CLINICAL STUDY PROTOCOL

NCT Number: NCT03922308

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

Study Number: SHP655-201

Protocol Version and Date:

Protocol Amendment 3.0 : 08-JUN-2020

PROTOCOL: SHP655-201

TITLE:	A Phase 2, multicenter, randomized, placebo-controlled, double-blind study in patients with acquired thrombotic thrombocytopenic purpura (aTTP) to evaluate the pharmacokinetics, safety, and efficacy of rADAMTS-13 (SHP655) administered in addition to standard of care (SoC) treatment
SHORT TITLE:	A Phase 2, randomized, placebo-controlled, double-blind study of rADAMTS-13 (SHP655) in the treatment of patients with aTTP
STUDY PHASE:	Phase 2
ACRONYM:	SOAR-HI (**S**tudy **O**f ADAMTS-13, **R**ecombinant in acquired t**H**rombocytopen**I**c purpura)
DRUG:	SHP655 (rADAMTS-13)
IND NUMBER:	018577
EUDRACT NUMBER:	2018-003775-35
SPONSOR:	Baxalta US Inc.*, 300 Shire Way, Lexington, MA 02421, USA AND Baxalta Innovations GmbH*, Industriestrasse 67, A-1221 Vienna *Baxalta is now part of Shire*
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter
PROTOCOL HISTORY:	**Protocol Amendment 3.0: 08 JUN 2020** **Replaces:** Protocol Amendment 2.1: 23 SEP 2019

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature:	**Date:**
[redacted], MD	

Investigator's Acknowledgement

I have read this protocol for Study SHP 655-201.

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

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 guidelines on Good Clinical Practice and with the applicable regulatory requirements.

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

Protocol Amendment 3.0		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3.0**	**Amendment Date** **08 JUN 2020**	**Country Specific**
Protocol Amendment Summary and Rationale: Added rescue therapy for subjects not adequately responding to treatment after 4 days.		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Made terms consistent, improved grammar and syntax throughout document.	Clarity.	Throughout document.
Updated dosing to allow for 10% buffer in calculation	Provided reasonable dosing buffer	Synopsis; Section 4.1; Section 4.3
Rewording of safety and efficacy endpoints in SOC	General clarification	Synopsis; Section 3.2; Section 9.5.2; Section 9.6.1
Added exclusion criterion precluding participation for subjects with conditions of severe immunodeficiency.	Clarification	Synopsis and Section 5.2
Added text stipulating that if the ADAMTS-13 levels (based on local labs) are <50% between discharge and first weekly follow-up visit then the investigator may treat the patient with the IP prior to the scheduled visit.	Clarification	Synopsis and Section 6.2.6
Clarified prior treatment must be documented for past 30 days	Consistency with rest of protocol	Section 6.8.1
Added interim analysis after 18 subjects have achieved remission and when approximately 50% of the planned sample size has been enrolled and treated in the three arms.	Allow for internal analysis and review of initial study results	Synopsis, Section 9.2, Section 9.5.2, Section 6.2.5
Clarified that the final study visit should be 3 months after remission	General clarification	Schedule of study activities
Added evaluation of schistocytes to screening criteria	Aligned inclusion criteria with schedule of study procedures	Schedule of study activities
Follow-up visits can be completed by a home healthcare provider/healthcare professional	Ensure accurate data collection	Schedule of study activities Section 8.1.3
Clarified that local ADAMTS13 could be used to determine eligibility	General clarification. It is not always logistically feasible to collect central lab screening samples prior to the initiation of PEX	Synopsis (Exclusion Criteria); Section 5.2

Protocol Amendment 3.0		
Summary of Change(s) Since the Last Version of the Approved Protocol		
Amendment Number **3.0**	**Amendment Date** **08 JUN 2020**	**Country Specific**
Protocol Amendment Summary and Rationale: Added rescue therapy for subjects not adequately responding to treatment after 4 days.		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Clarified the possibilities for administering the first PEX and IP	General clarification	Section 4.1
Removed references to ECG	General clarification; ECGs never included in study	Appendix 2.1
Added urine-albumin-creatinine ratio assessment	Increased monitoring for immune complexes and vasculitis	Schedule of activities; Section 8.2.3.4; Appendix 2.7
Removed physical exam from daily treatment period	Patients closely monitored as part of standard of care	Schedule of activities
Removed references to urine pregnancy tests	Serum β-hCG pregnancy test to be administered during screening	Section 5.2.1; Section 8.2.3.5
Changed timeframe at which Caplacizumab is exclusionary	Drug expected to be cleared within 1 month of last dosing	Section 6.8.4; Section 5.2; Section 1.1 Synopsis
Provided web-based data collection access	Ensure accuracy and completeness of data	Section 8.2.4.7
Specified which non-serious adverse events should be reported as study outcomes	Data captured as a study outcome	Section 8.2.3.2

See Appendix 6 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 Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Shire 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)/Shire 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 Shire medical monitor:

Shire Medical Monitor

[redacted], MD
Direct Line: [redacted]
Email: [redacted]

IQVIA medical monitor

[redacted], MD
Mobile: [redacted]
Email: [redacted]

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 Shire 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 Shire 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

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

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**
North and South America	PQC@shire.com
European Union and Rest of World	PQCROW@shire.com

Telephone number (provided for reference if needed):

Shire, Lexington, MA (USA)
1-800-828-2088

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol number: SHP655-201	**Drug**: SHP655 (rADAMTS-13)
Title of the study: A Phase 2, multicenter, randomized, placebo-controlled, double-blind study in patients with acquired thrombotic thrombocytopenic purpura (aTTP) to evaluate the pharmacokinetics, safety, and efficacy of rADAMTS-13 (SHP655) administered in addition to standard of care (SoC) treatment	
Short title: A Phase 2, randomized, placebo-controlled, double-blind study of rADAMTS-13 (SHP655) in the treatment of patients with aTTP	
Study phase: Phase 2	
Number of subjects (total and per treatment arm): Approximately 30 in total and 10 per treatment arm	
Investigator(s): multicenter study	
Site(s) and Region(s): Approximately 27 sites in North America and Europe are planned.	
Study period (planned): 2019-2021	**Clinical phase:** 2

Objectives:

Co-Primary:

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

Secondary:

PK/PD Objectives

1. Evaluate changes in levels of ADAMTS-13 binding and inhibitory autoantibodies from baseline in response to daily PEX, with or without SHP655 supplementation, during the acute episode and up to 30 days after the resolution of the acute aTTP episode
2. Evaluate ADAMTS-13 activity levels in subjects up to 30 days after acute aTTP episode remission
3. Specify dose(s) of SHP655 needed to achieve and maintain adequate plasma levels of rADAMTS-13 in order to support induction of remission and to reduce the number of PEX procedures needed for the treatment of acute aTTP episodes

Safety/Efficacy Objectives

1. Assess the safety and immunogenicity of two regimens of SHP655 supplementation administered during an acute TTP episode in subjects undergoing PEX treatment and immunosuppressant therapy as measured by AEs, changes in vital signs and laboratory parameters

2. Evaluate the occurrences of aTTP related complications, (including death, stroke, MI, and organ failure), aTTP relapses*, exacerbations** and end-organ function improvement
3. Evaluate the time to aTTP related complications (including death, stroke, MI, and organ failure), aTTP relapses*, exacerbations** and end-organ function improvement
4. Evaluate the occurrence of procedure (e.g. PEX, SHP655 infusions) related adverse events

Exploratory Objectives:

[redacted]

*Defined as >30 days after achieving remission

**Defined as ≤30 days after achieving remission

Rationale:

This study is needed to enable detailed assessment of ADAMTS-13 activity in aTTP subjects in the context of PEX, rADAMTS-13 supplementation and anti-ADAMTS-13 autoantibodies, all of which will acutely change plasma ADAMTS-13 activity.

The relationship between recovery of ADAMTS-13 activity and improvement in clinical outcomes will be explored. PK/PD analysis will be utilized to establish an SHP655 dosing regimen that assures achievement of adequate ADAMTS-13 activity levels, thus enabling a reduction in the number of PEX, a hypothesis which will be tested in the pivotal phase 3 study.

Investigational product, dose, and mode of administration:

- SHP655 40 IU/kg ±4 IU/kg once daily, i.v. or 40 IU/kg ±4 IU/kg, b.i.d., i.v.
- Placebo (0.9% saline)

Study Design

Subjects experiencing the onset of an acute TTP episode will receive a single PEX as part of SoC as soon as feasible, consent will be obtained, and subjects will undergo screening procedures. Eligible subjects will provisionally be randomized into one of three treatment arms, with a total enrollment of approximately 30 evaluable subjects. The first 2 on-study PEX (after the first SoC PEX) will be 1.5 plasma volume, followed by daily 1.0 plasma volume exchanges.

Arm 1 - SoC (n=10)

Subjects will receive daily PEX and will also receive placebo immediately after each PEX and at 12±1 hours after completion of each PEX.

Arm 2 - SoC with Supplementation once daily (n=10)

Subjects will receive daily PEX and will also receive 40 IU/kg ±4 IU/kg SHP655 immediately after each PEX and placebo at 12±1 hours after completion of each PEX.

Arm 3 - SoC with Supplementation twice daily (n=10)

Subjects will receive daily PEX and will also receive 40 IU/kg ±4 IU/kg SHP655 twice daily immediately after each PEX and at 12±1 hours after completion of each PEX.

Supplementation with SHP655 or placebo as appropriate will continue until all remission criteria are met: platelet count ≥150,000/μL and confirmation by a second platelet count ≥150,000/μL and LDH <2 ULN 48 hours following initial normalization. Furthermore, dosing will also be discontinued based on pre-PEX ADAMTS-13 activity levels as described later in this section.

If screening laboratory tests show:

- ADAMTS-13 activity >10%; or
- The absence of anti-ADAMTS-13 autoantibodies; or
- The presence of a known genetic mutation on both alleles consistent with cTTP

The subject will be discontinued from the study. A follow up safety visit will be scheduled 30 ±5 days after the last administration of study drug, but the subject will be excluded from the PK and efficacy analyses.

An immunosuppressive regimen of 1 g methylprednisolone iv once daily for 3 consecutive days, followed by 2.5 mg/kg/day, and 375 mg/m^2 rituximab administered weekly for 4 weeks will be initiated within 2 days of enrollment for all subjects. Steroid tapering is permitted per local SoC. Additional immunosuppressive therapy can be considered after consultation with the sponsor.

Subjects in each study arm will receive a dose of IP immediately after and at 12±1 hours after each PEX. In all study arms, the second daily dose (SHP655 or placebo 12h after PEX) will be terminated if a local lab pre-PEX ADAMTS-13 activity level is >150% or above the upper limit of quantification. If the ADAMTS-13 levels (based on local labs) are <50% between discharge and first weekly follow-up visit then the investigator may treat the patient with the IP prior to the scheduled visit. Any additional assessments may be conducted as per the investigator's judgement.

If the second dose has already been suspended and a subsequent local lab pre-PEX ADAMTS-13 activity level is >150% or above the upper limit of quantification, the first daily dose (SHP655 or placebo immediately after PEX) will be terminated.

After resolution of the TTP episode, subjects will be given additional IP (placebo for Arm 1, SHP655 40 IU/kg ±4 IU/kg for Arms 2 and 3) once weekly if ADAMTS-13 activity at the local lab is <50%.

Discretionary Rescue Therapy

Study investigators may elect to administer rescue therapy to a subject if platelet count have not increased at least 2-fold from screening and LDH remains above ULN after 4 days of treatment. Rescue therapy will be defined as any product with a known interruption to the PK/PD relationship between ADAMTS-13 activity, VWF activity, and platelet count. Additional administration of FFP, S/D treated plasma, and immunosuppressive therapies will not be considered rescue therapy unless otherwise agreed after consultation with the Sponsor. However, they may be prohibited medication after initiation of plasma exchange (refer to section 6.8.4). The rescue therapy treatment should follow local standard of care practices. If rescue therapy is initiated, the administration of IP (SHP655 or placebo) will be suspended for the duration of the study. The patient will continue to follow the same visit and assessment schedule to be monitored for safety. PK samples should continue to be collected to monitor safety and the subject should be followed for three months post remission.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Subject or legally authorized representative voluntarily signs informed consent. For subjects unable to provide consent, a fully recognized medical proxy may be used according to local laws.
2. Subject is 18 to 75 years old at the time of screening.
3. Subject has been diagnosed with primary or secondary autoimmune aTTP based on the following criteria:
   a. Thrombocytopenia [drop in platelet count ≥50% or platelet count < 100,000/µL];
      - No more than 3 subjects per arm may be enrolled with a screening platelet count ≥50,000/ µL.

b. Microangiopathic hemolytic anemia [elevation of lactate dehydrogenase (LDH) >2-fold or by presence or increase of schistocytes in peripheral blood smear].

4. Willingness to fully comply with study procedures and requirements, and intention to initiate plasma exchange (PEX). Subjects may be provisionally entered into the trial and undergo randomization pending the results of the ADAMTS-13 activity, anti-ADAMTS-13 antibody, and genetic testing for cTTP.
5. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study. Sexually active males must use an accepted and effective method of contraception during the treatment and until a minimum of 16 days after the last dose administered.

Exclusion Criteria:

1. Subject has been diagnosed with congenital TTP.
2. Subject has plasma ADAMTS-13 activity> 10% of normal at the central lab; if screening samples are not taken until after the first PEX, ADAMTS-13 activity from the local lab is permitted to determine eligibility.
3. Subject has been diagnosed with another cause of thrombotic microangiopathy (TMA) including: DIC, disseminated malignancy, malignant hypertension, hematopoietic stem cell transplantation, shiga toxin-related and atypical HUS, drug toxicity (e.g. gemcitabine, mitomycin C, clopidogrel) and pregnancy-related thrombocytopenia syndromes (e.g. HELLP, eclampsia).
4. Subject has been exposed to another IP within 30 days prior to enrollment or is scheduled to participate in another clinical study involving IP or investigational device during the course of the study.
5. Subject has received caplacizumab within 1 months prior to study enrollment.
6. Subject is human immunodeficiency virus positive (HIV+) with unstable disease or $CD4^+$ count $\leq$200 cells/mm^3 within 3 months screening.
7. Subjects with conditions of severe immunodeficiency.
8. Subject has had a previous aTTP event in the past 30 days.
9. Subject has another underlying progressive fatal disease and/or life expectancy of less than 3 months.
10. Subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
11. Subject suffers from a mental condition rendering him/her unable to understand the nature, scope, and possible consequences of the study and/or evidence of an uncooperative attitude. However, a fully recognized medical proxy will be permitted to provide consent.
12. If female, subject is pregnant or lactating.
13. Subject is a family member or employee of the Sponsor or investigator.
14. Any contraindication to PEX, methylprednisolone and/or rituximab as per prescribing information.
15. Known life-threatening hypersensitivity reaction, including anaphylaxis, to the parent molecule ADAMTS-13, hamster protein, or other constituents of SHP655.

Maximum duration of subject participation in the study:

6 months

- Planned duration of screening period: 1 day
  - Planned duration of enrollment period: 1 day
- Planned duration of treatment period: up to 3 months (dependent on time to remission)
- Planned duration of follow-up: 3 months

Endpoints and statistical analysis:

Analysis sets:

- Full Analysis Set (FAS): all enrolled aTTP subjects who are treated with study product and have ADAMTS-13 activity reading from at least one post infusion sample. Randomization errors are included in the treatment arm they are randomized to, not in the treatment arm of the treatment they receive.
- Safety Analysis Set:
  - Safety Analysis Set (enrolled) -- all subjects randomized and who received any dose of investigational product.
  - aTTP Safety Analysis Set -- all aTTP subjects in the Safety Analysis Set. Subjects provisionally randomized, and subsequently meet the non-aTTP criterion, are not part of this analysis set.
- PK/PD Analysis Set: all aTTP subjects who receive study treatment and obtain at least one post-infusion ADAMTS-13 activity level.

Endpoints

Primary endpoints

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

Secondary

Pharmacokinetic Endpoints

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

Safety and efficacy endpoints

1. Time to normalization of platelet count, defined as platelet count ≥ 150,000/μL, which must be confirmed by a second normal platelet count ≥ 150,000/μL and LDH <2 ULN 48 hours following initial normalization
2. Occurrence of remission, defined as a normal platelet count and LDH <2 ULN for at least 48 hours following initial normalization of platelet count (acute episode period)
3. Time to first exacerbation (aTTP episode ≤30 days following remission)
4. Time to relapse (aTTP episode >30 days following remission)
5. Occurrence of exacerbation
6. Occurrence of relapse
7. Occurrence of major clinical events related to TTP including:
    a. Death
    b. Stroke
    c. MI
    d. Organ dysfunction not normalized within the 90-day observation period
        i. Chronic renal insufficiency
        ii. Neurologic impairment
        iii. Neurocognitive deficits.
8. Incidence of major clinical events related to PEX, including clinically relevant bleeding (modified ITP score) or thrombosis at the site of line insertion, adverse reactions to plasma, including citrate reactions, allergic reactions, and TRALI
9. Changes in the titers of binding and inhibitory antibodies to ADAMTS-13 relative to baseline
10. Occurrence of antibodies to SHP655
11. Incidence of AEs and SAEs, and specifically product-related AEs and SAEs
12. Clinically relevant changes in vital signs, clinical chemistry, and hematology
13. Occurrence of subjects receiving rescue therapy
14. Occurrence of subjects meeting rescue criteria

[redacted]

[redacted]

Exploratory Endpoints

[redacted]

Statistical Methods

Statistical models used to analyze the primary endpoints:

A non-linear mixed effects model will be used to analyze the PK of ADAMTS-13 activity over time in the presence of anti-ADAMTS-13 antibodies and the administration of daily PEX, during treatment of an acute TTP event with or without SHP 655 supplementation.

A PK/PD model will be developed to study the temporal relationship between Platelet count or LDH levels with respect to the changes in ADAMTS-13 activity over time.

- Safety analysis

  AEs and SAEs will be tabulated and summarized according to the Medical Dictionary for Regulatory Activities, in total, by arm, and by relatedness to product or PEX procedure. The number and proportion of subjects experiencing these events will be tabulated for each arm.

  Individual and summary vital signs and clinical laboratory data will be presented in tabular form with mean, standard deviation, quartiles, and range as appropriate, by treatment arm and time point.

For the 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.

- Efficacy analysis

  All time to event efficacy endpoints will be analyzed by the non-parametric Kaplan Meier (KM) estimator of the survival curve. Estimates of the median time to event as well as proportions of subjects with event will be derived, together with two-sided, 95% confidence intervals.

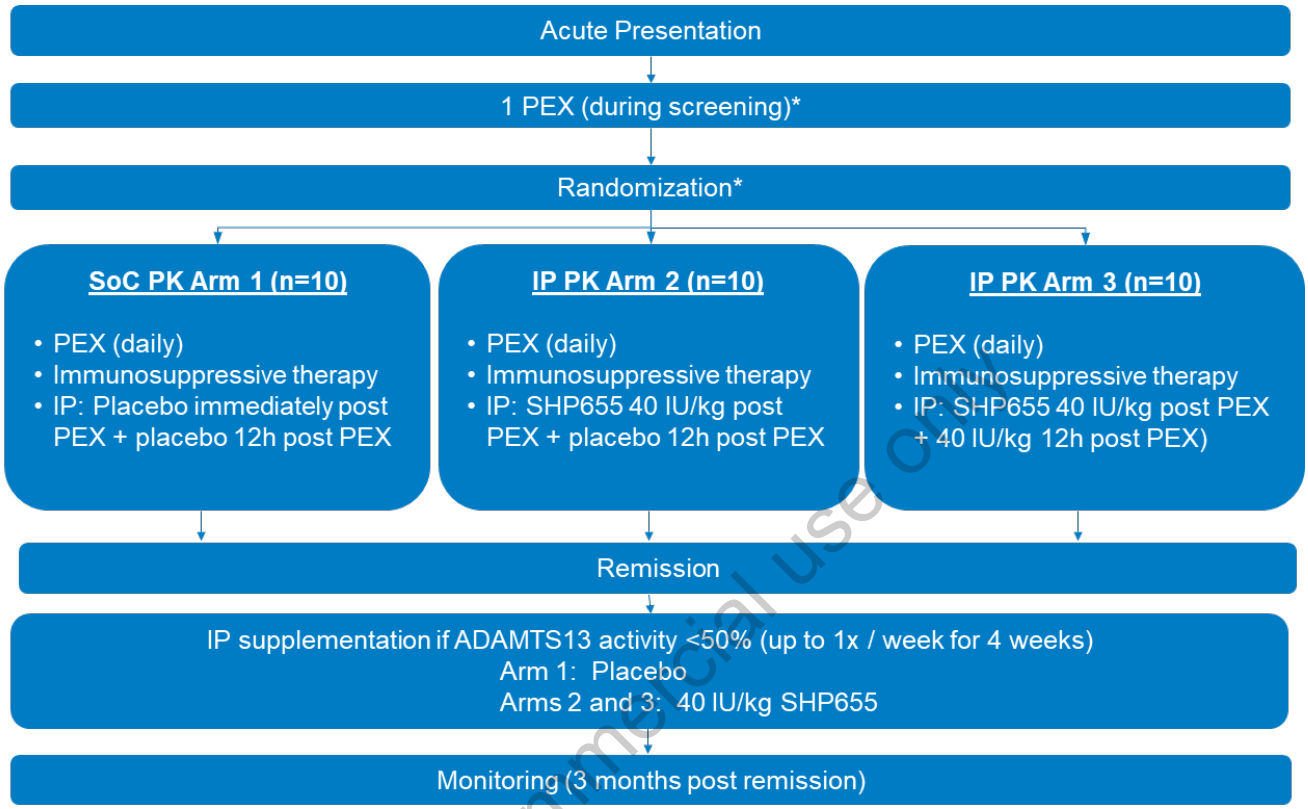
Summary statistics will be provided for the efficacy endpoints assessed by study arm. For continuous variables these will include mean, standard deviation and 95%, two-sided confidence interval (CI). For discrete variable these will include proportions, incidence, and their two-sided 95% CI.

- An interim analysis will be performed after 18 subjects have achieved remission and when approximately 50% of the planned sample size has been enrolled and treated in the three arms. The IA will include all data, collected by this time point, for all subjects enrolled in the study. IA results will be used to evaluate a preliminary treatment effect, assess initial PK/PD parameters, and inform the phase 3 clinical development planning. Access to results from the IA will be restricted to a small group of Takeda personnel designated as unblinded who thereafter will be removed from participation in oversight of daily conduct of this study. The interim analysis data and results may be used in regulatory interactions but will not be made public or used in scientific manuscripts.

Details on the specific analyses to be performed during the IA will be provided in the Statistical Analysis Plan.

1.2 Schema

Figure 1. Study Schematic Diagram



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

1.3 Schedule of Activities

Table 1. Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening/ Enrollment[a]	Interval Study Visits			Study Completion/ Termination Visit[c] (12 weeks ± 7 days following remission)
		Treatment Period (Daily)[b]	Weekly Follow Up Study Visits[l] (Q1Week ±3 days x4 weeks)	Biweekly Follow Up Study Visits[l] (Q2Week ±3 days x2 visits)	
Informed Consent[d]	X				
Eligibility Criteria	X				
Serum pregnancy test (females)	X				
Medical History	X				
Demographic and Baseline Characteristics	X				
Medications	X	X[q]	X[q]	X	X
Non-drug Therapies	X	X[q]	X[q]	X	X
Physical Exam[o] (including weight)	X		X	X	X
Adverse Events	X	X	X	X	X
Laboratories[g]	X	X[h]	X	X	X
Vital Signs	X	X	X	X	X
Evaluation of schistocytes	X				
Randomization[k]	X				
IP		X[e,q]	X[f,q]		
Plasma exchange	X	X[q]			
Cognitive assessment tests	X	X	X		
Modified ITP Bleeding Score	X	X			
ADAMTS-13 Antigen & Activity	X	X[h]	X[p]	X	X
Anti-rADAMTS-13 Binding antibodies, total Ig (IgG, IgA, IgM)[m]	X	X[h]	X	X	X
Anti-rADAMTS-13 Binding antibodies, IgE [n]					
Anti-ADAMTS-13 Inhibitory antibodies (for native protein)	X	X[h]	X	X	X

Table 1. Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening/ Enrollment[a]	Interval Study Visits			Study Completion/ Termination Visit[c] (12 weeks ± 7 days following remission)
		Treatment Period (Daily)[b]	Weekly Follow Up Study Visits[l] (Q1Week ±3 days x4 weeks)	Biweekly Follow Up Study Visits[l] (Q2Week ±3 days x2 visits)	
Anti-rADAMTS-13 Inhibitory antibodies	X				X
VWF antigen and multimers			X[i]		
Urine-albumin-creatinine ratio	X	X	X[r]		
Methylprednisolone (tapering permitted)		X[q]	X[b, q]		
Rituximab		X[b, q]	X[b, q]		
[redacted]					

a. Screening and enrollment occur at same visit.
b. Actual number of treatment dosing visits will vary.
c. Including for subjects who withdraw or discontinue.
d. Occurs at enrollment (prior to any study-specific procedure).
e. Double blind administration of placebo or SHP655 is given twice daily in all arms until remission is achieved. Supplementation post-remission is double blinded and administered only after local ADAMTS-13 activity levels are <50% (measured >72 hours after last IP dose).
f. Actual number of supplementation dosing visits and days will vary.
g. Hematology and clinical chemistry per section 8.2.3.4. See also Table 2.
h. See Table 2 for daily laboratory assessments during daily PEX. PK sampling is randomized to Schedule A or B (Table 3).
i. Weeks 1 and 4 only.

[redacted]

k. Randomization to study arm and independent randomization to PK sampling schedule A or B.
l. Follow up is in reference to when remission is achieved; follow-up visits may be conducted in the home setting by a healthcare professional if consistent with local procedures.
m. The assay measures both anti-native ADAMTS-13 and anti-rADAMTS-13 binding antibodies.
n. IgE assessment only in case of adverse events.
o. Height will be measured at screening only. Weight will be measured at screening, weekly during the treatment period, and at all follow up visits.
p. ADAMTS-13 activity during the weekly follow up period will be measured locally (in addition to centrally) for determining the need for IP supplementation in the first 4 weekly follow up visits.
q. Administration of rescue therapy will be at the discretion of the investigator and will not include IP.
r. Urine-albumin-creatinine ratio to be measured during the weekly follow-up period if IP is administered.

Table 2. Non-PK Laboratory Assessments in Screening and Treatment

Procedure/ Assessment	Screening/ Enrollment	Within 1 h Pre-PEX	Within 30 min prior to daily post-PEX IP infusion #2 [b]
ADAMTS-13 Gene mutation	C		
Blood type	L		
HIV1/2, HBV, HCV	C		
ADAMTS-13 Activity	L and B	L	
ADAMTS-13 Antigen	B		
Anti-rADAMTS-13 binding total Ig	B		
Anti-ADAMTS-13 inhibitory Ab	B		
Anti-rADAMTS-13 inhibitory Ab	B		
Complete blood count with platelets and leukocyte differential	L	L	L
Chemistry (except LDH)	L	L	
LDH	L	L	L
Schistocytes	L		
Urine-albumin-creatinine ratio	L	L	L
[redacted]			

L = local lab; C = Central (sponsor) lab; B= Bioanalytical specialty lab (sponsor)
[redacted]

[b] Subjects receiving rescue therapy should not have samples taken within 1 h Pre-PEX, IP should not be administered, and samples should be taken only within 30 minutes post-PEX.

Table 3. Treatment Period PK Laboratory Assessments
(Randomized to Schedule A or B)
SCHEDULE A: Days 1, 2, 3, 4, 6, 8, 11, and every 3 days thereafter
SCHEDULE B: Days 1, 2, 3, 5, 7, 9, 12, and every 3 days thereafter

Procedure/ Assessment	Within 15 min Pre-PEX	Within 15 min Post-PEX	Within 15 min post end of IP infusion #1[c]	0.5-3 h post end of IP infusion #1[c]	4-6 h post end of IP infusion #1[c]	Within 30 min pre-IP infusion #2 [d]	Within 15 min post end of IP infusion #2 [d]	0.5-3 h post end of IP infusion #2 [d]
ADAMTS-13 activity	X	X	X[a]	X[a]	X	X[b]	X[b]	X[b]
ADAMTS-13 antigen	X	X	X[a]	X[a]	X	X[b]	X[b]	X[b]
Anti-rADAMTS-13 binding Ig	X	X			X	X[b]		
Anti-ADAMTS-13 inhibitory antibodies	X	X			X	X[b]		

All labs to be performed at a bioanalytical specialty lab (sponsor)
[a] To be drawn if first dose of IP on study is administered prior to first PEX (see section 6.2.3).
[b] Do not collect if daily IP infusion #2 (dose 12h post-PEX) is discontinued (see section 6.2.6).
[c] Collect these time-points in relation to the end of PEX if IP infusion #1 (dose immediately post-PEX) is discontinued (see section 6.2.6) or if the subject is receiving rescue therapy.
[d] For subjects receiving rescue therapy, collect within 15 min post end of PEX and 0.5-3 h post end of PEX (no IP administered when on rescue therapy).

2. INTRODUCTION

Baxalta US Inc. (Baxalta), now part of Shire, has developed a recombinant A Disintegrin and Metalloproteinase with Thrombospondin Type-1 Motifs 13 candidate (rADAMTS-13, now designated as SHP655; formerly designated as BAX 930) for treating subjects with thrombotic thrombocytopenic purpura (TTP). TTP may occur in congenital (cTTP) or acquired (aTTP) forms. In aTTP, autoantibodies inhibit and/or accelerate clearance of ADAMTS-13. A severe deficiency of ADAMTS-13 leads to an accumulation of high molecular weight von Willebrand Factor (VWF) and a thrombotic microangiopathy (TMA) whose hallmarks are severe thrombocytopenia and schistocytosis. Clinical features that accompany the TMA classically are described as the pentad of fever, neurologic changes, renal insufficiency, thrombocytopenia, and microangiopathic hemolytic anemia. Due to the lethality of untreated aTTP, treatment often commences with suspicion of the diagnosis, prior to laboratory confirmation of ADAMTS-13 deficiency.

The overall goal of this study is to assess ADAMTS-13 activity in aTTP subjects in the context of plasma exchange (PEX) treatment, supplementation with rADAMTS-13 and the presence of anti-ADAMTS-13 autoantibodies, all of which will acutely change plasma ADAMTS-13 activity. The relationship between recovery of ADAMTS-13 activity and improvement in clinical outcomes will be explored. A pharmacometric analytical approach will be utilized to establish an SHP655 dosing regimen that achieves efficacious ADAMTS-13 activity levels with a reduced number of PEX for use in future studies.

Refer to the latest version of the SHP655 investigator's brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding the pharmacokinetics, efficacy, and safety of SHP655.

2.1 Indication and Current Treatment Options

2.1.1 Current Standard of Care (SoC)

Daily PEX is the cornerstone of the present standard of care (SoC) (Rock et al., 1991). Immunomodulatory drugs, such as corticosteroids, rituximab, vincristine, cyclosporine, cyclophosphamide as well as splenectomy, are recommended to reduce the production of autoantibodies for sustained remission (Saha et al., 2017). Other novel therapeutic modalities, such as a nanobody (caplacizumab) targeting the interaction between platelet glycoprotein Ib (GPIb) and VWF multimers were recently approved by EMA and FDA.

2.1.1.1 Plasma Exchange (PEX)

PEX became recognized as the SoC in 1991, following the publication of the landmark study of 102 adult TTP patients, in which PEX was more effective than plasma infusion in the treatment of TTP (Rock et al., 1991). This study showed a response rate (defined as a platelet count of >150 × 10^9/L and no new neurological events) by day 9 of 47% for PEX versus 25% for plasma infusion, P = 0.025, and 6-month survival of 78% for PEX versus 63% for plasma infusion, respectively, P = 0.04. Since then, PEX has reduced the mortality rate from up to 95% to 10–20% (Zheng, 2015).

As soon as a diagnosis of an acute TTP episode is established or suspected, PEX with frozen or solvent detergent plasma (both containing normal levels of ADAMTS-13, i.e., approximately 1 µg/mL) should be initiated (Allford et al., 2000, Rock et al., 2006) to replenish ADAMTS-13 activity and remove anti-ADAMTS-13 auto-antibodies (Kremer Hovinga et al., 2017, Rock et al., 1991).

A daily PEX at 1 to 1.5 times the patient's predicted plasma volume is generally given until clinical features related to organ manifestations (e.g., neurologic symptoms, increased troponin level, renal failure, abdominal pain due to enteritis or pancreatitis) are resolved, the platelet count and LDH are normalized, and hemolysis stops (Joly et al., 2017, Knöbl, 2014). A published UK TTP guideline recommends that PEX should be continued for a minimum of 2 days after the platelet count is normalized (> 150 x 10^9/L) (Scully et al., 2012).

After remission, a therapeutic PEX taper is sometimes used in clinical practice. However, there was no statistical difference in relapse rates comparing the taper and non-taper sub-groups, in a retrospective analysis of 115 patients with initial presentations of aTTP (Bandarenko and Brecher, 1998, Zheng, 2015).

2.1.1.2 Corticosteroids

Corticosteroids have long been utilized along with PEX as frontline therapy. Importantly, before the widespread use of PEX, response rates of 30/54 (55%) were reported among patients without considerable organ damage within 48-72 hours with the use of corticosteroids alone (Scully et al., 2012). A randomized, controlled trial comparing high-dose (10 mg/kg/d) and standard-dose (1 mg/kg/d) methylprednisolone as adjunct therapy to PEX in 60 newly diagnosed aTTP patients demonstrated 77% and 47% remission rates respectively (Balduini et al., 2010). The British TTP guidelines recommend the use of glucocorticoids (1 mg of oral prednisone per kilogram daily; or 1 g of methylprednisolone per day for three consecutive days) for all patients with aTTP (Scully et al., 2012).

2.1.1.3 Rituximab

Rituximab (humanized anti-CD20 monoclonal antibody) was first used in patients with suboptimal responses to PEX (i.e., exacerbation or refractoriness), typically at a dose of 375 mg/m^2 in 4 weekly doses) with excellent (89%) remission rates (Joly et al., 2017). These very positive results prompted an increase in frontline use of rituximab, which results in shorter hospitalization and fewer relapses (Scully et al., 2011, Vazquez-Mellado et al., 2016).

Response to rituximab was associated with a decrease in the anti-ADAMTS-13 antibodies with a resulting increase in the ADAMTS-13 activity (Cataland and Wu, 2015). Earlier administration (within 3 days) was associated with faster achievement of remission (12 vs. 20 days, $P < 0.001$), fewer PEX (16 vs. 24, $P = 0.03$) and shorter hospital stay (16 vs. 23 days, $P = 0.01$) (Westwood et al., 2013).

In addition, rituximab improved relapse-free survival when used for prophylactic treatment of patients with a history of aTTP and persistent ADAMTS-13 activity less than 10% in clinical remission (Hie et al., 2014, Westwood et al., 2013). Rituximab prophylaxis was associated with normalization of ADAMTS-13 levels within 3 months in all but one case, with only one acute relapse at follow-up (Westwood et al., 2013).

2.1.1.4 Caplacizumab

There is ongoing clinical evaluation of caplacizumab, an anti-VWF nanobody that inhibits the binding between platelet GPIb receptor and ULVWF multimers, thereby preventing platelet aggregation in the microcirculation, with the aim of decreasing the time to normalization of platelet count during PEX. In the Phase 3, controlled study, 145 patients underwent randomization (72 were assigned to receive caplacizumab, and 73 to receive placebo). In the caplacizumab group, 50% of patients had platelet normalization within 2.69 median days (95% confidence interval [CI], 1.89 to 2.83) compared to 2.88 median days in the placebo group (95% confidence interval 2.68 to 3.56, $P = 0.01$) and 75% of patients had platelet normalization in 2.95 days compared to 4.50 days in the placebo group (95% confidence interval). Three patients in the caplacizumab group had an exacerbation, as compared with 28 patients in the placebo group. Six patients in the caplacizumab group had a relapse in the first month after stopping the study drug, all of whom had ADAMTS-13 activity that remained below 10%, suggesting unresolved autoimmune activity. The median duration of exposure to caplacizumab was longer than the duration of exposure to placebo (35 days [range, 1 to 65] vs. 23 days [range, 2 to 66]). Bleeding-related adverse events (AEs), most of which were mild to moderate in severity, were more common with caplacizumab than with placebo (65% of patients vs. 48%). Bleeding events were severe in 3 patients in the caplacizumab group, and one patient had severe bleeding in the placebo group. Serious adverse events of bleeding were reported in 8 patients (11%) in the caplacizumab group and in 1 patient (1%) in the placebo group.

Normalization of the three organ-damage markers (lactate dehydrogenase, cardiac troponin I, and serum creatinine) occurred in 0 patients in the caplacizumab group versus 3 patients in the placebo group (P=0.06) (Peyvandi et al., 2016).

Although caplacizumab blocks the formation of microthrombi, it does not address the underlying pathophysiology, the ADAMTS-13 deficiency (Cataland and Wu, 2015). Clinical events including relapse, exacerbation, and organ damage may occur once it is discontinued if the potential to form the microthrombi remains. For instance, 8% on the caplacizumab and none on the placebo arms of the Phase 3 study had a recurrence during first month after discontinuing the therapy (Peyvandi et al., 2016).There have been no long-term safety studies to assess organ damage.

2.1.2 Unmet Medical Needs of Current Therapy

With current therapy, acute mortality rate of aTTP is still 10-20% (Alwan F et al., 2016), and in high-risk patients (older age, multiple organ involvement at presentation, etc.) it may reach 30-60% (Benhamou et al., 2012).

Although PEX is the standard treatment for TTP, it is frequently associated with complications related to both the procedure and the large volumes of plasma to which the patient is exposed. These complications include catheter-related sepsis, venous thrombosis, pneumothorax, hemorrhage, hypotension, allergic and anaphylactic reaction, citrate intolerance, and volume overload (Koyfman et al., 2011, Reutter et al., 2001).

Adverse events were reported as complications in about 26% of the PEX procedures (George, 2007). In a nine-year cohort study of 206 consecutive patients treated for TTP, five patients (2%) died of complications of PEX treatment; three patients died from hemorrhage related to the insertion of a central venous catheter and two from catheter-related sepsis. Fifty-three other patients had major complications attributed to PEX treatment, including systemic infection, venous thrombosis, and hypotension that required treatment.

Despite significant progress in plasma safety, infectious risk associated with blood-borne pathogens remains (Bryant and Klein, 2007, Humpe et al., 2000). Also, long-term PEX may become especially problematic in patients with poor venous access. Furthermore, PEX is associated with high healthcare resource utilization, is time consuming, specialized equipment and trained staff, and can be stressful for patients.

Recurrence (reemergence of clinical and laboratory signs and symptoms of TTP after the remission) has been reported in 20 to 50% of cases (Peyvandi et al., 2008). Most recurrences occur within the first year after the acute episode and less frequently thereafter.

Exacerbation within 30 days of remission occurs in up to 50% of aTTP patients in spite of daily PEX, and relapses have been reported in 20 to 40% of cases. Refractory disease occurs in up to 10% of aTTP patients regardless of intensive PEX (Coppo and Veyradier, 2012).

Even among patients who do not relapse, many experience a lower quality of life (QoL) in terms of general and mental health, and may continue to experience pain in the long run (Lewis et al., 2009). Patients in remission may suffer from lingering neurocognitive impairment (Han et al., 2015, Kessler et al., 2012). In one study following patients recovering from TTP for up to 16 years, the prevalence of hypertension, depression, and risk of death were increased (Deford et al., 2013). These underscore not only the ongoing therapeutic challenge in the treatment of the initial acute event, but also the need to decrease the long-term morbidity seen after its resolution.

2.2 Product Background and Clinical Information.

The active drug substance of SHP655, produced in a Chinese Hamster Ovary (CHO) mammalian expression system in a plasma-protein-free milieu, is the fully glycosylated recombinant human ADAMTS-13 protein that has undergone two dedicated virus reduction steps, solvent detergent [S/D] treatment and nanofiltration.

Preclinical studies show efficacy in aTTP. When TTP was triggered using 2000 U/kg rVWF in the presence of polyclonal antibody to ADAMTS-13 in SD rats, the animals displayed severe TTP-like symptoms, such as thrombocytopenia, hemolytic anemia, and VWF–rich thrombi in the kidneys and brain. Subsequent injection SHP655 prevented development of these symptoms. Analysis of plasma samples confirmed that SHP655 was able to override circulating anti-ADAMTS-13 inhibitory antibodies, resulting in restoration of ADAMTS-13 activity and degradation of ultra-large VWF multimers (Plaimauer et al., 2011, Plaimauer et al., 2015, Tersteeg et al., 2015, Tersteeg et al., 2016).

Results from the Phase 1 clinical study of cTTP show that rADAMTS-13 is safe and efficacious for cTTP. Pharmacokinetic parameters of rADAMTS-13 were comparable to those estimated in previous plasma infusion studies.

Dosing of SHP655 in aTTP subjects has not been studied previously and is complicated by the presence of binding and inhibitory autoantibodies and the effect of daily PEX, which removes plasma protein and replenishes ADAMTS-13 via donor plasma. In silico modeling that accounted for these factors, in addition to Phase 1 PK data of ADAMTS-13 activity in congenital TTP patients, were used to determine dosing in this study.

No interaction studies with other medicinal products have been performed to date.

Refer to the IB for details on the background and clinical information of the investigational product (IP).

2.3 Study Rationale

Despite advances in the knowledge of the pathophysiology of aTTP, the acute mortality rate has remained 10-20% for over twenty years (Alwan F et al., 2016). Moreover, TTP patients suffer from numerous devastating morbidities and decreased quality of life (Deford et al., 2013, Tersteeg et al., 2016). SHP655, has demonstrated efficacy of restoring VWF-cleaving activity in vitro in the presence of anti-ADAMTS-13 antibodies and in an animal model of aTTP. With sufficient rADAMTS-13 replacement, it is expected that aTTP patients can receive adequate therapy, leading to a reduction in the severity of TTP episodes and time to resolution. Such improvements in the therapy for aTTP patients are potentially reducing short- and long-term clinical complications including neurological impairment, renal failure, myocardial damage and stroke and improve quality of life.

This study is needed to assess ADAMTS-13 activity in aTTP subjects in the context of SHP655 dosing, PEX and anti-ADAMTS-13 autoantibodies, all of which will acutely change plasma ADAMTS-13 activity. The relationship between recovery of ADAMTS-13 activity and improvement in clinical outcomes will be explored. A PK/PD analysis will be utilized to establish an SHP655 dosing regimen that achieves efficacious ADAMTS-13 activity levels with a reduced number of PEX for use in future studies.

2.4 Benefit/Risk Assessment

SHP655 appeared to be safe and well tolerated following a single administration over a dose range of 5 to 40 U/kg in cTTP patients in Study 281101, and there was no evidence of an immune response to SHP655. The activity PK parameters were comparable to those estimated from fresh frozen plasma (FFP) studies and demonstrated dose proportionality with respect to C_{max} and AUC. Finally, there was evidence for SHP655 activity *in vivo*, including effects on VWF multimers, platelet count, and serum LDH. Overall, the data obtained in the first-in-human Phase 1 Study 281101 indicate that SHP655 is suitable for further clinical development and may have a positive benefit:risk ratio for patients with congenital TTP. Because the primary defect, i.e. ADAMTS-13 deficiency, is the same in congenital and acquired TTP, rADAMTS-13 replacement is anticipated to be safe and may provide benefit in acquired TTP if sufficient plasma concentrations of ADAMTS-13 can be achieved.

Refer to the latest version of the SHP655 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of SHP655.

2.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonization 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 Co-Primary Objectives

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

3.1.2 Secondary Objectives

PK/PD Objectives

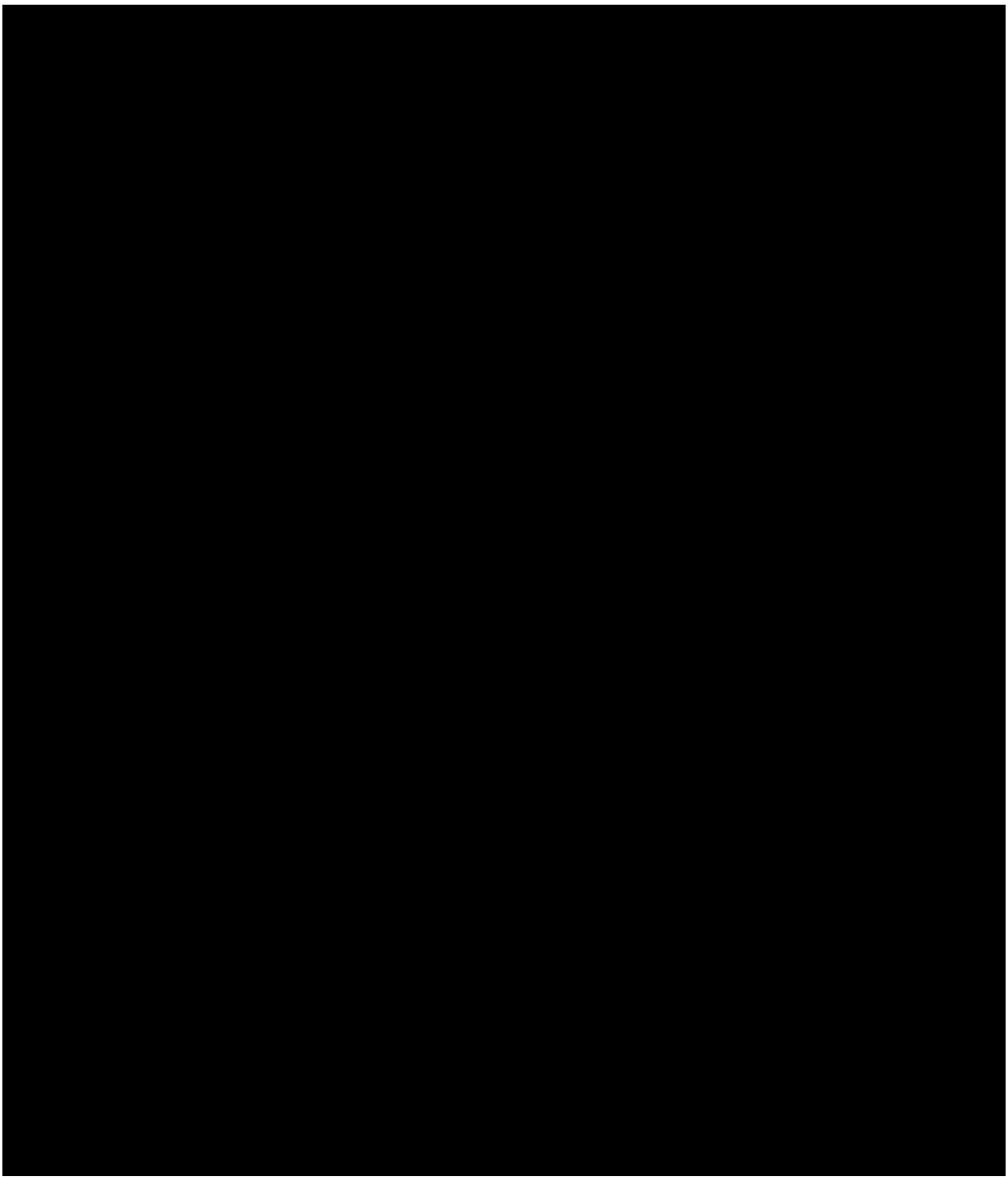
- Evaluate changes in levels of ADAMTS-13 binding and inhibitory autoantibodies from baseline in response to daily PEX, with or without SHP655 supplementation, during the acute episode and up to 30 days after the resolution of the acute aTTP episode
- Evaluate ADAMTS-13 activity levels in subjects up to 30 days after acute aTTP episode remission
- Specify dose(s) of SHP655 needed to achieve and maintain adequate plasma levels of rADAMTS-13 in order to support induction of remission and to reduce the number of PEX procedures needed for the treatment of acute aTTP episodes.

Safety/Efficacy Objectives

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

*Defined as >30 days after achieving remission
**Defined as ≤30 days after achieving remission

3.1.3 Exploratory Objectives



3.2 Study Endpoints

Table 4. Objectives and Endpoints

Objective	Endpoint(s)
Co-Primary	
• Assess the PK of ADAMTS-13 in aTTP subjects treated for an acute episode by daily plasma exchange (PEX), immunosuppressant therapy, with or without SHP655 supplementation • Study the PK/PD relationship between ADAMTS-13 activity levels and pathophysiological biomarkers as well as clinical efficacy parameters.	• ADAMTS-13 activity levels • Platelet count and LDH levels
Secondary	
PK/PD Objectives	
• Evaluate changes in levels of ADAMTS-13 binding and inhibitory autoantibodies in response to daily PEX, with or without SHP655 supplementation, during the acute episode and up to 30 days after the resolution of the TTP episode	• Changes in the titers of binding and inhibitory antibodies to ADAMTS-13 relative to baseline • Occurrence of antibodies to SHP655 • PK parameters such as incremental recovery, area under the curve, systemic and antibody induced clearance, maximum ADAMTS-13 activity between PEX or SHP 655 infusions, and trough levels prior PEX • The ADAMTS-13 binding and inhibitory autoantibody levels in response to daily PEX, with or without SHP655 supplementation, during the acute TTP episode and up to 30 days after resolution
• Evaluate ADAMTS-13 activity levels in subjects up to 30 days after TTP episode remission	• ADAMTS-13 activity levels in subjects receiving additional SHP655 for up to 30 days after the resolution of the TTP episode
• Specify dose(s) of SHP655 needed to achieve and maintain adequate plasma levels of rADAMTS-13 in order to support induction of remission and to reduce the number of PEX procedures needed for the treatment of acute aTTP episodes.	• The PK/PD temporal relationship of efficacy parameters (e.g., platelet count, LDH levels), as a function of ADAMTS-13 activity • The relationship between ADAMTS-13 activity and end-organ disease status (e.g., renal, neurologic, and cardiac)

Table 4. Objectives and Endpoints

Objective	Endpoint(s)
Safety/Efficacy Objectives	
• Assess the safety and immunogenicity of two regimens of SHP655 supplementation administered during an acute TTP episode in subjects undergoing PEX treatment and immunosuppressant therapy as measured by AEs, changes in vital signs and laboratory parameters	• Incidence of AEs and SAEs, and specifically product-related AEs and SAEs • Clinically relevant changes in vital signs, clinical chemistry, and hematology • Platelet count and LDH levels • Time to normalization of platelet count, defined as platelet count ≥ 150,000/μL, which must be confirmed by a second normal platelet count ≥ 150,000/μL and LDH <2 ULN 48 hours following initial normalization • Occurrence of remission, defined as a normal platelet count and LDH <2 ULN for at least 48 hours following initial normalization of platelet count (acute episode period) • Occurrence of subjects receiving rescue therapy • Occurrence of subjects meeting rescue criteria • Occurrence of antibodies to SHP655
• Evaluate the occurrences of aTTP related complications, (including death, stroke, MI, and organ failure), aTTP relapses, exacerbations and end-organ function improvement.	• Occurrence of exacerbation • Occurrence of relapse • Occurrence of major clinical events related to TTP including: (entire study) a. Death b. Stroke c. MI d. Organ dysfunction not normalized within the 90 day observation period i. Chronic renal insufficiency ii. Neurologic impairment iii. Neurocognitive deficits
• Evaluate the time to aTTP related complications (including death, stroke, MI, and organ failure), aTTP relapses*, exacerbations** and end-organ function improvement	• Time to first exacerbation (aTTP episode ≤30 days following remission) • Time to relapse (aTTP episode >30 days following remission)
• Evaluate the occurrence of procedure (e.g. PEX, SHP655 infusions) related adverse events	• Incidence of major clinical events related to PEX, including clinically relevant bleeding (modified ITP score) or thrombosis at the site of line insertion, adverse reactions to plasma, including citrate reactions, allergic reactions, and TRALI

Table 4. Objectives and Endpoints

Objective	Endpoint(s)
Exploratory Objectives	
[redacted]	

Table 4. Objectives and Endpoints

Objective	Endpoint(s)
[redacted]	[redacted]

4. STUDY DESIGN

4.1 Overall Design

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

Arm 1 – SoC plus placebo (n=10)

Subjects will receive daily PEX and placebo immediately after PEX and 12±1 hours after completion of PEX.

Arm 2 – SoC with SHP655 once daily (n=10)

Subjects will receive daily PEX and 40 IU/kg ±4 IU/kg SHP655 once daily immediately after PEX and placebo 12±1 hours after completion of PEX.

Arm 3 – SoC with SHP655 twice daily (n=10)

Subjects will receive daily plasma exchange and 40 IU/kg ±4 IU/kg SHP655 twice daily immediately after PEX and 12±1 hours after completion of PEX.

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

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

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

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

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

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

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

Discretionary Rescue Therapy

Study investigators may elect to administer rescue therapy to a subject if platelet count have not increased at least 2-fold from screening and LDH remains above ULN after 4 days of treatment. Rescue therapy will be defined as any product with a known interruption to the PK/PD relationship between ADAMTS-13 activity, VWF activity, and platelet count. Additional administration of FFP, S/D treated plasma, and immunosuppressive therapies will not be considered rescue therapy unless otherwise agreed after consultation with the Sponsor. However, they may be prohibited medication after initiation of plasma exchange (refer to section 6.8.4). The rescue therapy treatment should follow local standard of care practices. If rescue therapy is initiated, the administration of IP (SHP655 or placebo) will be suspended for the duration of the study. The patient will continue to follow the same visit and assessment schedule to be monitored for safety. PK samples should continue to be collected to monitor safety and the subject should be followed for three months post remission.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for control group

A control group of SoC alone plus placebo was chosen so that an independent effect of PEX and autoantibody can be modeled without the contribution from SHP655 dosing. Additional considerations are that use of a SoC control group will enable a comparison of efficacy endpoints between placebo and SHP655 dosed groups.

4.2.2 Rationale for Primary and Key Secondary Endpoints

Deficiency of ADAMTS-13 is the cause of aTTP. Thus, determining the PK of dosed rADAMTS-13 in the context of aTTP treatment will lead to an understanding of how to dose rADAMTS-13 to achieve remission, which is defined by consensus criteria as normalization of platelet account and LDH.

4.2.3 Justification for the use of placebo

The use of double-blind placebo offers several study design advantages. First, a double blinded placebo minimizes bias in AE reporting that could be influenced by knowledge of treatment allocation. Second, it minimizes bias in treatment decisions, PK blood sampling, and other procedures that could be influenced by knowledge of treatment allocation.

4.3 Justification for Dose

The dosing regimen of 40 IU/kg ±4 IU/kg was selected based on the Phase 1 single-dose study of SHP655 in subjects with cTTP (Study 281101). This dose was safe and well tolerated and is further supported by non-clinical safety studies (see 5.3.1 Non-clinical Studies).

In the Phase 1 study the pharmacokinetics of ADAMTS-13 was characterized in cTTP patients with no detectable anti-ADAMTS-13 antibodies. The mean terminal half-life was 59.2 hours using the FRETS-VWF73 assay. The geometric mean of IR was 0.0232 (U/mL x kg/U). The geometric mean C_{max} after a 40 U/kg infusion was 0.948 U/mL and the $AUC_{(0\text{-inf})}$ was 53.1 U·h/mL. In an aTTP population which will have the anti-ADAMTS-13 antibodies, Baxalta expects the clearance to be significantly increased. There may also be a decrease in the incremental recovery, as noted in Phase 1 Study 281101. In addition, PEX will remove anti-ADAMTS-13 antibodies and SHP655. Daily dosing therefore is needed to evaluate PK model that can predict doses needed for efficacious ADAMTS-13 levels. To augment the ability of the PK model to predict the efficacious dose and to evaluate safety at higher doses that the PK model may predict, a second regimen will be tested at 40 IU/kg ±4 IU/kg twice daily.

The proposed dosing supplementation regimen of SHP655 is not predicted to yield ADAMTS-13 activity levels that will exceed a safe threshold, even in a cTTP patient mistakenly diagnosed with aTTP. Daily PEX with donor plasma that has a presumed ADAMTS-13 activity of 100% will help normalize any excessively low or high ADAMTS-13 level.

4.4 Duration of Subject Participation and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 6 months, depending on the time needed to achieve remission plus 3 months' follow-up.

The study will be completed in approximately 1.5 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 follow-up visit or contact, whichever is later (refer to Section 8.1.3 for the defined follow-up period for this protocol).

4.5 Sites and Regions

The study will be conducted in approximately 27 sites across North America and Europe.

5. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent 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. Subject voluntarily signs informed consent. For subjects unable to provide consent, a fully recognized medical proxy may be used according to local laws.
2. Subject is 18 to 75 years old at the time of screening.
3. Subject has been diagnosed with primary or secondary autoimmune aTTP based on the following criteria:
   a. Thrombocytopenia [drop in platelet count ≥50% or platelet count < 100,000/μL];
      - No more than 3 subjects per arm may be enrolled with a screening platelet count ≥50,000/ μL.
   b. Microangiopathic hemolytic anemia [elevation of lactate dehydrogenase (LDH) >2-fold or by presence or increase of schistocytes in peripheral blood smear]
4. Willingness to fully comply with study procedures and requirements, and intention to initiate plasma exchange (PEX). Subjects may be provisionally entered into the trial and undergo randomization pending the results of the ADAMTS-13 activity, anti-ADAMTS-13 antibody, and genetic testing for cTTP
5. If female of childbearing potential, subject presents with a negative pregnancy test and agrees to employ adequate birth control measures for the duration of the study. Sexually active males must use an accepted and effective method of contraception during the treatment and until a minimum of 16 days after the last dose administered.

5.2 Exclusion Criteria

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

1. Subject has been diagnosed with congenital TTP
2. Subject has plasma ADAMTS-13 activity> 10% of normal at the central lab; if screening samples are not taken until after the first PEX, ADAMTS-13 activity from the local lab is permitted to determine eligibility
3. Subject has been diagnosed with another cause of thrombotic microangiopathy (TMA) including: DIC, disseminated malignancy, malignant hypertension, hematopoietic stem cell transplantation, shiga toxin-related and atypical HUS, drug toxicity (e.g. gemcitabine, mitomycin C, clopidogrel) and pregnancy-related thrombocytopenia syndromes (e.g. HELLP, eclampsia)

4. Subject has been exposed to another IP within 30 days prior to enrollment or is scheduled to participate in another clinical study involving IP or investigational device during the course of the study
5. Subject has received caplacizumab within 1 month prior to study enrollment.
6. Subject is human immunodeficiency virus positive (HIV+) with unstable disease or CD4+ count ≤200 cells/mm^3 within 3 months of screening
7. Subjects with conditions of severe immunodeficiency.
8. Subject has had a previous aTTP event in the past 30 days
9. Subject has another underlying progressive fatal disease and/or life expectancy of less than 3 months.
10. Subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
11. Subject suffers from a mental condition rendering him/her unable to understand the nature, scope, and possible consequences of the study and/or evidence of an uncooperative attitude. However, a fully recognized medical proxy will be permitted to provide consent.
12. If female, subject is pregnant or lactating.
13. Subject is a family member or employee of the Sponsor or investigator.
14. Any contraindication to PEX, methylprednisolone and/or rituximab as per prescribing information
15. Known life-threatening hypersensitivity reaction, including anaphylaxis, to the parent molecule ADAMTS-13, hamster protein, or other constituents of SHP655.

5.2.1 Contraception

Sexually active females of childbearing potential should use an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 16 days following the last dose of investigational product. If used, hormonal contraceptives should be administered according to the package insert.

Female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or

- Of childbearing potential with a negative serum β-hCG pregnancy test at the Screening/Enrollment Visit and prior to randomization. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

- Intrauterine devices plus condoms
- Double-barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (Visit 1), plus condoms. Note: If the subject becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

Sexually active males must exercise abstinence or use an accepted and effective method of contraception during the treatment and until a minimum of 16 days after the last dose administered.

6. STUDY INTERVENTION

6.1 Investigational Product

6.1.1 Identity of Investigational Product

SHP655 and placebo (0.9% saline)

Dosage form:
Lyophilized formulation

Dosage frequency:
Up to twice daily during treatment period and up to once weekly for 4 weeks after remission is achieved.

Mode of Administration:
Intravenous (i.v.)

The investigational product is SHP655 (rADAMTS-13), a recombinant ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that expresses the human ADAMTS cDNA. It will be provided in lyophilized formulation together with sterile water for reconstitution for intravenous administration. Additional information is provided in the current SHP655 Investigator's Brochure.

The reference/comparator product is placebo (0.9% saline) which will be provided in single use vial form.

6.1.2 Blinding the Treatment Assignment

Double blind administration of placebo or SHP655 is given twice daily in all Arms until remission is achieved. Supplementation with SHP655 after remission is also blinded.

6.2 Administration of Investigational Product

6.2.1 Hypersensitivity to SHP655

SHP655 should not be administered in patients with known hypersensitivity to any of the components of rADAMTS-13. 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.

6.2.2 Interactive Response Technology for Investigational Product Management

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

6.2.3 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 investigational product allocated to the subject, once eligibility has been determined.

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

Individual subject treatment is automatically assigned by the interactive response technology (IRT).

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

6.2.4 Dosing

SHP655 is administered by i.v. injection. The reconstituted solution of SHP655 should be clear and colorless in appearance. SHP655 should be administered at room temperature and within 3 hours of reconstitution.

Prior to administration of the IP, it should be ensured that the solution is clear and free of particles. In addition, it should be ensured that venous access via an i.v. cannula is available. A butterfly needle may be used if placed immediately prior to the IP infusion. Central venous catheters may be used for IP infusion.

SHP655 should be slowly infused (between 2 to 4 mL per minute). Syringes should be changed according to medical practice.

An unblinded investigational pharmacy at each site will coordinate the administration of IP. Placebo (0.9% normal saline) or SHP655 will be drawn into syringe with the appropriate study label that does not identify the IP as active drug or placebo, and a blinded study team member will administer the dose.

6.2.5 Unblinding the Treatment Assignment during the Placebo-Controlled Portion of the Study

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

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

The interim analysis (IA) data and results will be provided in unblinding fashion to a pre-specified sub-team of the current clinical team. Newly appointed members of the clinical team, who are blinded to the treatment assignments and unaware of the interim data and results will support the remaining portion of the study. The rest of the study team will remain blinded to the restricted data and the results of the interim statistical and PK analyses until the time after database lock and study unblinding. All individuals involved in the conduct of the trial post IA are to remain unaware of unblinding information related to the interim analysis. The study will continue after the IA as double blinded for the duration of the trial.

6.2.6 Dose Modification

In all study arms, the second daily dose (SHP655 or placebo given 12 hours after PEX completion) will be terminated if the pre-PEX ADAMTS-13 activity levels are >150% (local lab) or above the upper limit of the local lab quantification. After the second dose has been suspended, the first daily dose (SHP655 or placebo given immediately after PEX) will be terminated if pre-PEX ADAMTS-13 activity levels are >150% or above the upper limit of the local lab quantification. If the ADAMTS 13 levels (based on local labs) are <50% between discharge and first weekly follow-up visit then the investigator may treat the patient with the IP prior to the scheduled visit. Any additional assessments may be conducted as per the investigator's judgement.

After resolution of the TTP episode, subjects who received SHP655 during the treatment of the acute episode will be given additional supplementation with blinded IP once weekly (maximum of 4 doses of weekly 40 IU/kg ±4 IU/kg) if a weekly ADAMTS-13 activity at the local lab is <50% (drawn >72 hours after last IP infusion).

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 investigational product(s) container.

The sponsor will provide the investigator with packaged investigational product labeled in accordance with specific country regulatory requirements. All investigational product is labeled with a minimum of the following: protocol number, product identification number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements "For clinical trial use only" and/or "CAUTION: New Drug – Limited by Federal (or United States [US]) Law to Investigational Use," and the sponsor's name and address.

Additional labels (e.g., those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product 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.

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

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

SHP655 will be packaged in single boxes with 2 glass vials, 1 vial containing the lyophilized SHP655, the other containing the diluent. Further details are provided in the Pharmacy Manual.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product 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 distributed by the pharmacy or nominated member of the study team.

The investigator or designee will be blinded to the treatment and will be responsible for administering the investigational product.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product 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. 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 investigational product 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 investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

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

The investigator has overall responsibility for administering/dispensing investigational product. 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 investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered medication will be documented in the subject's source and/or other investigational product record. No investigational product stock or returned inventory from a Shire-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 investigational product 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 investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

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

6.5 Subject Compliance

Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.6 Plasma Exchange (PEX)

PEX procedures will be performed per the local SoC using the locally available automated apheresis device with citrate anticoagulant. Replacement fluid will be the plasma type(s) available through the local blood bank. Fresh frozen plasma, thawed plasma, solvent-detergent plasma, and cryoprecipitate-poor plasma are acceptable. Replacement with normal saline or albumin solutions are permitted per local SoC.

The first PEX prior to IP administration will be performed according to the local SoC. The first two PEX procedures on study (3rd PEX overall) will be 1.5 plasma volumes (per Rock et al., 1991). The 3rd and subsequent on-study PEX procedures will be 1.0 plasma volume. Planned PEX schedules or plasma volumes different than once daily must be pre-approved by the sponsor. In extenuating cases, urgent, unapproved changes to the PEX regimen may be required for optimal patient care, e.g. emergent stroke or MI.

The following PEX parameters will be recorded for each PEX procedure:

- Calculated plasma volume according to apheresis device
- Plasma volume exchanged
- Volume of anticoagulant used
- Volumes and types of replacement fluid(s) exchanged
- Blood loss (if applicable)
- Time of PEX (time connected to apheresis device)

Adverse events related to apheresis catheters, venous access, and/or PEX will be recorded as (S)AEs and managed per the local SoC. Citrate toxicity is recommended to be treated with pausing of the apheresis procedure and administration of iv calcium preparation. Low plasma ionized calcium concentrations are supportive evidence of citrate reactions but are not required for diagnosis.

All transfusion reactions of any severity must be documented and reported to the blood bank. Transfusion reactions will be managed according to the local SoC. It will be recorded whether PEX-related AEs lead to delays in the PEX procedure, an aborted procedure, and/or additional procedures (e.g. central venous catheter interventions, escalation in care).

6.7 Immunosuppression

- Methylprednisolone: Subjects will receive methylprednisolone 1g/day iv x 3 days starting on the first study treatment day. On Day 4, the methylprednisolone dose is recommended to start at 2.5 mg/kg/day. Corticosteroids administered prior to enrollment will be recorded as prior therapy. Adjustments in corticosteroid regimen deemed necessary by the principal investigator are allowed; the justification for the modification and the alternate treatment regimen will be recorded. Tapering of methylprednisolone, including transition to another corticosteroid, is permitted at the discretion of the principal investigator.
- Rituximab: recommended dose of 375mg/m^2 iv once weekly x 4 weeks. The first dose will be administered within two days of enrollment. All doses are recommended to be administered as soon after PEX as feasible (when applicable).

6.8 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/enrollment 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.

6.8.1 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 first dose of investigational product. Prior treatment information must be recorded in the subject's source document. It is anticipated that subjects will have received one SoC PEX prior to enrollment. Plasma infusion is permitted as prior treatment.

6.8.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the subject's source document.

6.8.3 Permitted Treatment

The following adjunctive treatments are allowed:

For PEX, antihistamines, calcium replacement, iv fluids, and albumin solution are permitted. Aspirin and heparin formulations are permitted per the local aTTP SoC.

Any treatment for comorbid conditions is permitted. Red blood cell transfusion is permitted at the investigator discretion. Medical treatments not otherwise specified in the protocol are permitted. Consultation with the study medical director is advised for any questions about concomitant treatments.

6.8.4 Prohibited Treatment

Caplacizumab is prohibited within 1 month prior to the study and during the study. During the study, Caplacizumab may be used as discretionary rescue therapy if part of the local standard of care and a subject's platelet count has not increased 2x from screening and LDH remains above ULN after 4 days of treatment. In this instance, the administration of all study IP should be suspended for the duration of the study.

Treatments for aTTP in addition to glucocorticoids and rituximab (e.g., bortezomib, N-acetylcysteine, cyclophosphamide, splenectomy, cyclosporine, vincristine) require prior approval by the sponsor.

Plasma infusion after PEX has been initiated is prohibited except for subjects receiving rescue therapy. Platelet transfusion and factor concentrates are prohibited except for instances of life-threatening hemorrhage.

Investigators should always use their clinical judgement to determine the best course of treatment for a patient. If prohibited treatments are administered, the Medical Monitor should be immediately notified to make a decision on continued participation in the study.

7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

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

Subjects who discontinue will be replaced at the discretion of the sponsor.

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 1 reason, each reason should be documented in the source and the most clinically relevant reason should be indicated.

Reasons for discontinuation include, but are not limited to:

- Not meeting confirmatory inclusion criteria, i.e. screening ADAMTS-13 >10% at sponsor bioanalytic lab, no ADAMTS-13 inhibitory antibody, or genetic mutation indicating congenital TTP
- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Sponsor withdrawal
- Major surgery
- Subject becomes pregnant
- Screen failure
- Other (must be specified in CRF)

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.

If 1) the subject withdraws or 2) a subject is not confirmed to be a case of aTTP because of ADAMTS-13 activity >10%, absence of anti-ADAMTS-13 autoantibody, or genetic confirmation of congenital TTP, IP administration and study procedures will stop, with the exception of a Termination/Completion Visit, which should occur within 1 week after the final dose of IP.

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 acknowledgement of receipt request) asking that the subject return to the site for final safety evaluations and return any unused investigational product.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Schedule

Refer to Table 1 for the schedule of study activities. Study assessments are detailed in Section 8.2.

8.1.1 Screening Period

Subjects may present with an initial or relapse aTTP episode. Screening will occur as soon as feasible after clinical presentation. Initial aTTP management until enrollment will be performed according to the local SoC, including the initial PEX. Screening will utilize local labs for initial eligibility determination.

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. Subjects who are screen failures may undergo a full re-screening with a new study identification number.

A subject is considered enrolled once randomized. Subjects may not re-enroll if previously randomized in this study.

8.1.1.1 Screening/Baseline Visit

Informed consent must be obtained by the subject or the subject's legally authorized representative before subjects are asked to prepare for any screening procedures.

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

8.1.2 Treatment Period

After screening, subjects will be randomly assigned to 1 of 3 Arms by a computer algorithm. In the event that enrollment in an Arm is full, subjects will be randomly assigned to the remaining Arm(s).

The treatment period begins after randomization with the first IP infusion up to 4 hours after the initial PEX, but preferably as soon as possible. For all Arms after remission is achieved, blinded IP supplementation is administered weekly for ADAMTS-13 activity levels <50% (measured >72 hours after the last dose of IP).

PEX will occur once daily during the treatment period. If the principal investigator deems that more intensive PEX is required for patient care, it is preferred that the volume of plasma treated be escalated to 1.5 or 2 plasma volumes before the frequency of PEX is increased. A planned increase in the frequency of treatment volume of PEX requires sponsor approval. Additional PEX after remission is not permitted except for subjects receiving rescue therapy.

8.1.2.1 Final Visit

The Final Visit is the Completion/Termination Visit.

8.1.3 Follow-up Period

The follow-up period is 3 months after remission. For subjects who receive SHP655 supplementation after remission, follow up after the last dose of IP will be 2 months if supplementation is given in week 4 after remission. Subjects maybe contacted for up to 6 months after study completion to correct or complete study data collection.

In the event of aTTP exacerbation or relapse during the study period, the subject will not receive additional IP, and treatment will be determined by the PI. During the treatment of a recurrence, subjects will follow the bi-weekly visit schedule and study procedures per Table 1 until remission is achieved or 4 months after the initial remission, whichever is sooner.

At the end of this period will be the Completion/Termination Visit. All AEs and SAEs that are not resolved at the time of this contact will be followed for up to 30 days (see Appendix 2.2).

All follow-up visits except the completion/termination visit may be conducted by a healthcare provider in the home setting if consistent with local procedures and all study requirements are met.

8.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

8.2 Study Assessments

8.2.1 Demographic and Other Baseline Characteristics

Subject demographic information including gender, age, and race will be collected prior to the subject receiving the first dose of investigational product.

8.2.1.1 Height and Weight

Height and weight will be measured and recorded in the subject's source documents. Current hospitalization records may be used for height and weight. Weight will be recorded in kg to one (1) decimal.

8.2.1.2 Medical, Medication History, and Non-drug Therapies

Medical, medication history, and non-drug therapies will be collected and recorded in the subject's source documents at screening/enrollment. Concurrent medication and non-drug therapies will be collected at every visit.

8.2.2 Efficacy

The Montreal Cognitive Assessment (MoCA) and Richmond Agitation Sedation Scale (RASS) assessments will be performed daily while inpatient until the subject performs in the normal range for two consecutive days on each scale. Once the subject performs in the normal range on two consecutive days on a scale, the assessment scale is discontinued. Scales may be performed during the treatment period and for the first 4 weekly follow up visits. For the MoCA, the normal range is a score of 26-30. A subjects' inability to perform the MoCA will be documented by study staff. For the RASS, a normal score is zero. Assessments are to be performed during the daytime at a similar time of day, where feasible. RASS may be recorded directly into the CRF.

Occurrence of stroke, MI, neurologic deficits, cognitive deficits, and renal insufficiency will be documented daily as present/absent based on local laboratory results and local consultants, as appropriate for the local SoC. If present, 1) a narrative description will be provided at the time of diagnosis; 2) the status of present or absent will be documented daily.

Occurrence of exacerbation or relapse will be determined by platelet count or the occurrence after remission of a major clinical event (e.g. MI, stroke, death) deemed by the investigator to be related to aTTP. Exacerbation is defined as recurrent thrombocytopenia following a response and requiring a reinitiation of daily plasma exchange treatment after ≥ 1 day but ≤ 30 days of no plasma exchange treatment.

8.2.3 Safety

Safety will be assessed by monitoring vital signs, clinical chemistry, hematology, clinically relevant bleeding (modified ITP score) or thrombosis at the site of line insertion, adverse reactions to plasma, including citrate reactions, allergic reactions, and TRALI. Adverse Events (AEs) and Serious Adverse Events (SAEs) will be assessed. The modified ITP Bleeding Score will be assessed by the study staff daily until remission is achieved.

Central and local laboratories will be used for all laboratory values required per protocol.

The presence of inhibitors (and total binding antibodies) against rADAMTS-13 will be assessed for up to 1 month ± 7 days following the last interval study visit.

The study DMC will evaluate safety as per the DMC charter. In addition, the safety will be monitored by the Sponsor's Medical Director as per the safety review plan.

8.2.3.1 Physical Examination

Complete and targeted physical examinations will be performed at the time points specified in Table 1. Complete physical examination includes the review of the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; eyes; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; back; and lymph nodes. Weight will be measured at screening, weekly during the treatment period, and at the time points specified in Table 1. Height will be measured at screening (Visit 1) only.

Changes after the screening visit that are deemed clinically significant in the opinion of the investigator will be recorded as an AE.

Abnormalities (such as neurologic deficits, skin lesions) identified at the screening visit (Visit 1) and at subsequent study visits will be recorded in the subject's source documents.

8.2.3.2 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), or disease (e.g., peritonitis, bacteremia, etc.) temporally associated with the use of an IP, whether or not related to the IP. An AE includes any event, regardless of the presumed causality between the event and the IP.

Events that do not necessarily meet the definition of AEs, regardless of causal association with IP, should be treated as AEs because they may be reportable to Regulatory Authorities according to AE reporting regulation; these include the following:

- IP overdose, whether accidental or intentional
- IP abuse
- An event occurring from IP withdrawal
- Any failure of expected pharmacological action
- Exposure to IP during pregnancy
- Unexpected therapeutic or clinical benefit from the IP
- Medication errors (i.e., incorrect route of administration, incorrect dosage, use of incorrect product)

For the purposes of this study, the following non-serious events experienced after the first IP exposure are collected under other study outcome measures and thus are not reportable on the AE CRF if related to a TTP event, nor will they be included in the analysis of AEs:

1. Increase of serum creatinine
2. Elevation of LDH >2×ULN
3. Neurological symptoms (e.g., confusion, visual changes, dysphonia, paresthesias, dysarthria, focal or general motor symptoms)
4. Abnormal ADAMTS-13 activity
5. Positive anti-ADAMTS-13 inhibitor
6. Decrease in platelet count
7. Increase of serum creatinine
8. An increase in schistocytes in peripheral blood smear
9. Fever (≥100.4°F/38°C)
10. Abdominal pain

8.2.3.3 Vital Signs

Vital signs will be assessed at each visit, if not stated otherwise:

- Blood pressure: Systolic/diastolic blood pressure (mmHg) baseline measurements will be measured after a 10-minute rest in the supine/semirecumbent position.
- Pulse rate: Pulse rate (beats/min) will be measured at the distal radial arteries under the same conditions as above.
- Respiratory rate: Respiratory rate (breaths/min) will be measured over a period of 1 minute under the same conditions as above.
- Temperature: Body temperature (°C or °F) may be determined by oral, rectal, axillary, or tympanic measurement at the discretion of the investigator. However, the same method should be used for all measurements in 1 subject.

During the treatment period, vital signs will be assessed 30±15 minutes prior to and 30±15 minutes after the first IP infusion on study and 30±15 minutes prior to and 30±15 minutes after the first and second post-PEX IP infusion each day thereafter.

Vital sign values are to be recorded on the vital signs CRF. For each abnormal vital sign value, the investigator will determine whether the value is considered an AE (see definition in Appendix 2.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded 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 (described in Appendix 2.1), 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 vital signs CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, 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.

8.2.3.4 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.

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

The clinical chemistry panel is performed locally and consists of ALT, AST, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

The measurement of urine-albumin-creatinine ratio should be completed daily in the local lab during the acute treatment period and the weekly follow-up period if IP is administered to monitor for early signs of vasculitis.

A complete list of the clinical laboratory tests to be performed is provided in Table 1 and Table 2.

8.2.3.5 Pregnancy Test

A beta human chorionic gonadotropin (β hCG) pregnancy test will be performed locally on all females of childbearing potential at the time points specified in Table 1; if pregnancy is suspected; or upon withdrawal of the subject from the study.

Pregnancy tests are not required for females of non-childbearing potential who have undergone hysterectomy or bilateral oophorectomy, have medically confirmed ovarian failure, or are medically confirmed postmenopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; postmenopausal status may be confirmed by FSH testing in females who have had 12 consecutive months of spontaneous amenorrhea and are 51 years of age or older).

8.2.4 Other

8.2.4.1 Clinical Pharmacokinetics

Pharmacokinetics (PK) will be assessed at the following time points in all patients on each of the pre-specified sampling days: within 15 minutes pre-PEX, within 15 minutes post end of PEX, within 15 minutes post end of IP or placebo infusion, 0.5-3 hours after end of IP or placebo infusion #1, 4-6 hours after end of IP or placebo infusion #1, within 30 minutes pre-IP or placebo #2, within 15 minutes post end of IP or placebo infusion #2, 0.5-3 hours post end of IP or placebo infusion #2. Patients in each study arm will be separated into two groups and follow Sampling Schedule A or B, respectively.

SCHEDULE A: Days 1, 2, 3, 4, 6, 8, 11, and every 3 days thereafter

SCHEDULE B: Days 1, 2, 3, 5, 7, 9, 12, and every 3 days thereafter

PK sampling should continue as scheduled for subjects receiving rescue therapy. A complete list of PK sampling schedules and timepoints is provided in Table 3.

8.2.4.2 Pharmacodynamics

Pharmacodynamics will be assessed during the treatment period with daily LDH concentration and platelet count. In the one-month post remission (with or without supplementation), VWF multimer analysis will be assessed at weeks 1 and 4 post remission (Table 2).

8.2.4.3 Genetics

Genetic sequencing of the ADAMTS-13 gene will be performed to exclude subjects with congenital TTP and will not be used for exploratory research purposes.

8.2.4.4 [redacted]

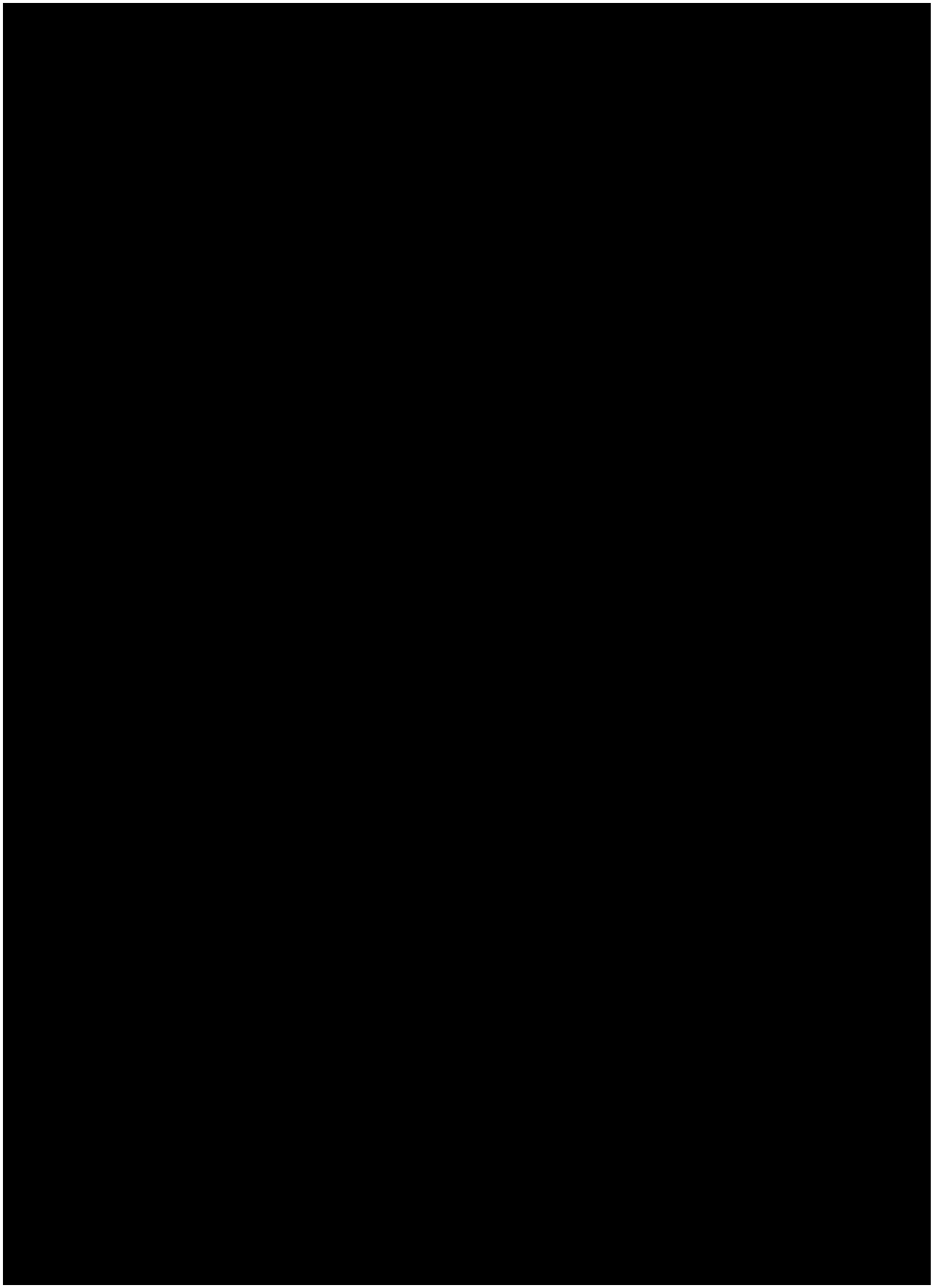
- [redacted]
  - [redacted]
  - [redacted]

8.2.4.5 [redacted]

- [redacted]

8.2.4.6 [redacted]

[redacted]



[redacted]

8.2.4.7 [redacted]

[redacted]

8.2.5 Volume of Blood to Be Drawn from Each Subject

Please refer to the study lab manual for volumes of blood to be drawn. The volume of blood to be drawn per subject will vary by how many PEX procedures are performed, with the accompanying post-PEX PK sampling.

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.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Process

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

The SAP will provide the statistical methods and definitions for the analysis of the efficacy, PK/PD and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed using SAS® software Version 9.3 or higher (SAS Institute, Cary, NC 27513).

Unless otherwise specified, summary tabulations will be presented by treatment group. All data listings will be sorted by treatment group, site, and subject number, and will include the subject's age, sex, and race.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation, minimum, and maximum values will be presented. For categorical data, the number of subjects, percentage, median, quartiles and range will be reported.

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

An interim analysis will be performed after 18 subjects have achieved remission and when approximately 50% of the planned sample size has been enrolled and treated in the three arms. The IA will include all data, collected by this time point, for all subjects enrolled in the study. IA results will be used to evaluate a preliminary treatment effect, assess initial PK/PD parameters, and inform the phase 3 clinical development planning. Access to results from the IA will be restricted to a small group of Takeda personnel designated as unblinded who thereafter will be removed from participation in oversight of daily conduct of this study. The interim analysis data and results may be used in regulatory interactions but will not be made public or used in scientific manuscripts. Details on the specific analyses to be performed during the Interim Analysis will be provided in the Statistical Analysis Plan.

An external DMC will be established to review the overall safety of the study subjects on an ongoing basis.

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

Further details regarding the DMC can be found in the DMC charter, which will be available before the administration of investigational product to any subject.
Analyses of the data for DMC review will be conducted according to the DMC charter and DMC SAP. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not applicable.

9.3 Sample Size and Power Considerations

The sample size for this study is not based on a power calculation. It is a Phase 2 study with PK modeling as one of the primary objectives and is being conducted in aTTP subjects which is a rare condition. The sample size of 10 subjects per treatment arm is selected to provide sufficient PK/PD data to develop the two models outlined in the co-primary objectives.

9.4 Statistical Analysis Set(s)

- The screened set will consist of all subjects who have signed an informed consent document.
- The randomized set will consist of all subjects in the screened set for whom a randomization number has been assigned.
- The safety set will consist of all subjects who have received at least 1 dose of investigational product.
- Full Analysis Set (FAS) will consist of all enrolled aTTP subjects who are treated with study product and have ADMATS13 activity reading from at least one post infusion sample. Randomization errors are included in the treatment arm they are randomized to, not in the treatment arm of the treatment they receive.
- The per-protocol set (PPS) will consist of all subjects in the FAS who do not have protocol deviations that may affect the efficacy endpoints.
- The PK set will consist of all subjects who have received at least 1 dose of investigational product and who have at least 1 evaluable post-dose PK concentration value. Samples from subjects receiving rescue medicine will be excluded from the primary and secondary endpoint analysis after the rescue medicine is initiated.

- The pharmacodynamics (PD) set will consist of all subjects who have received at least 1 dose of investigational product and who have at least 1 evaluable post-dose PD value. Samples from subjects receiving rescue medicine will be excluded from the primary and secondary endpoint analysis after the rescue medicine is initiated.

9.5 Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be based on the FAS and in the main efficacy analysis, subjects will be analyzed according to the treatment they actually received. There are no statistical hypotheses formulated for this study and no significant tests are planned. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

9.5.1 Primary Efficacy Endpoint

There is no Primary Efficacy Endpoint since the primary objective of the study is to assess PK of ADAMTS-13. PK analysis is described in Section 9.8.

9.5.2 Secondary Efficacy Endpoints

1. Time to normalization of platelet count, defined as platelet count ≥ 150,000/μL, which must be confirmed by a second normal platelet count ≥ 150,000/μL and LDH <2 ULN 48 hours following initial normalization
2. Occurrence of remission, defined as a normal platelet count and LDH <2 ULN for at least 48 hours following initial normalization of platelet count (acute episode period)
3. Time to first exacerbation (aTTP episode ≤30 days following remission)
4. Time to relapse (aTTP episode >30 days following remission)
5. Occurrence of exacerbation
6. Occurrence of relapse
7. Occurrence of major clinical events related to TTP including:
    a. Death
    b. Stroke
    c. MI
    d. Organ dysfunction not normalized within the 90-day observation period
        i. Chronic renal insufficiency
        ii. Neurologic impairment
        iii. Neurocognitive deficits.

8. Occurrence of subjects receiving rescue therapy
9. Occurrence of subjects meeting rescue criteria

All time to event efficacy endpoints will be analyzed by the non-parametric Kaplan Meier (KM) estimator of the survival curve. Estimates of the median time to event as well as proportions of subjects with event will be derived, together with two-sided, 95% confidence intervals.

Summary statistics will be provided for the secondary efficacy endpoints assessed by study arm. For continuous variables these will include mean, standard deviation and 95%, two-sided confidence interval (CI) for the mean. For discrete variable these will include proportions, incidence, and the two-sided 95% CI for the proportion.

Data handling and imputation approaches for subjects receiving rescue therapy will be described in the SAP.

An interim analysis will be performed after 18 subjects have achieved remission and when approximately 50% of the planned sample size has been enrolled and treated in the three arms. The IA will include all data, collected by this time point, for all subjects enrolled in the study. IA results will be used to evaluate a preliminary treatment effect, assess initial PK/PD parameters, and inform the phase 3 clinical development planning. Access to results from the IA will be restricted to a small group of Takeda personnel designated as unblinded who thereafter will be removed from participation in oversight of daily conduct of this study.

The interim statistical analysis will be performed by an unblinded CRO team which is separate from the CRO team that is involved in the conduct of the study. An interim population PK/PD analysis will be performed by an independent unblinded team at another CRO with no involvement in the conduct of the study.

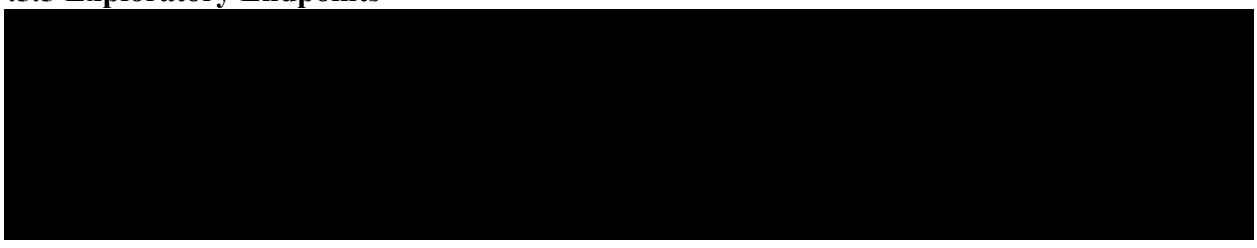
9.5.3 Multiplicity Adjustment

Not applicable.

9.5.4 Control of Type I Error

Not applicable.

9.5.5 Exploratory Endpoints



[redacted]

9.6 Safety Analyses

9.6.1 Secondary Safety Endpoints

1. Incidence of major clinical events related to PEX, including clinically relevant bleeding (modified ITP score) or thrombosis at the site of line insertion, adverse reactions to plasma, including citrate reactions, allergic reactions, and TRALI
2. Changes in the titers of binding and inhibitory antibodies to ADAMTS-13 relative to baseline
3. Occurrence of antibodies to SHP655
4. Incidence of AEs and SAEs, and specifically product-related AEs and SAEs
5. Clinically relevant changes in vital signs, clinical chemistry, and hematology

9.6.2 Safety Endpoint Analyses

AEs and SAEs will be tabulated and summarized according to the Medical Dictionary for Regulatory Activities, in total, by arm, and by relatedness to product or PEX procedure. The number and proportion of subjects experiencing these events will be tabulated for each arm.

Individual and summary vital signs and clinical laboratory data will be presented in tabular form with mean, standard deviation, quartiles, and range as appropriate, by treatment arm and time point.

For the 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.

9.7 [redacted]

9.7.1 [redacted]

9.7.2 [redacted]

9.7.3 [redacted]

9.7.4 [redacted]

[redacted]

9.8 Pharmacokinetic Analyses

9.8.1 Secondary PK/PD Endpoints

1. The PK/PD temporal relationship of efficacy parameters (e.g., platelet count, LDH levels), as a function of ADAMTS-13 activity
2. The ADAMTS-13 binding and inhibitory autoantibody levels in response to daily PEX, with or without SHP655 supplementation, during the acute TTP episode and up to 30 days after resolution
3. ADAMTS-13 activity levels in subjects receiving additional SHP655 for up to 30 days after the resolution of the TTP episode

4. The relationship between ADAMTS-13 activity and end-organ disease status (e.g., renal, neurologic, and cardiac)
5. PK parameters such as incremental recovery, area under the curve, systemic and antibody induced clearance, maximum ADAMTS-13 activity between PEX or SHP 655 infusions, and trough levels prior PEX
6. Occurrence of ADAMTS-13 activity trough levels >10%

9.8.2 PK/PD Analyses

All PK/PD analyses will be performed using the PK analysis set. ADMATS-13 activity levels will be tabulated and plotted by arm as data permit. PK will be assessed using a population PK modeling framework. A structural population PK model will be developed and validated. Standard model diagnostics including statistical measures of fit and goodness-of-fit plots will be used to discriminate between models. PK parameters of interest (e.g. clearance and volume) for ADMATS-13 activity will be reported for each subject and summarized using descriptive statistics. The model will attempt to quantify the influence of PEX, SHP655 as well as inhibitory autoantibody on ADAMTS-13 activity clearance. Full details will be provided in the population PK analysis plan.

10. 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 (e.g., 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.

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 of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

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. The sponsor will provide the ECs with a copy of the same summary.

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.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 © of Directive 2001/20/EC.

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.

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

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

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.

All data will have separate source documentation; no data except Richmond Agitation Sedation Scale (RASS) will be recorded directly onto the CRF.

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.

Incorrect entries must be crossed with a single line as to not obscure the original entry. Corrections must be made adjacent to the item to be altered, initialed, and dated by an authorized investigator or designee as stated in the site delegation log. Overwriting of this information or use of liquid correcting fluid is not allowed.

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

If the data are unclear or contradictory, queries are sent for corrections or verification of data.

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 and original clinical laboratory 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 (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc.). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., 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.

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).

Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation

When using controlled substances, biohazardous material, or substances for infectious diseases, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

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 entered into a clinical database as specified in the CRO's CRF completion guidelines and data handling plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

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.

Data Handling

Data that may potentially unblind the treatment assignment (i.e., investigational product serum concentrations, antibodies to SHP655 treatments, 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.

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 informed consent form 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 (i.e., 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 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 (i.e., 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.

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 and applicable regulatory authority 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.

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 one (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.

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.

Shire is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Shire will require the submission of all Shire-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 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Appendix 2.1 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.

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.

Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (i.e., 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

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or product labeling; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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.

Preexisting conditions prior to randomization are described in the medical history, and those that manifest with the same severity, frequency, or duration after drug exposure, are not to be recorded as AEs. However, when there is an increase in the severity, 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 (e.g., concomitant disease or expected disease evolution) is found for the abnormal values.

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 2.2 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 2.3 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.

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

If applicable, action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. 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 Shire Global Drug Safety Department and the CRO/Shire 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 2.8) unless they result in an SAE.

The investigator must complete, sign, and date the Shire "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 Shire Global Drug Safety Department. A copy of the Shire 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/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

Medical Device Safety Reporting

All serious injuries and UADEs must be reported to the sponsor as an SAE in the same process as described above. Serious injury (SI) is defined as:

- Led to death;
- Led to a serious deterioration in health of a patient, user, or others that
- Results in a life-threatening illness or injury
- Results in a permanent impairment/ damage of a body function or body structure
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in medical or surgical intervention to prevent permanent impairment/ damage to body function/ structure.
- Led to fetal distress, fetal death or a congenital abnormality/birth defect

Appendix 2.4 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 follow-up period stated in Section 8.1.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire 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 Shire Global Drug Safety Department within 24 hours of the reported first becoming aware of the event.

Appendix 2.5 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 informed consent form, 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 2.6 Fatal Outcome

Any SAE that results in the subject's death (e.g., 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 (e.g., 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 2.7 Pregnancy

All pregnancies are reported from the time informed consent is signed until the defined follow-up period stated in Section 8.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire 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/Shire 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.

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 Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form.

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

Appendix 2.8 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 2.1.

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 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., 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.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

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.

All investigational product provided to pediatric subjects should be supervised by the parent/legally authorized representative/caregiver.

Appendix 2.9 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 trial 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 trial or trials
- Any other immediate action taken in order to protect clinical trial 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 2.10 Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The sponsor and the CRO are responsible for notifying the relevant regulatory authorities (central IRBs/central 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).

Appendix 3 Genetics

Shire intends to apply genetic research across the SHP655 development program to differentiate participants with congenital (genetic) versus acquired TTP to determine eligibility to participate in this study.

Candidate genes which may be studied include those potentially related to the mechanism of action of SHP655 as well as those potentially responsible for absorption, disposition, metabolism, and excretion of SHP655.

A DNA sample will be drawn at screening. Samples will be collected from all subjects in order to meet inclusion criteria.

Samples will be labeled with the study protocol number, the subject's study identification number, and information related to the sample. No personal identifiers will be recorded on the sample labels.

Subjects terminating early from the study due to AE, tolerability, or drug-related issues should, where possible, be approached for their remaining protocol-defined samples at the earliest possible time. Unscheduled samples should be labeled with free text capturing study protocol number, subject's study identification number, and information related to the sample (RNA or protein, sampling date, and time). Samples will be shipped to and stored at biorepositories as detailed in the laboratory manual.

As an added level of security, the sample will be recoded with a new, unique number at the biorepository laboratory. This unique number is the only code used in any subsequent analysis and will be used to link a sample to a subject and to ensure that the subject's identity remains confidential.

A link file linking the first and second codes will be kept in a secure place at the sponsor, with restricted access. This will be in a secure environment outside of the clinical study database and separate to any analysis results. This file will be used to identify the relevant samples for analysis, facilitate correlation of any results with clinical data, allow regulatory audit, and trace samples for destruction in the case of withdrawal of consent.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 4 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. The link will also be destroyed at the same time as any remaining sample(s) are destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

Appendix 4 Diagnostic Criteria/Disease Classification

Female participants:

Female participants of childbearing potential and sexually active males are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomy A vasectomy in a male subject or a vasectomized partner for a female subject is a highly effective contraception method provided that the partner is the sole male sexual partner of the women of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment

Appendix 5 Abbreviations

Abbreviation	Definition
Ab	antibody
ADAMTS-13	a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
aTTP	Acquired thrombotic thrombocytopenic purpura
AUC	area under the curve
$AUC_{0\text{-inf}}$	area under the curve from time 0 to infinity
β-hCG	beta-human chorionic gonadotropin
B19V	parvovirus B19
BID	twice daily
BW	body weight
C	degree Celsius
CBC	complete blood count
CD4	cluster of differentiation 4
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CRF	case report form
CRO	contract research organization
cTTP	congenital thrombotic thrombocytopenic purpura
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
EMA	European Medicines Agency
[redacted]	[redacted]
EU	European Union
EUDRACT	European Union clinical trials database
F	degree Fahrenheit
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Definition
FFP	Fresh frozen plasma
FVIII	Factor VIII
GCP	Good Clinical Practice
GmbH	*Gesellschaft mit beschränkter Haftung* – German term for a company that does not trade its shares on the stock market
GPIb	glycoprotein Ib
HAV	hepatitis A virus
HBc	hepatitis B core
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
[redacted]	[redacted]
[redacted]	[redacted]
hTTP	hereditary thrombotic thrombocytopenic purpura; congenital thrombotic thrombocytopenic purpura
[redacted]	[redacted]
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IP	Investigational product
ID	intradermal(ly)
IM	Intramuscular
INR	international normalized ratio
IP	intraperitoneal(ly)
IR	Incremental recovery
IRB	institutional review board
IRT	interactive response technology
IV	intravenous(ly)
KM	Kaplan Meier
LDH	lactic dehydrogenase
Mab	monoclonal antibody
[redacted]	[redacted]
MCHC	mean corpuscular hemoglobin concentration

Abbreviation	Definition
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MI	Myocardial infarction
mmHg	millimeter(s) of mercury
NA	not applicable
NCS	not clinically significant
[redacted]	[redacted]
[redacted]	[redacted]
PEX	Plasma exchange
PD	Pharmacodynamics(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPS	per-protocol set
[redacted]	[redacted]
[redacted]	[redacted]
Q1W	every week
Q2W	every 2 weeks
QOD	every other day
QoL	quality of life
rADAMTS-13	a recombinant human disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13
RASS	Richmond Agitation Sedation Scale
RBC	red blood cell
RCo	ristocetin cofactor activity
Rituximab	humanized anti-CD20 monoclonal antibody
RNA	ribonucleic acid
RSI	reference safety information
rVWF	Recombinant von Willebrand factor
[redacted]	[redacted]
S/D	solvent/detergent
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SAS	statistical analysis system
SD	Sprague-Dawley
SI	serious injury
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TBD	to be determined
TEAE	treatment emergent serious adverse event (s)
TMA	thrombotic microangiopathy
TRALI	Transfusion-related acute lung injury
TTP	thrombotic thrombocytopenic purpura
U	unit(s)
UADE	unanticipated adverse device effect
UK	United Kingdom
UL VWF	ultra-large von Willebrand Factor
ULN	upper limit of normal
US	United States
V_{ss}	steady state volume of distribution
VWF	von Willebrand factor
WOCBP	women of childbearing potential
[redacted]	[redacted]

Appendix 6 Protocol History

Document	Date	Global/Country/Site Specific
Protocol Amendment 3.0	08 JUN 2020	Non – UK, CH, FR
Protocol Amendment 2.3	07 NOV 2019	France
Protocol Amendment 2.2	07 NOV 2019	UK
Protocol Amendment 2.1	23 SEP 2019	Non-UK
Protocol Amendment 1.3	18 JUN 2019	France
Protocol Amendment 1.2	01 APR 2019	Non-UK
Protocol Amendment 1.1	18 MAR 2019	UK
Original Protocol	03 OCT 2018	Global

11. REFERENCES

Allford, S. L., Harrison, P., Lawrie, A. S., Liesner, R., Mackie, I. J. & Machin, S. J. 2000. Von Willebrand factor--cleaving protease activity in congenital thrombotic thrombocytopenic purpura. *Br. J. Haematol,* 111**,** 1215-1222.

Alwan F, Vendramin C, Langley K & et al. 2016. Presenting ADAMTS13 Antigen Level Correlates with Clinical Outcome in Acute Thrombotic Thrombocytopenic Purpura. *Blood,* 128**,** 1365.

Balduini, C., Gugliotta, L., Luppi, M., Laurenti, L., Klersy, C., Pieresca, C., Quintini, G., Iuliano, F., Re, R., Spedini, P., Vianelli, N. & Zaccari 2010. High versus standard dose methylprednisolone in the acute phase of idiopathic thrombotic thrombocytopenic purpura: a randomized study. *Annals of Hematology,* 89**,** 591-596.

Bandarenko, N. & Brecher, M. E. 1998. United States thrombotic thrombocytopenic purpura apheresis study group (US TTP ASG): Multicenter survey and retrospective analysis of current efficacy of therapeutic plasma exchange. *Journal of Clinical Apheresis,* 13**,** 133-141.

Benhamou, Y., Assié, C., Boelle, P.-Y., Buffet, M., Grillberger, R., Malot, S., Wynckel, A., Presne, C., Choukroun, G., Poullin, P., Provôt, F., Gruson, D., Hamidou, M., Bordessoule, D., Pourrat, J., Mira, J.-P., Le Guern, V., Pouteil-Noble, C., Daubin, C., Vanhille, P., Rondeau, E., Palcoux, J.-B., Mousson, C., Vigneau, C., Bonmarchand, G., Guidet, B., Galicier, L., Azoulay, E. & Rottensteiner, H. 2012. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. *Haematologica,* 97**,** 1181-6.

Bryant, B. J. & Klein, H. G. 2007. Pathogen inactivation: the definitive safeguard for the blood supply. *Archives of Pathology & Laboratory Medicine,* 131**,** 719-33.

Cataland, S. R. & Wu, H. M. 2015. Acquired thrombotic thrombocytopenic purpura: New therapeutic options and their optimal use. *J Thromb Haemost,* 13 Suppl 1**,** s223-s229.

Coppo, P. & Veyradier, A. 2012. Current management and therapeutical perspectives in thrombotic thrombocytopenic purpura. *Presse Med,* 41**,** e163-e176.

Deford, C. C., Reese, J. A., Schwartz, L. H., Perdue, J. J., Kremer Hovinga, J. A., Lammle, B., Terrell, D. R., Vesely, S. K. & George, J. N. 2013. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood,* 122**,** 2023-2029.

George, J. N. 2007. Evaluation and management of patients with thrombotic thrombocytopenic purpura. *J. Intensive Care Med,* 22**,** 82-91.

Han, B., Page, E. E., Stewart, L. M., Deford, C. C., Scott, J. G., Schwartz, L. H., Perdue, J. J., Terrell, D. R., Vesely, S. K. & George, J. N. 2015. Depression and cognitive impairment following recovery from thrombotic thrombocytopenic purpura. *Am. J. Hematol,* 90**,** 709-14.

Hie, M., Gay, J., Galicier, L., Provôt, F., Presne, C., Poullin, P., Bonmarchand, G., Wynckel, A., Benhamou, Y., Vanhille, P., Servais, A., Bordessoule, D. & Coindre 2014. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. *Blood,* 124**,** 204-210.

Humpe, A., Legler, T. J., Nübling, C. M., Riggert, J., Unger, G., Wolf, C., Heermann, K.-H. & Köhler, M. 2000. Hepatitis C Virus Transmission through Quarantine Fresh-frozen Plasma. *Thrombosis and Haemostasis,* 83**,** 784-788.

Joly, B. S., Coppo, P. & Veyradier, A. 2017. Thrombotic thrombocytopenic purpura. *Blood,* 129**,** 2836-2846.

Kessler, C. S., Khan, B. A. & Lai-Miller, K. 2012. Thrombotic Thrombocytopenic Purpura: A Hematological Emergency. *Journal of Emergency Medicine,* 43**,** 538-544.

Knöbl, P. 2014. Inherited and acquired thrombotic thrombocytopenic purpura (TTP) in adults. *Semin. Thromb. Hemost,* 40**,** 493-502.

Koyfman, A., Brém, E. & Chiang, V. W. 2011. Thrombotic thrombocytopenic purpura. *Pediatr. Emerg. Care,* 27**,** 1085-1091.

Kremer Hovinga, J. A., Coppo, P., Lämmle, B., Moake, J. L., Miyata, T. & Vanhoorelbeke, K. 2017. Thrombotic thrombocytopenic purpura. *Nature Reviews Disease Primers,* 3**,** 17020.

Lewis, Q. F., Lanneau, M. S., Mathias, S. D., Terrell, D. R., Vesely, S. K. & George, J. N. 2009. Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura. *Transfusion,* 49**,** 118-124.

Peyvandi, F., Lavoretano, S., Palla, R., Feys, H. B., Vanhoorelbeke, K., Battaglioli, T., Valsecchi, C., Canciani, M. T., Fabris, F., Zver, S., Reti, M., Mikovic, D., Karimi, M., Giuffrida, G., Laurenti, L. & Mannucci, P. M. 2008. ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. *Haematologica,* 93**,** 232-239.

Peyvandi, F., Scully, M. F. & Kremer Hovinga, J. A. 2016. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med,* 374**,** 511-522.

Plaimauer, B., Kremer Hovinga, J. A., Juno, C., Wolfsegger, M. J., Skalicky, S., Schmidt, M., Grillberger, L., Hasslacher, M., Knöbl, P., Ehrlich, H. & Scheiflinger, F. 2011. Recombinant ADAMTS13 normalizes von Willebrand factor-cleaving activity in plasma of acquired TTP patients by overriding inhibitory antibodies. *J Thromb Haemost,* 9**,** 936-944.

Plaimauer, B., Schiviz, A., Kaufmann, S., Höllriegl, W., Rottensteiner, H. & Scheiflinger, F. 2015. Neutralization of inhibitory antibodies and restoration of therapeutic ADAMTS13 activity levels in inhibitor-treated rats through defined doses of recombinant ADAMTS13. *J Thromb Haemost,* 13**,** 2053-62.

Reutter, J. C., Sanders, K. F., Brecher, M. E., Jones, H. G. & Bandarenko, N. 2001. Incidence of allergic reactions with fresh frozen plasma or cryo-supernatant plasma in the treatment of thrombotic thrombocytopenic purpura. *J. Clin. Apher,* 16**,** 134-138.

Rock, G., Yousef, H., Neurath, D. & Lu, M. 2006. ADAMTS-13 levels in fresh, stored, and solvent detergent treated plasma. *Transfus Apher Sci,* 35**,** 235-238.

Rock, G. A., Shumak, K. H., Buskard, N. A., Blanchette, V. S., Kelton, J. G., Nair, R. C. & Spasoff, R. A. 1991. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med,* 325**,** 393-397.

Saha, M., McDaniel, J. K. & Zheng, X. L. 2017. Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. *Journal of Thrombosis and Haemostasis,* 15**,** 1889-1900.

Scully, M., Hunt, B. J., Benjamin, S., Liesner, R., Rose, P., Peyvandi, F., Cheung, B., Machin, S. J. & The British Committee for Standards in Haematology 2012. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br. J. Haematol,* 158**,** 323-335.

Scully, M., McDonald, V., Cavenagh, J., Hunt, B. J., Longair, I., Cohen, H. & Machin, S. J. 2011. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood,* 118**,** 1746-1753.

Tersteeg, C., Schiviz, A., De Meyer, S. F., Plaimauer, B., Scheiflinger, F., Rottensteiner, H. & Vanhoorelbeke, K. 2015. Potential for recombinant ADAMTS13 as an effective therapy for acquired thrombotic thrombocytopenic purpura. *Arterioscler Thromb Vasc Biol,* 35**,** 2336-2342.

Tersteeg, C., Verhenne, S., Roose, E., Schelpe, A. S., Deckmyn, H., De Meyer, S. F. & Vanhoorelbeke, K. 2016. ADAMTS13 and anti-ADAMTS13 autoantibodies in thrombotic thrombocytopenic purpura - current perspectives and new treatment strategies. *Expert Rev Hematol,* 9**,** 209-221.

Vazquez-Mellado, A., Pequeño-Luévano, M., Cantu-Rodriguez, O. G., Villarreal-Martínez, L., Jaime-Pérez, J. C., Gomez-De-Leon, A., De La Garza-Salazar, F., Gonzalez-Llano, O., Colunga-Pedraza, P., Sotomayor-Duque, G. & Gomez-Almaguer, D. 2016. More about low-dose rituximab and plasma exchange as front-line therapy for patients with thrombotic thrombocytopenic purpura. *Hematology,* 21**,** 311-6.

Westwood, J.-P., Webster, H., McGuckin, S., McDonald, V., Machin, S. J. & Scully, M. 2013. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. *Journal of Thrombosis and Haemostasis,* 11**,** 481-490.

Zheng, X. L. 2015. ADAMTS13 and von Willebrand factor in thrombotic thrombocytopenic purpura. *Annu. Rev. Med,* 66**,** 211-225.