or received any of these non-drug therapies during the study may be withdrawn from the study at the discretion of the sponsor.

6.7 Adverse event management

The mechanism of action of SHP655 reduces high molecular weight von Willebrand factor. SHP655 dosing theoretically could induce a von Willebrand disease phenotype. In the event of hemorrhage after SHP655 dosing consistent with DLT criteria in Section 6.2.3.2, treatment that replenishes von Willebrand factor may be indicated.

Immunogenicity to SHP655 theoretically could result in a TTP-like syndrome. In case of evolving thrombocytopenia, neurologic changes, or thrombotic microangiopathy that emerges after IP dosing, ADAMTS13 activity should be tested. Treatment of an immunogenicity-induced TTP event with standard TTP treatment would be expected to be beneficial.

SHP655 should not be administered in patients with known hypersensitivity to any of the components of rADAMTS13. As with any i.v. protein product, allergic-type hypersensitivity reactions are possible. Subjects must be closely monitored for any symptoms throughout the infusion period. Subjects should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented.

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7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If IP is discontinued, regardless of the reason, the evaluations listed for study completion visit will be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified evaluations at termination visit. Comments (spontaneous or elicited) or complaints made by the subject regarding discontinuation must be recorded in the source documents. The reason for discontinuation, date of discontinuation of the IP, and the total amount of IP administered must be recorded in the source documents.

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

7.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's source document. If a subject is discontinued for more than one reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

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Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Other (e.g., pregnancy)

7.3 Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

7.4 Subjects "Lost to Follow-up" Prior to the Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject who is lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact).

At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgment of receipt request) asking that the subject return to the site for final safety evaluations.

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8. STUDY ASSESSMENTS AND PROCEDURES

Prior to performing any study assessments that are not part of routine medical care for the subject, the investigator will obtain written informed consent as described in Appendix 1.5. Any subject who is randomized is considered a subject enrolled in the study.

The following series of numbers will comprise the subject identifier: The last three digits of the protocol identifier (i.e., 101), a 3-digit study site number (e.g., 002), and 4-digit subject number (e.g., 0003) assigned by the IRT system and reflecting the order of enrollment (i.e., signing the ICF). For example, the third subject who signed an ICF at study site 002 will be identified as Subject 101-002-0003. All study documents (e.g., case report forms [CRFs], clinical documentation, sample containers, drug accountability logs, etc.) will include the subject identifier. Subjects who fail to meet eligibility criteria may be re-screened during the open screening period of the study. A different subject identifier will be issued to all such subjects.

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8.1 Study Schedule

The overall study design is illustrated in Figure 1. Details on the assessments to be performed at each study visit, including screening, are provided in Table 1. Study assessments are detailed in Section 8.2.

8.1.1 Screening Visit

All screening procedures and confirmation of eligibility shall take place within 28 days prior to the first infusion of IP. If the IP is not infused within 28 days, all screening assessments must be repeated to reconfirm eligibility.

The study site is responsible for maintaining a screening and enrollment log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered IP. A complete or partial re-screen may also become necessary at the discretion of the investigator or sponsor.

8.1.2 Treatment Period

On Day 1, the subjects will be randomized to receive either SHP655 or placebo in a 3:1 ratio. Additional Day 1 procedures will be carried out in accordance with the Schedule of Assessment in Table 1.

Subjects with any ongoing AEs or SAEs at the time of scheduled discharge from the study center should remain at the study center until the investigator has determined that these events have been resolved or deemed as not clinically significant by the investigator.

The Treatment Period consists of the Day 1 IP infusion through the last planned PK/PD assessment.

8.1.3 Follow-up Period

The follow-up period for this protocol is 13 days. At the end of this period there will be a Follow-Up Visit query for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Appendix 3.2).

8.1.4 Study Completion/Termination Visit

After the follow-up period, all subjects will return to the study center for the EOS Visit. The EOS will be on Day 28 following IP infusion. Subjects who discontinue the study early will be asked to return to the study center for the termination visit.

Different procedures will be carried out in accordance with the Schedule of Assessments in Table 1.

8.1.5 Additional Care of Subjects after the Study

No aftercare is planned for this study.

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8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information and other baseline characteristics including gender, age, and race, vital signs, physical examination, height/weight, medical history, prior medications, AE, etc. will be collected prior to the subject receiving the first dose of IP.

8.2.2 Safety

8.2.2.1 Physical Examination

At screening and subsequent study visits (refer to Section 1.3), a physical examination will be performed by the investigator. A complete physical examination includes, general appearance, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, liver/gastrointestinal, extremities/musculoskeletal, skin/dermatological, neck/thyroid, lymph nodes, psychiatric/neurological systems.

Abnormalities identified at the Screening Visit and at subsequent study visits will be recorded in the subject's source documents. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

8.2.2.2 Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. Refer to Appendix 3 for AE definitions, assessment, collection time frame, and reporting procedures.

8.2.2.3 Vital Signs

Vital signs will be assessed pre- and post-infusion at each visit, if not stated otherwise:

- Height (cm) and weight (kg).
- Systolic/diastolic blood pressure (mmHg) baseline measurements will be measured after a 10-minute rest in the supine/semi-recumbent position.
- Pulse (beats/min) will be measured at the distal radial arteries under the same conditions as above.
- Respiratory rate (breaths/min) will be measured over a period of 1 minute under the same conditions as above.
- Body temperature (ºC or ºF) may be determined by oral, rectal, axillary, temporal, or tympanic measurement at the discretion of the investigator. However, the same method should be used for all measurements in 1 subject.

Vital signs, excluding height and weight, will be measured at screening and within 5 minutes before the 15-minutes and 1-hour PK samplings, and within 30 minutes before all other PK samplings and at each study visit, and at study completion/termination. Blood pressure will be measured when subjects are in the supine/semi-recumbent position.

The investigator will assess whether a change from the Baseline Visit in vital signs may be deemed clinically significant and whether the change should be considered and recorded as an AE. If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

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8.2.2.4 Clinical Laboratory Tests

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out of range changes which may be associated with, or constitute, an AE. The investigator should assess out of range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

A complete list of the clinical laboratory tests to be performed is provided in Appendix 2.

8.2.2.5 Pregnancy Test

A urine or serum pregnancy test will be performed on all females of childbearing potential at the screening visit (Visit 1) and Baseline Visit; if pregnancy is suspected; or on withdrawal of the subject from the study.

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8.2.3 Pharmacokinetics

Blood samples will be assessed to determine ADAMTS13 activity and ADAMTS13 antigen according to Schedule of Assessment presented in Table 1 as per the timepoints mentioned in Table 2. The actual date and time of dosing and of the blood sample collection will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate laboratory manual.

8.2.4 Pharmacodynamics

PD effects will be assessed by measuring VWF:Ag, VWF:RCo, and platelets, as specified in Table 2. The impact of plasma free hemoglobin and plasma thrombospondin levels will also be assessed.

The actual date and time of the sample collection will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate laboratory manual. The analytical methods used to measure these PD endpoints will be described in a separate bioanalytical report.

8.2.5 Additional Exploratory Biomarkers

Biomarkers of SCD severity and additional PD readouts that may be impacted by SHP655 will be assessed.

These evaluations may include, but are not limited to, [redacted].

The actual date and time of the sample collection or observation will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate laboratory manual.

8.2.6 Retention of Study Samples

Biologic samples will be retained in biostorage for up to 4 years after study completion. Consent will be obtained for any testing of these samples that are outside the objectives of this study.

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9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the safety, pharmacokinetic, and pharmacodynamic data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, IP exposure, and both prior and concomitant medications. It will also provide the preparation of tables, listings, and figure details.

The SAP will be finalized prior to final unblinding to preserve the integrity of the statistical analysis and study conclusions. Data handling approaches, including imputation of missing values, will be provided in the SAP.

Data will be summarized by dose level. The placebo group will be pooled for the presentation.

All statistical analyses will be performed using statistical analysis system (SAS®) (SAS Institute, Cary, NC 27513) Version 9.4 or above.

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9.2 Planned Interim Analysis, Adaptive Design, and Data Escalation Committee

Although no formal DMC will be involved in the management of this study, safety will be monitored by a Takeda Dose Escalation Committee. Please refer to Section 6.2.3.2 for more details.

9.3 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.

9.4 Statistical Analysis Set(s)

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 ***Safety Analysis Set*** will consist of all subjects randomized and who received any dose of IP.

The ***PK Analysis Set*** will contain all subjects who receive at least one 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 used for all PK summaries.

The ***PD Analysis Set*** will contain all subjects who receive at least one 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 used for all PD summaries.

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9.5 Safety Analyses

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

9.5.1 Primary Safety Endpoint

The 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.

9.5.2 Statistical Analysis of Safety Parameters

Safety, including immunogenicity data, will be assessed using descriptive summaries by dose cohort appropriate for the measure (e.g., number and percent for categorical measures and mean, standard deviation, quartiles, and range as appropriate for continuous measures).

For each measure, baseline is the last non-missing value reported prior to the first infusion of IP.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the infusion of IP.

The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment cohort. Treatment-emergent adverse events will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed. AEs and SAEs will be tabulated and summarized according to the Medical Dictionary for Regulatory Activities.

Individual and summary vital signs and clinical laboratory data will be presented in tabular form.

For laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

The number and proportion of subjects will be summarized by dose for incidence of binding and inhibitory antibodies to SHP655.

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9.6 Pharmacokinetic and Pharmacodynamic Analyses

The PK, PD, and PK/PD analyses are described below. Additional details will be provided in the SAP.

9.6.1 Pharmacokinetic Analysis

Pharmacokinetic parameters for ADAMTS13 activity and ADAMTS13: Ag following SHP655 or placebo infusion will be derived using non-compartmental methods, including but not limited to, where applicable and estimable:

- Incremental recovery
- Observed maximum concentration (Cmax)
- Time to reach Cmax (tmax)
- Terminal half-life (t1/2)
- Mean residence time from zero (predose) extrapolated to infinite time (MRT0-inf) and from zero (predose) to 72 hours postdose (MRT0-72)
- Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration (AUC0-last)
- Area under the concentration-time curve from zero (predose) to 72 hours postdose (AUC0-72) and/or partial AUC over other time intervals may be calculated as appropriate
- Area under the concentration-time curve from zero (predose) extrapolated to infinite time (AUC0-inf)

- Systemic clearance (CL)
- Volume of distribution at steady state (Vss)

Weight measured at the PK Baseline Visit on the IP infusion day will be used to calculate total dose. ADAMTS13 activity and ADAMTS13:Ag in SHP655 dosing solutions will be used to derive actual dose amount for calculating IR, CL, and V_{ss}.

Area under the curves will be calculated using linear up/log down trapezoidal summation.

For PK parameter calculations, should the measurement at pre-infusion of the respective PK infusion be above the lower limit of quantitation, baseline may be subtracted from post-infusion measurements, or used as a covariate as applicable if other analysis methods are employed.

PK concentrations and PK parameters will be listed and summarized by treatment and dose cohorts (and by scheduled time for PK concentrations). Individual and mean PK concentration-time profiles over time will be presented. Scatter plots of individual and geometric mean PK exposure parameters (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$) versus dose level will be presented for dose proportionality assessment. Additional figures may be generated as applicable.

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9.6.2 Pharmacodynamic Analysis

The observed PD measurements of plasma VWF:Ag, VWF:RCo, plasma free hemoglobin, plasma thrombospondin, and platelet count will be listed and summarized by treatment, dose level, and scheduled time. Ratio to baseline values will be calculated for VWF:Ag, VWF:RCo, and platelet count. Individual and mean PD profiles over time will be presented. The correlation of plasma free hemoglobin and thrombospondin with ADAMTS13 activity and VWF will be assessed.

9.6.3 Pharmacokinetic-Pharmacodynamic Relationship

The PK/PD assessments will be performed to evaluate the correlation of plasma free hemoglobin and thrombospondin with ADAMTS13 activity and VWF.

Graphical assessments of plasma free hemoglobin and thrombospondin versus ADAMTS13 activity and VWF activity will be generated.

Other assessments may be performed to evaluate the PK/PD relationships.

9.7 Efficacy Analyses

No efficacy analyses are planned.

9.8 Exploratory Analyses

The exploratory variables, including but not limited to [redacted] will be listed and summarized by treatment, dose level, and scheduled time.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

Appendix 1.1 Regulatory and Ethical Considerations

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

Appendix 1.2 Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

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Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

Indemnity/Liability and Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO and investigator as necessary.

Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

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Appendix 1.3 Investigator's Responsibilities

Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

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Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

Documentation and Retention of Records

Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

The CRFs should be approved by the investigator per study specifications and the sponsor's data delivery requirements.

Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's source documents.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

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Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

Appendix 1.4 Data Management Considerations

Data Collection

The investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines or similar for all data requiring transcription of the source. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

Data Management

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

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Data Handling

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, antibodies to SHP655, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits. Following the review of unblinded data for a completed dose cohort by the DEC, and a recommendation by the DEC that it is safe to proceed with enrollment of the next dose cohort, Sponsor study team will have access to the unblinded data for the completed dose cohort, as specified in the unblinding plan.

Appendix 1.5 Ethical Considerations

Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP.

Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject ICF or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the Sponsor with a copy of the consent form where applicable that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

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Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the CRO has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU, or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

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After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP655; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form.

The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of 1 year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

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At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Takeda is committed to transparent dissemination of all scientific, technical, and medical manuscripts generated from Takeda-supported research. Therefore, after 01 Jan 2018, Takeda will require the submission of all Takeda-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

Appendix 2 Clinical Laboratory Tests

The following clinical laboratory assessments will be performed:

Chemistry	[redacted] Creatinine [redacted] Alanine aminotransfarase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) [redacted] Albumin Total bilirubin (TBL) Blood Urea Nitrogen Glucose Sodium Potassium Chloride Bicarbonate
Hematology	Erythrocytes (Red Blood Cell [RBC]) Leukocytes (White Blood Cell [WBC]) Hemoglobin Hematocrit [redacted] Blood Group Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) WBC Differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) Platelet
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 (HbsAg)
Pregnancy Test	Urine human chorionic gonadotropin (HCG)[a]

1. Only women with childbearing potential (excluding menopausal women or women with surgical contraception) will receive the urine HCG test at Screening Period and, if necessary, during the study.

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Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Appendix 3.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causality is suspected (ICH Guidance E2A 1995).

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the investigational product or medicinal product.

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Serious Adverse Event

A serious adverse event (SAE) is any untoward clinical manifestation of signs, symptoms, or outcomes (whether considered related to investigational product or not and at any dose):

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs.
- For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:
- Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

Unexpected Adverse Event

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

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Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected disease progression and are part of the efficacy or effectiveness data collected in the study. Significant worsening of symptoms should be recorded as an AE.

When there is an increase in the severity of a pre-existing condition, duration or frequency of a preexisting condition, the event must be described on the AE CRF.

Clinical Laboratory and Other Safety Assessment

A change in the value of a clinical laboratory parameter, or vital sign measure can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), or vital sign values, which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

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The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, or vital sign is clinically significant and represents an AE.

Appendix 3.2 Collection of Adverse Events

All AEs/SAEs are collected from the time the informed consent document is signed until the defined follow-up period stated in Section 8.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Appendix 3.3 Assessment of Adverse Events

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity is captured as a new event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

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The medical assessment of severity is determined by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Table A1 Adverse Event Relationship Categorization

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

Outcome Categorization

The outcome of AEs must be documented in the source during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

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If applicable, action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF.

Appendix 3.4 Safety Reporting

Reference Safety Information

The RSI for this study is the IB which the sponsor has provided under separate cover to all investigators.

Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Takeda Global Drug Safety Department and the CRO/Takeda medical monitor within 24 hours of becoming aware of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Appendix 3.9) unless they result in an SAE.

The investigator must complete, sign, and date the Takeda "Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol", verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or e-mail the form to the Takeda Global Drug Safety Department. A copy of the Takeda Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol.

Appendix 3.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined EOS Visit stated in Section 8.1.3 and must be reported to the Takeda Global Drug Safety Department and the CRO/Takeda medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Takeda Global Drug Safety Department within 24 hours of the reported first becoming aware of the event.

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Appendix 3.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the ICF or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Appendix 3.7 Fatal Outcome

Any SAE that results in the subject's death (eg, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

Appendix 3.8 Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined EOS Visit stated in Section 8.1.3.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Takeda Global Drug Safety Department using the Takeda Investigational and Marketed Products Pregnancy Report Form.

A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

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Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Takeda Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.

A pregnancy that occurs in the partner of a study subject during the study must be reported and recorded on the appropriate CRF.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Takeda Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

Appendix 3.9 Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Appendix 3.9.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than one category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

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Appendix 3.10 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical study from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical study or studies
- Any other immediate action taken in order to protect clinical study participants from immediate hazard to their health and safety

The investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the sponsor. In the event(s) of an apparent direct hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, and within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

Appendix 3.11 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor and the CRO are responsible for notifying the relevant regulatory authorities: US central IRBs/ECs of related, unexpected SAEs.

In addition, the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP655 program.

The investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings that occur at his or her site as required by IRB/EC procedures (see Appendix 1.5).

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Appendix 4 Abbreviations

Abbreviation	Definition
ACS	Acute chest syndrome
ADAMTS13	A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B-core total antibodies
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from time 0 to infinity
AUC_{0-last}	Area under the curve from time 0 to the time of last concentration measured
β–hCG	Beta-human chorionic gonadotropin
CBC	Complete blood count
cDNA	Complementary deoxyribose nucleic acid
CHO	Chinese hamster ovary
CL	Systemic clearance
C_{max}	Observed maximum concentration
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
[redacted]	[redacted]
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EOS	End of study
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HMW	High molecular weight
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed consent form

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Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
IL	Interleukin
IP	Investigational product (SHP655 or Placebo)
IR	Incremental recovery
IRT	Interactive response technology
IV	Intravenous (ly)
[redacted]	[redacted]
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRT	Mean residence time
$MRT_{0\text{-}inf}$	Mean residence time from zero (predose) extrapolated to infinite time
n	Number of subjects
NOAEL	No-observed-adverse-effect-level
O_2	Oxygen
PD	Pharmacodynamic (s)
PK	Pharmacokinetic(s)
q4h	Every 4 hours
rADAMTS13	Recombinant a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SCD	Sickle cell disease
SIC	Subject identification code
$t_{1/2}$	Terminal half-life
TEAEs	Treatment-emergent adverse events
T_{max}	Time to reach maximum concentration
TNF	Tumor necrosis factor
TSP1	Thrombospondin 1
ULVWF	Ultralarge von Willebrand factor
US	United States

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Abbreviation	Definition
VOC	Vaso-occlusive crisis
V_{ss}	Apparent steady state volume of distribution
VWF	von Willebrand factor
VWF:Ag	VWF:antigen
VWF:RCo	VWF:Ristocetin cofactor activity
WBC	White blood cell
WHO	World Health Organization

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Appendix 5 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 2.0	12 JUL 2021	Global
Protocol Amendment 1.0	17 MAY 2019	Global
Original Protocol	28 MAR 2019	Global

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SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

- Original Protocol (28 MAR 2019)
- Protocol Amendment 1.0 (17 MAY 2019)

Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **17 MAY 2019**	**Global/Region/ Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: Changes were made in response to regulatory authority request.		
Description of Each Change and Rationale		**Section(s) Affected by Change**
• In Parts A and B of the study, the first 3 patients in each dose cohort will be dosed a minimum of 14 days apart to observe and interpret reactions and adverse events in order to ensure that no SAE requiring a pause or stop of the clinical trial has occurred in the most recently treated subject. • The booster dose was removed from the protocol.	Request by FDA.	Synopsis, Section 1.3, Section 4.1, Section 6.1.1, Section 6.2.3, Section 9.6.1
• Subjects 12-17 years old were removed from inclusion criteria; only adults aged 18 to 65 years old will be included in the study. • Specific criteria for organ dysfunction was added to inclusion criteria as follows: *The subject must have uncomplicated acute VOC (no significant organ dysfunction [ALT>3xULN of local lab; creatinine >2; symptomatic cardiac decompensation, no new neurologic symptoms] or signs or symptoms of systemic infection, or fever with body temperature ≥39ºC).* • The specific genotypes of sickle and beta thalassemia were added to the inclusion criteria. • Inclusion criteria #12 stated that if subject has uncomplicated UTI, body temperature < 38.5°C or costovertebral angle tenderness; or if subject had suspected minor viral syndromes, the subject had no symptoms suggestive of bacterial infection other than uncomplicated otitis media or uncomplicated streptococcal pharyngitis. This inclusion criteria was removed. In the exclusion criteria, the following was added: *Minor infection that does not meet the following criteria: uncomplicated urinary tract infection*	Request by FDA.	Synopsis, Section 5.1, Section 5.2, Section 8.2.7, Appendix 3.9, Appendix 5

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Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **17 MAY 2019**	**Global/Region/ Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: Changes were made in response to regulatory authority request.		
Description of Each Change and Rationale		**Section(s) Affected by Change**
with body temperature <38.5°C (101.3°F) and no costovertebral angle tenderness; or uncomplicated otitis media; or uncomplicated streptococcal pharyngitis. • The following exclusion criteria was added: *Any history of hemorrhagic stroke or bleeding diathesis.*		
Under pharmacodynamic endpoints, [redacted] was removed.	No longer considered a necessary test.	Synopsis, Section 1.2, Section 1.3, Section 3.2, Section 8.2.4, Section 9.6.2, Appendix 2
Health-related Quality of Life will not be assessed at screening.	Baseline assessments are sufficiently close to screening assessments, so redundancy removed.	Section 1.3
Added to the schedule of activities: *VAS is assessed at all PK sampling time points when awake and every 4 hours while awake during hospitalization.*	Clarification	Section 1.3
Information on the Q97R variant was added to the protocol.	Request by FDA	Section 2.2
The following text was added to section 2.4: *Enrollment will be stopped for any case of anaphylaxis, neutralizing antibody, life-threating condition, or death (see Section 9.2.1).* Also, Section 6.2.1 (Hypersensitivity of SHP655) was removed.	Clarification	Section 2.4, (6.2.1)
Parts A and B will be conducted at approximately 20 (instead of 3) sites in the United States and Europe.	Clarification	Section 4.5
Contraception methods of females were adjusted to	Clarification	Section 5.4.1,

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Protocol Amendment		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **1.0**	**Amendment Date** **17 MAY 2019**	**Global/Region/ Country/Site Specific** **Global**
Protocol Amendment Summary and Rationale: Changes were made in response to regulatory authority request.		
Description of Each Change and Rationale		**Section(s) Affected by Change**
include highly effective *or acceptable* methods of contraception. These are listed in Appendix 4, and are described in this section.		Section 6.2.3, Appendix 4
Stopping criteria were adjusted to define a study stop if a) 2 or more subjects in a given cohort receiving active drug have a severe AE in any vital organ or body system or b) any neutralizing antibody to SHP655 that develops after IP administration or c) any death occurs that is possibly related to SHP655 administration.	Request by FDA	Section 6.2.3.1
Section 6.2.3.2 Dose Limiting Toxicities was added. Section 6.2.5 was adjusted accordingly.	Request by FDA	Section 6.2.3.2. Section 6.2.5
The following text was added: *If AEs are observed within a dose cohort (Part A or Part B) that could meet DLT criteria, the Dose Escalation Committee will review treatment assignments to determine whether the DLT has been reached.* Section 6.2.5 was also adjusted accordingly.	Request by FDA	Section 6.2.3.3
Anticoagulant or anti-platelet medications were added to prohibited treatment.	Request by FDA	Section 6.6.4
Section 6.7 Adverse Event Management was added.	Request by FDA	Section 6.7
Efficacy assessments in pain score (VAS) were adjusted to use a consistent VAS scale. The first measure of time to discharge readiness was changed to: *1. A sustained 15 point decrease in on a linear 100 point VAS pain scale from baseline ore from baseline and transition to oral analgesia;*	Request by FDA	Section 8.2.6

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See Appendix 7 for protocol history, including all amendments.