Clinical Study Protocol

NCT Number: NCT03393975

Title: A Phase 3, Prospective, Randomized, Controlled, Open-label, Multicenter, 2 Period Crossover Study With a Single Arm Continuation Evaluating the Safety And Efficacy of BAX 930 (rADAMTS13) in the Prophylactic And On-demand Treatment of Subjects With Severe Congenital Thrombotic Thrombocytopenic Purpura (cTTP, Upshaw-Schulman Syndrome [USS], Hereditary Thrombotic Thrombocytopenic Purpura [hTTP])

Study Number: TAK-755-281102

Document Version and Date: Amendment 15.0, 18 November 2021

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

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

TAKEDA PHARMACEUTICALS

PROTOCOL:	281102
TITLE:	A phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of BAX 930 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP, Upshaw-Schulman Syndrome [USS], hereditary thrombotic thrombocytopenic purpura [hTTP])
SHORT TITLE:	A phase 3, randomized, controlled study of prophylactic and on-demand treatment of cTTP with BAX 930 (rADAMTS13)
STUDY PHASE:	Phase 3
DRUG:	BAX 930 / SHP655 / TAK-755 / rADAMTS13
IND NUMBER:	015219
EUDRACT NUMBER:	2017-000858-18
SPONSOR:	Takeda Development Center Americas, Inc. 95 Hayden Avenue, Lexington, MA 02421, USA and Baxalta Innovations GmbH, Industriestrasse 67, A-1221 Vienna
PROTOCOL HISTORY:	**AMENDMENT 15 (Global): 18-NOV-2021** **Replaces All Versions:** Amendment 14 (Germany): 2021 APR 30 Amendment 13 (Global): 2021 APR 28 Amendment 12 (Germany): 2021 MAR 25 Amendment 11 (Global): 2021 FEB 24 Amendment 10 (Germany): 2020 JUN 25 Amendment 9 (Global): 2020 MAR 06 Amendment 8 (UK): 2019 DEC 19 Amendment 7 (Switzerland): 2019 SEP 12 Amendment 6 (Germany): 2019 JUL 18 Amendment 5: 2018 DEC 06 Amendment 4 (UK): 2018 APR 11 Amendment 3 (UK): 2017 AUG 21 Amendment 2: 2017 MAY 09 Amendment 1: 2017 MAR 15 Original: 2017 FEB 13

PROTOCOL SIGNATURE PAGE

Sponsor's (Takeda) Approval

DocuSigned by:

Signature:	[redacted]	19-Nov-2021 | 13:22:29 EST
[redacted], MD		

Investigator's Acknowledgement

I have read this protocol for Study 281102.

Title: A phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of BAX 930 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP, Upshaw-Schulman Syndrome [USS], hereditary thrombotic thrombocytopenic purpura [hTTP])

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 of 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 handprint or type)	

Signature: _____ **Date:** _____

1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

[redacted], MD
[redacted]
Takeda Development Center Americas, Inc.

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator[s], sponsor's medical expert and study monitor, sponsor's representative[s], laboratories, steering committees, and oversight committees [including ethics committees {ECs}], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs), including suspected unexpected serious adverse reactions (SUSARS), to the ECs.

ALL SAEs, INCLUDING SUSARs, ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

Drug Safety contact information: see SAE Report form.
Refer to SAE Protocol Sections and the study team roster for further information.

For definitions and information on the assessment of these events, refer to the following:

- Adverse event (AE), Section 13.1
- SAE, Section 13.1.1.1
- SUSARs, Section 13.1.1.2
- Assessment of AEs, Section 13.1.2

3. SUMMARY OF CHANGES FROM PREVIOUS VERSION

An overview of the updates incorporated into Amendment 15 is presented below.

Summary of Change(s) Since Last Version of Approved Protocol

Description of Change	Purpose for Change	Section(s) Affected by Change
Sponsor name was updated to Takeda Development Center Americas, Inc.	Legal entity name change	Title page and throughout the document
Study completion dates updated as follows: • Study Primary Completion date changed from Feb 2023 to Nov 2023 • Study Completion from Jan 2024 to Mar 2024	Adjusted to account for enrollment of pediatric subjects.	Section 4, Synopsis
Footnote 'a' was added to the Table of TTP Definitions in the synopsis and body of the protocol: [a] In this instance, a laboratory measure refers to platelet counts or an LDH measurement	Added for clarity	Section 4, Synopsis Table 2
Terminology was aligned across document: • acute episodes of thrombotic thrombocytopenic purpura (TTP), and acute clinical events now thrombotic thrombocytopenic purpura (TTP) events • acute events or acute TTP events now acute TTP events throughout document • subacute events or subacute manifestations now subacute TTP events throughout document • Outcome measure or endpoint now outcome measure throughout document • Allergic manifestations now allergic reactions throughout the document	Clarification and alignment of terminology across the text	Throughout document
The definition of acute TTP event resolution was added to the synopsis	Language was reiterated for clarity	Section 4, Synopsis
Exploratory objective 2 was revised to the following: To assess the relationship between ADAMTS13 activity levels (measured and/or estimated from PK parameters) and time of occurrence of acute TTP events, subacute TTP events, and a composite of TTP manifestations in the prophylactic group	Revised for clarity	Section 4, Synopsis Section 8.4
Secondary Outcome Measure/ Efficacy #10 was updated (new text in **bold**): Incidence of acute TTP events while subjects are on their final dose and **dosing** regimen **in the study**	Language reverted to original for clarity	Section 4, Synopsis Section 9.4.2.1 Section 14.4.2.1
Added "Isolated TTP manifestations" definition to definitions tables; note that the definition did not change but it was summarized from other locations in the protocol and added to the table	Clarification of terminology and completeness of the table	Section 4, Synopsis Table 2
The following Health Related Quality of Life and Resource Utilization objective was moved to Efficacy Objectives: To evaluate the incidence of dose modification and supplemental dose for each treatment in the prophylactic cohort.	To align with general objectives of the study	Section 4, Synopsis Section 8.3.1

Summary of Change(s) Since Last Version of Approved Protocol

Description of Change	Purpose for Change	Section(s) Affected by Change
The following clarifying language was added; A PK-II evaluation is not applicable to subjects who received BAX930 SIN in Period 1 or Period 2	Language was reiterated for clarity	Section 9.2.2
New text added to sentence (in **bold**): ADAMTS13-mediated VWF cleavage products will be **analyzed using mass spectrometry or** visualized by SDS-poly-acrylamide gel electrophoresis followed by Western blot staining and quantitative densitometry.	Removed specificity to increase assay technique flexibility	Section 13.7.5.5
Reporting of TTP manifestations was clarified: **For the purpose of this study the TTP manifestations listed below, with an onset date after the first IP exposure, should be reported on the Adverse Event eCRF regardless of severity. Relationship to cTTP or to BAX 930 must be indicated. The TTP manifestations should be captured even if they were experienced as part of an acute or subacute event.** The bulleted list of TTP events was reorganized to match those presented in Table 3.	• Ensure TTP manifestations are reported and categorized on AE eCRF Ensured list of TTP symptoms matched those presented in the Definitions table	Section 13.1.2
Revised Secondary Outcome Measure Efficacy # 2 as follows (**new** and ~~removed text~~): 2. Time to resolution of **acute TTP events** ~~clinical symptomatology, if present, and normalization of laboratory parameters (platelet count ≥150,000/uL; LDH ≤1.5×ULN)~~ following initiation of treatment ~~in acute TTP episodes~~ with BAX 930 or SoC agent	Clarification of the terminology and alignment with present eCRF since clinical symptoms start and end time not tracked, only the start and end time of the TTP event.	Section 4, Synopsis Section 9.4.2.1 Section 14.4.2.1
Wording in secondary PK/PD outcome measure #4 was deleted and/or updated for clarity: #4 ~~Data allowing~~ **Assessment of the** impact of immunogenicity (immunogenicity status, time of onset) on ADAMTS13 antigen and activity PK parameters. ~~will be evaluated. Additionally, impact of immunogenicity (incidence, time of onset) on PD time profiles including VWF:RCo, VWF:Ag, VWF multimers and VWF cleavage products may be evaluated.~~	Prior wording was vague and was updated for clarity. Also, vWF:Ag, vWF multimers, and vWF cleavage products are exploratory outcome measures so should be removed from this section.	Section 4, Synopsis Section 9.4.2.3
Purpose of Protocol Amendment 15 was added: • provide clarification and alignment of various terms and definition throughout the text • include suggestions and options to reduce volume of blood samples collected from pediatric subjects to ensure the blood volume is within recommended limits • Other items listed in Summary of Changes	To provide a rationale for the changes included in Protocol Amendment 15	Section 9.1
Subjects who enroll into the TAK-755-3002 continuation study will complete the TAK-755-3002 Screening/Enrollment visit on the same day as the 281102 last IP infusion of Period 3.	To reduce the gap in treatment for cTTP subjects enrolled in both Phase 3 cTTP studies	Section 9.2.1.4

Summary of Change(s) Since Last Version of Approved Protocol

Description of Change	Purpose for Change	Section(s) Affected by Change
Sentence was removed: "Subjects who switch from the on-demand to the prophylaxis cohort upon resolution of the acute event will be excluded from the primary efficacy analysis."	The primary efficacy analysis will include all subjects that were treated in prophylaxis cohort, regardless of prior participation in the on-demand cohort.	Section 14.4
Clarified wording in PK/PD Secondary Objective #3/Secondary Outcome Measure #2 adding terms in bold: #3 To assess ADAMTS13 activity (pre-infusion ADAMTS13 levels) and **select** VWF parameters prior to each **PK** infusion of SoC or BAX 930 ~~and at the time of acute TTP event presentation~~ in the prophylactic cohort #2 Assessment of **PD markers, such as** VWF:Ag, and VWF: RCo, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment	To provide clarification and consistency with the schedule of assessments.	Section 4, Synopsis Throughout document
Secondary outcome measure 8 was revised to (**new** text in bold): 8. Incidence of supplemental doses prompted by **subacute TTP events** ~~isolated TTP manifestations~~	Updated to reflect new definitions of TTP events.	Section 4, Synopsis Section 9.4.2.1
General editing made throughout document to ensure alignment of wording/phrasing across the document.	Ensure alignment and reduce ambiguity.	Throughout document
Sentence regarding dose calculation was added: Note that the weight from the subject's previous visit can be used to calculate the dose as long as the weight was collected less than 6 weeks prior for adult subjects (≥12 years of age) and less than 4 weeks prior for pediatric subjects (<12 years of age).	To provide more flexibility to the sites while ensuring the patient receives the correct dose per weight. A weight measurement taken at a prior visit falls within a reasonable timeframe in which weight is not expected to change significantly enough to adversely affect the dose delivered in the study	Section 9.7.3
Revised wording so that pediatric PK sample blood collection schedules for pediatric subjects <6 years old may be optimized by the Investigator and Sponsor to accommodate for local blood collection volume considerations. The timing of related assessments to be modified in accordance with the optimized schedule.	To address blood volume limitations in young pediatric subjects.	Section 9.2.1.1.1, Section 9.2.1.1.3, Section 9.7.2, Section 11.3.1, Section 12.2, Section 12.2.1, Section 13.7.1, Section 13.7.2, Section 13.7.6.2, Section 13.8, Table 7, Table 9, Table 10, Table 12 Table 13, Table A1

Summary of Change(s) Since Last Version of Approved Protocol

Description of Change	Purpose for Change	Section(s) Affected by Change
The interim assessment was eliminated (note that the interim analysis is retained).	Study timing is such that the interim assessment is no longer feasible	Section 4, Synopsis Section 14
Statistical analyses wording was refined to: • Update wording as needed in regard to the elimination of the interim assessment • Provide clarification of the summary statistics	• The timing of the interim analysis was changed. • To align with changes in the SAP.	Section 4, Synopsis Section 14
Direct-to-Patient shipments of Investigational Product will be permitted for subjects having infusions at home, additional information will be provided in the Pharmacy Manual and Home Nursing documentation.	To accommodate for subjects receiving IP in a home setting.	Section 9.7.5
Withdrawal and discontinuation criteria was updated to reflect the follow-up procedures for subjects experiencing allergic reactions upon exposure, and ongoing AEs	Updated for clarity	Section 10.3
Study assessments were updated to indicate that, for subjects 0-<6 years old (prophylactic subjects only), if available and at the discretion of the Investigator, growth, development, and cognitive performance metrics may be recorded and reviewed from a subject's medical record at the Screening/Enrollment Visit, the start of every Treatment Period or annually, and at the Final Visit.	DMC recommendation to include key pediatric outcomes such as the child's growth, development, and cognitive performance.	Section 11.3.2
Realigned format of Secondary Objectives in synopsis to match the presentation in the body of the document.	In prior version (13), the Secondary Objectives were listed in numerical order in Synopsis but subcategorized by topic (eg., Efficacy, Safety, etc) in the body of the document. Now they are aligned.	Section 4, Synopsis
Germany-specific requirements, which were formally presented in a Germany-specific protocol, are now presented in the current Global version and are addressed in a German-specific Appendix 1, Table A1 that (for German sites only) replaces Table 8. Notes were added throughout the text accordingly.	Allow for elimination of a country-specific protocol by including all country-specific relevant text in the Global protocol.	Section 13.6, Section 13.8 Table A1
The second bullet of the statistical efficacy analysis section were revised, and the third bullet was removed (**new** text in bold): **• For acute TTP events, a Kaplan-Meier curve for each treatment group will be drawn based on each subject's time to resolution of the acute TTP event, defined as the time from initial treatment of the event to the end of the acute TTP event for pooled prophylactic and on-demand cohort data, and separately. Only the first acute TTP event for each subject will be included in the analysis. The median time to resolution will be presented for each treatment, along with the corresponding 95% CI.**	Text was revised and condensed for clarity	Section 14.4.2.1

Summary of Change(s) Since Last Version of Approved Protocol

Description of Change	Purpose for Change	Section(s) Affected by Change
Footnote 'v' (Table 10) and footnote 'q' (Table 11) was added to clarify cardiac marker measurement procedures: a. Testing is only applicable if available at local laboratory.	To allow flexibility at sites where local cardiac marker testing is not available	Table 9 and Table 10)
Figure 2 was updated	Updated for visual clarity of study flow	Section 20.1 (Figure 2)

4. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	BAX 930 / SHP655 / TAK-755
Name(s) of Active Ingredient(s)	rADAMTS13
CLINICAL CONDITION(S)/INDICATION(S) • Congenital thrombotic thrombocytopenic purpura (cTTP) (Upshaw-Schulman Syndrome) (hereditary thrombotic thrombocytopenia purpura) (hTTP)	
PROTOCOL ID	281102
PROTOCOL TITLE	A phase 3, prospective, randomized, controlled, open-label, multicenter, 2-period crossover study with a single arm continuation evaluating the safety and efficacy of BAX 930 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP, Upshaw-Schulman Syndrome [USS], hereditary thrombotic thrombocytopenic purpura [hTTP])
Short Title	A phase 3, randomized, controlled study of prophylactic and on-demand treatment of cTTP with BAX 930 (rADAMTS13)
STUDY PHASE	Ph3
PLANNED STUDY PERIOD	
Initiation	2017 OCT
Primary Completion	2023 NOV
Study Completion	2024 MAR
Duration	approximately 70 months
STUDY OBJECTIVES AND PURPOSE	
Study Purpose To assess safety and efficacy of BAX 930 in the prevention and treatment of acute thrombotic thrombocytopenic purpura (TTP) events in subjects with severe congenital deficiency of ADAMTS13 (cTTP; defined as plasma ADAMTS13 <10%, as measured by the fluorescent resonance energy transfer-VWF73 [FRETS] assay)	
Primary Objective 1. To determine the incidence of acute TTP events in subjects with severe cTTP receiving either standard of care (SoC) or BAX 930 as a prophylactic treatment.	

Secondary Objectives

Efficacy

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

Safety

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

Pharmacokinetics/Pharmacodynamics

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

Health Related Quality of Life and Resource Utilization

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

Exploratory Objectives

1. To evaluate the incidence of subacute TTP events in subjects receiving the respective prophylactic treatment.

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

STUDY DESIGN

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

The bulk drug substance (BDS) manufacturing location in Orth, Austria will move to the manufacturing facility located in Singapore in the middle of Phase 3 study. A PK comparability between BAX 930 ORT and BAX 930 SIN will be conducted.

Prophylaxis Treatment Cohort

The principal part of the study involves the prophylactic treatment of cTTP. There are 3 periods, 2 crossover PK assessments and 1 end-of-study PK assessment.

After informed consent has been obtained, all subjects will undergo a minimum washout period of 1 week from their last prophylactic infusion. Upon completion of the washout period, subjects will undergo screening procedures for the determination of eligibility. Subjects who meet eligibility criteria based on the inclusion/exclusion criteria and consent to treatment in the prophylaxis cohort will be randomized equally to 1 of 2 treatment orders: BAX 930-SoC or SoC-BAX 930. Subjects randomized into the SoC treatment arm for Period 1 will receive a single dose of BAX 930 to evaluate PK (i.e., PK dose) followed by a PK dose of their current SoC product 14 days [±2 days] later. Subjects randomized into the BAX 930 treatment arm for Period 1 will receive a PK dose of their current SoC product followed by a PK dose of BAX 930 14 days [±2 days] later. This crossover PK evaluation is PK-I. Subjects will then receive either BAX 930 or SoC for the first 6 months (one month=28 days) treatment period (Period 1) as randomized. For each subject, the SoC regimen will be determined by the investigator and defined by their treatment product and dosing regimen at the time of entry into the study. After completing Period 1 with either BAX 930 or SoC, subjects will enter Period 2 and crossover to the alternative treatment (BAX 930 for subjects who start on the SoC and SoC for subjects who start on BAX 930) and remain on that treatment for another 6 months during Period 2. Once Period 2 is completed, subjects will enter Period 3.

Availability of BAX 930 SIN material and the date (before or after 30 September 2021), will guide the specific study design each subject will follow. For adult and pediatric subjects starting on BAX 930 ORT, following the first randomized crossover PK evaluation of both the subject's SoC product and BAX 930 ORT, which is PK-I, subjects will receive 6 months (one month=28 days) of prophylaxis treatment with SoC product and 6 months of prophylaxis treatment with BAX 930 ORT. Once Period 2 is completed, subjects will enter Period 3.

Subjects will receive treatment with BAX 930 ORT in Period 3 until BAX 930 SIN is available at their site. Once BAX 930 SIN is available, subjects who received BAX 930 ORT in PK-I will initiate a randomized crossover PK evaluation between BAX 930 ORT and BAX 930 SIN, which is PK-II and then initiate an additional 6 months of prophylaxis treatment with BAX 930 SIN in Period 3. After the last IP infusion of Period 3, a subset of total subjects from the prophylactic cohort may undergo another PK assessment i.e., PK-III, following which they will be enrolled and followed in the continuation study. The PK-III assessment will be conducted in all subjects in the prophylactic cohort who initiate the study with BAX 930 SIN, pediatric subjects (<12 years old), subjects on QW1 schedule, and on-demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort. PK-III will be voluntary for all other subjects who receive BAX 930 SIN in Period 3. A minimum of 4 adult subjects (≥18 years), and 2 pediatric and adolescent subjects (age 0-17 years) may undergo the end-of-study PK-III assessment. Subjects will be allowed to remain in Study 281102 until the continuation study is open for enrollment. Subjects randomized to the prophylactic treatment who experience an acute TTP event will be treated with the agent the subject is receiving during the current period. Following acute TTP event recovery, subjects will continue with the prescribed prophylactic treatment.

For subjects who are screened after 30 September 2021, these subjects first undergo PK-I as a randomized crossover between BAX 930 SIN and SoC. No PK-II will be conducted for these subjects. Following PK-I, these subjects will continue through Period 1, Period 2 and Period 3 with BAX 930 SIN material. At the end of Period 3, these subjects will undergo PK-III.

During prophylactic treatment, and if deemed necessary and acceptable by the Investigator, subjects will be given the option to have at-home infusion of BAX 930 by a healthcare provider. Subjects will be required to come to the clinic for an acute/subacute TTP event. Subjects will also be required to have in clinic visits periodically throughout the trial, further details will be provided in a Home Nursing Manual.

An interim analysis (for regulatory filing purposes) will be performed after 30 adult (≥18 years old) or adolescent (>12-≤17 years old) subjects in the prophylactic treatment group complete the study. All data collected by that time point in Study 281102, as well as the continuation Study TAK-755-3002 will be included in the statistical analysis. The interim analysis will include final data from at least 30 subjects in the prophylactic cohort who completed the end-of-study visit. The interim analysis will be performed on a cleaned snapshot of the study database. The interim analysis data will be used in regulatory submissions and scientific manuscripts.

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

TTP Event Definitions			
	Acute TTP Event	**Subacute TTP Event**	**Isolated TTP Manifestations**
Criteria	Both of the following laboratory measures[a]	At least 2 of the following; at least 1 of which must include a laboratory measure[a]	Any of the following
Thrombocytopenia	Drop in platelet count ≥50% of baseline or a platelet count <100,000/µL	Drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/µL	Drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/µL
Microangiopathic Hemolytic Anemia	Elevation of LDH >2 x of baseline or >2 x ULN	Elevation of LDH >1.5 x of baseline or >1.5 x ULN	Elevation of LDH >1.5 x of baseline or >1.5 x ULN

TTP-related Clinical Signs/Symptoms	Not required to meet criteria but to be recorded if observed	Organ-specific signs and symptoms, including but not limited to: • Renal signs, as defined by increase of serum creatinine >1.5 × baseline • Neurological symptoms (eg, headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures) • Fever (≥100.4°F/38°C) • Fatigue/lethargy • Abdominal pain	Organ-specific signs and symptoms, including but not limited to: • Renal signs, as defined by increase of serum creatinine >1.5 × baseline • Neurological symptoms (eg, headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures) • Fever (≥100.4°F/38°C) • Fatigue/lethargy • Abdominal pain

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

- Standard of care treatment (6 months[i]) (Period 1 or 2, depending on randomization)
  - ➢ Subjects will receive the investigator-recommended standard prophylaxis treatment regimen for 6 months
  - o Dose modifications to increase the dose or frequency of SoC therapy, to the extent possible, is recommended if any of the following conditions are met:
    - One acute TTP event
    - Two separate occurrences of any laboratory deviations:
      - Drop in platelet count ≥25% of baseline or a platelet count <150,000/μL; OR
      - Elevation of LDH >1.5× of baseline or >1.5× ULN
    - Three separate occurrences of any organ-specific signs or symptoms, with or without changes in platelet count or LDH
      - o Neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR
      - o Abdominal pain; OR
      - o Increase of serum creatinine >1.5×baseline
  - ➢ Subjects will receive the investigator-recommended standard treatment and dosing regimen during the acute TTP event
  - ➢ Acute management:
  - o Subjects experiencing an acute TTP event during the prophylaxis period will receive the investigator-recommended standard treatment and dosing regimen during the acute TTP event
  - o Subjects will continue prophylaxis therapy 1 week after their last acute treatment dose

[i] The length of Period 1 and Period 2 is 6 months each. If a subject cannot switch to the next period at the end of month 6, for either logistical or medical reasons, the length of Period 1 and Period 2 can be extended to up to 7 months total. For subjects enrolled before November 2017, Period 1 can be extended until the global amendment to lift the temporary study halt is approved.

Acute TTP events are considered resolved when:

- Platelet count is ≥150,000/ μL or platelet count is within 25% of baseline
- Elevation of LDH ≤1.5 x baseline or ≤1.5 x ULN
  - ➢ Subacute management:
    - o Investigators may elect to treat a subacute TTP event with 1 or 2 additional daily doses of SoC
- BAX 930 treatment (6 months[ii]) (Period 1 or 2, depending on randomization and Period 3)
  - ➢ Subjects will receive BAX 930 prophylactically for 6 months
    - o Initial prophylactic dose and dosing regimen:
      - ▪ Subjects currently treated Q1W with fresh frozen plasma (FFP) or a solvent/detergent (S/D) treated plasma replacement product will start BAX 930 treatment with 40 IU/kg [±4 IU/kg] Q1W
      - ▪ All other subjects will receive a starting prophylaxis dose of 40 IU/kg [±4 IU/kg] every 2 weeks (Q2W)
    - o Dose modification based on clinical response:
      - ▪ Dose modifications to 40 IU/kg [±4 IU/kg] Q1W will be required if any of the following conditions is met:
        - One acute TTP event
        - Two separate occurrences of laboratory deviations:
          - Drop in platelet count ≥25% of baseline or a platelet count <150,000/μL; OR
          - Elevation of LDH >1.5× of baseline or >1.5× ULN
        - Three separate occurrences of organ-specific signs or symptoms, with or without changes in platelet count or LDH
          - Neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR
          - Abdominal pain; OR
          - Increase of serum creatinine >1.5×baseline
  - ➢ Acute management:
    - o Subjects experiencing an acute TTP event during the prophylaxis period will receive the following dose and dosing regimen:
      - ▪ Subjects will receive an initial dose of 40 IU/kg [±4 IU/kg] BAX 930
      - ▪ Subjects will receive a subsequent dose of 20 IU/kg [±2 IU/kg] BAX 930 on Day 2
      - ▪ Subjects will receive an additional daily dose of 15 IU/kg [±1.5 IU/kg] BAX 930 until 2 days after the acute TTP event is resolved

[ii] The length of Period 1 and Period 2 is 6 months each. If a subject cannot switch to the next period at the end of month 6, for either logistical or medical reasons, the length of Period 1 and Period 2 can be extended to up to 7 months. For subjects enrolled before November 2017, Period 1 can be extended until the global amendment to lift the temporary study halt is approved. The length of Period 3 is approximately 6 months or when the continuation study has opened at the subject's site.

- Subjects will continue prophylactic therapy 1 week after their last acute treatment dose

➢ Subacute management:

- Investigators may elect to treat a subacute TTP event- with 1 or 2 additional daily doses of 40 IU/kg BAX 930.

On-Demand Treatment Cohort

Subjects experiencing an acute TTP event, meeting all other inclusion criteria, and entering and consenting to treatment in the study through the on-demand cohort will be randomized to receive urgent treatment with either the SoC or BAX 930. Upon resolution of the acute TTP event, subjects may choose to move to the prophylaxis cohort of the study and continue with assigned treatment or discontinue entirely. Subjects electing to move to the prophylaxis cohort will move directly to Period 1 and PK-I will not be conducted. Re-enrollment of an on-demand subject who has finished the study into the on-demand treatment cohort is allowed if he/she experiences a new acute TTP event.

Switching to BAX 930 SIN: Beginning on 1 October 2021, subjects entering the study will no longer receive BAX 930 ORT in Period 1, or any subsequent period thereafter. At this point, all subjects will receive BAX 930 SIN or SoC only, depending on randomization, beginning with PK-I, and continuing throughout the study. For subjects randomized to receive BAX 930 in the on-demand arm will receive treatment with BAX 930 ORT until BAX 930 SIN becomes available. If a subject is randomized to receive BAX 930 ORT and BAX 930 SIN becomes available prior to Period 1, subjects will continue to receive BAX 930 ORT until completion of Period 1 or Period 2, depending on randomization. Once BAX 930 SIN is available, on-demand subjects will receive BAX 930 SIN or SoC per their randomization schedule. Subjects who move to prophylactic treatment will continue with treatment assigned during their on-demand treatment and receive BAX 930 SIN in either Period 1 or Period 2, per randomization schedule.in other per randomization schedule during Period 1.

Pediatric subjects: Pediatric subjects (<12 years old) will be able to switch to BAX 930 SIN material after the cut-off date of 30 September 2021. At sites where BAX 930 SIN becomes available prior to the cut-off date, pediatric subjects who initiate the study with BAX 930 ORT, will not switch to BAX 930 SIN if or until initiation of prophylactic treatment.

- Standard of care treatment:
  - ➢ Subjects will receive the investigator-recommended standard treatment and dosing regimen during the acute TTP event
- BAX 930 treatment:
  - ➢ Subjects will receive an initial dose of 40 IU/kg [±4 IU/kg] BAX 930
  - ➢ Subjects will receive a subsequent dose of 20 IU/kg [±2 IU/kg] BAX 930 on Day 2
  - ➢ Subjects will receive an additional daily dose of 15 IU/kg [±1.5 IU/kg] BAX 930 until 2 days after the acute TTP event is resolved
  - ➢ Enrollment:
    - Subjects with a confirmed diagnosis of cTTP may provisionally enroll in the on-demand treatment cohort if a clinician believes the subject is undergoing an acute TTP event, based on platelet count and LDH irrespective of clinical symptomatology. Continuation in the study will be dependent on the confirmation of an acute TTP episode and compliance with all inclusion criteria and a determination that no exclusion criteria apply.

	Efficacy data from such subjects will be excluded from the efficacy analysis if subsequent laboratory tests provide evidence that the subject did not experience an acute TTP event or was ineligible to participate in the study. All investigational product (IP)-related safety data will be included in the final study analysis.
Safety • Enrollment will be paused pending Data Monitoring Committee (DMC) evaluation if there are ≥3 product related SAEs, including the development of inhibitory antibodies to BAX 930 • The study will be stopped if 2 or more subjects develop confirmed ADAMTS13 inhibitory antibodies defined as ≥0.6 BU in the central laboratory on 2 separate assays performed within a 1-month period.	
Study Type/ Classification/ Discipline	Bioavailability, Efficacy, Pharmacodynamics, Pharmacoeconomics, Pharmacokinetic, Safety (eg, Immunogenicity)
Control Type	Concurrent (Active)
Study Indication Type	Prevention, Treatment
Intervention model	2-period crossover with a single arm continuation
Blinding/Masking	Open-label
Study Design	This is a Phase 3, prospective, randomized, controlled, prospective, open-label, multicenter, 2-period crossover study with a single arm continuation evaluating the safety and efficacy of BAX 930 in a total of approximately 57 subjects (48 subjects starting in the prophylaxis cohort, and 9 subjects in the on-demand cohort) with severe cTTP.
Planned Duration of Subject Participation	Approximately 22 months in the prophylaxis cohort and approximately 1 month in the on-demand cohort.
Primary Outcome Measure 1. Incidence of acute TTP events among subjects receiving either BAX 930 or SoC prophylactically during the corresponding treatment periods.	
Secondary Outcome Measures **Efficacy** 1. Proportion of acute TTP events responding to BAX 930, defined as not requiring the use of another ADAMTS13-containing agent 2. Time to resolution of acute TTP events following initiation of treatment with BAX 930 or SoC agent 3. Incidence of thrombocytopenia defined as a drop in platelet count ≥25% of baseline or a platelet count <150,000/μL 4. Incidence of microangiopathic hemolytic anemia defined as an elevation of LDH >1.5× of baseline or >1.5× ULN 5. Incidence of neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) 6. Incidence of renal dysfunction defined as an increase in serum creatinine >1.5×baseline 7. Incidence of abdominal pain 8. Incidence of supplemental doses prompted by subacute TTP events	

9. Incidence of dose modification not prompted by an acute TTP event
10. Incidence of acute TTP events while subjects are on their final dose and dosing regimen in the study

Safety/Immunogenicity

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

Pharmacokinetics/Pharmacodynamics

1. Assessment of the PK parameters (incremental recovery [IR], area under the plasma curve [AUC], terminal half-life [$t_{1/2}$], mean residence time [MRT], systemic clearance [CL], steady state volume of distribution [V_{ss}], and maximum concentration following infusion [C_{max}]) for ADMATS13 activity and ADMATS13 antigen for both the SoC agent and BAX 930
2. Assessment of PD markers, such as VWF:Ag and VWF:RCo, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment
3. Assessment of ADAMTS13 activity (pre-infusion ADAMTS13 levels) and select VWF parameters prior to each PK infusion of SoC or BAX 930
4. Assessment of the impact of immunogenicity (immunogenicity status, time of onset) on ADAMTS13 antigen and activity PK parameters

Health Related Quality of Life and Resource Utilization

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

Exploratory Outcome Measures

Efficacy

1. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), while receiving prophylactic treatment with BAX 930 or SoC during the 6 months of the corresponding treatment
2. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), while receiving the final prophylactic treatment regimen with BAX 930 or SoC.
3. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), requiring supplemental dose treatment.
4. Incidence of the subacute TTP events in subjects receiving prophylactic treatment.

5. Assessment of additional exploratory PD biomarkers including but not limited to VWF multimer patterns, ADAMTS13 mediated VWF cleavage products, and coagulation readouts, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment.

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

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	**BAX 930** **Dosage form:** Lyophilized formulation **Dosage frequency:** Daily (on-demand cohort) or once every 1-2 weeks (Q1W or Q2W) (prophylaxis cohort) **Mode of Administration:** Intravenous (i.v.)
Standard of Care	**FFP, pooled solvent/detergent (S/D) treated plasma, or factor VIII (FVIII): VWF concentrates** **Dosage form:** Liquid **Dosage frequency:** Daily (on-demand cohort) or once every 1-2 weeks (Q1W or Q2W) (prophylaxis cohort) **Mode of Administration:** i.v.
SUBJECT SELECTION	
Targeted Accrual	Approximately 57 subjects; including approximately 36 adult (≥18 years old) subjects and 12 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects starting in the prophylaxis cohort, and approximately 6 adult (≥18 years old) subjects and 3 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects in the on-demand cohort. Enrollment will conclude following enrollment of: • The last dosing visit of the fourth pediatric subject in the 0- to <6-year pediatric cohort; and • At least 30 adult subjects in the prophylaxis cohort
Number of Cohorts	2 (prophylaxis and on-demand)

Inclusion Criteria

1. Subject or legally authorized representative has provided signed informed consent (≥18 years of age) and/or assent form (signed by legal representative if subject is <18 years of age).
2. Subject is 0 to 70 years of age, inclusive, at the time of screening. (Subjects <18 years of age will be enrolled only after at least 5 adults (≥18 years of age) each have at least 10 exposures with BAX 930 and reviewed by the DMC. In France, no subjects younger than 18 years of age will be enrolled into the study before the first adult subject has been treated with BAX 930 for a minimum of 6 months.).

3. Subject has a documented diagnosis of severe hereditary ADAMTS13 deficiency, defined as:
   - Confirmed by molecular genetic testing, documented in subject history or at screening, and
   - ADAMTS13 activity <10% as measured by the FRETS-VWF73 assay, documented in subject history or at screening (subjects currently receiving SoC prophylactic therapy may exceed 10% ADAMTS13 activity at screening).

   Note: Subjects currently receiving prophylactic therapy will be screened immediately prior to their usual prophylactic infusion
4. Subject does not display any severe TTP signs (platelet count <100,000/µL and elevation of LDH >2× ULN) at screening. (prophylactic cohort only).
5. Subject is currently on a prophylactic dosing regimen or has a documented history of at least 1 TTP event and an ability to tolerate SoC prophylactic dosing (prophylactic cohort only).
6. Subjects ≥16 years of age must have a Karnofsky score ≥70% and subjects <16 years of age must have a Lansky score ≥80%.
7. Subject is hepatitis C virus (HCV)-negative as confirmed by antibody or polymerase chain reaction testing OR HCV-positive if their disease is chronic but stable.
8. If female of childbearing potential, subject presents with a negative blood or urine pregnancy test, confirmed no more than 7 days before the first administration, and agrees to employ adequate birth control measures for the duration of the study and to undergo quarterly pregnancy testing.
9. 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.
10. Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. Subject has been diagnosed with any other TTP-like disorder (microangiopathic hemolytic anemia), including acquired TTP.
2. Subject has known hypersensitivity to hamster proteins.
3. Subject has experienced an acute TTP episode less than 30 days prior to screening (**prophylactic cohort only**).
4. Subject has a medical history or presence of a functional ADAMTS13 inhibitor at screening.
5. Subject has a medical history of a genetic or acquired immune deficiency that would interfere with the assessment of product immunogenicity, including subjects who are human immunodeficiency virus (HIV)-positive with an absolute cluster of differentiation 4 (CD4) count <200/mm^3 or who are receiving chronic immunosuppressive drugs.
6. Subject has been diagnosed with severe cardiovascular disease (New York Heart Association classes 3 to 4).
7. Subject with end stage renal disease requiring chronic dialysis.
8. Subject has been diagnosed with hepatic dysfunction, as evidenced by, but not limited to, any of the following:
   a. Serum alanine aminotransferase (ALT) ≥2xULN
   b. Severe hypoalbuminemia <24 g/L
   c. Portal vein hypertension (eg, presence of otherwise unexplained splenomegaly, history of esophageal varices)

9. In the opinion of the investigator, the subject has another clinically significant concomitant disease that may pose additional risks for the subject.
10. Subject has been treated with an immunomodulatory drug, excluding topical treatment (eg, ointments, nasal sprays), within 30 days prior to enrollment. Use of corticosteroids in conjunction with administration of FFP to prevent allergic reactions is permitted.
11. Subject has an acute illness (eg, influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, bronchial asthma) at the time of screening (prophylaxis cohort only).
12. Subject is receiving or anticipates receiving another investigational drug and/or interventional drug within 30 days before enrollment.
13. Subject has a history of drug and/or alcohol abuse within the last 2 years.
14. Subject has a progressive fatal disease and/or life expectancy of less than 3 months.
15. Subject is identified by the investigator as being unable or unwilling to cooperate with study procedures.
16. 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.
17. Subject is a family member or employee of the sponsor or investigator.
18. If female, subject is pregnant or lactating at the time of enrollment.
19. Any contraindication to standard of care medicinal product(s) as per local prescribing information.

STATISTICAL ANALYSIS

Sample Size Determination

In total, approximately 42 adult (≥18 years old) subjects and 15 adolescent (>12-≤17 years old) or pediatric (<12 years old) subjects will be enrolled in this study, including approximately 36 adult subjects and 12 adolescent or pediatric subjects starting in the prophylaxis cohort, and approximately 6 adult subjects and 3 adolescent or pediatric subjects, in the on-demand cohort. The sample size is limited by the extremely low prevalence of the disease (0.5 to 4 per million) (Mansouri Taleghani et al., 2013). The updated approximate number of subjects reflects the current observed enrollment patterns and accounts for a 10% dropout rate. The number of subjects starting enrollment in the prophylactic cohort should allow an overall assessment of efficacy and safety of BAX 930, including immunogenicity, and PK.

The sample size of approximately 36 adult (≥18 years old) subjects and 12 adolescent (4 subjects age >12-≤17) or pediatric subjects (4 subjects age ≥6-<12, and 4 subjects age 0-< 6) in the prophylaxis cohort, will be evaluated for the safety and efficacy of the investigational product.

If 15 of the 30 adult and adolescent prophylaxis subjects receive FFP and each subject receiving FFP will have at least 14 infusions per treatment period, there will be 210 total FFP infusions. With 210 FFP infusions, there is a >99% probability that at least 1 SAE will be observed, if as reported in the literature, the rate of serious adverse reactions (SARs) is 6% (Huisman et al., 2014).

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

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

Planned Statistical Analysis

Efficacy

The overall treatment effect of BAX 930 will be assessed on the totality of evidence provided by efficacy, safety, PRO, and PK data. The statistical analysis for the prophylactic cohort will be carried out in 2 steps: (a) an interim analysis (with interim clinical study report) will be performed after 30 adults and adolescent subjects in the prophylactic cohort, complete the study; (b) a final analysis will be done at the end of the study when all efficacy, safety, PRO and PK data collected become available for both adult and pediatric subjects.

The interim analysis will be performed on a cleaned snapshot of the study database. The interim analysis results will be used in regulatory submissions and scientific manuscripts. An efficacy analysis for the on-demand cohort based on available data at the time of the snapshot will also be included in the interim analysis.

Analyses will be performed separately for the prophylaxis and on-demand cohorts on applicable outcome measures and will be presented by treatment group for each cohort, unless otherwise stated.

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

Prophylaxis cohort

The primary efficacy analysis will provide the number and incidence rate of acute TTP events for each treatment arm in the prophylactic cohort, with the corresponding 95%, 2-sided confidence intervals (CIs). The ratio of the 2 treatment incidence rates and a 95%, 2-sided CI will be estimated using a generalized linear mixed-effects model with the negative binomial distribution as a family and with a logarithmic link function (the default), if data facilitate convergence of the model; this approach will utilize the paired counts for each subject obtained under each of the 2 treatments. Summaries of the numbers and incidence rates of the two treatments will be provided also by period and by age groups.

The number and incidence rates of the following: (a) thrombocytopenia, defined as a drop in platelet count ≥25% of baseline or a platelet count <150,000/μL; (b) microangiopathic anemia defined as an elevation of LDH >1.5× of baseline or >1.5× ULN; (c) neurological symptoms (TTP related); (d) renal disfunction defined as an increase in serum creatinine >1.5×baseline and (e) abdominal pain (TTP related) will be tabulated by treatment arm for the prophylactic cohort. The number and incidence rate of (a) dose modification and (b) supplemental dose while on either the BAX 930 or SoC treatment arm will be reported by treatment arm for the prophylactic cohort.

For acute TTP events, the number and the proportion of acute TTP events responding to treatment will be summarized, for the pooled prophylactic and on-demand cohort data, and separately. A Kaplan-Meier curve for each treatment group will be drawn based on each subject's time to resolution of the acute TTP event, defined as the time from the initial treatment to resolution of the acute TTP event. Only the first acute TTP event for each subject will be included in the analysis.

Safety

The number and percentage of treatment-emergent adverse events will be calculated overall, by system organ class, by preferred term, and by treatment group for each cohort. Treatment-emergent adverse events will be further summarized by seriousness, severity, and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Incidence of binding and inhibitory antibody formation will be tabulated and summarized.

Vital signs and clinical laboratory results (clinical chemistry, hematology, and urinalysis), observed and change from baseline, will be summarized by study visit, treatment, and age group (as applicable) using descriptive statistics.

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.

The estimated total quantity of ADAMTS13 administered during the treatment of acute TTP events will be listed by subject and summarized by treatment cohort (prophylactic or on-demand) using descriptive statistics.

Pharmacokinetics/Pharmacodynamics

Standard PK parameters for ADAMTS13 activity and ADAMTS13:Ag including IR, AUC, MRT, systemic CL, V_{ss}, and C_{max} after single infusions of BAX 930 will be estimated for each subject utilizing a non-compartmental approach. Plasma VWF:RCo, VWF:Ag, and VWF multimer structure analysis prior to and following a single infusion (PK studies) and following each subsequent infusion (treatment periods) of BAX 930, FFP, or other ADAMTS13 replacement product will also be measured. Additional summary statistics like median, coefficient of variation, geometric mean, and the corresponding 90% CIs will be reported.

Health Related Quality of Life

Health related quality of life and resource utilization will be tabulated by treatment group.

5. TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

6. LIST OF ABBREVIATIONS

Abbreviation	Definition
λ_z	apparent terminal rate constant
ADAMTS13	a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13
AE	adverse event
Ag	antigen
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma curve
$AUC_{(0\text{-inf})}$	area under the plasma-time concentration curve from zero to infinity
$AUC_{(0\text{-last})}$	area under the plasma-time concentration curve from zero to the last measured timepoint
$AUMC_{(0\text{-inf})}$	area under the moment curve from zero to infinity
B19V	parvovirus B19
BAX 930	rADAMTS13
BAX 930 ORT	rADAMTS13 manufactured in Orth
BAX 930 SIN	rADAMTS13 manufactured in Singapore
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
CK-MB	creatine kinase myocardial band
CL	clearance
C_{max}	maximum concentration (following infusion)
CNS	central nervous system
CRF	case report form
CTA	Clinical Trial Agreement
cTnI	cardiac troponin I
cTnT	cardiac troponin T
cTTP	congenital thrombotic thrombocytopenic purpura
DMC	data monitoring committee
EC	ethics committee

Abbreviation	Definition
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EQ-5D-3L	EuroQol 5 Dimensions Questionnaire 3-Level
EQ-5D-Y	EuroQol 5 Dimensions Questionnaire Youth version
EU	European Union
°F	degree Fahrenheit
FAS	full analysis set
FDP	Final Drug Product
FFP	fresh frozen plasma
FRET	fluorescent resonance energy transfer
FVIII	factor VIII
GCP	good clinical practice
GLP	good laboratory practice
GmbH	*Gesellschaft mit beschränkter Haftung* – German term for a company that does not trade its shares on the stock market
hr	hour(s)
HAV	hepatitis A virus
HBc	hepatitis B core
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
hTTP	hereditary thrombotic thrombocytopenic purpura; congenital thrombotic thrombocytopenic purpura
i.a.	intra-arterial
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IR	incremental recovery
i.v.	intravenous(ly)
IVR	in vivo recovery

Abbreviation	Definition
ko	knockout
LDH	lactate dehydrogenase
LLOQ	lower levels of quantification
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
min	minute(s)
MRT	mean residence time
NMC	non-medical complaint
NOAEL	no-observed-adverse-effect-level
NSE	neuron-specific enolase
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PP	per-protocol
PRO	patient reported outcome
Q1W	every week
Q2W	every 2 weeks
rADAMTS13	a recombinant human disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13
RBC	red blood cell
RCo	ristocetin cofactor activity
RSI	Reference Safety Information
S100B	S100 calcium-binding protein B
S/D	solvent/detergent
SAE	serious adverse event
SAP	statistical analysis plan
SD	Sprague-Dawley
SDS	sodium dodecyl sulfate
SF-36	36-Item Short Form Health Survey
SIC	subject identification code
SoC	standard of care
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life

Abbreviation	Definition
TBD	to be determined
TEAE	treatment emergent adverse event (s)
t_{max}	time to maximum concentration
TSQM-9	abbreviated 9-item Treatment Satisfaction Questionnaire for Medication
TTP	thrombotic thrombocytopenic purpura
U	unit(s)
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
VWF:Ag	von Willebrand factor: antigen
VWF:RCo	von Willebrand factor: ristocetin cofactor activity
w/w	weight-to-weight ratio

7. BACKGROUND INFORMATION

7.1 Description of Investigational Product

Baxalta Innovations GmbH/Baxalta US Inc (later Shire and now Takeda, hereafter referred to as Takeda or sponsor) has developed a recombinant ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) named BAX 930, which is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that expresses the human ADAMTS cDNA. To address concerns regarding the risk of transmission of blood-borne pathogens that may be introduced by human plasma, no exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final product. A plasma-protein-free method and 2 virus inactivation steps are used in this process. This process virtually eliminates any risk of transmission of human blood-borne viruses or other adventitious agents that could, in theory, be introduced by the use of animal- or human-derived raw materials. The only proteins present in the final product other than BAX 930 are trace quantities of host cell (i.e., CHO) protein. The biologic product is a lyophilized formulation of human rADAMTS13 for intravenous (i.v.) injection intended for use as on-demand and prophylactic treatment of patients with thrombotic thrombocytopenic purpura (TTP).

See Section 9.7 for further information on the investigational product (IP) and its usage in this study. A detailed description of BAX 930 is also provided in the investigator's brochure (IB).

7.2 Clinical Condition/Indication

Thrombotic thrombocytopenic purpura is a rare, life-threatening microvascular disease characterized by single or recurrent episodes of thrombocytopenia, microangiopathic hemolytic anemia, and widespread microvascular thrombosis, which leads to the ischemic damage of multiple organs (mainly kidney, heart, and brain) (George, 2006).

Defective processing of von Willebrand factor (VWF), a large plasma glycoprotein that plays a central role in both primary and secondary hemostasis, is central to the pathophysiology of TTP. Patients with TTP display abnormally large VWF multimers in their plasma; the thrombi in TTP are enriched in VWF and platelets; and VWF is present on the surface of platelets in patients with TTP (Tsai, 2003).

Two forms of TTP are recognized: congenital and acquired. The distinction is clinically important because of the different mechanisms of disease and treatment protocols.

The congenital form of TTP (cTTP) comprises no more than 5% of all TTP cases. The exact prevalence of cTTP is not known but is estimated to be less than 1/1,000,000 patients.

It exhibits an autosomal recessive mode of inheritance caused by homozygous or double heterozygous mutations in both ADAMTS13 alleles on chromosome 9. The nature of these mutations is quite diverse and includes missense, nonsense, and splice site mutations as well as deletions and insertions less commonly (Lotta et al., 2010). A severe deficiency of ADAMTS13 results in the accumulation of VWF multimers of ultra-large molecular weight (UL VWF), a characterizing feature of TTP (Moake and McPherson, 1989).

The clinical presentation of cTTP is quite variable. Although symptoms develop soon after birth in approximately 50% of patients, in others, symptoms do not occur until the second or third decade of life. Moreover, while some patients present with relatively asymptomatic anemia and thrombocytopenia, progressive organ dysfunction is frequently encountered and rapidly progressive life-threatening organ failure may also be encountered (Furlan and Lämmle, 2001; Schneppenheim et al., 2003; Schneppenheim et al., 2006). Among patients presenting soon after birth, severe neonatal jaundice requiring exchange transfusion is commonly encountered. Often, the disease is initially misdiagnosed as idiopathic thrombocytopenia purpura and the initiation of appropriate therapy is delayed. A highly sensitive detection system (surface-enhanced laser desorption/ionization time-of-flight mass spectrometry) has demonstrated that residual ADAMTS13 activity correlates with the genotype of the disease and the severity of the clinical phenotype (Lotta et al., 2012).

Often, conditions that are associated with increases in circulating VWF levels, such as second or third trimester pregnancy and infection, are triggers for acute TTP events. These observations suggest that while only very low levels of circulating ADAMTS13 activity are generally required to maintain an appropriate VWF multimer size distribution, the increased release of endothelial stores of VWF can overwhelm this limited capacity and result in a clinically apparent syndrome.

Plasma therapy was proposed empirically in patients with TTP long before its logic was demonstrated. Two preparations are presently in use: quarantine-stored fresh frozen plasma (FFP) and solvent/detergent (S/D)-treated plasma. Both contain normal levels of ADAMTS13, i.e., approximately 1 µg/mL (Allford et al., 2000; Furlan et al., 1999; Heger et al., 2007; Kentouche et al., 2002; Rock et al., 2006).

Fresh frozen plasma is a single donor plasma preparation produced by whole blood fractionation or by automated plasmapheresis. The plasma units are rapidly frozen within 6 hours (hr) after donation.

The residual risk of transmitting human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) is reduced by quarantine storage for 6 months and adjacent second donor screening for these blood-borne viruses. The FFP contains physiologic levels of functionally active plasma proteins according to their respective intra-individual variations.

The FFP involves a very small but not negligible risk of transmitting blood-borne viruses (Hellstern et al., 2002). The FFP units contain all clotting factors and inhibitors of hemostasis and fibrinolysis, with average activities of 100 U/dL and considerable variations corresponding to inter-individual variability (Heim et al., 2009).

For treating TTP episodes, 10 to 20 mL/kg FFP rescues acute episodes, with cessation of hemolysis within 24 hr and improvement of platelet count within a few days. Nevertheless, rescue infusions may not prevent central nervous system (CNS) and renal involvement. In neonates, exchange transfusion is generally indicated because of the severe hyperbilirubinemia. Platelet infusions are contraindicated, as they may trigger thrombotic complications.

The general use of prophylaxis in cTTP has been proposed as rescue infusions may not prevent CNS and renal involvement (Loirat et al., 2006). In prophylactic treatment, 10 mL/kg FFP every 2 or 3 weeks (80% of patients), or in some patients (about 10%) only every 4 weeks, are necessary to maintain remission (Allford et al., 2003; Barbot et al., 2001). Approximately 10% of patients require prophylactic treatment every week to maintain remission[iii].

Low levels of ADAMTS13, generally <10%, are sufficient to prevent clinical manifestations (Kiss, 2010). The half-life of ADAMTS13 in FFP is 2 to 4 days (Furlan et al., 1999; Kovarova et al., 2018), and its protective effect persists for at least 14 days (George, 2007). A proposed explanation to this long-lasting effect, even at low plasma concentrations, has been that ADAMTS13 may "dock" to the endothelium where it is able to cleave UL VWF over a longer period of time (Loirat et al., 2006).

In practice, the interval between 2 FFP infusions is typically decided based upon clinical symptomatology and laboratory parameters such as platelet count and lactate dehydrogenase (LDH) levels. Pharmacokinetic modeling suggests that currently employed regimens maintain ADAMTS13 levels above most or all of the treatment period.

In order to cover triggering events, intensification of plasma therapy (10 mL/kg FFP infusion even if the interval since last infusion is <1 to 2 weeks) is typically considered any time an infection occurs. Close monitoring of LDH and hemoglobin levels have been proposed as an indication to administer FFP when the platelet count drops below 150 $\times 10^9$/L (Willis and Bandarenko, 2005). A similar approach has been recommended for vaccinations. In case of surgery, prophylactic administration of FFP is justified. Lastly, it is recommended that plasma therapy is intensified during pregnancy.

[iii] Kremer J. Personal Communication, Clinical Trial Identifier NCT01257269.

Whether the intensification (eg, weekly infusions of FFP) needs to be started at the beginning of the third trimester or earlier has not been established.

7.3 Population to be Studied

A total of approximately 57 eligible subjects diagnosed with severe congenital ADAMTS13 deficiency (cTTP; defined as plasma ADAMTS13 activity <10%) between 0 and 70 years of age, inclusive, as applicable at time of enrollment, are planned to be enrolled. Approximately 36 adult (≥18 years old) subjects and 12 adolescent (≥12-≤17 years old) or pediatric (0-<12 years old) subjects will be enrolled in the prophylactic cohort. A total of approximately 6 adult subjects (≥18 years old) and 3 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects will be enrolled in the on-demand cohort, as applicable, and depending on the minimum age permitted in each individual country.

Enrolled subjects (i.e., subjects who have signed the informed consent form [ICF] or provided assent [<18 years of age]) will be eligible to participate in the study if they meet all of the inclusion criteria (see Section 10.1) and none of the exclusion criteria (see Section 10.2).

7.4 Findings from Nonclinical and Clinical Studies

The current investigational product BAX 930 consists of a mixture of the native protein and a protein variant Q97R (A single nucleotide change of “A” to “G” in the ADAMTS13 nucleotide sequence leads to a change of amino acid glutamine “Q” to arginine “R” at position 97 at the protein level, resulting in the sequence variant Q97R).

All nonclinical studies and the Phase 1 clinical study were performed with the two-variant product. No safety concerns were raised in the nonclinical toxicology studies or among subjects participating in the Phase 1 clinical study. Refer to the BAX 930 IB for information on findings from nonclinical and clinical studies. Potential risks and efficacy of BAX 930 are summarized in the following sections.

7.4.1 Nonclinical Studies

Nonclinical studies have been performed in vitro and in vivo to characterize the safety, efficacy, pharmacokinetics (PK), and toxicity of BAX 930.

An overview of the nonclinical studies is summarized in Table 1.

Table 1. Overview of Nonclinical Studies for BAX 930

Study Number	Study	Species
527739	Repeat Dose Toxicity (5 days)[a]	SD Rat
PV2511001	Repeat Dose Toxicity (4 weeks)[a]	SD Rat
523430	Repeat Dose Toxicity (26 weeks)[a]	Rat
8234215	Escalating Dose and Repeat Dose Toxicity (4 weeks)[a]	Cynomolgus monkey
8243420	Repeat Dose Toxicity (4 weeks) including cardiovascular investigations[a]	Cynomolgus monkey
PV2541101	Local Tolerance[a]	Rabbit
495388	Placental Transfer Feasibility	SD Rat
496821	Pre- and Post-natal Development[a]	SD Rat
497081	Female Fertility and Embryo-fetal Development[a]	SD Rat
PV2521007	PK[a]	ADAMTS13 ko mouse
PV2531005	PK[a]	Rat
8234215	PK[a]	Cynomolgus monkey
WH0610	Efficacy of prophylactic administration	ADAMTS13 ko mouse
WH0211	Efficacy of prophylactic administration over time	ADAMTS13 ko mouse
WH0710	Efficacy of therapeutic administration	ADAMTS13 ko mouse
248.220.5098	Efficacy of therapeutic administration at different doses	ADAMTS13 ko mouse
ATS0007101	In Vitro Functional Activity	Plasma from ADAMTS13 ko mouse, SD rat, guinea pig, minipig, and cynomolgus monkey

ko=knockout; PK=pharmacokinetics; SD=Sprague-Dawley.

a. GLP compliant according to the following: US Code of Regulations, 21 CFR 58 – GLP for Nonclinical Laboratory Studies; Organisation de Coopération et de Développement Economiques - Principles of GLP, ENV/MC/CHEM(98)17 (as revised in 1997); Austrian Federal Law Gazette II No. 450/2006 – Regulation of the Minister of Health and Women on GLP; Austrian Federal Law Gazette II No. 211/2000 - Regulation of the Minister of Agriculture, Forestry, Environment and Water Management on the Application of Principles of GLP and the monitoring of compliance (Chemicals GLP Inspection Regulation – GLP-V); Austrian Federal Law Gazette No. 501/1989 - Animal Experiments Act; and Japanese Ordinance No. 21/1997, GLP Standard for Conduct of Nonclinical Safety Studies of Drugs.

7.4.1.1 Nonclinical Pharmacology

Primary pharmacodynamics studies were performed to evaluate the efficacy of both prophylactic and therapeutic administration of BAX 930 in ADAMTS13 knockout (ko) mice using a TTP model developed by (Schiviz et al., 2012).

Briefly, TTP like symptoms are induced in ADAMTS13 ko mice by injecting a high dose of a recombinant human von Willebrand factor (rVWF) preparation containing UL VWF multimers.

These mice are not able to cleave human high-molecular weight VWF multimers; therefore, rVWF triggers TTP-like symptoms.

Efficacy of the test item was defined as the degree of prevention of platelet drop and prevention of increase in LDH, both parameters being markers of TTP. In addition, organ damage was assessed histologically. In all 4 efficacy studies (WH0610, WH0710, WH0211, 248.220.5098[iv]), body weight loss, severe thrombocytopenia, increase in serum LDH, and thrombotic changes in the heart were present in all animals in the negative control groups, confirming that the induction of TTP like symptoms is homogeneous, stable, and reproducible.

In all 4 studies, animals treated with buffer and challenged with a high dose of rVWF served as negative controls. Untreated animals served as background controls.

Both prophylactic and therapeutic treatment with BAX 930 was efficacious in the rVWF-induced TTP model in ADAMTS13 ko mice. The efficacy of BAX 930 was interval- and dose-dependent when administered before or after induction of TTP. Treatment with BAX 930 showed similar or slightly improved efficacy to treatment with fresh frozen human plasma, the current standard of care.

Regarding safety pharmacology, the influence of administration of BAX 930 on vital functions (cardiovascular and respiratory parameters) was tested in the repeat dose toxicity study in cynomolgus monkeys (Study 8243429). Treatment with BAX 930 was well-tolerated and did not result in any adverse effect on the cardiovascular or respiratory system in cynomolgus monkeys up to a dose of 400 U/kg body weight (BW), which was the highest dose tested and which is 10 times the maximum anticipated human dose in the Phase 3 clinical trial.

7.4.1.2 Nonclinical Pharmacokinetics

Pharmacokinetic studies were performed in 3 animal species (ADAMTS13 ko mice, Sprague-Dawley [SD] rats and cynomolgus monkeys). Citrated plasma samples were analyzed for ADAMTS13 activity by a validated ADAMTS13 activity assay (FRETS-VWF73 assay). ADAMTS13 antigen was measured using a validated antigen ELISA.

7.4.1.2.1 Pharmacokinetic Study in ADAMTS13 ko Mice

The pharmacokinetic profile of BAX 930 was evaluated in ADAMTS13 ko mice after intravenous bolus administration of 40, 80, or 200 U/kg BW.

[iv] Studies WH0610, WH0710, WH0211, and 248.220.5098 data on file at Takeda

The study followed a serial sacrifice design. For each arm, 10 animals (5 male/5 female) at each of 9 timepoints were bled by cardiac puncture under anesthesia[v].

Similar dose-adjusted values (average) of area under the plasma-time concentration curve from zero to infinity ($AUC_{(0\text{-}inf)}$) were observed for all 3 doses, for both the ADAMTS13 activity and the ADAMTS13 antigen (approximately 0.13 hr* U/mL / U/kg and approximately 0.13 hr*µg/mL/µg/kg). Both the ADAMTS13 activity and antigen values showed similar results for in vivo recovery (IVR), incremental recovery (IR), clearance (CL), and also for mean residence time (MRT), terminal half-life ($t_{1/2}$), and steady state volume of distribution (V_{ss}).

7.4.1.2.2 Pharmacokinetic Study in Rats

The pharmacokinetics and dose proportionality of BAX 930 were evaluated in SD rats (Study PV2531005[vi]) after single intravenous (bolus) administration of 80, 200, or 400 U/kg BW. A single animal design was used with 10 animals in each dose group.

The geometric means, following analysis for ADAMTS13 activity, for dose-adjusted area under the plasma-time concentration curve from zero to the last measured timepoint ($AUC_{(0\text{-}last)}$) (hr*U/mL/U/kg) were 0.326, 0.384, and 0.458 for the low, mid, and high doses, respectively. The geometric means for antigen for dose-adjusted $AUC_{(0\text{-}last)}$ (hr*µg/mL/µg/kg) were 0.301, 0.285, and 0.283, respectively. The ratios of $AUC_{(0\text{-}last)}$ and $AUC_{(0\text{-}inf)}$ for both activity and antigen indicated good coverage of the drug exposure for all doses during the observational period of the study. Terminal half-lives ranged from 16.7 to 25.6 hr and 23.5 to 24.0 hr for activity and antigen, respectively.

Mean residence times ranged from 22.8 to 30.8 hr and 28.3 to 29.7 hr for activity and antigen, respectively, and IVR ranged from 60% to 66%, and 49% to 57% for activity and antigen, respectively.

7.4.1.2.3 Pharmacokinetic Study in Cynomolgus Monkeys

Pharmacokinetics of BAX 930 in cynomolgus monkeys was assessed in Study 8234215[vii]. Three males and 3 females received the test (800 U/kg BW) and control item by slow bolus i.v. injection once weekly during the repeated dose phase of this study.

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[v] Study PV251007 data on file at Takeda
[vi] Study PV2531005 data on file at Takeda
[vii] Study 8234215 data on file at Takeda

The geometric mean of dose-adjusted $AUC_{(0\text{-last})}$ [hr* U/mL/U/kg] for combined sexes was 0.377 (95% confidence interval [CI]: 0.357 to 0.398) and 0.401 (95% CI: 0.379 to 0.423) at Days 1 and 15, respectively. This slight increase was also observed with antigen: geometric mean of dose-adjusted $AUC_{(0\text{-last})}$ [hr*µg/mL / µg/kg] for combined sexes. Further, $t_{1/2}$ and MRTs were comparable between Days 1 and 15 for combined sexes for both analytes.

7.4.1.3 Nonclinical Toxicology

Sprague-Dawley rats and cynomolgus monkeys were selected as suitable species for evaluation of safety and toxicity of BAX 930. Species suitability was shown by demonstrating that (BAX 930 can cleave endogenous monkey and rat VWF in vitro and in vivo. Only one species (SD rat) was used for long-term toxicity assessment and DART (developmental and reproductive toxicity) assessment based on the following reasons:

- In the 1-month repeat-dose toxicity studies, the safety profile of BAX 930 in SD rats and cynomolgus monkeys was comparable
- In the 1-month repeat-dose toxicity study in the cynomolgus monkey, formation of neutralizing anti-drug antibodies was observed which resulted in a decrease in exposure and in development of TTP-like symptoms after repeated dosing. Cynomolgus monkeys are therefore not considered suitable for long-term studies with BAX 930.

7.4.1.3.1 Repeat Dose Toxicity Study in Rats

In Study 527739[viii], the toxicity and toxicokinetics of BAX 930 were evaluated in SD rats when intravenously dosed for 5 consecutive days. Treatment with BAX 930 at 80, 200, or 400 U/kg BW for 5 consecutive days was well tolerated in rats and did not cause any adverse treatment related effects. The NOAEL for BAX 930 in this study was 400 U/kg, which was the highest dose tested.

Study PV2511001[ix] assessed the toxicity of BAX 930 in rats after repeated i.v. administration every third day over a 28-day period (10 applications) and a 2-week recovery phase.

Treatment with 80, 400, and 800 U/kg BAX 930 every third day for 28 days was well-tolerated and did not cause any adverse treatment related effects. The NOAEL for BAX 930 for this study in rats was 800 U/kg, which was the highest dose tested.

[viii] Study 527739 data on file at Takeda
[ix] Study PV2511001 data on file at Takeda

7.4.1.3.2 Escalating Dose- and Repeat Dose Toxicity Study in Cynomolgus Monkeys

Study 8234215[x] was conducted to assess the PK profile of BAX 930 and to determine the NOAEL and a suitable dose level for repeated application in the cynomolgus monkey following i.v. administration (4 males and 4 females for the escalating dose phase and 3 males and 3 females for the repeated dose phase).

Treatment with BAX 930 at 800 U/kg i.v. once a week for a total of 5 weeks (repeat dose phase) was well-tolerated and did not reveal any adverse treatment related changes in general. The formation of antibodies against BAX 930 is an expected immune response after repeated application of heterologous proteins to cynomolgus monkeys and was not regarded as adverse. The NOAEL was the high dose of 800 U/kg under the conditions of this repeated dose phase study. Based on data available from the escalating dose phase, the NOAEL for this phase of study was the high dose of 1790 U/kg.

7.4.1.3.3 Repeat Dose Toxicity Study in Cynomolgus Monkeys

Study 8243420[xi] aimed to determine the toxicity of the test item BAX 930, following i.v. administration to the cynomolgus monkey for 4 weeks and to assess the reversibility of effects observed during a 2-week recovery phase.

BAX 930 was administered i.v. to 3 groups (5/sex/group) of cynomolgus monkeys by bolus injection at doses of 0, 80, 200, and 400 U/kg every 7 days (weekly) for 29 days (5 doses). Another group of cynomolgus monkeys (5/sex) received vehicle (buffer for BAX 930) at the highest dosing volume of 1.117 mL/kg. Two animals per sex in each group were maintained on study for a 2-week recovery period.

Treatment with BAX 930 was well-tolerated at either dose and did not reveal any adverse clinical symptoms or findings that could be clearly attributed to the test item. The formation of antibodies against BAX 930 is an expected immune reaction after repeated application of heterologous proteins to cynomolgus monkeys. The NOAEL was the high dose of 400 U/kg.

7.4.1.3.4 Reproductive and Developmental Toxicity and Placental Transfer Feasibility Study in Rats

Study 495388[xii] was performed to assess the potential of BAX 930 to cross the placenta. Sprague-Dawley rats received a single i.v. (bolus) injection of BAX 930 of a dose level of 0 (vehicle control group) and 3200 U/kg (test group) on Day 21 gestation, via the lateral tail vein at a dose volume of 5 mL/kg.

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[x] Study 8234215 data on file at Takeda
[xi] Study 8243420 data on file at Takeda
[xii] Study 495388, BAX 930: A Reproductive Toxicity and Placental Transfer Feasibility Study in Rats, data on file at Takeda

Incomplete placental transfer of BAX 930 was detected in SD rats following a single administration on Day 21 of gestation at a level of 3200 U/kg. ADAMTS13 antigen concentration was measured up to only 0.6% of the concentration detected in maternal serum.

In Study 497081[xiii], the effect of BAX 930 on female fertility and pregnancy was assessed in SD rats after intravenous administration every third day for 2 weeks before mating, throughout mating, and up to approximately day 16 of gestation. BAX 930 was administered at doses of 80, 200, or 400 U/kg BW (20 females per group). The formulation buffer of BAX 930 served as vehicle control. In conclusion, treatment with BAX 930 at 80, 200, and 400 U/kg BW in female rats was not associated with any adverse maternal findings or treatment related effects on fertility, pregnancy performance, or fetal development. In addition, no binding anti-drug antibodies were detected in any animals during the study. The highest dose tested, 400 U/kg BW, was therefore considered to be the maternal and fetal NOAEL in this study.

In Study 496821[xiv], the effects of BAX 930 on pregnant/parturient/lactating rats and on the development of the conceptus and offspring to sexual maturity was assessed after repeated intravenous administration. BAX 930 was administered at doses of 80, 200, or 400 U/kg BW (24 females per group). The formulation buffer of BAX 930 served as vehicle control. There was no effect on the physical or functional development of the F1 generation or their reproductive function. Both the maternal and the reproductive NOAEL were determined to be 400 U/kg which was the highest dose tested.

7.4.1.3.5 Local Tolerance in Rabbits

Study PV2541101[xv] investigated the local tolerance of BAX 930 after i.v. (clinical application route), intra-arterial (i.a.), and paravenous (possible misapplication routes) application in rabbits in comparison with buffer for BAX 930 (vehicle control) and saline (negative control). Each item was injected i.v. or i.a. at a volume of 5 mL per animal (within 2 minutes), or paravenously at a volume of 0.5 mL per animal (bolus injection), into the right ear of each of 4 rabbits (2 male, 2 female; total of 24 tested animals). The animals' behavior was observed, and the injection sites examined macroscopically for possible changes in the first 30 minutes after treatment and thereafter intermittently up to 6 hours and again at 24, 48, and 72 hours.

No changes in behavior and no macroscopic changes at the injection sites were observed after administration of BAX 930 for any of the administration routes tested. Histopathologically, no adverse lesions regarding local tissue tolerability of the test item were detected.

[xiii] Study 497081 data on file at Takeda

[xiv] Study 496821 data on file at Takeda

[xv] Study PV2541101 data on file at Takeda

BAX 930 was well-tolerated after i.v. (intended clinical administration route), i.a., and paravenous administration.

7.4.2 Clinical Studies

A first in man, Phase 1, prospective, open-label, multicenter, dose-escalation study[xvi] to evaluate safety including immunogenicity and PK of BAX 930 in a total of at least 14 subjects diagnosed with severe cTTP (plasma ADAMTS13 activity <6%) assigned to either 1 of 3 dose cohorts (i.e., 5, or 20, or 40 U/kg) has been completed. Overall, 16 subjects were enrolled, of whom 15 received the IP and completed the study.

7.4.2.1 Safety

No severe treatment emergent adverse events (TEAEs), deaths, serious AEs (SAEs), or TEAEs leading to discontinuation from the study or from the investigational product, or breakthrough TEAEs were observed in the study. Although most of the subjects in the study reported TEAEs, a greater proportion of the TEAEs were mild in severity and assessed as not related to the IP or study procedure. The most commonly reported TEAEs were in the system organ class nervous system disorders, gastrointestinal disorders, and infections and infestations. All the TEAEs reported in the study resolved.

No safety signals were evident by shifts in laboratory values. After BAX 930 infusion, platelet counts increased and LDH levels decreased before returning to baseline levels, consistent with ADAMTS13 activity.

7.4.2.2 Immunogenicity

All subjects tested negative at all scheduled timepoints for neutralizing anti-ADAMTS13 antibodies, anti-CHO protein antibodies, and anti-BAX 930 binding antibodies.

7.4.2.3 Pharmacokinetics

Low levels below the limit of quantification (quantified using FRETS-VWF73) of ADAMTS13:antigen (Ag) and limited ADAMTS13 activity were measured in most subjects at predose baseline. Following single-dose administration of BAX 930 at 5, 20, and 40 U/kg to adults, dose-related increases in individual ADAMTS13:Ag and activity were observed and reached a maximum at approximately 1 hour or earlier. Similar ADAMTS13:Ag and ADAMTS13 FRETS-VWF73, profiles notwithstanding some differences due to different lower levels of quantification (LLOQs), suggested a good correlation between protein concentrations (ADAMTS13:Ag) and activity. ADAMTS13:Ag and activity coverage was higher than baseline (predose) value for most data points over the 288-hour sample collection window.

[xvi] Full Clinical Study Report 281101, BAX 930 (rADAMTS13).

The most robust PK data were derived from the 40 U/kg dose cohort, in which the greatest number of subjects (9 subjects, including 7 adults) were enrolled and values above the LLOQ observed. The protein antigen and activity PK parameters of BAX 930 were comparable to those estimated from previous FFP studies (Furlan et al., 1999; Fujimura et al., 2015). In the 40 U/kg cohort, the geometric mean of IR was 0.0232 (U/mL x kg/U) and mean half-life was 59.2 hours for ADAMTS13 FRETS-VWF73.

The geometric mean of ADAMTS13:Ag CL was 61.5 mL/h and of V_{ss} was 5300 mL (at 40 U/kg dose level), suggesting the protein distributed primarily within the intravascular compartment. There was approximate dose proportionality with respect to the maximum concentration following infusion (C_{max}; geometric means of 0.323 µg/mL after 20 U/kg infusion and 0.672 µg/mL after 40 U/kg infusion) and $AUC_{(0\text{-inf})}$ (geometric means of 18.3 µg·h/mL after 20 U/kg infusion and 36.0 µg·h/mL after 40 U/kg infusion). Likewise, ADAMTS13 activity (FRETS-VWF73) C_{max} and total exposures increased approximately in proportion to the dose escalations. The geometric mean C_{max} was 0.398 U/mL after 20 U/kg infusion and 0.948 U/mL after 40 U/kg infusion; and geometric mean $AUC_{(0\text{-inf})}$ was 19.1 U·h/mL after 20 U/kg infusion and 53.1 U·h/mL after 40 U/kg infusion.

No apparent differences were observed for ADAMTS13 activity and ADAMTS13:Ag between adolescents (N=2) and adults (N=7), where data were available. Pediatric PK parameters could not be accurately estimated due to insufficient data from the sparse sampling scheme of 2 adolescent subjects and the absence of younger pediatric subjects to support parameter calculations.

7.4.2.4 Pharmacodynamics

Detectable ADAMTS13-mediated VWF cleavage products were present in all subjects (100%) up to 3, 24, and 48 hours postdose at 5, 20, and 40 U/kg, respectively. A trend for decreasing large multimers, a fraction of which also included ultra-large multimers, and increasing levels of the intermediate fraction was observed over the first 24 hours post-infusion in individual profiles at BAX 930 doses of 20 or 40 U/kg. In addition, the function of VWF to bind platelet GP1b, as measured by the VWF:RCo assay, decreased by almost 30% in the first 9 hours.

There was an increase in the platelet count in all dosing groups and a decrease of LDH in the first 96 hours. Taken together, these findings provide evidence of in vivo ADAMTS13 activity following BAX 930 IP administration.

7.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

Currently, acute TTP events are treated with FFP infusions, typically 10 to 20 mL/kg BW for 3 or more days or until the platelet count rises to above 150,000 per µL. There is currently no approved treatment for cTTP, therefore BAX 930 represents a new therapeutic to improve current treatment (Plaimauer and Scheiflinger, 2004; Plaimauer et al., 2011). Takeda intends to evaluate BAX 930 as replacement therapy in a fashion analogous to the use of FFP, the current standard clinical therapy for TTP.

Based on the retrospective analysis of available peptide mapping data, the composition of Q97 native and Q97R variant protein appears to have been consistent throughout development. The evaluation further confirmed no differences in the structure/function relationship of the native and variant protein in the composition observed and demonstrated consistency of the product throughout preclinical and clinical development with a Q97R protein abundance of between 52% and 72%.

Evaluation of biochemical, enzymatic and pharmacokinetic characteristics of BAX 930 which contains both the native dominant Q97 and variant Q97R proteins, concluded (1) no differences in the structure/function relationship of the native vs. variant protein and (2) that they closely reflect the properties of plasma-derived ADAMTS13. The amino acid exchange position is located away from the proposed VWF binding sites that are critical for cleavage and metal ion binding, significantly reducing the possibility of any effect it may have on regulation of these binding domains.

No safety concerns were raised in the nonclinical toxicology studies or among subjects participating in the Phase 1 clinical study - none of the study subjects developed antibodies to ADAMTS13 following treatment with BAX 930. An *in silico* assessment of immunogenicity has been performed (utilizing the Immune Epitope Database), indicating no generation of novel immune-dominant MHC II T cell epitopes as result of the Q97R amino acid exchange.

Over the course of evaluation of ADAMTS13 variability in the human population, the ADAMTS13 protein variant identified in BAX 930 resembles a benign missense mutation, which was also supported by an immunogenicity assessment based on non-clinical study results as well as an in-silico assessment which did not provide any data pointing to new immune epitopes formed by the variant.

BAX 930 is therefore expected to behave in the same way as endogenous ADAMTS13, as demonstrated in several non-clinical in vitro and in vivo studies. Replacement therapy with BAX 930 promotes increased plasma levels of ADAMTS13, which are absent or greatly reduced in subjects with cTTP.

The temporary correction of the enzyme deficiency results in improvement of VWF cleaving activity and prevention of the clinical symptoms. Due to the lack of clinical experience with BAX 930, there is no known risk of formation of inhibitors to ADAMTS13.

There is no experience with the therapeutic use of Takeda's BAX 930 in pediatric or geriatric TTP subjects; however, with respect to the anticipated efficacy and safety of BAX 930, no differences are expected between adults and children as treatment with current SoC replacement products is similar in the 2 populations. It is now well established that FFP and virus-inactivated plasma replace active ADAMTS13 in subjects with TTP (Loirat et al., 2006). There is only 1 example of a subject developing an inhibitor to ADAMTS13 reported in the literature (Raval et al., 2015).

While the treatment of TTP via plasma infusions is effective, the therapy can cause complications such as allergic reaction (i.e., urticaria and anaphylaxis). Plasma infusions also carry the following risks: infection associated with exposure to blood-borne pathogens; volume overload, and hyperviscosity associated with rapid infusion of plasma volumes that are required in order to increase the plasma ADAMTS13 levels significantly (Hellstern et al., 2002); and in subjects undergoing long-term prophylaxis, hemorrhage related to the insertion of a central venous catheter, venous thrombosis, and systemic infection (Howard et al., 2006). Furthermore, an additional risk involves the availability of FFP, which can fluctuate due to its use in market as a source material for plasma protein preparations (Hellstern et al., 2002).

BAX 930 should be administered with caution in subjects with known hypersensitivity to any of the components of rADAMTS13. As with any i.v. protein product, allergic-type hypersensitivity reactions are possible. Subjects must be closely monitored for any symptoms throughout the infusion period.

Subjects should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented.

Please refer to the BAX 930 IB for further details on benefits and risks of the IP.

7.6 Compliance Statement

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

8. STUDY PURPOSE AND OBJECTIVES

8.1 Study Purpose

The purpose of the study is to assess safety and efficacy of BAX 930 in the prevention and treatment of acute TTP events in subjects with severe congenital deficiency of ADAMTS13 (cTTP; defined as plasma ADAMTS13 <10%, as measured by the FRETS-VWF73 assay).

8.2 Primary Objective

The primary objective of the study is:

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

8.3 Secondary Objectives

8.3.1 Efficacy

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

8.3.2 Safety

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

8.3.3 Pharmacokinetics/Pharmacodynamics

1. For both adult and pediatric subjects two crossover PK evaluations and an end-of-study ADAMTS13 PK evaluation (PK-III) may be performed for up to 288 hours post-infusion in the prophylactic cohort
    1) PK-I: To characterize the baseline PK of ADAMTS13 activity after administration of BAX 930 ORT or BAX 930 SIN and SoC prior to Period 1

2) PK-II: To assess the PK comparability between BAX 930 SIN and BAX 930 ORT, in subjects who received BAX 930 ORT in PK-I.

3) PK-III: To assess if any time dependent PK changes occur due to long-term exposure to BAX 930 SIN at the end of period 3.

2. To assess VWF:antigen (VWF:Ag), and VWF:ristocetin cofactor activity (RCo) at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment in the prophylactic cohort.
3. To assess ADAMTS13 activity (pre-infusion ADAMTS13 levels) and select VWF parameters prior to each PK infusion of SoC or BAX 930 in the prophylactic cohort.
4. To evaluate the effect of immunogenicity on the PK profile of ADAMTS13

8.3.4 Health Related Quality of Life and Resource Utilization

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

8.4 Exploratory Objectives

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

9. STUDY DESIGN

9.1 Brief Summary and Amendment Rationale

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

The primary purpose of Protocol Amendment 15 is to 1) provide clarification and alignment of various terms and definition throughout the text and 2) include suggestions and options to reduce volume of blood samples collected from pediatric subjects to ensure the blood volume is within recommended limits. Refer to Section 3 for a summary of all changes from the prior version.

9.2 Overall Study Design

The overall study design is illustrated in Figure 1. The principal part of the study involves the prophylactic treatment of cTTP. There are 3 periods, 2 crossover PK and one end-of-study PK assessment. Adult, adolescent, and pediatric subjects, who are screened prior to 01 October 2021, will initiate the study with BAX 930 ORT. Following the first randomized crossover PK evaluation (PK-I) of both the subject's SoC product and BAX 930 ORT, subjects will receive 6 months of prophylaxis treatment with SoC product and 6 months of prophylaxis treatment with BAX 930 ORT. Once Period 2 is completed, subjects will enter Period 3. Subjects will receive treatment with BAX 930 ORT in Period 3 until BAX 930 SIN is available at their site. Once BAX 930 SIN is available, subjects randomized to the study after the temporary study halt will initiate a crossover PK evaluation, which is PK-II (see Section 9.2.1.1.2 for PK-II exceptions), and then initiate an additional 6 months of prophylaxis treatment with BAX 930 SIN in Period 3.

To briefly describe PK-1, after informed consent has been obtained, all adult and pediatric subjects will undergo a minimum washout period of 1 week from their last prophylactic infusion. For subjects receiving factor VIII (FVIII):VWF concentrates, the minimum required SoC PK dose washout period may be reduced to 5 days. Upon completion of the washout period, subjects will undergo screening procedures for the determination of eligibility. Subjects who meet all eligibility criteria based on the inclusion/exclusion criteria (see Section 10.1 and Section 10.2, respectively) and consent to treatment in the prophylactic cohort will be randomized equally to 1 of 2 treatment orders: BAX 930-SoC or SoC-BAX 930. Subjects randomized into the SoC treatment arm for Period 1 will receive a single dose of BAX 930 to evaluate pharmacokinetics (i.e., PK dose) followed by a PK dose of their current SoC product 14 days [±2 days] later. An exception will be permitted for subjects on Q1W dosing if the investigator is concerned that delaying an infusion would impact subject safety. These subjects will be permitted to receive their current SoC product 7 days [±0.5 days] after the BAX 930 PK dose.

Subjects randomized into the BAX 930 treatment arm for Period 1 will receive a PK dose of their current SoC product followed by a PK dose of BAX 930 14 days [±2 days] later.

Following PK-I, subjects will then receive either BAX 930 ORT or SoC for the first 6-month treatment period (Period 1) as randomized. For each subject, the SoC regimen will be determined by the investigator and defined by their treatment product and dosing regimen at the time of entry into the study.

After completing Period 1 with either BAX 930 ORT or SoC, subjects will enter Period 2 and crossover to the alternative treatment (BAX 930 ORT for subjects who start on the SoC and SoC for subjects who start on BAX 930 ORT) and remain on that treatment for another 6 months during Period 2. Once Period 2 is completed, subjects will enter Period 3. Subjects will receive treatment with BAX 930 ORT in Period 3 until BAX 930 SIN is available at their site. Once BAX 930 SIN is available, adult and adolescent (≥12 years old) subjects randomized to the study after the temporary study halt will initiate a crossover PK evaluation, which is PK-II (see Section 9.2.1.1.2 for PK-II exceptions). Then, subjects will start Period 3 and receive an additional 6 months of treatment with BAX 930 SIN. Subjects randomized to the study prior to the temporary study halt, will receive prophylactic treatment with BAX 930 ORT in Period 3. After the last IP infusion of Period 3, an end-of-study, PK-III assessment may be implemented for a subset of subjects including; 1.) Any subject in the prophylactic cohort, including any subject who switches from on-demand treatment to prophylactic treatment, who initiates the study with BAX 930 SIN, and 2.) A minimum of 4 adults (≥18 years old), and a minimum of 2 pediatric or adolescent subjects (age 0-17 years) who receive BAX 930 SIN in Period 3. Pediatric subjects (<12 years old) and subjects who receive weekly (Q1Week) dosing regimen will undergo the PK-III assessment. Subjects will be allowed to remain in the 281102 study until the continuation study is open for enrollment. Dosing, visits and assessments will be continued unchanged and as per protocol description of Period 3 (See Section 9.2.1.4), until their transfer to the continuation study.

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

During prophylactic treatment, and if deemed necessary and acceptable by the investigator, subjects will be given the option to have at-home infusion of BAX 30 by a healthcare provider. Subjects will be required to come to the clinic for an acute/subacute TTP event. Subjects will also be required to have in-clinic visits periodically throughout the trial, further details regarding at-home visits can be found in the Home Nursing Manual.

An interim analysis will be performed after 30 adult or adolescent subjects in the prophylactic cohort, who were randomized to the prophylactic cohort, complete the study. The interim analysis will be performed on a cleaned snapshot of the study database. The interim analysis will include final data from at least 30 subjects in the prophylactic cohort who have completed the study. The interim analysis data will be used in regulatory submissions and scientific manuscripts.

It is anticipated that TTP-related events will occur during the study. These events will be classified as acute TTP events, isolated TTP manifestations, or subacute TTP events according to the following classifications (refer also to Section 13.1.2 regarding the reporting of TTP-related events and adverse events):

Table 2. TTP Event Definitions

	Acute TTP Event	Subacute TTP Event	Isolated TTP Manifestations
Criteria	Both of the following laboratory measures[a]	At least 2 of the following; at least 1 of which must include a laboratory measure[a]	Any of the following
Thrombocytopenia	Drop in platelet count ≥50% of baseline or a platelet count <100,000/µL	Drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/µL	Drop in platelet count ≥25% of baseline or a drop in platelet count <150,000/µL
Microangiopathic Hemolytic Anemia	Elevation of LDH >2 x of baseline or >2 x ULN	Elevation of LDH >1.5 x of baseline or >1.5 x ULN	Elevation of LDH >1.5 x of baseline or > 1.5 x ULN
TTP-related Clinical Signs/Symptoms	Not required to meet criteria but to be recorded if observed	Organ-specific signs and symptoms, including but not limited to: • Renal signs, as defined by increase of serum creatinine >1.5 × baseline • Neurological symptoms (eg, headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures) • Fever (≥100.4°F/38°C) • Fatigue/lethargy • Abdominal pain	Organ-specific signs and symptoms, including but not limited to: • Renal signs, as defined by increase of serum creatinine >1.5 × baseline • Neurological symptoms (eg, headache, confusion, memory issues, irritability, paresthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures) • Fever (≥100.4°F/38°C) • Fatigue/lethargy • Abdominal pain

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

Acute TTP events will be managed by intensification of the replacement regimen using the same therapeutic agent (SoC or BAX 930) as employed for prophylaxis at that time. The occurrence of these events may also necessitate a change in the prophylactic regimen according to pre-specified criteria.

Subjects experiencing an acute TTP event, meeting all other inclusion criteria, and entering and consenting to treatment in the study through the on-demand cohort will be randomized to receive urgent treatment with either the SoC or BAX 930. Upon resolution of the acute TTP event, subjects may choose to move to the prophylaxis cohort of the study or discontinue entirely. Subjects electing to move from on-demand cohort to the prophylaxis cohort will move directly to Period 1 and will not receive PK-I infusions. Subjects switching from on-demand treatment cohort to prophylaxis cohort will receive the same treatment in Period 1 as the randomized on-demand treatment, and alternative in Period 2.

Re-enrollment of on-demand subjects who has finished the study into the on-demand treatment cohort is allowed if he/she experiences a new acute TTP event.

9.2.1 Prophylaxis Treatment Cohort and PK Assessments

9.2.1.1 Pharmacokinetic Assessments

Three PK evaluations of ADAMTS13 will be performed: 1) PK-I: To characterize the baseline PK of ADAMTS13 activity after administration of BAX 930 and SoC prior to Period 1; 2) PK-II: To assess the PK comparability between BAX 930 SIN and BAX 930 ORT at the beginning of Period 3 for those subjects treated with BAX 930 ORT during Period 1 or 2; 3) PK-III: To characterize the PK profile of ADAMT13 activity at the end of the study following long term exposure to BAX 930.

In case of an acute TTP event occurring during the PK study, PK sampling should be redone for PK-I and PK-II, if there are less than 7 post-dose PK timepoints collected up to the time of the acute TTP event and the last time point is shorter than 168 hr [±12 hr].

For PK-I, for subjects receiving weekly treatment as part of their SoC prophylaxis regimen, all washout periods can be reduced to 1 week at the discretion of the investigator. Due to lower content of ADAMT13 in factor VIII (FVIII):VWF concentrates (Peyvandi et al., 2013), subjects receiving factor VIII (FVIII):VWF concentrates or who are undergoing weekly prophylactic treatment, the minimum required SoC PK dose washout period may be reduced to 5 days. For PK-II, samples from subjects on prophylaxis treatment will be collected and included in the PK analysis.

For PK-III, a subset of subjects may undergo ADAMTS13 activity PK assessments after the last dose with BAX 930 SIN in Period 3.

9.2.1.1.1 PK-I

PK-I is a randomized two-way crossover PK evaluation. Depending upon the availability of BAX 930 SIN material, either BAX 930 ORT or BAX 930 SIN will be administered in PK-I. When BAX 930 SIN is not available, prior to the cut-off date of 01 Oct 2021, subjects in the prophylaxis treatment cohort randomized into the SoC treatment arm for Period 1 will receive a single infusion of 40 IU/kg BAX 930 ORT, no less than 1 week after their previous prophylactic dose (washout period during screening). For subjects receiving factor VIII (FVIII):VWF concentrates, the minimum required SoC PK dose washout period may be reduced to 5 days. After subjects receive their BAX 930 ORT PK dose, they will then receive a single infusion of their current SoC product at their usual prophylactic dose 14 days [±2 days] later. See exceptions in Section 9.2.

Similarly, all subjects randomized into the BAX 930 ORT treatment arm for Period 1 will receive a single infusion of their current SoC product at their usual prophylactic dose, no less than 1 week after their previous prophylactic dose (washout period). For subjects receiving FVIII:VWF concentrates, the minimum required BAX 930 ORT PK dose washout period may be reduced to 5 days. Subjects will then receive a PK dose of 40 IU/kg BAX 930 ORT 14 days [±2 days] later. See exceptions in Section 9.2.

PK assessments will be conducted at the timepoints described in Table 11 (adult and adolescent subjects ≥12 years) and Table 12 (pediatric subjects <12 years). Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

9.2.1.1.2 PK-II

PK-II is applicable to all subjects who received BAX 930 ORT in PK-I, Period 1 or Period 2. It is not applicable to subjects who received BAX 930 SIN in PK-I, Period 1 or Period 2. After Period 2, before study subjects are switched from BAX 930 ORT to BAX 930 SIN, a 1:1 randomized, single-dose, crossover PK assessment of 40 IU/kg BAX 930 ORT and 40 IU/kg BAX 930 SIN will be conducted in subjects that received BAX 930 ORT during Period 1 or Period 2.

Subjects on weekly treatment at the end of period 2, pediatric subjects <12 years of age, subjects randomized to the study prior to the temporary study halt, and on-demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort are to be excluded from the PK-II assessments.

Once the PK sampling is completed, subjects randomized to the study after the temporary study halt will start treatment of BAX 930 SIN for 6 months in Period 3. The amount of time between the two PK infusions (washout) will be 14 days [±2 days]. For subjects receiving FVIII:VWF concentrates or undergoing weekly prophylactic treatment during Period 1 and Period 2, the minimum required BAX 930 PK dose washout period may be reduced to 5 days.

PK assessments will be conducted at the timepoints described in Table 11 (adult and adolescent subjects ≥12 years).

9.2.1.1.3 PK-III

An end-of-study PK-III assessment of ADAMTS13 activity will be conducted after the last BAX 930 SIN dose in Period 3. PK-III assessments will be conducted for any subject in the prophylactic cohort who initiates the study with BAX 930 SIN, including any subject who switches from on-demand treatment to prophylactic treatment.

All subjects who receive BAX 930 SIN in Period 3 may voluntarily receive an end-of-study PK-III assessment, with a total study minimum of 4 adult subjects (≥18 years old), and 2 pediatric or adolescent subjects (age 0-17 years).

Pediatric subjects (<12 years old), subjects who receive a weekly (Q1Week) dosing regimen, and on-demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort, will undergo a PK-III assessment. PK-III assessments will be conducted at the timepoints described in Table 13. Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

For subjects that consent to PK-III, the assessments will occur at the last IP Infusion of Period 3. Subjects will not need to come back for a separate infusion visit to participate in PK-III.

For subjects who decide to enroll in the TAK-755-3002 continuation study, they will complete the TAK-755-3002 Screening/Enrollment visit on the same day as the 281102 last IP infusion of Period 3.

Their 281102 Study Completion date will be documented as the last day of PK-III assessments (i.e. 72-hr PK sample for Q1W subjects >12 years old, 168-hr PK sample for Q1W subjects <12 years old, and 288-hr PK sample for all Q2W subjects). All adverse events that occur through the final PK-III assessment will be reported in the 281102 EDC.

If the last PK-III assessment occurs on the same day as the first dosing visit for TAK-755-3002:

- The 281102 PK-III assessments (blood-draw and vital signs) must occur pre-infusion.
- Adverse events that occur prior to IP infusion will be reported in 281102.
- Adverse events that occur at the time of IP infusion or after, will be reported in the TAK-755-3002.

As detailed in Section 13.1.2, any reported adverse events that are ongoing at the Study Completion date will remain ongoing in 281102 database and imported to the TAK-755-3002 continuation study and followed within the TAK-755-3002 eCRF.

9.2.1.2 Switching to BAX 930 SIN

Adult Subjects

Beginning after 30 September 2021, subjects entering the study will no longer receive BAX 930 ORT in Period 1, or any subsequent period thereafter. At this point, all subjects will receive BAX 930 SIN or SoC only, depending on randomization, beginning with PK-I, and continuing throughout the study. Prior to 01 October 2021, subjects who have entered Period 1 on BAX 930 ORT, will continue to receive BAX 930 ORT until the end of Period 2. Thereafter, subjects will switch to BAX 930 SIN in Period 3.

Pediatric Subjects

Pediatric subjects (<12 years old) will initiate the study with BAX 930 SIN after 30 September 2021. Prior to 01 October 2021, pediatric subjects who have entered Period 1 on BAX 930 ORT, will continue to receive BAX 930 ORT until the end of Period 2. Thereafter, subjects will switch to BAX 930 SIN in Period 3.

9.2.1.3 Standard of Care Treatment Arm (6 Months[xvii]) (Period 1 or 2, Depending on Randomization)

Subjects will receive the investigator-recommended standard treatment regimens for 6 months. We strongly suggest investigators follow SoC treatment at intervals of Q1W or Q2W. Q3W will be accepted but not encouraged. Subjects experiencing an acute TTP event during the prophylaxis period will receive the investigator-recommended standard treatment and dosing regimen during the acute TTP event. Subjects will resume the previous prophylactic regimen 1 week after their last acute treatment dose. Subjects requiring a vaccination during treatment should schedule the vaccination administration within 72 hours after a prophylactic treatment dose.

Subjects receiving a COVID-19 vaccination during the study period should be monitored frequently by telephonic health checks and for thrombocytopenia for 14 consecutive days following vaccination, as deemed appropriate by the investigator. Elective surgeries should be scheduled 24 hours after the last prophylactic dose and ADAMTS13 levels should be obtained daily for up to 7 days or until hospital discharge post-surgery after surgery.

Dose modifications to increase the dose or frequency of SoC therapy, to the extent possible, is recommended if any of the following conditions are met:

- One acute TTP event or,
- Two separate occurrences of any laboratory deviations:
  - Drop in platelet count ≥25% of baseline, or a platelet count <150,000/μL; OR
  - Elevation of LDH >1.5× of baseline or >1.5 x ULN
- Three separate occurrences of any organ-specific signs or symptoms, with or without changes in platelet count or LDH
  - Neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR
  - Abdominal pain; OR
  - Increase of serum creatinine >1.5×baseline

Subjects experiencing an acute TTP event during the SoC prophylaxis period will receive the investigator-recommended SoC treatment and dosing regimen during the acute TTP event.

[xvii] The length of Period 1 and Period 2 is 6 months each. If a subject cannot switch to the next period at the end of month 6, for either logistical or medical reasons, the length of Period 1 and Period 2 can be extended to up to 7 months. For subjects enrolled before November 2017, Period 1 can be extended until the global amendment to lift the temporary study halt is approved.

Although not required, investigators may also elect to treat subacute TTP events (refer to Table 2 for definitions) with 1 or 2 additional daily doses of SoC; these treatments will be tabulated separately in the statistical analysis.

9.2.1.4 BAX 930 Treatment Arm (6 Months[xviii]) (Period 1 or 2, Depending on Randomization and Period 3)

Most of the subjects will receive BAX 930 ORT prophylactically for 6 months for Period 1 or 2; BAX 930 SIN will replace BAX 930 ORT during Period 3. Subjects randomized after the temporary study halt will receive BAX 930 SIN prophylactically for 6 months for Period 3.

After the last IP infusion of Period 3, subjects will be enrolled and followed in the continuation study. Subjects will be allowed to remain in the 281102 study until the continuation study is open for enrollment. Dosing, visits and assessments will be continued according to the protocol / visits in period 3 until their transfer to the continuation study.

Subjects who enroll into the TAK-755-3002 continuation study will complete the TAK-755-3002 Screening/Enrollment visit on the same day as the 281102 last IP infusion of Period 3.

Subjects requiring a vaccination during treatment should schedule the vaccination administration within 72 hours after a prophylactic treatment dose. Subjects receiving a COVID-19 vaccination during the study period should be monitored frequently by telephonic health checks and for thrombocytopenia for 14 consecutive days following vaccination, as deemed appropriate by the investigator.

Elective surgeries should be scheduled 24 hours after the last prophylactic dose and ADAMTS13 levels should be obtained daily for up to 7 days or until hospital discharge post-surgery.

Although not required, investigators may also elect to treat subacute TTP events with 1 or 2 additional daily doses of BAX 930; these treatments will be tabulated separately in the statistical analysis.

[xviii] The length of Period 1 and Period 2 is 6 months each. If a subject cannot switch to the next period at the end of month 6, for either logistical or medical reasons, the length of Period 1 and Period 2 can be extended to up to 7 months. For subjects enrolled before November 2017, Period 1 can be extended until the global amendment to lift the temporary study halt is approved. The length of Period 3 is approximately 6 months or when the continuation study has opened at the subject's site.

9.2.1.4.1 Initial BAX 930 Prophylactic Dose and Dosing Regimen

Subjects currently treated Q1W with FFP or S/D treated plasma replacement product will start BAX 930 treatment with 40 IU/kg [±4 IU/kg] Q1W. All other subjects will receive a starting prophylaxis dose of 40 IU/kg [±4 IU/kg] every 2 weeks (Q2W).

9.2.1.4.2 Dose Modification Based on Clinical Response

Dose modifications to 40 IU/kg Q1W will be required if any of the following conditions -are met:

- One acute TTP event or,
  - Two separate occurrences of laboratory deviations: Drop in platelet count ≥25% of baseline, or a platelet count <150,000/μL; OR
  - Elevation of LDH >1.5× of baseline or >1.5 × ULN
- Three separate occurrences of organ-specific signs or symptoms, with or without changes in platelet count or LDH
  - Neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures) as per the opinion of the investigator; OR
  - Abdominal pain; OR
  - Increase of serum creatinine >1.5×baseline

9.2.1.4.3 Acute Management

Subjects experiencing an acute TTP event during the prophylaxis period will receive the following dose and dosing regimen:

- Subjects will receive an initial dose of 40 IU/kg [±4 IU/kg] BAX 930
- Subjects will receive a subsequent dose of 20 IU/kg [±2 IU/kg] BAX 930 on Day 2
- Subjects will receive an additional daily dose of 15 IU/kg [±1.5 IU/kg] BAX 930 until 2 days after the acute TTP event is resolved

Subjects in Q1W and Q2W will recommence their prophylaxis therapy 1 week after their last acute treatment dose and receive BAX 930 40 IU/kg Q1W.

Acute TTP events are considered resolved when:

- Platelet count is ≥150,000/ μL or platelet count is within 25% of baseline
- Elevation of LDH ≤1.5 x baseline or ≤1.5 x ULN

Investigators may elect to treat subacute TTP events (refer to Table 2 for definitions) with 1 or 2 additional daily doses of 40 IU/kg BAX 930.

9.2.2 On-Demand Treatment Cohort

Subjects experiencing an acute TTP event, meeting all other inclusion criteria, and entering and consenting to treatment in the study through the on-demand cohort will be randomized to receive urgent treatment with either the SoC or BAX 930. Upon resolution of the acute TTP event, subjects may choose to move to the prophylaxis cohort of the study or discontinue entirely. Re-enrollment of on-demand subject who has finished the study into the on-demand treatment cohort is allowed if he/she experiences a new acute TTP event. Subjects electing to move to the prophylaxis cohort will move directly to Period 1 and will not go through PK-I assessment but will be subject to PK-II evaluation later after completion of Period 2.A PK-II evaluation is not applicable to subjects who received BAX930 SIN in Period 1 or Period 2. Subjects randomized to receive SoC in the on-demand cohort will receive SoC in Period 1 of the prophylaxis cohort and BAX 930 in Period 2 and 3. Subjects randomized to receive BAX 930 in the on-demand arm will receive BAX 930 in Period 1, SoC in Period 2, and BAX 930 in Period 3. If a subject is randomized to BAX 930 and BAX 930 SIN is available at the time of enrollment, that subject will receive BAX 930 SIN during prophylactic treatment. Subjects who initiate on-demand treatment with BAX 930 SIN may voluntarily receive prophylactic treatment with BAX 930 SIN following resolution of an acute TTP event, and will undergo an end-of-study, PK-III evaluation.

Standard of Care On-demand Treatment

Subjects will receive the investigator-recommended standard treatment and dosing regimen during the acute TTP event. Standard of care treatment should contain ADAMTS13 in a quantifiable amount for each administered dose.

9.2.2.1 BAX 930

On-demand Treatment

During acute TTP events:

- Subjects will receive an initial dose of 40 IU/kg [±4 IU/kg] BAX 930
- Subjects will receive a subsequent dose of 20 IU/kg [±2 IU/kg] BAX 930 on Day 2
- Subjects will receive an additional daily dose of 15 IU/kg [±1.5 IU/kg] BAX 930 until 2 days after the acute TTP event is resolved

Acute TTP events are considered resolved when:

- Platelet count is ≥150,000/ μL or platelet count is within 25% of baseline

And

- Elevation of LDH ≤1.5× of baseline or ≤1.5× ULN

Switching to BAX 930 SIN

Adult subjects randomized to receive BAX 930 will receive on-demand treatment with BAX 930 ORT until BAX 930 SIN becomes available. Once BAX 930 SIN is available, subjects randomized to receive BAX 930 will start on-demand treatment with BAX 930 SIN and continue treatment with BAX 930 SIN during prophylactic treatment.

Pediatric subjects

Pediatric subjects (<12 years old) may initiate the study with BAX 930 SIN beginning on 01 October 2021. At sites where BAX 930 SIN becomes available prior to the cut-off date, pediatric subjects who initiate the study with BAX 930 ORT in the on-demand cohort, will not switch until completing Period 2.

Enrollment

Subjects with a confirmed diagnosis of cTTP may provisionally enroll in the on-demand treatment cohort if a clinician believes the subject is undergoing an acute TTP event, based on platelet count and LDH irrespective of clinical symptomatology.

Continuation in the study will be dependent on the confirmation of an acute TTP episode and compliance with all inclusion criteria and no exclusion criteria apply. Efficacy data will be excluded from the analysis if subsequent laboratory tests provide evidence that the subject did not experience an acute TTP event or was ineligible to participate in the study. All IP-related safety data will be included in the final study analysis.

9.2.3 Safety

Enrollment will be paused pending Data Monitoring Committee (DMC) evaluation (see Section 15.4) if there are ≥3 product-related SAEs, including the development of inhibitory antibodies to BAX 930.

The study will be stopped if 2 or more subjects develop confirmed ADAMTS13 inhibitory antibodies defined as ≥0.6 BU in the central laboratory on 2 separate assays within a 1-month period.

9.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 70 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The recruitment period is approximately 24 months.

Depending on date of subject enrollment and treatment regimen, the subject participation period is approximately 22 months (1 month=28 days) from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

9.4 Outcome Measures

9.4.1 Primary Outcome Measures

The primary outcome measure is:

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

9.4.2 Secondary Outcome Measures

9.4.2.1 Efficacy

1. Proportion of acute TTP events responding to BAX 930, defined as not requiring the use of another ADAMTS13-containing agent
2. Time to resolution of acute TTP events following initiation of treatment with BAX 930 or SoC agent
3. Incidence of thrombocytopenia defined as a drop in platelet count ≥25% of baseline or a platelet count <150,000/μL
4. Incidence of microangiopathic hemolytic anemia defined as an elevation of LDH >1.5× of baseline or >1.5 x ULN
5. Incidence of neurological symptoms (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures)
6. Incidence of renal dysfunction defined as an increase in serum creatinine >1.5×baseline
7. Incidence of abdominal pain
8. Incidence of supplemental doses prompted by subacute TTP events
9. Incidence of dose modification not prompted by an acute TTP event
10. Incidence of acute TTP events while subjects are on their final dose and dosing regimen in the study

9.4.2.2 Safety

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

9.4.2.3 Pharmacokinetics/Pharmacodynamics

1. Assessment of the PK parameters (incremental recovery [IR], area under the plasma curve [AUC], terminal half-life [$t_{1/2}$], mean residence time [MRT], systemic clearance [CL], steady state volume of distribution [V_{ss}], and maximum concentration following infusion [C_{max}]) for ADMATS13 activity and ADMATS13 antigen for both the SoC agent and BAX 930
2. Assessment of PD markers, such as VWF:Ag and VWF:RCo, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment
3. Assessment of ADAMTS13 activity (pre-infusion ADAMTS13 levels) and select VWF parameters prior to each PK infusion of SoC or BAX 930
4. Assessment of the impact of immunogenicity (immunogenicity status, time of onset) on ADAMTS13 antigen and activity PK parameters

9.4.2.4 Health Related Quality of Life and Resource Utilization

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

9.4.3 Exploratory Outcome Measures

1. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), while receiving prophylactic treatment with BAX 930 or SoC during the 6 months of the corresponding treatment
2. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), while receiving the final prophylactic treatment regimen with BAX 930 or SoC
3. Incidence of TTP manifestations, defined as a composite[a] of secondary outcome measures (secondary efficacy outcome measures 3 to 7), requiring supplemental dose treatment
4. Incidence of the subacute TTP events in subjects receiving prophylactic treatment.
5. Assessment of additional exploratory PD biomarkers including but not limited to VWF multimer patterns, ADAMTS13-mediated VWF cleavage products, and coagulation biomarkers, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment.

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

9.5 Randomization and Blinding

This is a randomized, open-label, active-controlled clinical study. Subjects in the prophylaxis cohort will be randomized equally using a permuted block algorithm to randomly assign treatment order (BAX 930 – SoC or SoC – BAX 930). Subjects in the on-demand cohort will be randomized equally using a permuted block algorithm to either BAX 930 or SoC.

After the Period 2, subjects in the prophylaxis cohort will be randomized to the infusion sequence for PK-II (BAX 930 ORT followed by BAX 930 SIN, or BAX 930 SIN followed by BAX 930 ORT) in a 1:1 ratio stratifying for the sequence for PK-I.

9.6 Study Stopping Rules

Enrollment will be paused pending DMC evaluation (see Section 15.4) if there are ≥3 product-related SAEs, including the development of inhibitory antibodies to BAX 930.

This study will be stopped if 2 or more subjects develop confirmed ADAMTS13 inhibitory antibodies defined as ≥0.6 BU in the central laboratory on 2 separate assays within a 1-month period.

If this study is halted for reasons listed in this section, restarting the trial will require a substantial amendment.

9.7 Investigational Product(s)

9.7.1 Packaging, Labeling, and Storage

BAX 930 will be packaged in single boxes with 2 glass vials, 1 vial containing the lyophilized BAX 930, the other containing the diluent. Further details are provided in the Pharmacy Manual. BAX 930 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 BAX 930 is 2 to 8°C. The expiration date for BAX 930 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 BAX 930 IB and/or other specific instructions provided by the sponsor.

9.7.2 Administration

BAX 930 is administered by i.v. injection.

The reconstituted solution of BAX 930 should be clear and colorless in appearance. BAX 930 should be administered at room temperature and within 3 hr 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; however, for the IP infusion, the butterfly needle may be inserted immediately prior to the infusion.

A tourniquet should be applied, and the injection site prepared by wiping the skin well with an alcohol swab.

The supplied butterfly infusion set should be used if possible, or an i.v. catheter, if available. The butterfly needle should be placed into a vein of the opposite forearm to that used for blood draws. Samples for PK analysis should be drawn from the opposite arm to that used for BAX 930 or SoC infusion during the first 24 hours post-infusion of BAX 930 or SoC. Either arm can be used for blood draw of samples upon completing 24 hours post-infusion. The butterfly needle or i.v. catheter should be secured as suggested by standard medical care.

Following removal of the tourniquet, placement of the needle/i.v. catheter should be ensured and BAX 930 slowly infused (between 2 to 4 mL per minute [min]). Syringes should be changed according to medical practice.

For adult and adolescent subjects (≥12 years of age), vital signs should be recorded within 1 hr before PK infusion and at the following timepoints post-infusion: 15±5 min, 60±5 min, 3±0.5 hr, 9±2 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 hr, 216±24 hr, and 288±24 hr. For pediatric subjects (<12 years of age), vital signs should be recorded within 1 hr before PK infusion and at the following timepoints post infusion: 30±5 min, 12±2 hr, 24±2 hr, 48±2 hr, 96±2 hr and 168±4 hr. Refer to the Schedule of Study Procedures and Assessments in Section 20.3 for the overall timing of vital signs collection.

Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

Should a significant increase in pulse rate occur or a significant drop in blood pressure, as determined by the investigator, the rate of administration should be reduced or the injection temporarily halted, which usually allows the symptoms to disappear promptly. If symptoms are progressive for 15 min, despite discontinuation of the infusion, emergency measures should be considered.

Upon completion of the infusion, the butterfly catheter should be flushed with at least 1 mL saline solution prior to removal of the needle. In case of a (central) venous access device, the flush should be with at least 10 mL of saline solution.

Finally, the butterfly should be removed but the i.v. catheter left, if placed on the same site (optional).

9.7.3 Description of Treatment

BAX 930 is formulated as a sterile, highly purified protein preparation appearing as a compact white lyophilized cake. The active drug substance is a fully glycosylated BAX 930 protein produced in a CHO cell line. For reconstitution and administration of the product as i.v. solution, a vial of diluent (5 mL sterilized Water for Injections), a butterfly infusion set with Luer Lock syringes (B.Braun Omnifix, 3, 5, 10, and 20 mL) and a needleless transfer device (BAXJECT II Hi-Flow) are provided. BAXJECT II Hi-Flow system is a needleless transfer device with the primary function of transferring diluent from its vial into an evacuated vial containing lyophilized product requiring reconstitution prior to infusion.

Upon reconstitution with sterile water for injection, the final drug product (FDP) contains purified BAX 930 together with excipients (mannitol, L-histidine, Tween 80 [polysorbate80], sodium chloride, calcium chloride, and sucrose). The reconstituted solution has a nominal strength of 300 U/mL.

Dose for administration should be calculated based on the subject's BW as measured at each dosing visit. Note that the weight from the subject's previous visit can be used to calculate the dose as long as the weight was collected less than 6 weeks prior for adult subjects (≥12 years of age) and less than 4 weeks prior for pediatric subjects (<12 years of age). For most subjects, the final volume of infusion after reconstitution of FDP will be between 5 and 14 mL, to be calculated by subject weight and the required number of units.

A list of all the components of BAX 930 FDP is shown in Table 3.

Table 3. Composition of BAX 930 FDP

Name of Constituent	Unit (and/or Percentage Formula)	Function	Reference to Standards
rADAMTS13	300 IU/mL reconstituted	Active ingredient	Takeda specification
Sodium chloride	30 mM	Tonicity modifier	USP, EP, JP
Calcium chloride	2 mM	Stabilizing Agent	USP, EP, JP
L-Histidine	20 mM	Buffer	USP, EP, JP
Mannitol	3% (w/w)	Bulking agent	USP, EP, JP
Sucrose	1% (w/w)	Bulking Agent	USP, EP
Polysorbate 80 (Tween 80)	0.05% (w/w)	Surfactant	USP, EP, JP

EP=European Pharmacopeia; JP=Japanese Pharmacopeia; USP=United States Pharmacopeia; w/w=weight-to-weight ratio

For those subjects who are randomized to receive SoC in the prophylactic cohort (see Section 9.2.1.3 and Figure 1), SoC will be provided with their routine prophylactic dose of either FFP, pooled S/D treated plasma, or FVIII: VWF concentrates. Subjects switching from the on-demand treatment cohort to the prophylaxis cohort will receive the same treatment in Period 1 as the randomized on-demand treatment, and alternative in Period 2. In the on-demand treatment cohort, subjects will receive investigator-recommended standard treatment and dosing regimen during the acute TTP event. Investigator-recommended standard treatment should contain ADAMTS13 as a measurable and quantifiable administered dose. SoC treatment type and dose will be recorded in subject CRFs. The SoC treatments will be in liquid form and administered intravenously.

For those subjects randomized to receive BAX 930 in the prophylactic cohort, subjects will receive BAX 930 40 IU/kg prophylactically (see Section 9.2.1.4 and Figure 1). For the on-demand treatment cohort, subjects will receive an initial dose of 40 IU/kg BAX 930 followed by treatment with 20 IU/kg on Day 2, then 15 IU/kg BAX 930 until 2 days after the acute TTP event is resolved (see Section 9.2.2.1).

Most subjects in the prophylactic cohort will receive BAX 930 SIN treatment during Period 3.

9.7.4 Dosing Justification

As cTTP may be considered a classical deficiency disease and BAX 930 represents a substitution therapy with a well characterized mechanism of action. There was no safety concern with infusions between 5 to 40 U/kg BAX 930 observed during the Phase 1 clinical study 281101. The pharmacokinetic parameters for BAX 930 were like FFP, specifically, a mean incremental recover of approximately 2.4 U/dL per U/kg infused and a mean plasma half-life of approximately 2.5 days (60 hours).

Recognizing that the ADAMTS13 content of FFP is approximately 1U/ mL, the dose exceeds current replacement strategies and would provide both a higher C_{max} and AUC level than is currently employed with SoC agents.

Based on data from Study 281101, the proposed dosing regimen of BAX 930 for acute TTP events should result in complete normalization of ADAMTS13 levels with mean ADAMTS13 levels between approximately 90 and 125 IU/dL (90% and 125% of normal). In a low case assumption of both an IR and $t_{1/2}$ of 50% of the means, the range of ADAMTS13 levels expected is predicted to be between approximately 50% of normal throughout the treatment period.

9.7.5 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received, and disposition. IP(s) must be dispensed only at the study site or other suitable location (eg, infusion center). Direct-to-Patient shipments of Investigational Product will be permitted for subjects having infusions at home, additional information will be provided in the Pharmacy Manual and Home Nursing documentation. Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

9.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and CRFs, see Section 17.2. The use of subject diaries is described in Section 11.5.

10. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

10.1 Inclusion Criteria

Subjects who meet **ALL** the following criteria are eligible for this study:

1. Subject or legally authorized representative has provided signed informed consent (≥18 years of age) and/or assent form (signed by legal representative if subject is <18 years of age)
2. Subject is 0 to 70 years of age, inclusive, at the time of screening. (Subjects <18 years of age will be enrolled only after at least 5 adults (≥18 years of age) each have at least 10 exposures with BAX 930 and reviewed by the DMC. In France, no subjects younger than 18 years of age will be enrolled into the study before the first adult subject has been treated with BAX 930 for a minimum of 6 months.
3. Subject has a documented diagnosis of severe hereditary ADAMTS13 deficiency, defined as:
   - Confirmed by molecular genetic testing, documented in subject history or at screening, and
   - ADAMTS13 activity <10% as measured by the FRETS-VWF73 assay, documented in subject history or at screening (subjects currently receiving SoC prophylactic therapy may exceed 10% ADAMTS13 activity at screening)

   Note: Subjects currently receiving prophylactic therapy will be screened immediately prior to their usual prophylactic infusion
4. Subject does not display any severe TTP signs (platelet count <100,000/μL and elevation of LDH >2 x ULN) at screening. (prophylactic cohort only).
5. Subject is currently on a prophylactic dosing regimen or has a documented history of at least 1 TTP event and an ability to tolerate SoC prophylactic dosing (prophylactic cohort only).
6. Subjects ≥16 years of age must have a Karnofsky score ≥70% and subjects <16 years of age must have a Lansky score ≥80%
7. Subject is HCV-negative as confirmed by antibody or polymerase chain reaction testing OR HCV-positive if their disease is chronic but stable

8. If female of childbearing potential, subject presents with a negative blood or urine pregnancy test, confirmed no more than 7 days before the first administration, and agrees to employ adequate birth control measures for the duration of the study and to undergo quarterly pregnancy testing[xix]
9. 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.
10. Subject is willing and able to comply with the requirements of the protocol

10.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject has been diagnosed with any other TTP-like disorder (microangiopathic hemolytic anemia), including acquired TTP
2. Subject has known hypersensitivity to hamster proteins
3. Subject has experienced an acute TTP episode less than 30 days prior to screening (prophylactic cohort only)
4. Subject has a medical history or presence of a functional ADAMTS13 inhibitor at screening
5. Subject has a medical history of genetic or acquired immune deficiency that would interfere with the assessment of product immunogenicity, including subjects who are HIV-positive with an absolute cluster of differentiation 4 (CD4) count <200/mm^3 or who are receiving chronic immunosuppressive drugs.
6. Subject has been diagnosed with severe cardiovascular disease (New York Heart Association classes 3 to 4)
7. Subject with end stage renal disease requiring chronic dialysis
8. Subject has been diagnosed with hepatic dysfunction, as evidenced by, but not limited to, any of the following:
   a. Serum alanine aminotransferase (ALT) ≥2×ULN
   b. Severe hypoalbuminemia <24 g/L
   c. Portal vein hypertension (eg, presence of otherwise unexplained splenomegaly, history of esophageal varices)
9. In the opinion of the investigator, the subject has another clinically significant concomitant disease that may pose additional risks for the subject

[xix] See Section 20.5 for a list of adequate contraceptive methods for females of childbearing potential

10. Subject has been treated with an immunomodulatory drug, excluding topical treatment (eg, ointments, nasal sprays), within 30 days prior to enrollment. Use of corticosteroids in conjunction with administration of FFP to prevent allergic reactions is permitted.
11. Subject has an acute illness (eg, influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, bronchial asthma) at the time of screening (prophylaxis cohort only)
12. Subject is receiving or anticipates receiving another investigational drug and/or interventional drug within 30 days before enrollment
13. Subject has a history of drug and/or alcohol abuse within the last 2 years
14. Subject has a progressive fatal disease and/or life expectancy of less than 3 months
15. Subject is identified by the investigator as being unable or unwilling to cooperate with study procedures
16. 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
17. Subject is a family member or employee of the sponsor or investigator
18. If female, subject is pregnant or lactating at the time of enrollment
19. Any contraindication to standard of care medicinal product(s) as per local prescribing information.

10.3 Withdrawal and Discontinuation

Enrollment will be paused pending DMC evaluation (see Section 15.4) if there are ≥3 product-related SAEs, including the development of inhibitory antibodies to BAX 930.

The study will be stopped if 2 or more subjects develop confirmed ADAMTS13 inhibitory antibodies defined as ≥0.6 BU in the central laboratory on 2 separate assays within a 1-month period.

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study CRF. Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) are described in Section 11.5 and Section 20.3.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action).

Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

1. The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow the subject through completion of the pregnancy and up to 1 year post-delivery, if feasible. The investigator will record a narrative description of the course of the pregnancy and its outcome.
2. The subject frequently misses administration of IP. The subject will be discontinued from further participation in the study.
3. Subjects who experience allergic reactions (eg, for anaphylaxis) upon exposure to BAX 930 and subjects who develop an inhibitory antibody to ADAMTS13 or any other safety issue will be discontinued from study treatment. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first; follow-up information is to be documented in the CRF.

   Subjects who develop allergic reactions to their standard of care treatment will be discontinued from the study. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first; follow-up information is to be documented in the CRF.

11. STUDY PROCEDURES

11.1 Informed Consent

Any subject who provides informed consent (i.e., signs and dates the ICF and assent form, if applicable) is considered as a subject in the study.

11.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (eg, 281102) to be provided by the sponsor, 3-digit study site number (eg, 002) to be provided by the sponsor, and 3-digit subject number (eg, 003) reflecting the order of providing informed consent. For example, the third subject who signed an ICF at study site 002 will be identified as Subject 281102-002003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC.

11.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF (or assent, if applicable), new SIC, and new CRF are required for that subject.

The overall study design is illustrated in the Figure 1 and Figure 2. Details on the procedures to be performed at each study visit, including screening, can be found in Section 20.3 Schedule of Study Procedures and Assessments and Section 20.4 Clinical Laboratory Assessments. For study sites in Germany only, please refer to the complete Schedule of Assessments in Table A1.

11.3.1 Screening and Study Visits for Pediatric Subjects

For pediatric subjects up to 12 years of age, the screening visits may be spread to several days to limit the amount of the blood drawn in one day. Since PK tests, immunogenicity (tiered approach for antibody testing), and genetic testing have the longest turnaround time, these tests should be performed first. Other tests can be done afterwards. Below is a suggested lab assessments order:

Day 1: Blood sampling for PK tests (without back-up samples), immunogenicity (total binding ABs only), genetic testing (if applicable)

Day 2: Immunogenicity (neutralizing Abs only); blood sampling for PK tests (back-up samples only),

Day 3: Blood sampling for Clinical Chemistry and CBC

Day 4: Blood sampling for Viral Serology

For pediatric subjects 0 to <6, if additional considerations are needed to not exceed the country-specific EC and applicable regulatory guidelines for daily and monthly limits, the following options (based on the subject weight at screening) to be discussed and, if agreed upon with the Sponsor, may be applied:

- Allowing pre-infusion samples to be collected up to 72 hours prior to infusion
- Omitting some PK/PD time points
- Not collecting samples that would be used for exploratory analysis
- Only collecting certain back-up samples

Refer to the Laboratory Manual for further information.

11.3.2 Pediatric Development Assessments

For subjects 0 to <6 years old (prophylactic subjects only), if available and at the discretion of the Investigator, growth, development and cognitive performance metrics may be collected from a subject's medical record and reviewed at the Screening/Enrollment Visit, the start of every Treatment Period or annually, and at the Final Visit.

11.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the study:

1. Medications:
    - Immunomodulatory drugs
    - Corticosteroids with an equivalent to hydrocortisone greater than 10 mg/day, excluding topical treatment (eg, ointments, nasal spray) are not permitted except as part of an established pre-medication regimen during the Standard of Care period of the study
    - Another IP or interventional drug A subject who has taken any of these medications or received any of these non-drug therapies will be considered a protocol deviation.

The following medications and non-drug therapies are permitted within 30 days before study entry and during the study:

1. Medications:
    - FFP or any other ADAMTS13-containing products interfering with ADAMTS13 PK will have to be paused at least 14 days [±2 days] prior to the IP infusion for PK assessment. However, for PK-I, if subjects are receiving weekly treatment as part of their SoC prophylaxis regimen, washout periods can be reduced to 1 week at the discretion of the investigator. For subjects receiving factor VIII (FVIII):VWF concentrates, the minimum required SoC PK dose washout period may be reduced to 5 days.
    - Use of corticosteroids in conjunction with administration of FFP to prevent allergic reactions is permitted

11.5 Subject Reported Outcomes

Subject (patient) reported outcomes, based on relevant questionnaires, will be captured at screening and at the end of each period visit (i.e., end of Period 1 visit, end of Period 2 visit, and end of Period 3 visit), and if subjects have an early termination, during the termination visit, in an electronic subject diary to assess chronic TTP-related symptoms and disabilities, including cognitive function. In the eventuality of nonfunctional electronic diaries, a web back-up option will be available for temporary use. Lower scores indicate worse HRQoL. The PRO instruments to be measured in this study are described in Table 4.

Subjects and/or their legally authorized representatives will be trained on use of the diary. The diary will be provided in electronic format and will remain at the site for the duration of the study. In the eventuality of non-functional electronic diaries, a web back-up option will be available for temporary use. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Subject entries in the diary will serve as source records. During study participation the investigator has access to the database holding the subject diary data. After study closure, the investigator will receive the diary records for their subjects, including audit trail records, in an archive disk. The data will be transmitted to the CRF by a validated transfer.

11.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, completed all study procedures according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Termination CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive disease, non-compliance with IP/protocol violation[s], recovery), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a subject terminates participation in the study and does not return for the completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) can be found in Section 20.3 Schedule of Study Procedures and Assessments and Section 20.4 Clinical Laboratory Assessments.

In the event of subject discontinuation due to an AE, clinical, and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

11.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at home or at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11.8 Acute TTP events During PK Assessment

Acute TTP events occurring during PK-I should be treated with the agent the subject is receiving. If less than 7 PK timepoint assessments have been collected at the time of the acute TTP event, PK assessments should be repeated. Acute TTP events occurring during PK-II should be treated with BAX 930 ORT.

12. ASSESSMENT OF EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS

12.1 Assessment of Efficacy: Acute TTP Events

The efficacy of BAX 930 will be assessed by the number and incidence of acute TTP events, where an acute TTP event is defined as having both:

1. Reduction in platelet count ≥50% of baseline, or a platelet count <100,000/µL;

and

2. Elevation of LDH by >2× of baseline or >2 x ULN

Laboratory (see Section 13.7) and vital sign measurements (see Section 13.8) will be used to identify acute TTP events.

12.2 Assessment of Pharmacokinetics and Pharmacodynamics

The date and time of the infusion start and stop, as well as start/stop of any infusion interruptions and restart of the infusion, and the actual volume infused (and lot number as applicable) will be recorded for all infusions.

The time and date of collection for each sample and any missing blood draws will be recorded. The details regarding sample processing are described in the Laboratory Manual.

The PK and PD assessments will be performed in adult and pediatric subjects for the prophylaxis cohort at screening during the initial SoC or BAX 930 infusions of Period 1 and after Period 3, and at each dosing visit as shown in Section 20.4. Additional details regarding PK sampling can be found in Section 9.2.1.

The PK, PD assay panel (PK: ADAMTS13 activity [see Section 13.7.5], ADAMTS13:Ag [see Section 13.7.5.2]; PD: VWF:RCo [see Section 13.7.5.3], VWF:Ag [see Section 13.7.5.4], and VWF multimer analysis and ADAMTS13 mediated VWF cleavage products [see Section 13.7.5.5]) will be assessed in a central laboratory.

Blood samples will be drawn at the following standardized timepoints for adult and adolescent subjects (≥12 years of age): pre-infusion (within 60 min prior to the start of the infusion), and relative to the end of the infusion for all following timepoints, at 15±5 min, 60±5 min, 3 hr±0.5 hr, 9 hr±2 hr, 24 hr±2 hr, 72 hr±4 hr, 120 hr±12 hr, 168 hr±12hr, 216 hr±24 and 288 hr±24 hr.

PK Post-Infusion Laboratory Assessments for subjects undergoing Q1W dosing should not be performed at 168±12 hrs, 216±12 hrs and 288±12 hrs timepoints, after PK Infusion #1. However, PK assessments up to 168±12 hrs timepoint should be performed after PK Infusion #2. Please refer to Table 11 to see the assessment schedule for subjects undergoing Q1W dosing. PK assessments for subjects on Q3W SoC treatment, are to be performed at the same timepoints as the subjects undergoing Q2W SoC treatment.

Timepoints for pediatric subjects (<12 years of age) include: pre-infusion (within 60 min prior to the start of the infusion) and, relative to the end of the infusion for all following timepoints, at 30 min±5 min, 12 hr±2 hr, 24 hr±2 hr, 48 hr±2 hr, 96 hr±2 hr, and 168 hr±4 hr.

Timepoints for subjects who undergo PK-III include: pre-infusion (within 60 min prior to the start of the infusion) and, relative to the end of infusion for all following timepoints, at 15±5 min, 30±5 min, 60 min±5 min, 9 hr±2 hr, 72 hr±8 hr, 168 hr±12 hr, and 288 hr±24 hr.

Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

See Section 14.4.2.3.1 for PK parameters to be calculated.

12.2.1 Pediatric Subjects (<6 Years Old)

If additional considerations are needed to not exceed the country-specific EC and applicable regulatory guidelines for daily and monthly limits that are based on the subject weight at screening, the following options to be discussed and, if agreed upon with the Sponsor, may be applied:

- Allowing pre-infusion samples to be collected up to 72 hours prior to infusion
- Omitting some PK/PD time points as agreed upon with the Sponsor
- Not collecting samples that would be used for exploratory analysis
- Only collecting certain back-up samples.

This list is not all inclusive; further information will be provided in the Laboratory Manual and recommendations tailored to the subject's weight will be provided prior to Screening.

Note that the timing of the collection of vital signs or other assessments associated with sample collections mentioned throughout this protocol will be adjusted accordingly.

13. ASSESSMENT OF SAFETY

13.1 Adverse Events

13.1.1 Definitions

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

13.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

1. Outcome is fatal/results in death (including fetal death)
2. Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay
4. Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
5. Is a congenital anomaly/birth defect
6. Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definitions above. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
    - Reviewed and confirmed seroconversion for HIV, hepatitis A virus (HAV), HBV, HCV,[xx] hepatitis E virus (HEV), or parvovirus B19 (B19V)
    - Severe hypersensitivity/allergic reactions to BAX 930

[xx] Patients with HCV can be included if the disease is chronic and stable. These subjects will have already seroconverted so will have anti-HCV antibodies detectable in the blood.

Uncomplicated pregnancies, following maternal or paternal exposure to IP are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective, or spontaneous abortion shall be considered an SAE.

13.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

- The sponsor will notify country's regulatory authorities (wherever the trial has been initiated) and all participating investigators regarding all serious and unexpected suspected adverse reactions within 15 days.
- All unexpected fatal or life threatening suspected adverse reactions must be reported in under 7 days.

13.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

13.1.1.4 Unexpected Adverse Events

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 and/or prescribing information 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 and/or prescribing information 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.

13.1.1.5 Preexisting Diseases

Preexisting diseases that are present before entry to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease after IP exposure, the event must be described on the AE CRF.

13.1.2 Assessment of Adverse Events

For the purpose of this study the TTP manifestations listed below, with an onset date after the first IP exposure, should be reported on the Adverse Event eCRF regardless of severity. Relationship to cTTP or to BAX 930 must be indicated. The TTP manifestations should be captured even if they were experienced as part of an acute or subacute event.

TTP manifestations, including but not limited to:

- Renal signs, as defined by increase of serum creatinine >1.5 × baseline
- Neurological symptoms, such as:
    - headache
    - confusion
    - memory issues
    - irritability
    - paresthesia
    - dysarthria
    - dysphonia
    - visual disturbances
    - focal or general motor symptoms including seizures
- Fever (≥100.4°F/38°C)
- Fatigue/lethargy
- Abdominal pain

All other AEs from the first IP exposure until study completion/discontinuation will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 13.1). Each AE will be evaluated by the investigator for:

1. Seriousness as defined in Section 13.1.1.1
2. Severity as defined in Section 13.1.2.1

3. Causal relationship to IP exposure or study procedure as defined in Section 13.1.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and 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. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first); follow-up information is to be documented in the CRF.

Subjects with reported ongoing AEs at the study completion date (date of last IP infusion or last date of PK-III assessments) who move on to the continuation study prior to the end of the 30-day AE follow up period will have all AE-related information captured and locked in the eCRF of Study 281102. At the time of enrollment into the continuation study, details surrounding an ongoing AE will be imported from Study 281102 into the subject's eCRF for Study TAK-755-3002. Resolution of an AE that occurs in 281102, but is resolved in TAK-755-3002, will be captured in the subject's eCRF for TAK-755-3002 only. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing, underdosing, abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form to the Takeda Global Drug Safety Department and followed-up at estimated date of delivery and 1 year post-delivery, if feasible.

If an investigator becomes aware of an SAE occurring in a subject within 2 weeks after study completion, the SAE must be reported on the provided SAE Report Form within 24 hr after awareness; no additional reporting on CRFs is necessary.

13.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

1. Mild
    - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level
    - The AE resolves spontaneously or may require minimal therapeutic intervention
2. Moderate
    - The AE produces limited impairment of function and may require therapeutic intervention
    - The AE produces no sequela/sequelae
3. Severe
    - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern
    - The AE produces sequela/sequelae, which require (prolonged) therapeutic intervention

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

13.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

1. Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
    - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
2. Unlikely related (either 1 or both circumstances are met)
    - Has little or no temporal relationship to the IP
    - A more likely alternative etiology exists

3. Possibly related (both circumstances must be met)
    - Follows a reasonable temporal relationship to the administration of IP
    - An alternative etiology is equally or less likely compared to the potential relationship to the IP
4. Probably related (both circumstances must be met)
    - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
        - Reappearance of a similar reaction upon re-administration (positive rechallenge)
        - Positive results in a drug sensitivity test (skin test, etc.)
        - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
    - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

13.2 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. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

1. Immediate change in study design or study procedures
2. Temporary or permanent halt of a given clinical trial or trials
3. Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate 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, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committees (ECs) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

13.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 13.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (i.e., from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF and on the SAE Report Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

13.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE.** Non-medical complaints include but are not limited to the following:

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
2. Missing components
3. Damage to the product or unit carton
4. A mislabeled product (eg, potential counterfeiting/tampering)
5. 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

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

13.5 Medical, Medication, and Non-Drug Therapy History

At screening (and during Period 1 of the on-demand cohort only), the subject's medical history will be described for the following body systems including severity (defined in Section 13.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

13.6 Physical Examinations

At screening and study completion/termination (see Section 20.3), a physical examination will be performed on the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF.

If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 13.1.1.5), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

For study sites in Germany only, refer to Appendix 1.1: Country-Specific Information for physical examination frequency and Table A1 Germany-specific Schedule of Assessments.

13.7 Clinical Laboratory Parameters

Clinical laboratory assessments are presented in Section 20.4, Table 9, and Table 10.

13.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of a complete blood count (CBC): red blood cell (RBC) count, hemoglobin, hematocrit, haptoglobin, reticulocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocytes (i.e., white blood cell count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts:

- In adult and adolescent subjects (≥12 years of age), samples for CBC analysis will be taken within 1 hr prior to infusion and, relative to the end of the infusion for all following timepoints, at 15±5 min, 9±1 hr, 24±2 hr, 72±4 hr, 216±24 hr, and 288±24 hr post-infusion (see Section 20.4).
- In pediatric subjects (<12 years of age), samples for CBC analysis will be taken within 1 hr prior to infusion and at 48±2 hr post-infusion (see Section 20.4, Table 12).

The clinical chemistry panel will consist of sodium, potassium, chloride, ALT, aspartate aminotransferase (AST), LDH, bilirubin, albumin (only at screening), alkaline phosphatase, blood urea nitrogen, creatinine, and glucose:

- In adult and adolescent subjects (≥12 years of age), samples for clinical chemistry analysis will be taken within 1 hr prior to infusion and, relative to the end of the infusion for all following timepoints, at 9±1 hr, 24±2 hr, 72±4 hr, 216±24 hr, and 288±24 hr post-infusion (see Section 20.4).
- In pediatric subjects (<12 years of age), samples for clinical chemistry analysis will be taken within 1 hr prior to infusion and at 48 ±2 hr post-infusion (see Section 20.4, Table 12).

Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted; refer also to Section 11.3.1 and Section 12.2.1.

Blood will be obtained for assessment of hematology and clinical chemistry parameters at screening, within 60 min of the start of the initial infusions of Period 1 and Period 2, interval study visits (i.e., every 3 months during SoC and BAX 930 treatment phases of Period 1 and Period 2), and at study completion/termination (see Section 20.4, Table 9 and Table 10). Hematology and clinical chemistry assessments will be performed on ethylenediaminetetraacetic acid-anticoagulated whole blood and serum, respectively, at the central laboratory (all assessments) and the local laboratory.

Blood group will be determined at screening only if not available in subject's medical history.

13.7.2 Biomarkers of Organ Damage

The biomarkers panel will consist of cTnT and cTnI, CK-MB, NSE, S100B:

- In adult and adolescent subjects (≥12 years of age), samples for biomarker analysis will be taken within 1 hr prior to infusion and, relative to the end of the infusion for all following timepoints, at 9±1 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 and 288±24 hr post-infusion (see Section 20.4, Table 10, and Table 13).
- In pediatric subjects (<12 years of age), samples for biomarker analysis will be taken within 1 hr prior to infusion and at 48±2 hr, and 168±4 hr post-infusion (see Section 20.4, Table 12 and Table 13).

Blood samples collected from subjects <18 years of age, for exploratory outcome measures, can be collected at the discretion of the investigator and are not to exceed the local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits.

Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted; refer also to Section 11.3.1 and Section 12.2.1.

13.7.2.1 Cardiac Troponin

Cardiac troponin T and I are sensitive biochemical markers of myocardial cell necrosis; these markers are superior to classical enzyme markers of necrosis due to their cardio-specificity.

13.7.3 Creatine Kinase Myocardial Band Fraction

Creatine kinase is a biochemical marker used as an indicator of organ damage. This parameter will also be measured at the local laboratory at specified timepoints further described in Section 20.4 (see Table 9 and Table 10) to look for signs of an acute TTP relapse.

13.7.3.1 Neuron-specific Enolase

Neuron-specific enolase is a glycolytic enzyme and a brain-specific biochemical seromarker for neuronal integrity, thus indicative for brain impairment.

13.7.3.2 S100 Calcium-binding Protein B

S100B is a calcium-binding protein, localized in astroglial and Schwann cells. Detectable serum levels of S100B are indicative for the acute phase of brain damage.

13.7.4 Urinalysis

Urinalysis dipstick assessments will be performed at screening and will consist of erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH.

13.7.5 Pharmacokinetics and Pharmacodynamic Tests

ADAMTS13 activity, ADAMTS13 antigen, VWF:RCo, VWF:Ag, VWF multimer analysis, and ADAMTS13 mediated VWF cleavage products will be measured at specified timepoints. For the adult sampling scheme, see Section 12.2, Section 20.4, and Table 11; for the pediatric sampling scheme see Section 12.2, Section 20.4, and Table 12.

Blood samples collected from subjects <18 years of age, for exploratory outcome measures, can be collected at the discretion of the investigator and are not to exceed the local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits.

Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted; refer also to Section 11.3.1 and Section 12.2.1.

13.7.5.1 ADAMTS13 Activity

ADAMTS13 activity will be measured by the FRETS-VWF73 assay. Results for samples with hemoglobin and bilirubin levels above the acceptable limit will be invalidated and excluded from reporting (not reportable).

13.7.5.2 ADAMTS13 Antigen (ADAMTS13:Ag)

ADAMTS13 antigen detects the status of total ADAMTS13 protein that may include free protein, protein in complex with antibody inhibitor, and ADAMTS13 bound to other carrier proteins, and will be measured using a commercial ADAMTS13 ELISA.

13.7.5.3 VWF Ristocetin Cofactor Activity (VWF:RCo)

The VWF:RCo provides a measure of the ability of VWF to bind platelet glycoprotein Ib, a key step in primary hemostasis. Stabilized platelets are agglutinated in the presence of VWF and the antibiotic Ristocetin.

13.7.5.4 VWF Antigen (VWF:Ag)

The VWF:Ag, a measure of total VWF protein, will be assessed using a sandwich ELISA employing anti-human-VWF antibodies.

13.7.5.5 VWF Multimer Analysis and ADAMTS13 mediated VWF cleavage products

The relative distribution of VWF multimers pattern (small, intermediate, large, and ultra large) over time will be assessed using low-resolution sodium dodecyl sulfate (SDS)-agarose gel electrophoresis. These analyses will employ Western blot with luminescence video imaging. In addition, the same high resolution SDS-agarose gel electrophoresis will be used to qualitatively determine the satellite band structure of VWF. ADAMTS13-mediated VWF cleavage products will be analyzed using mass spectrometry or visualized by SDS-poly-acrylamide gel electrophoresis followed by Western blot staining and quantitative densitometry.

13.7.6 Immunogenicity

Plasma will be assayed for the presence of antibodies against ADAMTS13 and CHO protein using validated immunoassays at the timepoints presented in Section 20.4, Table 9, and Table 10. The date/time of sample collection will be recorded in the eCRF.

Antibody-containing samples will be identified in a screening assay followed by a confirmatory assay to exclude false positive results.

A tiered approach for antibody testing will be followed:

- Total binding (total Ig) antibodies to ADAMTS13 (BAX 930) (screening and confirmation) will be tested initially. Absence of total binding antibodies to ADAMTS13 is an indication of the absence of neutralizing (activity inhibition) antibodies to ADAMTS13 and no further antibody assessments will be conducted on the sample.
- If total binding (total Ig) antibodies to ADAMTS13 are positive, binding Ab titer and the presence and levels of neutralizing (activity inhibition) antibodies to both plasma-derived ADAMTS13 and BAX 930 will be tested.

13.7.6.1 Anti-ADAMTS13 Antibodies

Caution is advised in interpreting positive results. Any clinical association, changes in the natural history of the disease, effect of therapy, etc. need to be considered for final judgement.
The sponsor's Medical Director should be consulted for additional advice. As part of the AE follow-up, any sample testing positive needs to be confirmed after 2 to 4 weeks and documented for AE follow-up. Only confirmed neutralizing anti-ADAMTS13 antibodies (biological assays) are considered inhibitors.

Subjects who develop an inhibitory antibody to ADAMTS13, will not receive any further IP infusion, however, will be followed until study completion and all remaining study procedures such as clinical and laboratory assessments will be completed. As an additional safety measure, ADAMTS13 specific IgE antibodies will only be assessed in case of allergic reactions.

13.7.6.1.1 Total Binding Antibodies to ADAMTS13

Total binding antibodies to ADAMTS13 will be measured by an ELISA-based assay, detecting total immunoglobulins (IgG, IgA, and IgM).

13.7.6.1.2 Neutralizing Antibodies to ADAMTS13

Neutralizing antibodies to ADAMTS13 will be measured by a Bethesda method with Nijmegen modification using the ADAMTS13 FRETS-VWF73 activity assay. Test plasma will be mixed and incubated with equal volume of test control at approximately 1 IU/mL, and the residual ADAMTS13 activity in the mixed samples will be determined by the FRETS-VWF73 assay.

13.7.6.2 Anti-CHO Protein Antibodies

Total immunoglobulin antibodies (Immunoglobulin G [IgG], A [IgA], and M [IgM]) against CHO protein will be analyzed. For this assay (ELISA), CHO protein derived from cultures of untransfected cells and propagated under the identical cell culture conditions used for recombinant antihemophilic factor-protein-free method production will be coated onto a microtiter plate, then incubated with dilutions of the positive control, negative control, or test sample.

Antibodies against CHO protein that are present in the samples bind to the coated antigen and will be detected with a horseradish peroxidase-coupled goat anti-human antibody (secondary antibody). A positive result without known hypersensitivity to hamster proteins, such as a history of anaphylactic or anaphylactoid reactions or other severe allergic reactions upon exposure to hamster-derived substances, will not constitute an exclusion criteria for randomization.

For subjects <6 years of age, anti-CHO protein Ab assessments may be omitted to not exceed local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits.

13.7.7 Viral Serology

Virus serology will be established during the screening period and at completion of standard of care treatment.

The following viral seromarkers will be assessed:

1. HIV: anti-HIV 1, HIV 2
2. Hepatitis A virus: anti-HAV (IgG and IgM)
3. HBV: hepatitis B surface antigen, anti-Hepatitis B core, anti-hepatitis B surface antibody
4. HCV: Chemiluminescence anti-HCV
5. HEV: anti-HEV
6. Parvovirus B19: anti-B19V (IgG and IgM)
7. CD4 levels (at screening in HIV-positive subjects)

13.7.8 Genetic Testing

A cell pellet (buffy coat and erythrocytes) will be retained for ADAMTS13 gene mutational analysis at Screening if the information is not already available in the subject's medical history.

13.7.9 Pregnancy Test

A blood or urine pregnancy test for females of child-bearing potential will be performed at screening, within 7 days prior to first dosing with BAX 930, interval study visits (i.e., every 3 months during SoC and BAX 930 treatment phases of Period 1, Period 2 and Period 3), and at study completion/termination (see Section 20.4, Table 9 and Table 10).

13.7.10 Assessment of Laboratory Values

13.7.10.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each abnormal laboratory value will be recorded on the CRF (note: there is no need for recording of normal local laboratory values on the CRF, with four exceptions: a) Coombs test, and b) the evaluation of schistocytes, c) platelet count, and d) LDH for which normal laboratory values should be reported). For each hematology and chemistry abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 13.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 13.1.1.5), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for HIV, HAV, HBV, HCV, HEV, or B19V shall be re-tested.

13.7.11 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used, for example, for re-testing, follow-up of an AE(s) or other test results, and/or assay development. After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

For this study, no samples will be taken or stored long-term in a biobank for future analyses.

13.8 Vital Signs and 12-lead Electrocardiogram

Vital signs will be collected at each dosing visit within 1 hour before and after IP infusion, and will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

For adult and adolescent subjects (≥12 years of age), vital signs should be recorded within 1 hr before PK infusion and at the following timepoints post-infusion: 15±5 min, 60±5 min, 3±0.5 hr, 9±2 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 hr, 216±24 hr, and 288±24 hr, as well as at each dosing visit.

For pediatric subjects (<12 years of age), vital signs should be recorded within 1 hr before PK infusion and at the following timepoints post infusion: 30±5 min, 12±2 hr, 24±2 hr, 48±2 hr, 96±2 hr and 168±4 hr, and as well as at each dosing visit.

Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments, such as vital signed, associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

Blood pressure will be measured when subjects are in the supine position.

Height will be measured at screening only for subjects >=12 years of age. Height will be measured at screening, Day 1, dosing visits and at study completion/termination, for subjects <12 years of age. Weight will be measured for all subjects at screening, Day 1, PK 2 infusion (if BAX 930 is being administered for this infusion), PK 3 infusion, PK 4 infusion, dosing visits and at study completion/termination.

A 12-lead electrocardiogram (ECG) will be measured at screening and at study completion/termination.

Vital signs and 12-lead ECG are to be recorded on the CRF. For each assessment, the investigator will determine whether or not to report an AE (see definition in Section 13.1) and record the medical diagnosis (preferably), symptom, or sign on the AE CRF.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

For study sites in Germany only, refer to Appendix 1.2: Country-Specific Information for 12-lead ECG frequency and Table A1 Germany-specific Schedule of Assessments.

13.9 Health-related Quality of Life

Patient reported outcomes, based on relevant questionnaires, will be captured at screening and at the end of each period visit (i.e., end of Period 1 visit, end of Period 2 visit, and end of Period 3 visit), and if subjects have an early termination, during the termination visit, to assess chronic TTP-related symptoms and disabilities, including cognitive function. Lower scores indicate worse HRQoL.

The PRO instruments to be measured in this study are described in Table 4.

Table 4. Patient Reported Outcome (PRO) Instruments

PRO	Assessment	Time of Measurement
SF-36v2	Self-administered, validated questionnaire. This 36-item questionnaire measures 8 domains, including: • Physical functioning • Role-physical • Bodily pain • General health • Vitality • Social functioning • Role emotional • Mental health. Two summary scores can be calculated: • Physical Component Score • Mental Component Score Additionally, scores can be calculated for each of the 8 domains.	• Screening • Prophylactic cohort: Period 1, and end of Periods 1, 2, and 3, and at early termination visit, if applicable. • On-demand cohort: End of Period 1 and at early termination visit, if applicable.
EQ-5D-3L or EQ-5D-Y	The EQ-5D-3L is a generic measure of health, consisting of a descriptive system. It captures the following domains: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Self-rated health is captured using a visual analog scale. The youth version contains the same features but uses more child-friendly wording.	• Screening • Prophylactic cohort: end of Periods 1, 2, and 3, and at early termination visit, if applicable. • On-demand cohort: End of Period 1
PedsQL[a]: Age 2-4 (Parent proxy, 21 items) Age 5-7 (Parent proxy, 23 items) Age 8-12 (Child version, 23 items) Age 13-18 (Child version, 23 items)—It will only be administered to subjects aged 13-17 years	The PedsQL is a generic HRQoL instrument designed specifically for a pediatric population. It captures the following domains: • Physical functioning • Emotional functioning • School functioning • Social functioning • Psychosocial summary • Physical health • Total score	• Screening • Prophylactic cohort: end of Periods 1, 2, and 3, and at early termination visit, if applicable. • On-demand cohort: End of Period 1

Table 4. Patient Reported Outcome (PRO) Instruments

PRO	Assessment	Time of Measurement
TSQM-9 (Bharmal et al., 2009)	The TSQM-9 questionnaire is a validated measure consisting of 3 domains (efficacy, convenience, and overall satisfaction) and 9 questions	• Screening • Prophylactic cohort: end of Periods 1, 2, and 3, and at early termination visit, if applicable. • On-demand cohort: End of Period 1
Health resource use items	This information will be gathered by the sites as part of the eCRF. It assesses: • Number of hospitalizations and length of stay • Number of acute care visits • Number of emergency room visits • Number of days missed from school, daycare or work (i.e., grade school, kindergarten, daycare)	• Via eCRF after randomization
cTTP PRO assessment	The cTTP PRO assessment is focused on measuring the symptoms and impacts of the disease. It is a 26-item questionnaire assessing several concepts, including the following: • Fatigue • Pain (joint, muscle, abdominal, chest) • Neuro-cognitive impairment • Vision difficulties • Headaches • Bruising • Emotional functioning • Impact on daily activities	• Screening • Prophylactic cohort: end of Periods 1, 2, and 3, and at early termination visit, if applicable. • On-demand cohort: End of Period 1

eCRF, electronic case report form; EQ-5D-3L, EuroQol 5 Dimensions Questionnaire 3 Level; EQ 5D Y, EQ-5D-youth; HRQoL, health-related quality of life; cTTP, congenital thrombotic thrombocytopenic purpura; PedsQL, Pediatric Quality of Life Inventory; PRO (patient reported outcome); SF 36v2, 36 Item Short Form Health Survey version 2; TSQM-9, Treatment Satisfaction Questionnaire for Medication.

[a] Subjects should be given the same questionnaire at follow-up that they were given at Screening, even if they move up an age range during the study.

14. STATISTICS

14.1 Sample Size Determination

In total, approximately 42 adult (≥18 years old) subjects and 15 adolescent (>12-≤17 years old) or pediatric (<12 years old) subjects will be enrolled in this study, including approximately 36 adult subjects and 12 adolescent or pediatric subjects starting in the prophylaxis cohort, and approximately 6 adult subjects and 3 adolescent or pediatric subjects, in the on-demand cohort. The sample size is limited by the extremely low prevalence of the disease (0.5 to 4 per million) (Mansouri Taleghani et al., 2013). The updated approximate number of subjects reflects the current, observed enrollment patterns and accounts for a 10% dropout rate. The number of subjects starting enrollment in the prophylactic cohort should allow an overall assessment of efficacy and safety of BAX 930, including immunogenicity, and PK following infusion.

The sample size of approximately 36 adult (≥18 years old) subjects and 12 adolescent (4 subjects age >12-≤17) or pediatric subjects (4 subjects age ≥6-<12, and 4 subjects age 0-<6) in the prophylaxis cohort, will also provide an estimate of the safety and efficacy of the IP.

If 15 of the 30 enrolled adult and adolescent prophylaxis subjects receive FFP and each subject receiving FFP will have at least 14 infusions per treatment period, there will be 210 total FFP infusions. With 210 FFP infusions, there is a >99% probability that at least 1 SAE will be observed, if as reported in the literature, the rate of serious adverse reactions (SARs) is 6% (Huisman et al., 2014).

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

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

14.2 Analysis Sets

14.2.1 All Subjects Enrolled Set

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

14.2.2 Full Analysis Set (FAS)

The full analysis set (FAS) will include all subjects with a confirmed cTTP diagnosis receiving at least 1 dose of BAX 930 or SoC treatment after randomization.

14.2.3 Modified Full Analysis Set (MFAS)

The modified full analysis set (MFAS) is based on the FAS, with the following modifications:

- For subjects enrolled prior to the study hold in November 2017, if BAX 930 was the randomized treatment for period 1 and were treated on SoC because BAX 930 was not available, the subjects will be excluded from the MFAS.
- For subjects enrolled prior to the study hold in November 2017, if SoC was the randomized treatment for period 1 and were treated on SoC because BAX 930 was not available, only the primary efficacy data for period 1 collected prior to the Month 6 visit will be used in the MFAS-based primary efficacy analysis.

14.2.4 Per-protocol Analysis Set

The per-protocol (PP) analysis set will include all subjects in the MFAS who have no major protocol deviations from the protocol affecting the efficacy outcome or treatment of the subject. Further information on major protocol deviations will be provided in the Statistical Analysis Plan (SAP).

14.2.5 Safety Analysis Set

The safety analysis set will include all subjects treated with at least 1 dose of BAX 930 or SoC treatment after randomization. All safety analyses will be performed on the safety analysis set.

14.2.6 Pharmacokinetic and Pharmacodynamic Analysis Sets

The PK Full Analysis Set (PKFAS) will be a subset of the FAS and will contain all subjects who receive at least 1 dose of investigational product and provide adequate postdose PK measurements for at least 1 of the PK analytes and have no major protocol deviations or events that may affect the integrity of the PK data. Subjects in this population will be used for all respective PK concentration and parameter summaries.

The PD analysis set will be a subset of FAS and will contain all subjects who receive at least 1 dose of investigational product and provide at least 1 valid data point postdose of the respective infusion for at least 1 PD measurement for any of the PD outcome measures, and have no major protocol deviations or events that may affect the integrity of the PD data. Subjects in this population will be used for all respective PD concentration summaries.

14.3 Handling of Missing, Unused, and Spurious Data

In general, missing data will not be imputed. However, if body weight at the time of infusion is missing for a subject then the last available body weight measurement will be carried forward in order to compute weight-adjusted BAX 930 consumption.

For PK data, if any concentration data are considered spurious (eg, lack of biological plausibility), they will be excluded from the analysis, and the reason for exclusion from the analysis will be documented.

Regarding missing data in AE records:

- Handling of unknown causality assessment:
  - If a subject experiences an AE with missing causality assessment, the relationship of the AE will be counted as "related." However, all efforts will be made to discuss with the investigator for a causality assessment.
- Handling of unknown severity grades:
  - If a subject experiences more than 1 AE categorized under the same preferred term, 1 of them is categorized as "severe" and 1 of them is categorized as "unknown", the severity of this AE will be counted as "severe"
  - If a subject experiences more than 1 AE categorized under the same preferred term, 1 of them is categorized as "mild" or "moderate" and 1 of them is categorized as "unknown," the severity of this AE will be counted as "unknown"

14.4 Methods of Analysis

The overall assessment of BAX 930 treatment will be based on the totality of evidence provided by efficacy, safety, PRO, and PK data. The statistical analysis for the prophylactic cohort will be carried out in 2 steps: (a) an interim analysis (with an interim clinical study report) will be performed after 30 adults and adolescent subjects in prophylactic cohort complete the study; (b) a final analysis will be done at the end of the study when all efficacy, safety, PRO and PK data collected become available for both adult and pediatric subjects.

Analyses will be performed separately for the prophylaxis and on-demand cohorts on applicable outcome measures and will be presented by treatment group for each cohort, unless otherwise stated.

Details on the specific analyses to be performed for this study will be provided in the SAP.

14.4.1 Primary Outcome Measure

The primary outcome measure is:

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

14.4.1.1 Incidence of Acute TTP Events

The number of acute TTP events and the incidence rate of acute TTP events will be summarized by treatment group (BAX 930 or SoC) and treatment period.

The acute TTP event annualized rate will be assumed to have a negative binomial distribution, and the mean acute TTP rate will be estimated using a generalized linear mixed-effects model with a negative binomial distribution as a family and a logarithmic link function (the default) with treatment as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset. The model-based mean annual rate and corresponding 95% CI will be presented for each treatment for the prophylactic cohort, as well as the ratio of the two treatment incidence rates, accompanied by a two-sided, 95% CI. If the model fails to converge, descriptive statistics on event rates will be reported without a statistical model.

Additional summaries of the number of acute TTP events and incidence rates of the two treatments will be provided by treatment group, treatment period and age group.

Efficacy analysis for the pediatric subjects will be performed separately.

The primary efficacy analysis will be based on the MFAS for the prophylactic cohort. A sensitivity analysis will be performed based on the FAS for the prophylactic cohort.

14.4.2 Secondary Outcome Measures

14.4.2.1 Efficacy

The methods of analysis for the secondary efficacy outcome measures (see Section 9.4.2.1) are:

- The proportion of acute TTP events responding to BAX 930 will be summarized including 95% CI by treatment for both the prophylactic and on-demand cohorts
- For acute TTP events, a Kaplan-Meier curve for each treatment group will be drawn based on each subject's time to resolution of the acute TTP event, defined as the time from initial treatment of the event to the end of the acute TTP event for pooled prophylactic and on-demand cohort data, and separately. Only the first acute TTP event for each subject will be included in the analysis. The median time to resolution will be presented for each treatment, along with the corresponding 95% CI.
- Incidence of thrombocytopenia defined as a drop in platelet count ≥25% of baseline, or a platelet count <150,000/µl, will be reported by treatment arm for the prophylactic cohort
- Incidence of microangiopathic hemolytic anemia defined as an elevation of LDH >1.5× baseline or >1.5×ULN, will be reported by treatment arm for the prophylactic cohort

- Incidence of neurological symptoms (TTP related) (eg, confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures), will be reported by treatment arm for the prophylactic cohort
- Incidence of renal dysfunction, defined as an increase in serum creatinine >1.5×baseline, will be reported by treatment arm for the prophylactic cohort
- Incidence of abdominal pain (TTP related) will be reported by treatment arm for the prophylactic cohort
- The incidence of supplemental doses prompted by subacute TTP events will be summarized by treatment for the prophylactic cohort
- The incidence of dose modifications not prompted by an acute TTP event will be summarized by treatment for the prophylactic cohort
- The incidence of acute TTP events while subjects are on their final dose and dosing regimen in the study will be summarized by treatment for the prophylactic cohort

14.4.2.2 Safety

Safety outcome measures (see Section 9.4.2.2) are:

- The number and percentage of treatment-emergent adverse events will be calculated overall, by system organ class, by preferred term, and by treatment group for each cohort. Treatment-emergent adverse events will be further summarized by seriousness, severity, and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.
- Incidence of binding and inhibitory antibody will be tabulated and summarized.
- Vital signs and clinical laboratory results (clinical chemistry, hematology, and urinalysis), observed and change from baseline, will be summarized by study visit, treatment, and age group (as applicable) using descriptive statistics.
- 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.
- The estimated total quantity of ADAMTS13 administered during the treatment of acute TTP events will be listed by subject and summarized by treatment cohort (prophylactic or on-demand) using descriptive statistics.

14.4.2.3 Pharmacokinetics/Pharmacodynamics

The methods for analysis of PK and PD outcome measures (see Section 9.4.2.3) are outlined in Section 14.4.2.3.1, Section 14.4.2.3.2, and Section 14.4.2.3.3.

14.4.2.3.1 Pharmacokinetics

Pharmacokinetic parameters for ADAMTS13 activity and ADAMTS13:Ag following SoC or BAX 930 infusion will be derived for adults using non compartmental methods, including, where estimable:

- IR
- C_{max}
- Time to reach C_{max} (t_{max})
- Apparent terminal rate constant (λ_z)
- $t_{1/2}$
- MRT
- Area under the plasma concentration/activity/time curve (AUC) including:
  - AUC from time zero to the time of the last concentration ($AUC_{(0\text{-last})}$)
  - AUC from time zero to infinity ($AUC_{(0\text{-inf})}$)
- Area under the moment curve from time zero to infinity ($AUMC_{(0\text{-inf})}$)
- Systemic CL
- V_{ss}

Potency of ADAMTS13 activity and ADAMTS13:Ag in the SoC or BAX 930 dosing solutions will be used to derive actual dose amount for calculating IR, CL, and V_{ss}.

For BAX 930 and SoC activity, FRETS-VWF73 will be used to measure potency.

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

Pharmacokinetic parameters for pediatric subjects will be assessed separately. An attempt will be made to determine PK parameters using a non-compartmental method for pediatric subjects based on the reduced sampling schedule and may include C_{max}, t_{max}, and appropriate estimates of AUC over the sampling period. Other analysis methods may be used to analyze pediatric data.

The PK levels and PK parameters for adult and pediatric subjects will be listed and summarized by age group, treatment cohort (prophylaxis or on-demand), treatment arm, and study visit (and by scheduled time for PK levels). Individual and mean PK profiles over time will be presented. Impact of immunogenicity on ADAMTS13 antigen and activity time profiles and PK parameters will be assessed.

Immunogenicity status, time of onset of immunogenicity for both binding and inhibitory antibodies will be used to assess this impact. Additional figures may be generated as applicable. Additional details will be provided in the SAP and Clinical Pharmacology Analysis Plan.

A nonlinear mixed effects model approach will be used to derive a population PK model for ADAMTS13. The modeling report will be reported separately.

14.4.2.3.2 Pharmacodynamics

The PD measurement of plasma VWF:RCo and VWF:Ag will be listed and summarized by age group, treatment cohort (prophylaxis or on-demand), treatment arm, study visit, and scheduled time. Individual and mean PD profiles over time will be presented. Data allowing impact of immunogenicity (immunogenicity status, time of onset) on VWF:RCo and VWF:Ag may be evaluated. Additional figures may be generated as applicable.

14.4.2.3.3 Pharmacokinetic/Pharmacodynamic

The relationship between ADAMTS13 activity levels and/or PK parameters and the presence of and/or time of occurrence of acute TTP events and subacute TTP events will be explored.

14.4.2.4 Health Related Quality of Life and Resource Utilization

The methods of analysis for the secondary HRQoL and resource utilization outcome measures (see Section 9.4.2.4) are:

- HRQoL and resource utilization will be tabulated by treatment period and treatment cohort (prophylaxis or on-demand)
- Differences observed between treatments will be assessed for each treatment cohort (prophylactic or on-demand) by significance tests

14.4.3 Exploratory Outcome Measures

Exploratory outcome measures based on incidence of events, where applicable, will be assessed using a generalized linear mixed-effects model assuming a negative binomial distribution and a logarithmic link function (the default) with treatment as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset. The model-based mean annual rate and corresponding 95% CI will be presented for each treatment for the prophylactic cohort, as well as the ratio of the two treatment incidence rates, accompanied by a two-sided, 95% CI. If the model fails to converge, descriptive statistics on event rates will be reported without a statistical model.

The PD measurement of ADAMTS13 mediated VWF cleavage products (if available) will be listed and summarized by age group, treatment cohort (prophylaxis or on-demand), treatment arm, study visit, and scheduled time. Individual and mean PD profiles over time will be presented. Additional figures may be generated as applicable.

14.4.4 Other Analyses

All other analyses, including analyses on subject disposition, demographics, disease characteristics, medications, histories etc. will be further defined in the SAP.

14.4.4.1 Planned Interim Analyses of the Study:

An interim analysis will be performed after 30 adult or adolescent subjects in the prophylactic treatment group complete the study. All data collected by that time point will be included in the statistical analysis.

The interim analysis will be performed on a cleaned snapshot of the study database and will include all data for adults, adolescent, and pediatric subjects in the study.

The interim analysis data will be used in regulatory submissions and scientific manuscripts. The interim analysis will include all analyses outlined in Section 14.4.1, Section 14.4.2, Section 14.4.3, and Section 14.4.4. Further details will be provided in the SAP.

14.5 Direct Access to Source Data/Documents

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored by an external DMC.

The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the field of hemophilia clinical care and research who are not actively recruiting subjects. The DMC can stop a trial if it finds toxicities or if treatment is proven to be not beneficial.

Enrollment will be paused pending DMC evaluation if there are ≥3 product-related SAEs, including the development of inhibitory antibodies to BAX 930. In addition, the DMC will review the enrollment of pediatric subjects in line with Table 5.

The study will be stopped if 2 or more subjects develop confirmed ADAMTS13 inhibitory antibodies defined as ≥0.6 BU in the central laboratory on 2 separate assays within a 1-month period.

This trial will also include a safety evaluation after first 6 subjects each have at least 3 BAX 930 SIN infusions (including PK infusions) to evaluate the ADAMTS13 activity.

15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate 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, but within 1 calendar day after the change is implemented. Takeda will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

Not applicable; a central laboratory/reader will be used for all clinical assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before subjects participate in this study, the protocol, ICF, any promotional material/advertisements, and any other written information will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval.

16.3 Informed Consent

Investigators will choose subjects for participation considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All subjects and/or their legally authorized representative must sign an ICF before entering the study according to applicable national and local regulatory requirements and ICH GCP. An assent form may be provided and should be signed by the legally authorized representative for subjects less than 18 years of age. Before use, the ICF will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2). The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. subjects or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the ICF, subjects or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised ICF, approved by the applicable EC and regulatory authorities where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the CTA.

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 9.8), records detailing the progress of the study for each subject, signed ICFs, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, Serious Adverse Event Reports, laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. Case report forms will be provided in electronic form.

If paper format CRFs are provided by the sponsor, all required study data, including corrections, will be clearly and accurately recorded by authorized study site personnel on the CRFs. The CRFs will remain at the site until they are reviewed by the study monitor or sponsor's representative. All original CRFs will be collected by the study monitor, and an identical copy of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the document and data retention policy (see Section 17.2).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Alternative approaches may be used to ensure data quality and integrity as well as maintaining subject safety (eg, remote source data verification (SDV) or telephone contact). See the monitoring plan for the detailed approach.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the CTA.

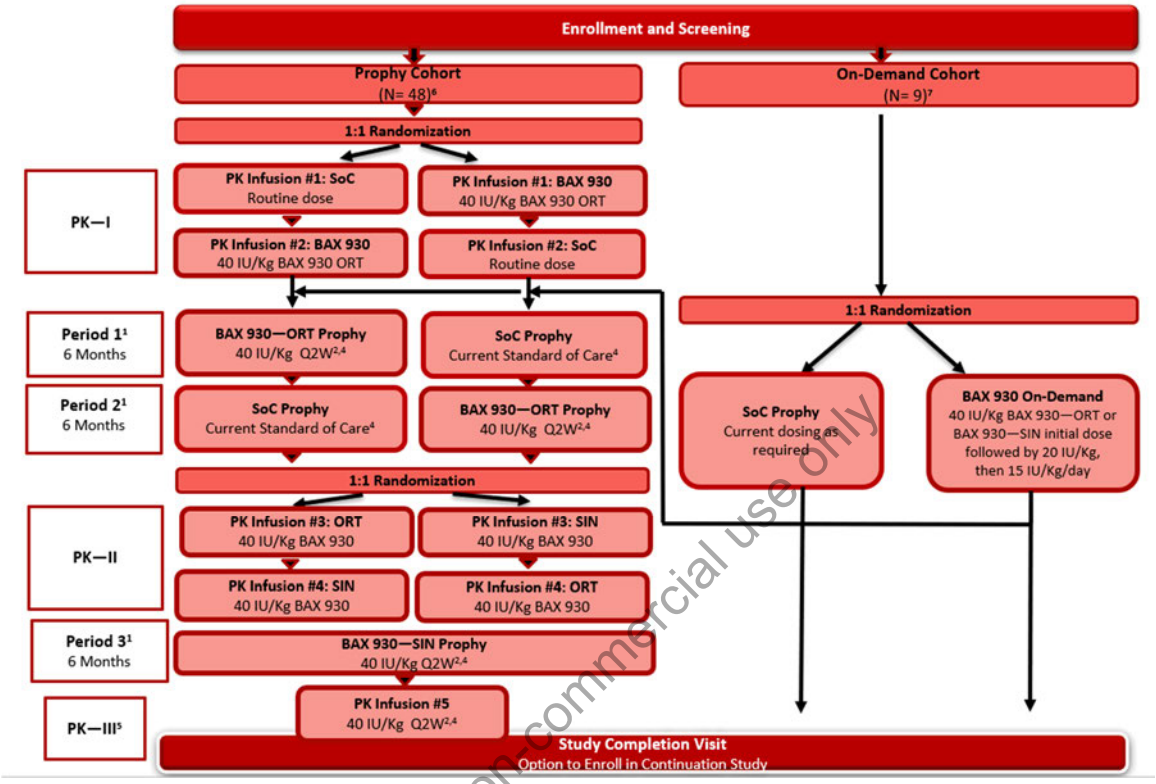
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

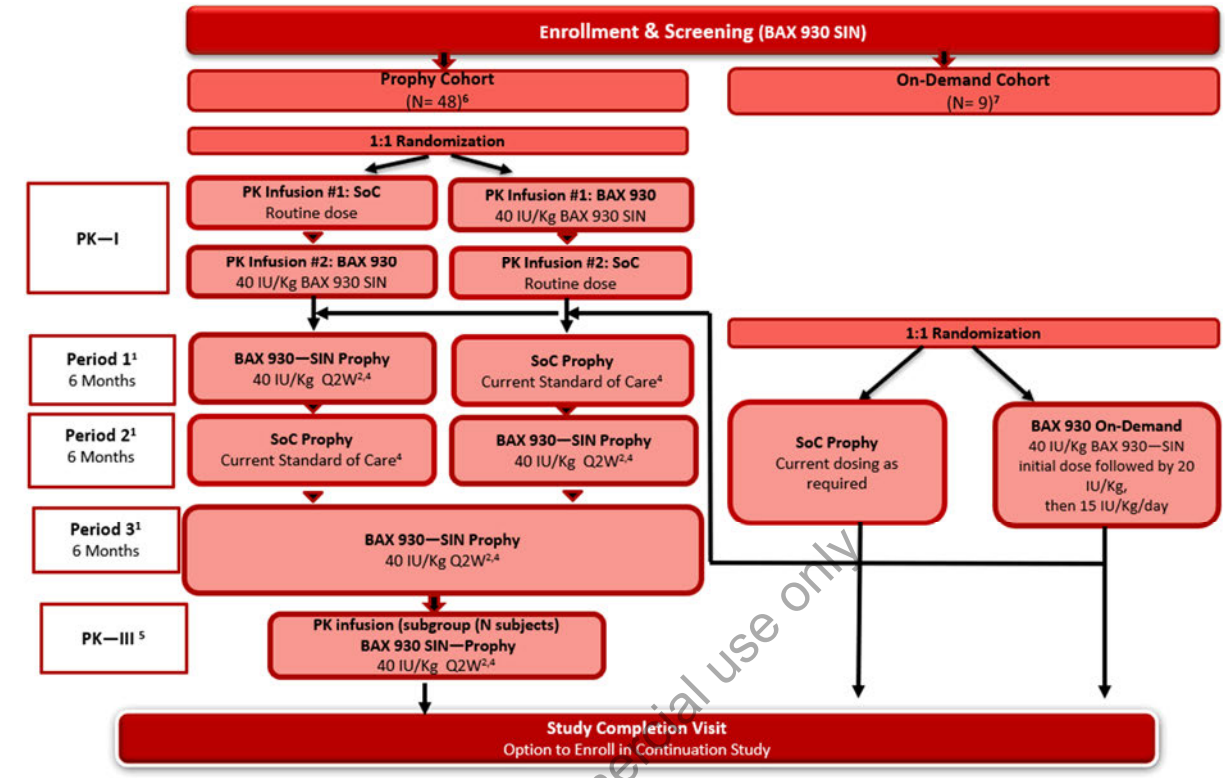
20.1 Study Flow Chart

Figure 1. Study Design for Subjects Entering Study with BAX 930 ORT



1. Acute TTP events in the prophylaxis arm will be treated with the treatment agent the subject is receiving in the current period.
2. Initial prophylactic dose and dosing regimen may be adjusted based on current SoC treatment (i.e., Q1Week) for subjects currently receiving FFP or S/D plasma Q1Week.
3. Interval visits will be every 3 months.
4. A single dose modification may be mandated based on clinical outcomes.
5. PK-III will be conducted on a smaller subset of subjects who receive BAX 930 SIN in Period 3 (adults ≥18 years, N=4, pediatric and adolescent subjects 0-17 years, N=2). It will be required for pediatric subjects (<12 years old) and subjects who receive a weekly (Q1Week) dosing regimen.
6. A total of at least 12 subjects in the prophylactic cohort will be pediatric or adolescent subjects (0-17 years).
7. A total of at least 3 pediatric or adolescent subjects are to be enrolled in the on-demand cohort.

Figure 2. Study Design for Subjects Entering Study with BAX 930 SIN



1. Acute TTP events in the prophylaxis arm will be treated with the treatment agent the subject is receiving in the current period.
2. Initial prophylactic dose and dosing regimen may be adjusted based on current SoC treatment (i.e., Q1Week) for subjects currently receiving FFP or S/D plasma Q1Week.
3. Interval visits will be every 3 months.
4. A single dose modification may be mandated based on clinical outcomes.
5. PK-III will be conducted on all subjects in the prophylactic cohort who initiate the study with BAX 930 SIN.
6. A total of at least 12 subjects in the prophylactic cohort will be pediatric or adolescent subjects (0-17 years).
7. A total of at least 3 pediatric subjects are to be enrolled in the on-demand cohort.

20.2 Pediatric Subjects

20.2.1 Prophylactic Cohort

This Phase 3 study will include 12 pediatric or adolescent subjects with all age groups in the prophylactic cohort which are represented and enrolled in the following distribution:

Table 5. Pediatric Enrollment (Prophylactic Cohort)

Age	Number of Pediatric Subjects	Criteria	DMC Review Required
≥12-≤17	4	5 adult subjects each have at least 10 exposures with BAX 930	Yes
≥6-<12	4	NA	No
0-<6	4	NA	No

Enrollment for subjects 12-17 years of age started after 5 adult subjects each had at least 10 exposures of BAX 930 in the prophylaxis cohort, collected data was reviewed by the DMC and endorsement was obtained. Pediatric and adolescent subjects age 0-17 who enter the study prior to the availability of BAX 930 SIN in Period 1, will initiate treatment with BAX 930 ORT during Period 1 or Period 2 and switch to BAX 930 SIN during Period 3. Once BAX 930 SIN is available, pediatric subjects will initiate Period 1 or Period 2 with BAX 930 SIN and continue treatment with BAX 930 SIN until completion of Period 3. Pediatric subjects, age 0-17 will be permitted to receive BAX 930 SIN when 5 adult subjects have had 10 exposures with BAX 930 SIN. In France, no subjects younger than 18 years of age will be enrolled into the study before the first adult subject has been treated with BAX 930 for a minimum of 6 months.

In line with the Pediatric Information Plan (P/0048/2012), the prophylactic cohort of the study is planned to enroll a total of 12 children from birth to less than 18 years of age, at least 6 of whom will be less than 12 years old. Pediatric and adolescent subjects will be replaced for drop out if they have less than 6 months' exposure of BAX 930, up to 2 subjects per age cohort unless 3 pediatric or adolescent subjects have each had 6 months' exposure of BAX 930 at the time of drop out. The replaced subject will be assigned into the same slot (i.e., BAX 930 – SoC or SoC - BAX 930) as the discontinued subject. Pediatric subjects who replace dropout subjects will receive BAX 930 ORT, per randomization schedule until 01 Oct 2021.

Each subject in the prophylactic cohort of the study is planned to have a full or limited PK evaluation, based on age, which can be used to further guide the initial treatment regimen.

Based on available registry data, the proposed dosing strategy for the pediatric initial dose at all age groups will be the same as the initial adult dose.

20.2.2 On-demand Cohort

The availability of potential subjects for the on-demand cohort is extremely limited. Although symptoms develop soon after birth in approximately 50% of subjects, in others, symptoms do not occur until the second or third decade of life. It should also be noted that the occurrence of an acute TTP event is potentially life-threatening, and subjects who have previously experienced an event will most likely be placed on prophylactic treatment with the current SoC. This Phase 3 study will include at least 3 pediatric subjects in the on-demand cohort which will be represented and enrolled in the following distribution:

Table 6. Pediatric Enrollment (On-demand Cohort)

Age	Number of Pediatric Subjects
≥12-≤17	1-3
≥6-<12	0-1
0-<6	0-1

20.3 Schedule of Study Procedures and Assessments

Table 7. Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments*	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[o,r]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	
Informed Consent[f]	X															
Eligibility Criteria	X															
Randomization[n]		X[n]						X								
Medical History	X															
ECG	X															X
Physical Exam	X															X
Concomitant Medications and non-Drug Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Infusion[g] (see Section 9.2.1)		X		X[h]		X	X	X		X[h]		X	X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories[i]	X	X[j]	X[j]	X[j]	X[j]	X	X	X[j]	X[j]	X[j]	X[j]	X	X	X	X	X
Vital Signs	X	X[j]	X[j]	X[j]	X[j]	X[m]	X[m]	X[j]	X[j]	X[j]	X[j]	X[m]	X	X	X	X
Height/ Weight[k]	X	X[k]		X[k]		X[k]	X[k]	X[k]		X[k]		X[k]	X[k]		X[k]	X

Table 7. Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments*	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[o,r]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	
Pediatric Development Markers[q]	X					X	X					X				X
HRQoL[l]	X[p]					X[p]	X[p]					X[p]				X[p]
Schedule Next Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Testing at central laboratory; CBC=complete blood count; CD4=cluster of differentiation 4; CHO=Chinese hamster ovary; ECG=electrocardiogram; EQ-5D-3L=EuroQol 5 Dimensions Questionnaire 3-Level; EQ-5D-Y=EQ-5D-youth; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=health related quality of life; cTTP=congenital thrombotic thrombocytopenic purpura; IP=investigational product; L=Testing at local laboratory; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; Ped QL=Pediatric Quality of Life Inventory; PK=pharmacokinetic; PRO=patient reported outcome; RBC=red blood cell; SF-36=36-Item Short Form Health Survey; SoC=Standard of Care; TSQM-9=Treatment Satisfaction Questionnaire for Medication; TTP=thrombotic thrombocytopenic purpura; VWF=von Willebrand factor; VWF:Ag=von Willebrand factor: antigen; VWF:RCo=von Willebrand factor: ristocetin cofactor activity

Note: Subjects of less than 18 years of age will be enrolled according to the criteria defined in Table 5.

* Sites in Germany should refer to Table A1 for assessments.

a. The length of Period 1 and Period 2 is 6 months each. If a subject cannot switch to the next period at the end of month 6, due to either logistic or medical reasons, the length of Period 1 and Period 2 can be extended to up to 7 months. For subjects enrolled before November 2017, Period 1 can be extended to up to 24 months. The length of Period 3 is 6 months or until the continuation study is open at the subject's study site.
b. If the subject received SoC agent to treat an acute episode of TTP, at least 15 days (360 hr) must have elapsed and the subject must not show any TTP-related symptoms.
c. See Table 11 for adult visit schedule. See Table 12 for pediatric visit schedule. See Table 13 for PK-III adult and pediatric visit schedule.
d. Assumes Q2W dosing. Visit schedule and accompanying tests should be modified based on dosing frequency (see Section 9.2.1.3 for SoC dosing and Section 9.2.1.4 for BAX 930 dosing). For subjects on Q1W treatment, labs will be drawn on Q2W schedule. Subjects on Q3W SoC treatment should have labs, vital signs and all assessment at the time of their visits according to the Q3W schedule.
e. Also applies to subjects who prematurely withdraw from the study.
f. Occurs at enrollment (prior to any study-specific procedure).

Table 7. Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments*	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[o,r]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	

g. Subjects requiring a vaccination during the course of treatment should schedule the vaccination administration within 72 hours after a prophylactic treatment dose. Subjects receiving a COVID-19 vaccination during the study period should be monitored frequently by telephonic health checks and for thrombocytopenia for 14 consecutive days following vaccination, as deemed appropriate by the investigator. Elective surgeries should be scheduled 24 hours after the last prophylactic dose and ADAMTS13 levels should be monitored after surgery.

h. The infusion (SoC, BAX 930 ORT, or BAX 930 SIN depending on randomization) on Day 13 is to be administered after the 288-hr PK sample has been collected.

i. For laboratory assessments, see Table 9.

j. PK assessments will be done at the following timepoints post-PK infusion for subjects undergoing Q2W and Q3W: 15 ±5 min, 60±5 min, 3±0.5 hr, 9±2 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 hr, 216±24 hr, and 288±24 hr. Vital signs for adult and adolescent subjects (≥12 years of age), should be recorded within 1 hr before PK infusion and at the following timepoints post infusion: 15±5 min, 60±5 min, 3±0.5 hr, 9±2 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 hr, 216±24 hr, and 288±24 hr. For pediatric subjects (<12 years of age), vital signs should be recorded within 1 hr before PK infusion and at the following timepoints post infusion: 30±5 min, 12±2 hr, 24±2 hr, 48±2 hr, 96±2 hr and 168±4 hr. Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1. PK Post-Infusion Laboratory Assessments for subjects undergoing Q1W dosing should not be performed at 168±12 hrs, 216±12 hrs and 288±12 hrs timepoints, after PK Infusion #1. However, PK assessments up to 168±12 hrs timepoint should be performed after PK Infusion #2, and PK #3. Please refer to the tables below to see the assessment schedule for subjects undergoing Q1W dosing. PK timepoints for subjects in Q3W dosing will be the same as subjects on Q2W dosing.

k. Height will be measured at screening only for subjects >=12 years of age. Height will be measured at screening, Visit1/Day 1, dosing visits and at study completion/termination for subjects <12 years of age. Weight will be measured for all subjects at screening, Day 1, PK 2 infusion (if BAX 930 is being administered for this infusion), PK 3 infusion, PK 4 infusion, PK 5 infusion, prophy dosing visits and at study completion/termination.

l. SF-36v2, TSQM-9, EQ-5D-3L or EQ-5D-Y, PedsQL, and a cTTP-specific PRO and health-resource use items.

m. Vital signs will be collected at each dosing visit within 1 hour before and after PI infusion.

n. Randomization can be done on day 1 or the day before day 1. IP dispensation will be allowed on the day before the visit.

o. PK-III assessments may be conducted in a minimum of 4 adult (≥18 years), and 2 pediatric (0-17 years) subjects who receive BAX 930 SIN in Period 3 on a voluntary basis. It will be required for pediatric subjects (<12 years old), subjects who receive a weekly (Q1Week) dosing regimen, and all subjects who receive BAX 930 SIN in PK-I, Period 1, or Period 2.

p. HRQoL assessments will be conducted only at the screening visits and at the end of the period (i.e., the last visit in the period, or at the early termination visit, if applicable).

q. For subjects 0-<6 years old, pediatric growth, development, and cognitive performance will be assessed if/when applicable, per the Investigator's discretion.

Table 7. Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments*	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[o,r]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	

r. Subjects enrolling into the continuation study will be allowed to remain in the 281102 study until the continuation study is open for enrolment. After the last IP Infusion, subjects will be enrolled and followed in the continuation study. Subjects who experience an acute TTP event will be treated with the assigned treatment at the time of said acute TTP event, before rolling over into the continuation study.

Table 8. Schedule of Study Procedures and Assessments for Subjects on On-Demand Cohort

Procedures/ Assessments	Screening Visit and Dosing Visit 1 Day 1	Period 1 On-Demand (SoC or BAX 930) V 2 Stabilization[b] Day 2, 3, 4, 5, 6, 7[c]	Study Completion/ Termination Visit[a] 28 ±3 days after the last IP infusion or termination of treatment phase
Informed Consent[d]	X		
Eligibility Criteria	X		
Medical History	X	X	
ECG	X		X
Physical Exam	X		X
Concomitant Medications and non-Drug Therapy	X	X	X
IP Infusion (see Section 9.2.2)	X	Current dosing as required	
Adverse Events	X	X	X
Laboratories[e]	X	X	X
Vital Signs	X	X	X
Height/Weight[f]	X		X
HRQoL[g]	X[i]	X[h]	X[j]
Schedule Next Visit	X	X	

Table 8. Schedule of Study Procedures and Assessments for Subjects on On-Demand Cohort

Procedures/ Assessments	Screening Visit and Dosing Visit 1 Day 1	Period 1 On-Demand (SoC or BAX 930) V 2 Stabilization[b] Day 2, 3, 4, 5, 6, 7[c]	Study Completion/ Termination Visit[a] 28 ±3 days after the last IP infusion or termination of treatment phase

ECG=electrocardiogram; EQ-5D-3L=EuroQol 5 Dimensions Questionnaire 3-Level; EQ-5D-Y=EQ-5D-youth; HRQoL=health related quality of life; cTTP=congenital thrombotic thrombocytopenic purpura; IP=investigational product; LDH=lactate dehydrogenase; Ped QL=Pediatric Quality of Life Inventory; PK=pharmacokinetic; PRO=patient reported outcome; SF-36=36-Item Short Form Health Survey; TSQM-9=Treatment Satisfaction Questionnaire for Medication

Note: Subjects of less than 18 years of age will be enrolled according to the criteria defined in Table 5.

a. Also applies to subjects who prematurely withdraw from the study. Subjects who are unable to move into prophylactic cohort due to data lock timelines may rollover directly into the continuation study.
b. Actual number of visits will vary. Subjects will receive treatment until 2 days after the acute TTP event is resolved.
c. Based on number of visits.
d. Occurs at enrollment (prior to any study-specific procedure).
e. For laboratory assessments, see Table 10.
f. Height will be measured at screening only. Weight will be measured at Screening/Visit1/Day 1, and at study completion/termination.
g. SF-36v2, TSQM-9, EQ-5D-3L or EQ-5D-Y, Ped QL, health-resource use items and a cTTP-specific PRO.
h. This assessment will be done only at the end of Period 1 (i.e., the last visit in the period).
i. Only at screening.
j. Only required if a subject terminates the study early.

20.4 Clinical Laboratory Assessments

Table 9. Clinical Laboratory Assessments: Prophylaxis Treatment (Prophylaxis Cohort)*

Assessments	Screening Visit	SoC PK Infusion and BAX 930 PK Infusion #1, 2, 3, 4& 5[a,b]	Prophy Dosing Visits (Every 2 weeks ±2 day[c])	Interval Study Visits (Every 3 months ±2 weeks during SoC and BAX 930 treatment phases of Periods 1, 2, & 3 to align with dosing visits)[s]	Acute TTP event Dosing Visits (Daily until 2 days following the resolution of the acute TTP event)	Study Completion/ Termination Visit[d] 28 ±3 days after the last IP infusion
Complete Blood Count[e]	C	C, L[f, p]	C, L[p]	C, L[p]	C, L[p]	C
Clinical Chemistry[g]	C	C, L[f, q]	C, L[q]	C, L[q]	C, L[q]	C
Urinalysis[h]	C					C
PK Tests[i]	C	C[i]				
Pre-Infusion ADAMTS13			C[f]		C[f]	
Post-Infusion ADAMTS13			C[n]		C[n]	
Immunogenicity[j]	C	C[f]	C[r]		C[f]	C
cTnT, cTnI, CK-MB[u]		C[f]			L[t,v]	L[v]
S100B, NSE[u]		C[f]		C[f]	C	C
Viral Serology[k]	C[k]			C[k]		
Genetic Testing[l]	C					
Blood Group[m]	L					
Pregnancy Test	L°/C	L°/C		C		C
Coombs test					L[f]	
Evaluation of Schistocytes					L[f]	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Testing at central laboratory; CBC=complete blood count; CD4=cluster of differentiation 4; CHO=Chinese hamster ovary; CK-MB=creatine kinase myocardial band; cTnI=cardiac troponin I, cTnT=cardiac troponin T; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; L=Testing at local laboratory; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration;

Table 9. Clinical Laboratory Assessments: Prophylaxis Treatment (Prophylaxis Cohort)*

Assessments	Screening Visit	SoC PK Infusion and BAX 930 PK Infusion #1, 2, 3, 4& 5[a,b]	Prophy Dosing Visits (Every 2 weeks ±2 day[c])	Interval Study Visits (Every 3 months ±2 weeks during SoC and BAX 930 treatment phases of Periods 1, 2, & 3 to align with dosing visits)[s]	Acute TTP event Dosing Visits (Daily until 2 days following the resolution of the acute TTP event)	Study Completion/ Termination Visit[d] 28 ±3 days after the last IP infusion

MCV=mean corpuscular volume; NSE=neuron-specific enolase; PK=pharmacokinetic; RBC=red blood cell; S100B=calcium binding protein B; SoC=Standard of Care; TTP=thrombotic thrombocytopenic purpura; VWF=von Willebrand factor; VWF:Ag=von Willebrand factor: antigen; VWF:RCo=von Willebrand factor: ristocetin cofactor activity

a. If the subject received SoC agent to treat an acute episode of TTP at least 15 days (360 hr) must have elapsed and the subject must not show any TTP-related symptoms.
b. PK Infusions to occur 14 days ±2 days.
c. Assumes Q2W dosing. Visit schedule and accompanying tests should be modified based on dosing frequency (see Section 9.2.1.3 for SoC dosing and Section 9.2.1.4 for BAX 930 dosing). For subjects on Q1W treatment, labs will be drawn on Q2W schedule. Subjects on Q3W SoC treatment should have labs, vital signs and all assessments at the time of their visits according to the Q3W schedule.
d. Also applies to subjects who prematurely withdraw from the study.
e. CBC: RBC count, hemoglobin, hematocrit, haptoglobin, reticulocyte count, MCV, MCH, MCHC, leukocytes (i.e., white blood cell count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, and neutrophils) and platelet counts.
f. Sampling within 60 min prior to start of infusion
g. Clinical chemistry assessments: sodium, potassium, chloride, ALT, AST, LDH, bilirubin, albumin (screening only), alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.
h. Urinalysis dipstick assessments: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH.
i. Samples for ADAMTS13 activity, ADAMTS13 antigen, VWF:RCo, VWF:Ag, VWF multimer analysis in adult and adolescent subjects (≥12 years of age) will done according to Table 11. Sampling for pediatric subjects (<12 years of age) will be done according to Table 12. Samples specific to PK-III are found in Table 13
j. Immunogenicity assessments and antibodies to other proteins: BAX 930 binding antibody, plasma-derived ADAMTS13 and BAX 930 neutralizing antibody and anti-CHO protein antibodies. ADAMTS13 specific IgE antibodies will be assessed in case of allergic reactions as an additional safety measure.
k. Viral serology: anti-HIV 1, HIV 2, anti-HAV, HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HEV, and anti-parvovirus B19 will be tested at screening and at completion of standard of care treatment. CD4 levels will be determined at screening in HIV-positive subjects.
l. Genetic testing: cell pellet (buffy coat and erythrocytes) will be retained for ADAMTS13 gene mutational analysis unless the information is already available.
m. Only if not available in subject's medical history.
n. Sampling within 60 ±5 min following infusion
o. Serum or urine pregnancy test should be done locally; if not available, serum pregnancy test will be done centrally. Negative pregnancy test is required no more than 7 days before first dosing for subjects receiving first administration of BAX 930 at PK infusion #1, or receiving first administration of BAX 930 at PK infusion #2.
p. Only platelet count is required to be run locally; local lab results should be entered in CRF
q. Only LDH is required to be run locally; local lab results should be entered in CRF.
r. Immunogenicity assessments should be run every 4 weeks and at the last IP infusion visit of in Period 3. All antibody samples should be collected prior dosing.
s. If an Interval Study Visit and Prophy Dosing Visit are combined, all laboratory samples applicable to both visits will be collected but CBC and Clinical Chemistry assessments will not be performed twice.
t. If subject is symptomatic and cardiac markers are abnormal, testing will be repeated at dosing until it becomes normal. If cardiac markers are normal, it will not be re-tested.

Table 9. Clinical Laboratory Assessments: Prophylaxis Treatment (Prophylaxis Cohort)*

Assessments	Screening Visit	SoC PK Infusion and BAX 930 PK Infusion #1, 2, 3, 4& 5[a,b]	Prophy Dosing Visits (Every 2 weeks ±2 day[c])	Interval Study Visits (Every 3 months ±2 weeks during SoC and BAX 930 treatment phases of Periods 1, 2, & 3 to align with dosing visits)[s]	Acute TTP event Dosing Visits (Daily until 2 days following the resolution of the acute TTP event)	Study Completion/ Termination Visit[d] 28 ±3 days after the last IP infusion

u. Blood samples collected from subjects <18 years of age, for exploratory outcome measures, can be collected at the discretion of the investigator and are not to exceed the local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits.
v. Testing is only applicable if available at local laboratory.

* Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

Table 10. Clinical Laboratory Assessments: Acute Treatment (On-Demand Cohort)*

Assessments	Screening Visit[a]	Dosing Visits (Daily until 2 days following the resolution of the acute TTP event)	Study Completion/ Termination Visit[b] 28 ±3 days after the last IP infusion
Complete Blood Count[c]	C	C, L[l]	C
Clinical Chemistry[d]	C	C, L[m]	C
Urinalysis[e]	C		C
Pre-Infusion ADAMTS13		C[f]	
Post-Infusion ADAMTS13		C[g]	
Immunogenicity[h]	C		C
cTnT, cTnI, CK-MB[p]	L[q]	L[o,q]	L[q]
S100B, NSE[p]	C	C	C
Viral Serology[i]	C[i]		C[i]
Genetic Testing[j]	C		
Blood Group[k]	L		
Pregnancy Test	L[n]/C		C
Coombs test		L[f]	
Evaluation of Schistocytes		L[f]	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Testing at central laboratory; CBC=complete blood count; CD4=cluster of differentiation 4; CHO=Chinese hamster ovary; CK-MB=creatine kinase myocardial band; cTnI=cardiac troponin I; cTnT=cardiac troponin T; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; L=Testing at local laboratory; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NSE=neuron-specific enolase; PK=pharmacokinetic; RBC=red blood cell; SoC=Standard of Care; S100B= calcium binding protein B; TTP=thrombotic thrombocytopenic purpura; VWF=von Willebrand factor; VWF:Ag=von Willebrand factor: antigen; VWF:RCo=von Willebrand factor: ristocetin cofactor activity

a. Subjects in the on-demand cohort will have their screening and first dosing visit on Day 1
b. Also applies to subjects who prematurely withdraw from the study.
c. CBC: RBC count, hemoglobin, hematocrit, haptoglobin, reticulocyte count, MCV, MCH, MCHC, leukocytes (i.e., white blood cell count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, and neutrophils) and platelet counts.
d. Clinical chemistry assessments: sodium, potassium, chloride, ALT, AST, LDH, bilirubin, albumin (screening only), alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.
e. Urinalysis dipstick assessments: erythrocytes, specific gravity, urobilinogen, ketones, glucose, protein, bilirubin, nitrite, and pH.
f. Sampling within 60 min prior to start of infusion
g. Sampling within 60 ±5 min following infusion
h. Immunogenicity assessments and antibodies to other proteins: anti-ADAMTS13 antibody (binding and neutralizing) and anti-CHO protein antibodies. Anti-ADAMTS13 Ab and anti-CHO Ab samples should be collected prior dosing. ADAMTS13 specific IgE antibodies will be assessed in case of allergic reactions as an additional safety measure.
i. Viral serology: anti-HIV 1, HIV 2, anti-HAV, HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HEV, and anti-parvovirus B19 will be tested at screening and at completion of standard of care treatment. CD4 levels will be determined at screening in HIV-positive subjects.
j. Genetic testing: cell pellet (buffy coat and erythrocytes) will be retained for ADAMTS13 gene mutational analysis unless the information is already available.
k. Only if not available in subject's medical history.
l. Only platelet count is required to be run locally; local lab results should be entered in eCRF
m. Only LDH is required to be run locally; local lab results should be entered in eCRF
n. Serum or urine pregnancy test should be done locally; if not available, serum pregnancy test will be done centrally. Negative pregnancy test required no more than 7 days before first dosing

Table 10. Clinical Laboratory Assessments: Acute Treatment (On-Demand Cohort)*

Assessments	Screening Visit[a]	Dosing Visits (Daily until 2 days following the resolution of the acute TTP event)	Study Completion/ Termination Visit[b] 28 ±3 days after the last IP infusion

o. If subject is symptomatic and cardiac markers are abnormal, testing will be repeated at dosing until it becomes normal. If cardiac markers are normal, it will not be re-tested.
p. Blood samples collected from subjects <18 years of age, for exploratory outcome measures, can be collected at the discretion of the investigator and are not to exceed the local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits.
q. Testing is only applicable if available at local laboratory.

* Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

Table 11. Adult and Adolescent Subjects (≥12 Years of Age) PK Laboratory Assessments

Procedure/ Assessment	Within 1 hr pre-inf[e]	15 ±5 min	60 ±5 min	3 ±0.5 hr	9 ±2 hr	24 ±2 hr	72 ±4 hr	120 ±12 hr	168 ±12 hr	216 ±24 hr	288 ±24 hr
CBC with differential[a]	X	X			X	X	X			X	X
Serum chemistry panel[b]	X				X	X	X			X	X
cTnT, cTnI, CK-MB, NSE, S100B[c]	X				X	X	X	X	X		X
PK[d/f]	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[g]	X										

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; CK-MB=creatine kinase myocardial band; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NSE=neuron-specific enolase; PK=pharmacokinetic; RBC=red blood cell; cTnT=cardiac troponin T; cTnI=cardiac troponin I; WF=von Willebrand factor; VWF:Ag=von Willebrand factor: antigen; VWF:RCo=von Willebrand factor: ristocetin cofactor activity

a. CBC: RBC count, hemoglobin, hematocrit, haptoglobin, reticulocyte count, MCV, MCH, MCHC, leukocytes (i.e., white blood cell count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts
b. Clinical chemistry assessments: sodium, potassium, chloride, ALT, AST, LDH, bilirubin, albumin (screening only), alkaline phosphatase, blood urea nitrogen, creatinine, and glucose
c. Blood samples collected from subjects <18 years of age, for exploratory outcome measures, can be collected at the discretion of the investigator and are not to exceed the local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits.[xxi]
d. ADAMTS13 activity, ADAMTS13 antigen, VWF:RCo, VWF:Ag, and VWF multimer pattern.
e. 1mL of fresh frozen plasma from each bag infused will be drawn and analyzed for ADAMTS13:Ag and ADAMTS13 activity.
f. PK sampling for subjects undergoing Q1W should not be performed at 168±12hrs, 216±12hrs and 288±12hrs timepoints, after PK Infusion #1, PK assessments up to 168±12hrs timepoint should be performed after PK Infusion #2
g. Sampling will be conducted within 60 min prior to start of infusion. Immunogenicity assessments and antibodies to other proteins: BAX 930 binding antibody, plasma-derived ADAMTS13 and BAX 930 neutralizing antibody and anti-CHO protein antibodies. ADAMTS13 specific IgE antibodies will be assessed in case of allergic reactions as an additional safety measure

[xxi] Maximum allowable blood draw volumes. Seattle Children's Hospital website. www.seattlechildrens.org/pdf/blood-volume-chart.pdf. Updated August 21, 2001. Accessed January 27, 2017.

Table 12. Pediatric (<12 Years of Age) PK Laboratory Assessment Adolescent Subjects*

Procedure/Assessment	Within 1 hr pre-inf[e]	30 ±5 min	12 ±2 hr	24 ±2hr	48 ±2 hr	96 ±2 hr	168 ±4 hr
CBC with differential[a]	X				X		
Serum chemistry panel[b]	X				X		
TnT, TNI, CK-MB, NSE, S100B[c]	X				X		X
PK[d]	X	X	X	X	X	X	X
Immunogenicity[f]	X						

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; CK-MB=creatine kinase myocardial band; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NSE=neuron-specific enolase; PK=pharmacokinetic; RBC=red blood cell; cTnT=cardiac troponin T; cTnI=cardiac troponin I; WF=von Willebrand factor; VWF:Ag=von Willebrand factor: antigen; VWF:RCo=von Willebrand factor: ristocetin cofactor activity

a. CBC: RBC count, hemoglobin, hematocrit, haptoglobin, reticulocyte count, MCV, MCH, MCHC, leukocytes (i.e., white blood cell count) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts
b. Clinical chemistry assessments: sodium, potassium, chloride, ALT, AST, LDH, albumin (screening only),bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose
c. Blood samples collected from subjects <18 years of age, for exploratory outcome measures, can be collected at the discretion of the investigator and are not to exceed the local EC and applicable regulatory guidelines for daily and monthly maximum blood volume limits
d. ADAMTS13 activity, ADAMTS13 antigen, VWF:RCo, VWF:Ag, VWF multimer pattern. Timepoints may be adjusted to optimize the sampling scheme as pediatric data become available.
e. 1 mL of fresh frozen plasma from each bag infused will be drawn and analyzed for ADAMTS13:Ag and ADAMTS13 activity.
f. Sampling will be conducted within 60 min prior to start of infusion. Immunogenicity assessments and antibodies to other proteins: BAX 930 binding antibody, plasma-derived ADAMTS13 and BAX 930 neutralizing antibody and anti-CHO protein antibodies. ADAMTS13 specific IgE antibodies will be assessed in case of allergic reactions as an additional safety measure

* Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

Table 13. End of Study, PK-III Assessment, PK Laboratory Assessments by Age

	Within 1 hr pre-inf	15 ±5 min	30 ±5 min	60 ±5 min	9±2hr	72 ±8 hr	168 ±12 hr	288±24 hr[b]
Adult and adolescent subject ≥12 years[a,c]	X	X		X	X	X		X
Pediatric subjects <12 years[a,c,d]	X		X		X	X	X	X

a. ADAMTS13 activity, ADAMTS13 antigen. Timepoints may be adjusted to optimize the sampling scheme as pediatric data become available.
b. PK sampling for subjects on Q1W treatment should not be performed at 288±24 hours.
c. Vital signs should be collected at the same time points that blood samples are collected.
d. Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1.

20.5 Contraceptive Methods for Female Subjects of Childbearing Potential

In this study, subjects who are women of childbearing potential must agree to utilize a highly effective contraceptive measure throughout the course of the study and for 30 days after the last administration of investigational product. In accordance with the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials (version 2014-09-15)[xxii], birth control methods which may be considered as highly effective include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable[xxiii]
- Intrauterine device (IUD)[xxiii]
- Intrauterine hormone-releasing system (IUS)[xxiii]
- Bilateral tubal occlusion[xxiii]
- Vasectomised partner(s)[xxiii]
- Sexual abstinence during the entire study period

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

[xxii] Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials: cTTP://www.hma.eu/fileadmin/dateien/ Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

[xxiii] Contraception methods that are considered to have low user dependency.

20.6 Contraceptive Method for Male Subjects

In this study, sexually active males with women of childbearing potential must use an acceptable and effective method of contraception (such as condom with spermicide) during the treatment and until a minimum of 16 days after the last dose of IP administered.

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Appendix 1 Country-Specific Information

The following study procedure adaptations pertain to sites in Germany only.

Appendix 1.1 Physical Examinations

At study sites in Germany, subjects will have physical examinations at Screening and every 3 months (±2 weeks), until study completion/termination.

Appendix 1.2 12-lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be measured at screening, 3 and 6 months of first IP treatment period, before the start of Period 3 and at study completion/termination.

See Table A1 for the country-specific complete Schedule of Events.

Table A1 Germany Study Sites: Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[q,t]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	
Informed Consent[f]	X															
Eligibility Criteria	X															
Randomization[n]		X[n]						X								
Medical History	X															
ECG	X					X[o]	X[o]					X[o]				X
Physical Exam	X					X[p]	X[p]					X[p]				X
Concomitant Medications and non-Drug Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Infusion[g] (see Section 9.2.1)		X		X[h]		X	X	X		X[h]		X	X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratories[i]	X	X[j]	X[j]	X[j]	X[j]	X	X	X[j]	X[j]	X[j]	X[j]	X	X	X	X	X
Vital Signs	X	X[j]	X[j]	X[j]	X[j]	X[m]	X[m]	X[j]	X[j]	X[j]	X[j]	X[m]	X	X	X	X
Height/ Weight[k]	X	X[k]		X[k]		X[k]	X[k]	X[k]		X[k]		X[k]	X[k]		X[k]	X
Pediatric Development Markers[s]	X					X	X					X				X

Table A1 Germany Study Sites: Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[q,t]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e]
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	28 ±3 days after the last IP infusion
HRQoL[l]	X[r]					X[r]	X[r]					X[r]				X[r]
Schedule Next Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=Testing at central laboratory; CBC=complete blood count; CD4=cluster of differentiation 4; CHO=Chinese hamster ovary; ECG=electrocardiogram; EQ-5D-3L=EuroQol 5 Dimensions Questionnaire 3-Level; EQ-5D-Y=EQ-5D-youth; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRQoL=health related quality of life; cTTP=congenital thrombotic thrombocytopenic purpura; IP=investigational product; L=Testing at local laboratory; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; Ped QL=Pediatric Quality of Life Inventory; PK=pharmacokinetic; PRO=patient reported outcome; RBC=red blood cell; SF-36=36-Item Short Form Health Survey; SoC=Standard of Care; TSQM-9=Treatment Satisfaction Questionnaire for Medication; TTP=thrombotic thrombocytopenic purpura; VWF=von Willebrand factor; VWF:Ag=von Willebrand factor: antigen; VWF:RCo=von Willebrand factor: ristocetin cofactor activity

Note: Subjects of less than 18 years of age will be enrolled according to the criteria defined in Table 5.

a. The length of Period 1 and Period 2 is 6 months each. If a subject cannot switch to the next period at the end of month 6, due to either logistic or medical reasons, the length of Period 1 and Period 2 can be extended to up to 7 months. For subjects enrolled before November 2017, Period 1 can be extended to up to 24 months. The length of Period 3 is 6 months or until the continuation study is open at the subject's study site.
b. If the subject received SoC agent to treat an acute episode of TTP, at least 15 days (360 hr) must have elapsed and the subject must not show any TTP-related symptoms.
c. See Table 11 for adult visit schedule. See Table 12 for pediatric visit schedule. See Table 14 for PK-III adult and pediatric visit schedule.
d. Assumes Q2W dosing. Visit schedule and accompanying tests should be modified based on dosing frequency (see Section 9.2.1.3 for SoC dosing and Section 9.2.1.4 for BAX 930 dosing). For subjects on Q1W treatment will draw labs on Q2W schedule. Subjects on Q3W SoC treatment should have labs, vital signs and all assessment at the time of their visits according to the Q3W schedule.
e. Also applies to subjects who prematurely withdraw from the study.
f. Occurs at enrollment (prior to any study-specific procedure).
g. Subjects requiring a vaccination during the course of treatment should schedule the vaccination administration within 72 hours after a prophylactic treatment dose. Subjects receiving a COVID-19 vaccination during the study period should be monitored frequently by telephonic health checks and for thrombocytopenia for 14 consecutive days following vaccination, as deemed appropriate by the investigator. Elective surgeries should be scheduled 24 hours after the last prophylactic dose and ADAMTS13 levels should be monitored after surgery.

Table A1 Germany Study Sites: Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[q,t]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	

h. The infusion (SoC, BAX 930 ORT, or BAX 930 SIN depending on randomization) on Day 13 is to be administered after the 288-hr PK sample has been collected.
i. For laboratory assessments, see Table 9.
j. PK assessments will be done at the following timepoints post-PK infusion for subjects undergoing Q2W and Q3W: 15 ±5 min, 60±5 min, 3±0.5 hr, 9±2 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 hr, 216±24 hr, and 288±24 hr. Vital signs for adult and adolescent subjects (≥12 years of age), should be recorded within 1 hr before PK infusion and at the following timepoints post infusion: 15±5 min, 60±5 min, 3±0.5 hr, 9±2 hr, 24±2 hr, 72±4 hr, 120±12 hr, 168±12 hr, 216±24 hr, and 288±24 hr. For pediatric subjects (<12 years of age), vital signs should be recorded within 1 hr before PK infusion and at the following timepoints post infusion: 30±5 min, 12±2 hr, 24±2 hr, 48±2 hr, 96±2 hr and 168±4 hr. Note that, subject to discussion and agreement with the Sponsor, blood collection timepoints for pediatric subjects <6 years of age may be adjusted and/or omitted and the timing of assessments associated with blood collections will be adjusted accordingly; refer also to Section 11.3.1 and Section 12.2.1. PK Post-Infusion Laboratory Assessments for subjects undergoing Q1W dosing should not be performed at 168±12 hrs, 216±12 hrs and 288±12 hrs timepoints, after PK Infusion #1. However, PK assessments up to 168±12 hrs timepoint should be performed after PK Infusion #2, and PK #3. Please refer to the tables below to see the assessment schedule for subjects undergoing Q1W dosing. PK timepoints for subjects in Q3W dosing will be the same as subjects on Q2W dosing.
k. Height will be measured at screening only for subjects >=12 years of age. Height will be measured at screening, Visit1/Day 1, dosing visits and at study completion/termination for subjects <12 years of age. Weight will be measured for all subjects at screening, Day 1, PK 2 infusion (if BAX 930 is being administered for this infusion), PK 3 infusion, PK 4 infusion, PK 5 infusion, prophy dosing visits and at study completion/termination.
l. SF-36v2, TSQM-9, EQ-5D-3L or EQ-5D-Y, PedsQL, and a cTTP-specific PRO and health-resource use items.
m. Vital signs will be collected at each dosing visit within 1 hour before and after PI infusion.
n. Randomization can be done on day 1 or the day before day 1. IP dispensation will be allowed on the day before the visit.
o. ECG will be measured at screening, 3 and 6 months of the first IP treatment period (Period 1 or Period 2, depending on randomization), before the start of Period 3 and at study completion.
p. Physical examination will be performed at screening and every 3 months (±2 weeks), until study completion/termination.
q. PK-III assessments may be subjects in the prophylactic cohort who initiate the study with BAX 930 SIN, including a minimum of 4 adult (≥18 years), and 2 pediatric (0-17 years) subjects who receive BAX 930 SIN in Period 3 on a voluntary basis. It will be required for pediatric subjects (<12 years old) and subjects who receive a weekly (Q1Week) dosing regimen.
r. HRQoL assessments will be conducted only at the screening visits and at the end of the period (i.e., the last visit in the period, or at the early termination visit, if applicable).
s. For subjects <6 years old, pediatric growth, development, and cognitive performance will be assessed if/when applicable, per the Investigator's discretion.

Table A1 Germany Study Sites: Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort

Procedures/ Assessments	Screening Visit Day -28 to 0	PK-I				Period 1 Prophylaxis (6 months)[a]	Period 2 Prophylaxis (6-months)[a]	PK-II				Period 3 Prophylaxis (6 months)[a]	PK-III[q,t]		Period 1, 2, or 3 Acute TTP Event	Study Completion/ Termination Visit[e] 28 ±3 days after the last IP infusion
		PK 1 Infusion	PK 1 blood draws[c,i]	PK 2 Infusion[b] ±2 days	PK 2 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 3 Infusion[b] ±2 days	PK 3 blood draws[c,i]	PK 4 Infusion[b] ±2 days	PK 4 blood draws[c,i]	Bi-Weekly Follow up Study Visits (Q2 week+/ -2 days for 6 months[a,d]	PK 5 Infusion[b] ±2 days	PK 5 blood draws[c,i]	As Needed	

t. Subjects enrolling into the continuation study will be allowed to remain in the 281102 study until the continuation study is open for enrolment. After the last IP Infusion, subjects will be enrolled and followed in the continuation study. Subjects who experience an acute TTP event will be treated with the assigned treatment at the time of said acute TTP event, before rolling over into the continuation study.

3. SUMMARY OF CHANGES FROM PREVIOUS VERSION

An overview of the updates incorporated into Amendment 11 and 13 is provided in the Table below

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
[redacted], MD was added as the signatory Investigator on the protocol signature page.	To reflect current study monitoring**.**	Protocol Signature Page Section 1, Study Personnel
The estimated study completion date was changed from June 2023 to January 2024.	Based on current enrollment patterns and delays related to the COVID-19 public health emergency, the estimated completion date is expected to be extended.	Section 4, Synopsis
An interim assessment may be conducted in 30 evaluable adult (≥18 years old) or adolescent (>12-≤17 years old) subjects from the prophylactic treatment group upon completion of PK-II by all subjects (ORT and SIN material crossover PK)	For a regulatory filing in the US, pending evidence of biocomparability between BAX 930 ORT and BAX 930 SIN, and FDA agreement for such filing	Section 4, Synopsis Section 9.2 Section 14.4 Section 14.4.4.1
Subjects who are excluded from PK-II; Pediatric subjects (<12 years old), subjects who receive a weekly (Q1Week) dosing regimen, and on demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort, will undergo a PK-III assessment.	In these subjects, an initial PK assessment (PK-I) with BAX 930 ORT and an end-of-study PK assessment (PK-III) with BAX 930 SIN, is sufficient to investigate the effect of BAX 930 ORT versus BAX 930 SIN on PK parameters.	Section 4, Synopsis Section 9.2.1.1.3 Section 20.3 (Table 7)
The total duration of the study is increased from 60 months to 70 months.	Enrollment delays related to COVID-19 has extended the estimated study duration.	Section 4, Synopsis Section 9.3
Exploratory outcome measures 1-3 were updated, by replacing the text, “subacute manifestations”, with “cTTP manifestations”. Footnote “a” was added for context.	These exploratory outcome measures were updated to reflect accuracy of the measurement and alignment with the information provided in Table 3. A footnote was added to explain the definition of *composite*.	Section 4, Synopsis Section 9.4.3 Section 14.4.3
Assessment of von Willebrand factor (VWF) multimer patterns will be evaluated as an exploratory endpoint. The new exploratory outcome measure aims to assess PD biomarkers including but not limited to VWF multimer patterns, ADAMTS13 mediated VWF cleavage products, and coagulation readouts, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment.	Alignment with intended use of data, i.e., for exploratory biomarker analyses.	Section 4, Synopsis Section 8.3.3 Section 8.4 Section 9.4.2.3 Section 9.4.3 Section 14.4.2.3.2

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Text was updated to reflect removal of the staggered pediatric enrollment. Pediatric subjects 0 to <12 years and 12 to ≤17 years may initiate Period 1 without a staggered enrollment approach.	No safety or immunogenicity concerns with BAX 930 have been identified in adult or pediatric subjects based on preliminary safety data and information from named-patient treatment of a neonate with BAX 930. The goal of the staggered approach, to introduce the youngest subjects after adequate safety and immunogenicity data were available from adults and the older pediatric population, is no longer required to support the safety of BAX 930 in pediatric subjects. Safety data from the adult and adolescent subjects currently enrolled in this study, coupled with the lack of adverse reactions and positive tolerability observed in the named-patient neonate, support the removal of the staggered enrollment approach. the Data Monitoring Committee endorsed removing the staggered enrollment approach.	Section 4, Synopsis Section 9.1 Section 9.2 Section 20.2.1
The total number of subjects was redefined as follows; **Prophylactic cohort:** Approximately 36 adult (≥18 years old) subjects and 12 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects. **On-demand cohort:** Approximately 6 adult (≥18 years old) subjects and 3 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects.	Due to the low global prevalence of congenital thrombotic thrombocytopenic purpura (cTTP; resulting in a low number of eligible study subjects), coupled with the current enrollment status of this study, it was determined that a wide range of total subjects (36-68 subjects) is no longer appropriate. The updated approximate number of subjects reflects the current, observed enrollment patterns and accounts for a 10% dropout rate.	Section 4, Synopsis Section 7.3 Section 14.1 Section 20.1 (Figure 1 and Figure 2)
After 30 September 2021, screened subjects in the prophylactic cohort may initiate the study with BAX 930 SIN.	A clear cut-off date of 30 September 2021 was established to provide guidance on switching subjects from BAX 930 ORT material to BAX 930 SIN material.	Section 4, Synopsis Section 9.2.1.2 Section 9.2.2.1 Section 20.2.1

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Figure 2 was generated to depict study flow in subjects who begin the study on BAX 930 SIN material. Figure 1 and Figure 2 were edited to reflect the updated study sample size and the addition of the PK-III assessment.	Figure 1 was updated to reflect additional study components. Figure 2 was added to improve study design clarity.	Section 20.1, Study Flow Chart (Figure 1 and Figure 2)
Secondary efficacy outcome measures text was changed from "number and incidence of acute TTP episodes…" to "proportion of acute TTP episodes…"	The proportion of subjects with TTP episodes more clearly reflects the goals of the secondary objective of the study, which is to determine the number of subjects who experience acute TTP episodes with BAX 930 vs standard of care (SoC).	Section 4, Synopsis Section 9.4.2.1 Section 14.4.2.1
Text was added to reflect the option of at-home BAX 930 infusions for subjects receiving prophylactic treatment.	At-home infusions reduce subject burden and COVID-19-related risks.	Section 4, Synopsis Section 9.1 Section 9.2 Section 11.7
An interim analysis will be performed after 30 adult (≥18 years old) or adolescent (>12-≤17 years) subjects in the prophylactic cohort complete the study. All data collected by that time point in Study 281102, as well as the continuation Study TAK-755-3002 will be included in the statistical analysis. Data generated from this interim analysis will be used in the first data filing for an FDA submission. The interim analysis will include final data from at least 30 subjects in the prophylactic cohort who completed the study.	The population of subjects included in the interim analysis was further defined for clarity.	Section 4, Synopsis Section 9.2 Section 14.4.4.1
Text was updated to describe that subjects receiving factor VIII:VWF concentrates prophylactic treatments qualify for a reduced SoC pharmacokinetic (PK) washout period of 5 days.	Factor VIII contains very small amounts of ADAMTS13 (circulation levels of 0.1 IU/mL or below expected to be achieved within 5 days) (Peyvandi et al., 2013).	Section 9.2.1
Text was clarified to describe that adult and adolescent subjects (≥12 years old) who enroll in the study with BAX 930 ORT material will undergo two randomized crossover PK assessments. This will include PK-I (BAX 930 ORT and SoC) and PK-II (BAX 930 ORT and BAX 930 SIN).	Protocol text was revised to clarify that adult and pediatric subjects will initiate the study with PK-I (BAX 930 ORT and SoC) and subsequently receive BAX 930 ORT. Subjects who are screened after 30 September 2021 will not receive BAX 930 ORT. In this case, the subjects will initiate the study with BAX 930 SIN, PK-I will consist of a crossover between BAX 930 SIN and SoC and no PK-II will be conducted.	Section 9.2 Section 9.2.1.1.2

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
A brief summary and rationale for this protocol amendment was updated to include the removal of staggered pediatric enrollment, named-patient favorable outcome to treatment, availability of at-home infusions, and switching of BAX 930 material production from Orth, Austria, to Singapore. Crossover comparability PK assessments will be conducted to ensure safety.	The summary and rationale were updated to promote safe and logistically appropriate conduct of this trial.	Section 9.1
Clarifying text was added to explain that once subjects begin on-demand treatment with newly available BAX 930 SIN, subjects will continue prophylactic treatment with BAX 930 SIN.	Text was added for clarity.	Section 9.2.2.1
Clarifying text was added to explain that subjects in the prophylactic cohort who enroll with BAX 930 SIN will have a randomized crossover PK comparison with SoC in PK-I. PK-II is not applicable in these subjects. Following PK-I these subjects will go through Periods 1, 2, and 3 with BAX 930 SIN.	Protocol text was revised to clarify that adult and adolescent subjects will initiate the study with PK-I (BAX 930 ORT and SoC) and subsequently receive BAX 930 ORT. Subjects who are screened after 30 September 2021 will initiate the study with BAX 930 SIN. In this case, PK-I will consist of a crossover between BAX 930 SIN and SoC and no PK-II will be conducted.	Section 4, Synopsis Section 9.2.1
Standard of care treatment administered as the Investigator's best judgment should include ADAMTS13 in a quantifiable dose. The administered dose will be recorded. Subjects who experience an allergic reaction to ADAMTS13-containing forms of SoC may be discontinued from the study.	For proper PK evaluation, ADAMTS13 must be detectable in blood samples as a result of a specific given dose.	Section 9.2.2 Section 9.7.3 Section 10.3
Recording of subject (patient) reported outcomes will be captured with electronic diaries, and a web-backup option will be available for temporary use.	Paper diaries are no longer appropriate for the purpose of this clinical trial.	Section 11.5
Text was added to clarify that subject-reported outcomes will also be measured at the termination visit.	Text was added for clarity.	Section 11.5 Section 13.9 Table 4 Section 20.3 (Table 7)
Compliance will be monitored at at-home visits by a licensed healthcare professional.	Compliance will be captured at-home to accommodate for subjects receiving IV infusions at home	Section 11.7

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Subjects with reported ongoing AEs at the end-of-study visit, who move on to the continuation study prior to the end of the 30-day AE follow up period will have all AE-related information captured and locked in the eCRF of Study 281102. At the time of enrollment into the continuation study, details surrounding an ongoing AE will be imported from Study 281102 into the subject's eCRF for Study TAK-755-3002. Resolution of an AE that occurs in 281102, but is resolved in TAK-755-3002, will be captured in the subject's eCRF for TAK-755-3002 only. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE).	Clarifying text was added to capture AE reporting for subjects who enter the continuation study prior to AE resolution in the pivotal, 281102 study.	Section 13.1.2
The biochemical marker, creatine kinase myocardial band fraction (CK-MB) will be measured at a local laboratory rather than at the central laboratory.	CK-MB is a key cardiovascular biomarker. A local laboratory will have the ability to return test results more quickly than a central laboratory.	Section 13.7.3 Section 20.4 (Table 9 and Table 10)
Alternative approaches to data monitoring may be employed to maintain data quality and integrity, and subject safety.	In-clinic visits may be limited due to global COVID-19 pandemic. Alternative monitoring approaches may be employed to decrease risk to study subjects.	Section 17
The list of clinical laboratory assessments was updated to include the following biomarkers; cTnT, cTnI, CK-MB, S100B, and NSE.	These are biomarkers of organ damage (heart, brain) that will be analyzed as part of the exploratory endpoints	Section 20.4 (Table 9 and Table 10)
An end-of-study, PK-III assessment may be implemented for a subset of subjects including; 1) Any subject in the prophylactic cohort, including any subject who switches from on-demand treatment to prophylactic treatment, who initiates the study with BAX 930 SIN, and 2) A minimum of 4 adults (≥18 years old), and a minimum of 2 pediatric or adolescent subjects (age 0-17 years) who received BAX 930 SIN in Period 3. Subjects who do not initiate the clinical trial with BAX 930 SIN may voluntarily opt for a PK-III assessment, regardless of the treatment administered at study initiation.	PK-III is added to assess the impact of time on long-term exposure to BAX 930 SIN.	Section 4, Synopsis Section 8.3.3 Section 9.2 Section 9.2.1.1.3 Section 9.2.2 Section 12.2 Section 20.1 (Figure 1 and Figure 2) Section 20.3 (Table 7 and Table 13)

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Pediatric subjects (<12 years old), subjects who receive a weekly (Q1Week) dosing regimen, and on demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort, will undergo a PK-III assessment. PK 5 infusion was added below the PK-III subheading in Table 7 to indicate sequential PK infusions and blood draws. Table 13 was added to indicate PK-III assessments and timepoints.		
The incidence of subacute manifestations in subjects receiving prophylactic treatment is added as an exploratory outcome measure.	The exploratory outcome measures were updated for accuracy and to reflect the exploratory objectives of this study	Section 4, Synopsis Section 8.4 Section 9.4.3
The impact of immunogenicity on ADAMTS13 PK parameters and pharmacodynamic (PD) variables is included as a PK/PD study objective and will be assessed as a secondary PK/PD outcome measure, accordingly.	The impact of immunogenicity on PK/PD is included to present a more comprehensive understanding of potential SoC or BAX 930-derived immunogenicity, beyond the previous, limited scope of safety and efficacy.	Section 4, Synopsis Section 8.3.3 Section 9.4.2.3 Section 20.4 (Table 11 and Table 12)
The following exploratory objective measure was added, "to characterize the PK profile of ADAMTS13 activity at the end of the study".	This exploratory objective was added to highlight the importance of characterizing the PK profile of ADAMTS13 activity throughout the duration of the study.	Section 4, Synopsis Section 8.4
Subjects who experience an acute event will be treated with the assigned treatment at the time of said acute event, before rolling over into the continuation study.	Text was added for clarity in the case of an acute event.	Section 20.3 (Table 7)
Subjects who were unable to move into the prophylactic cohort due to data lock timelines may move into the continuation study.	Subjects in the on-demand cohort are likely to qualify for enrollment in the Phase 3b continuation study. This allowance gives subjects an opportunity to receive prophylactic treatment following lock timelines.	Section 20.3 (Table 8)
A footnote was added to Table 11 to indicate the immunogenicity assessments and antibody proteins to be measured as an additional safety measure.	Text was added as a footnote to clarify sampling and corresponds to safety immunogenicity objectives in the body of the protocol.	Section 20.4 (Table 11 and Table 12)
One month was defined as 28 days. Study participants are referred to as "subjects," instead of "subjects" and "patients" used interchangeably.	Text was added to improve clarity and accuracy.	Throughout document

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
The table numbering was updated throughout to reflect the removal of the previously numbered, Table 1 from the synopsis. Continuous table numbering is initiated in the body of the protocol only. The contents of the table in the synopsis is retained and is provided in Table 3 of the body of the protocol.	The Synopsis is a stand-alone document and should include external links to Sections or Tables in the body of the protocol.	Throughout the document

Summary of Change(s) Since Protocol Amendment 11 (Global)		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Subjects receiving a COVID-19 vaccination during the study period should be monitored frequently by telephonic health checks and for thrombocytopenia for 14 consecutive days following vaccination, as deemed appropriate by the investigator.	Based on safety concerns following the recent pause of the Johnson & Johnson and AstraZeneca COVID-19 vaccines, subjects receiving COVID-19 vaccinations during the study should be monitored closely as a safety precaution. This change was introduced following the submission of Protocol Amendment 11 (Global) in the US.	Section 9.2.1.3 Section 9.2.1.4 Section 20.3 (Table 7)

3. SUMMARY OF CHANGES FROM PREVIOUS VERSION

An overview of the updates incorporated into Amendment 11 is provided in the Table below

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
[redacted], MD was added as the signatory Investigator on the protocol signature page.	To reflect current study monitoring.	Protocol Signature Page Section 1, Study Personnel
The estimated study completion date was changed from June 2023 to January 2024.	Based on current enrollment patterns and delays related to the COVID-19 public health emergency, the estimated completion date is expected to be extended.	Section 4, Synopsis
An interim assessment may be conducted in 30 evaluable adult (≥18 years old) or adolescent (>12-≤17 years old) subjects from the prophylactic treatment group upon completion of PK-II by all subjects (ORT and SIN material crossover PK)	For a regulatory filing in the US, pending evidence of biocomparability between BAX 930 ORT and BAX 930 SIN, and FDA agreement for such filing	Section 4, Synopsis Section 9.2 Section 14.4 Section 14.4.4.1
Subjects who are excluded from PK-II; Pediatric subjects (<12 years old), subjects who receive a weekly (Q1Week) dosing regimen, and on demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort, will undergo a PK-III assessment.	In these subjects, an initial PK assessment (PK-I) with BAX 930 ORT and an end-of-study PK assessment (PK-III) with BAX 930 SIN, is sufficient to investigate the effect of BAX 930 ORT versus BAX 930 SIN on PK parameters.	Section 4, Synopsis Section 9.2.1.1.3 Section 20.3 (Table 7)
The total duration of the study is increased from 60 months to 70 months.	Enrollment delays related to COVID-19 has extended the estimated study duration.	Section 4, Synopsis Section 9.3
Exploratory outcome measures 1-3 were updated, by replacing the text, “subacute manifestations”, with “cTTP manifestations”. Footnote “a” was added for context.	These exploratory outcome measures were updated to reflect accuracy of the measurement and alignment with the information provided in Table 3. A footnote was added to explain the definition of *composite*.	Section 4, Synopsis Section 9.4.3 Section 14.4.3
Assessment of von Willebrand factor (VWF) multimer patterns will be evaluated as an exploratory endpoint. The new exploratory outcome measure aims to assess PD biomarkers including but not limited to VWF multimer patterns, ADAMTS13 mediated VWF cleavage products, and coagulation readouts, at baseline and following infusion of the SoC agent and BAX 930 treatment during the initial PK assessment.	Alignment with intended use of data, i.e., for exploratory biomarker analyses.	Section 4, Synopsis Section 8.3.3 Section 8.4 Section 9.4.2.3 Section 9.4.3 Section 14.4.2.3.2

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Text was updated to reflect removal of the staggered pediatric enrollment. Pediatric subjects 0 to <12 years and 12 to ≤17 years may initiate Period 1 without a staggered enrollment approach.	No safety or immunogenicity concerns with BAX 930 have been identified in adult or pediatric subjects based on preliminary safety data and information from named-patient treatment of a neonate with BAX 930. The goal of the staggered approach, to introduce the youngest subjects after adequate safety and immunogenicity data were available from adults and the older pediatric population, is no longer required to support the safety of BAX 930 in pediatric subjects. Safety data from the adult and adolescent subjects currently enrolled in this study, coupled with the lack of adverse reactions and positive tolerability observed in the named-patient neonate, support the removal of the staggered enrollment approach. the Data Monitoring Committee endorsed removing the staggered enrollment approach.	Section 4, Synopsis Section 9.1 Section 9.2 Section 20.2.1
The total number of subjects was redefined as follows; **Prophylactic cohort:** Approximately 36 adult (≥18 years old) subjects and 12 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects. **On-demand cohort:** Approximately 6 adult (≥18 years old) subjects and 3 adolescent (>12-≤17 years old) or pediatric (0-<12 years old) subjects.	Due to the low global prevalence of congenital thrombotic thrombocytopenic purpura (cTTP; resulting in a low number of eligible study subjects), coupled with the current enrollment status of this study, it was determined that a wide range of total subjects (36-68 subjects) is no longer appropriate. The updated approximate number of subjects reflects the current, observed enrollment patterns and accounts for a 10% dropout rate.	Section 4, Synopsis Section 7.3 Section 14.1 Section 20.1 (Figure 1 and Figure 2)
After 30 September 2021, screened subjects in the prophylactic cohort may initiate the study with BAX 930 SIN.	A clear cut-off date of 30 September 2021 was established to provide guidance on switching subjects from BAX 930 ORT material to BAX 930 SIN material.	Section 4, Synopsis Section 9.2.1.2 Section 9.2.2.1 Section 20.2.1

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Figure 2 was generated to depict study flow in subjects who begin the study on BAX 930 SIN material. Figure 1 and Figure 2 were edited to reflect the updated study sample size and the addition of the PK-III assessment.	Figure 1 was updated to reflect additional study components. Figure 2 was added to improve study design clarity.	Section 20.1, Study Flow Chart (Figure 1 and Figure 2)
Secondary efficacy outcome measures text was changed from "number and incidence of acute TTP episodes…" to "proportion of acute TTP episodes…"	The proportion of subjects with TTP episodes more clearly reflects the goals of the secondary objective of the study, which is to determine the number of subjects who experience acute TTP episodes with BAX 930 vs standard of care (SoC).	Section 4, Synopsis Section 9.4.2.1 Section 14.4.2.1
Text was added to reflect the option of at-home BAX 930 infusions for subjects receiving prophylactic treatment.	At-home infusions reduce subject burden and COVID-19-related risks.	Section 4, Synopsis Section 9.1 Section 9.2 Section 11.7
An interim analysis will be performed after 30 adult (≥18 years old) or adolescent (>12-≤17 years) subjects in the prophylactic cohort complete the study. All data collected by that time point in Study 281102, as well as the continuation Study TAK-755-3002 will be included in the statistical analysis. Data generated from this interim analysis will be used in the first data filing for an FDA submission. The interim analysis will include final data from at least 30 subjects in the prophylactic cohort who completed the study.	The population of subjects included in the interim analysis was further defined for clarity.	Section 4, Synopsis Section 9.2 Section 14.4.4.1
Text was updated to describe that subjects receiving factor VIII:VWF concentrates prophylactic treatments qualify for a reduced SoC pharmacokinetic (PK) washout period of 5 days.	Factor VIII contains very small amounts of ADAMTS13 (circulation levels of 0.1 IU/mL or below expected to be achieved within 5 days) (Peyvandi et al., 2013).	Section 9.2.1
Text was clarified to describe that adult and adolescent subjects (≥12 years old) who enroll in the study with BAX 930 ORT material will undergo two randomized crossover PK assessments. This will include PK-I (BAX 930 ORT and SoC) and PK-II (BAX 930 ORT and BAX 930 SIN).	Protocol text was revised to clarify that adult and pediatric subjects will initiate the study with PK-I (BAX 930 ORT and SoC) and subsequently receive BAX 930 ORT. Subjects who are screened after 30 September 2021 will not receive BAX 930 ORT. In this case, the subjects will initiate the study with BAX 930 SIN, PK-I will consist of a crossover between BAX 930 SIN and SoC and no PK-II will be conducted.	Section 9.2 Section 9.2.1.1.2

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
A brief summary and rationale for this protocol amendment was updated to include the removal of staggered pediatric enrollment, named-patient favorable outcome to treatment, availability of at-home infusions, and switching of BAX 930 material production from Orth, Austria, to Singapore. Crossover comparability PK assessments will be conducted to ensure safety.	The summary and rationale were updated to promote safe and logistically appropriate conduct of this trial.	Section 9.1
Clarifying text was added to explain that once subjects begin on-demand treatment with newly available BAX 930 SIN, subjects will continue prophylactic treatment with BAX 930 SIN.	Text was added for clarity.	Section 9.2.2.1
Clarifying text was added to explain that subjects in the prophylactic cohort who enroll with BAX 930 SIN will have a randomized crossover PK comparison with SoC in PK-I. PK-II is not applicable in these subjects. Following PK-I these subjects will go through Periods 1, 2, and 3 with BAX 930 SIN.	Protocol text was revised to clarify that adult and adolescent subjects will initiate the study with PK-I (BAX 930 ORT and SoC) and subsequently receive BAX 930 ORT. Subjects who are screened after 30 September 2021 will initiate the study with BAX 930 SIN. In this case, PK-I will consist of a crossover between BAX 930 SIN and SoC and no PK-II will be conducted.	Section 4, Synopsis Section 9.2.1
Standard of care treatment administered as the Investigator's best judgment should include ADAMTS13 in a quantifiable dose. The administered dose will be recorded. Subjects who experience an allergic reaction to ADAMTS13-containing forms of SoC may be discontinued from the study.	For proper PK evaluation, ADAMTS13 must be detectable in blood samples as a result of a specific given dose.	Section 9.2.2 Section 9.7.3 Section 10.3
Recording of subject (patient) reported outcomes will be captured with electronic diaries, and a web-backup option will be available for temporary use.	Paper diaries are no longer appropriate for the purpose of this clinical trial.	Section 11.5
Text was added to clarify that subject-reported outcomes will also be measured at the termination visit.	Text was added for clarity.	Section 11.5 Section 13.9 Table 4 Section 20.3 (Table 7)
Compliance will be monitored at at-home visits by a licensed healthcare professional.	Compliance will be captured at-home to accommodate for subjects receiving IV infusions at home	Section 11.7

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Subjects with reported ongoing AEs at the end-of-study visit, who move on to the continuation study prior to the end of the 30-day AE follow up period will have all AE-related information captured and locked in the eCRF of Study 281102. At the time of enrollment into the continuation study, details surrounding an ongoing AE will be imported from Study 281102 into the subject's eCRF for Study TAK-755-3002. Resolution of an AE that occurs in 281102, but is resolved in TAK-755-3002, will be captured in the subject's eCRF for TAK-755-3002 only. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE).	Clarifying text was added to capture AE reporting for subjects who enter the continuation study prior to AE resolution in the pivotal, 281102 study.	Section 13.1.2
The biochemical marker, creatine kinase myocardial band fraction (CK-MB) will be measured at a local laboratory rather than at the central laboratory.	CK-MB is a key cardiovascular biomarker. A local laboratory will have the ability to return test results more quickly than a central laboratory.	Section 13.7.3 Section 20.4 (Table 9 and Table 10)
Alternative approaches to data monitoring may be employed to maintain data quality and integrity, and subject safety.	In-clinic visits may be limited due to global COVID-19 pandemic. Alternative monitoring approaches may be employed to decrease risk to study subjects.	Section 17
The list of clinical laboratory assessments was updated to include the following biomarkers; cTnT, cTnI, CK-MB, S100B, and NSE.	These are biomarkers of organ damage (heart, brain) that will be analyzed as part of the exploratory endpoints	Section 20.4 (Table 9 and Table 10)
An end-of-study, PK-III assessment may be implemented for a subset of subjects including; 1) Any subject in the prophylactic cohort, including any subject who switches from on-demand treatment to prophylactic treatment, who initiates the study with BAX 930 SIN, and 2) A minimum of 4 adults (≥18 years old), and a minimum of 2 pediatric or adolescent subjects (age 0-17 years) who received BAX 930 SIN in Period 3. Subjects who do not initiate the clinical trial with BAX 930 SIN may voluntarily opt for a PK-III assessment, regardless of the treatment administered at study initiation.	PK-III is added to assess the impact of time on long-term exposure to BAX 930 SIN.	Section 4, Synopsis Section 8.3.3 Section 9.2 Section 9.2.1.1.3 Section 9.2.2 Section 12.2 Section 20.1 (Figure 1 and Figure 2) Section 20.3 (Table 7 and Table 13)

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
Pediatric subjects (<12 years old), subjects who receive a weekly (Q1Week) dosing regimen, and on demand subjects that were treated with BAX 930 SIN and continue into the prophylactic cohort, will undergo a PK-III assessment. PK 5 infusion was added below the PK-III subheading in Table 7 to indicate sequential PK infusions and blood draws. Table 13 was added to indicate PK-III assessments and timepoints.		
The incidence of subacute manifestations in subjects receiving prophylactic treatment is added as an exploratory outcome measure.	The exploratory outcome measures were updated for accuracy and to reflect the exploratory objectives of this study	Section 4, Synopsis Section 8.4 Section 9.4.3
The impact of immunogenicity on ADAMTS13 PK parameters and pharmacodynamic (PD) variables is included as a PK/PD study objective and will be assessed as a secondary PK/PD outcome measure, accordingly.	The impact of immunogenicity on PK/PD is included to present a more comprehensive understanding of potential SoC or BAX 930-derived immunogenicity, beyond the previous, limited scope of safety and efficacy.	Section 4, Synopsis Section 8.3.3 Section 9.4.2.3 Section 20.4 (Table 11 and Table 12)
The following exploratory objective measure was added, "to characterize the PK profile of ADAMTS13 activity at the end of the study".	This exploratory objective was added to highlight the importance of characterizing the PK profile of ADAMTS13 activity throughout the duration of the study.	Section 4, Synopsis Section 8.4
Subjects who experience an acute event will be treated with the assigned treatment at the time of said acute event, before rolling over into the continuation study.	Text was added for clarity in the case of an acute event.	Section 20.3 (Table 7)
Subjects who were unable to move into the prophylactic cohort due to data lock timelines may move into the continuation study.	Subjects in the on-demand cohort are likely to qualify for enrollment in the Phase 3b continuation study. This allowance gives subjects an opportunity to receive prophylactic treatment following lock timelines.	Section 20.3 (Table 8)
A footnote was added to Table 11 to indicate the immunogenicity assessments and antibody proteins to be measured as an additional safety measure.	Text was added as a footnote to clarify sampling and corresponds to safety immunogenicity objectives in the body of the protocol.	Section 20.4 (Table 11 and Table 12)
One month was defined as 28 days. Study participants are referred to as "subjects," instead of "subjects" and "patients" used interchangeably.	Text was added to improve clarity and accuracy.	Throughout document

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Purpose for Change**	**Section(s) Affected by Change**
The table numbering was updated throughout to reflect the removal of the previously numbered, Table 1 from the synopsis. Continuous table numbering is initiated in the body of the protocol only. The contents of the table in the synopsis is retained and is provided in Table 3 of the body of the protocol.	The Synopsis is a stand-alone document and should include external links to Sections or Tables in the body of the protocol.	Throughout the document

22. SUMMARY OF CHANGES

Protocol 281102: Global Amendment 9 2020 MAR 06

Replaces: Global Amendment 5 2018 DEC 06[xxiv]

In this section, changes from Global Protocol Amendment 5, dated 2018 DEC 06, are described and their rationale is given.

1. **Title page, throughout document**

   Description of Change:

   Addition of TAK-755, as the newer name given to SHP655 by its current sponsor, Baxalta, now part of Shire, at first mention.

2. **Throughout document**

   Description of Change:

   Syntax or grammar have been improved, or minor clarifications have been added.

3. **Section 1, Throughout document**

   Description of Change:

   Some study personnel were updated due to organizational changes.

4. **Section 3 Study Synopsis, Section 6.3, Section 8.2**

   Description of Change:

   - *6 more subjects have been added to the study, in the prophylaxis cohort. Subject Selection section updated accordingly.*
   - *Planned study period was changed, to reflect current situation.*
   - *It was clarified that prophy subjects will receive a cross-over PK evaluation after period 2 and once BAX 930 SIN is available with the exception of subjects enrolled prior the temporary study halt.*
   - *Study design was changed to remove information on a previous protocol amendment. Some clarifications were made to the text for example to clarify that Period 3 would last until the continuation study had opened at the subject's study site.*

[xxiv] This also replaces all local amendments that followed Global Amendment 5. However, only changes made to Global Amendment 5 are detailed in this section.

- *The statistical section was amended accordingly, and some clarifying statements were added.*
- *It was clarified that for subjects receiving factor VIII (FVIII):VWF concentrates, the minimum required SoC PK dose washout period may be reduced to 5 days.*

5. Section 7.3.4 Health Related Quality of Life and Resource Utilization

Description of Change:
Health Related Quality of Life and Resource Utilization moved to be included under secondary objectives.

6. Section 8.2 Overall Study Design

Description of Change:
Clarification regarding switching to BAX 930 SIN material added.

7. Section 8.2.1.1.1 PK-II

Description of Change: *Clarification regarding exclusion from PK-II assessments.*

8. Section 8.7.2 Administration

Description of Change:
Clarification regarding blood draw sampling and vital signs recording.

9. Section 10.2 Subject Identification Code

Description of Change: *Subject digit numbering system was updated.*

10. Section 10.5 Patient Reported Outcomes

Description of Change: *Information on subject diaries was clarified.*

11. Section 10.8 Acute events during PK Assessment

Description of Change:
Information on acute events during PK assessment was clarified.

12. Section 11.2 Assessment of Pharmacokinetics and Pharmacodynamics

Description of Change:
PK timepoints added for subjects undergoing Q1W dosing. PK assessments for subjects on Q3W clarified.

13. Section 12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Description of Change: *Update to SUSAR reporting section.*

14. **Section 12.7.5.5 VWF Multimer Analysis and ADAMTS13 mediated VWF cleavage products**

    Description of Change: *VWF multimer analysis was updated.*

15. **Section 12.7.6.2 Anti-CHO Protein**

    Description of Change:

    The following text was added:

    A positive result without known hypersensitivity to hamster proteins, such as a history of anaphylactic or anaphylactoid reactions or other severe allergic manifestations upon exposure to hamster-derived substances, will not constitute an exclusion criteria for randomization..

16. **Section 12.7.7 Viral Serology**

    Description of Change: *Information on viral serology testing was clarified.*

17. **Section 12.7.8 Genetic Testing**

    Description of Change: *HLA genotype determination was removed.*

18. **Section 12.7.9 Pregnancy Test**

    Description of Change: *Information on pregnancy test requirements was added.*

19. **Section 12.8 Vital Signs and 12-lead Electrocardiogram**

    Description of Change: *Timing of vital signs testing was clarified.*

20. **Section 12.9 Health-related Quality of Life / Table 5**

    Description of Change:
    PRO section- Ped QL was updated, clarifications were added.

21. **Section 13 STATISTICS,**
    Section 20 SUPPLEMENTS

    Description of Change:
    Changes to number of subjects in the study were reflected in the text; clarifications were made including the age groups in Tables 6a and 6b.

22. Section 20.3 Schedule of Study Procedures and Assessments / Table 7

Description of Change: *Table 7 updated to reflect changes in protocol procedures.*

23. Section 20.4 Clinical Laboratory Assessments / Table 9, Table 11, Table 12

Description of Change:
Tables 9 and 11 were updated and Table 12 was added to reflect changes in protocol procedures.

22. SUMMARY OF CHANGES

Protocol 281102: Global Amendment 5 2018 DEC 06

Replaces: Global Amendment 2 2017 MAY 09

In this section, changes from Global Protocol Amendment 2, dated 2017 MAY 09, are described and their rationale is given.

1. **Throughout the document**

   Description of Change:

   Particularly on the title page and all pages preceding the document text, changes have been made to make the document align better with the current Shire protocol template. The address of Baxalta US, Inc., has also been updated.

   Change of hereditary TTP to its current name: congenital TTP.

   Addition of SHP655, as the newer name given to BAX 930 by its current sponsor, Shire at first mention.

2. **Section 3 Study Synopsis**

   Description of Change:

   Nomenclature of BAX 930 adjusted to include its newer name: SHP655 at first instance.

   Study period updated to reflect current status

   PK comparability aspect of study added to reflect current planned study conduct

   Numbers of subjects for planned enrollment (ie sample size), enrollment of pediatric subjects, duration of time for subjects in the prophylaxis cohort, and planned study period dates and study duration were amended.

   Windows (+/-) were added to planned dose levels.

   Inclusion criteria were slightly amended/clarified.

   Small changes to the exclusion criteria were made.

   Specific information on the planned interim analysis was added.

3. Section 6.3

Description of Change:

Sample size amended from 60 to 62.

4. Section 6.4

Description of Change:

Description of Q97R sequence variant added.

5. Section 6.4.2.3

Mention of the Technozym ADAMTS13 activity ELISA removed.

6. Section 6.5

Description of Change:

Information on Q97R variant added.

7. Section 7.3.3

Description of Change:

PK/PD points added to reflect the PK comparability study.

8. Section 8.1

Description of Change:

Information on this amendment and its purpose was added, to specify study conduct after the temporary study halt.

9. Section 8.2

Description of Change:

Information on the PK comparability study and interim analysis were added to study design.

10. Section 8.3

Description of Change:

Length of subject participation in the study updated.

11. Section 8.5

Description of Change:

Additional randomization sequence added, as part of the PK comparability study.

12. Section 8.6

Description of Change:

The following statement was added:

If this study is halted for reasons listed in this section, restarting the trial will require a substantial amendment.

13. Section 8.7

Description of Change:

Changes were made to the timing of testing for vital signs, timing of pulse rate monitoring, measurement of body weight, and Section 8.7.4 (dosing justification) was added to the document.

14. Section 9.1

Description of Change:

Inclusion criterium 2 was amendment as follows:

Subject is 0 to 70 years of age, inclusive, at the time of screening. (Subjects <18 years of age will be enrolled only after at least **5 adults (≥18 years of age) each have at least 10 exposures with BAX 930 and reviewed by the DMC. In France, no patients younger than 18 years of age will be enrolled into the study before the first adult patient has been treated with BAX 930 for a minimum of 6 months.**

Inclusion criteria 8 and 9 were amended as follows:

If female of childbearing potential, subject presents with a negative blood or urine pregnancy test, **confirmed no more than 7 days before the first administration**, and agrees to employ adequate birth control measures for the duration of the study and to undergo quarterly pregnancy testing

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.

15. Section 9.2

Description of Change:

Point 8 on patients with diagnosed hepatic dysfunction removed the exclusion criterion that international normalized ratio would be >1.5. The following exclusion criterion was also added:

16. Section 10.3.1

Description of Change:

Section added to describe screening process for pediatric subjects.

17. Section 10.4

Description of Change:

The third point under Medications (not permitted within 30 days before study entry and during the course of the study) was changed to read:

Another IP or interventional drug ~~**within 30 days prior to enrollment**~~

The first point under Medications (permitted within 30 days before study entry and during the course of the study) was changed to read:

- FFP or any other ADAMTS13-containing products interfering with ADAMTS13 PK will have to be paused at least **14 days [+/- 2 days]** prior to the IP infusion for PK assessment. **However, for PK-I, if subjects are receiving weekly treatment as part of their SoC prophylaxis regimen, washout periods can be reduced to 1 week at the discretion of the investigator.**

18. Section 10.8

Description of Change:

Section added to describe treatment of acute events during PK assessment.

19. Section 11.2, Section 12.7.1, 12.7.2, 12.7.3, and Tables 9, 10 and 11

Description of Change:

Timing of blood sample draws was changed. Albumin was added to clinical chemistry panel to be taken at screening. Creatine kinase parameter specified to be measured at the central laboratory.

20. Section 12.7.5.1

Description of Change:

Section rewritten to reflect that the FRETS assay will measure ADAMTS13 activity.

21. Section 12.7.6 and in Table 9

Description of Change:

Tiered approach to antibody testing added. Addition of IgE antibody testing in case of allergic reactions.

22. Section 12.7.7

Description of Change:

Viral seromarkers 4 was changed, and 5 was added as follows:

HCV: **Chemiluminescence**

HEV: anti-HEV

23. Section 12.7.9

Description of Change:

Period 3 treatment phase added.

24. Section 12.7.10

Description of Change:

Excluded from lab values recorded on CRF to include platelet count and LDH.

25. Section 12.8

Description of Change:

Timing of vital signs measurements and height and weight measurements changed.

26. Section 12.9

Description of Change:

Table 5 changed to include HRU questions in the eDiary/daily evening report.

27. Section 13

Description of Change:

Sample revised to 62 subjects; cohort sizes changed; MFAS analysis set added and described; interim analysis added; Section 13.4 (Methods of Analysis) expanded and updated; analyses of pediatric subjects and of the various cohorts described and expanded upon; references to Technozym ADAMTS13 activity assay removed.

28. Section 15

Description of Change:

The following statement was added:

This trial will also include a safety evaluation after first 6 subjects each have at least 3 BAX 930 SIN infusions (including PK infusions) to evaluate the ADAMTS13 activity.

29. Section 20

Description of Change:

Section was updated to include and describe study conduct of PK comparability study, interim analyses, prophylactic and on-demand cohorts, pediatric patients (except in France, where pediatric patients under 18 years of age will not be enrolled in the study until the first adult patient in the study has been treated for at least 6 months), updated timing of study procedures and assessments, and contraceptive requirements for male subjects during the study.

22. SUMMARY OF CHANGES

Protocol 281102: Amendment 2 2017 MAY 09
Replaces: Amendment 1 2017 MAR 15

In this section, changes from Protocol Amendment 1, dated 2017 MAR 15, are described and their rationale is given.

1. **Section 3 Study Synopsis**

   Description of Change:

   Clarified PK treatment order following randomization

   ADAMTS13 trough levels re-defined as pre-infusion ADAMTS13

   Clarified that subjects in the SoC prophylaxis cohort can have dose adjustments based on clinical symptoms and laboratory signs at the investigator's discretion

   Defined severe TTP signs

   Clarified secondary outcome measures

   Specified that subjects enrolling in the on-demand cohort and moving to the prophylaxis cohort will be analyzed separately and will not count towards the 40 patient cap on the prophylaxis cohort

   Clarified how subjects can move from the on-demand cohort to the prophylaxis cohort

   Update the planned population PK analysis

2. **Section 6.3 Population To Be Studied**

   Description of Change:

   Specified that subjects enrolling in the on-demand cohort and moving to the prophylaxis cohort will not count towards the 40 patient cap on the prophylaxis cohort

3. **Section 7.3 Secondary Outcome measures**

   Description of Change:

   ADAMTS13 trough levels re-defined as pre-infusion ADAMTS13

4. Section 8.2 Overall Study Design

Description of Change:

Clarified PK treatment order following randomization

5. Section 8.2.1 Prophylaxis Treatment Cohort

Description of Change:

Clarified that subjects in the SoC prophylaxis cohort can have dose adjustments based on clinical symptoms and laboratory signs at the investigator's discretion

6. Section 8.2.2 On-Demand Treatment Cohort

Description of Change:

Clarified how subjects can move from the on-demand cohort to the prophylaxis cohort

7. Section 8.4.2 Secondary Outcome Measures

Description of Change:

Clarified secondary outcome measures

8. Section 8.4.3 Exploratory Outcome Measures

Description of Change:

Clarified exploratory outcome measures

9. Section 9.1 Inclusion Criteria

Description of Change:

Defined severe TTP signs

Specified that subjects in the prophylactic cohort must have the ability to tolerate SoC prophylactic dosing

Updated criteria for enrolling adolescent subjects

10. Section 12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Description of Change:

Clarified how the FDA will be notified of AEs

11. Section 12.7.10.1 Assessment of Abnormal Laboratory Values

Description of Change:

Noted that normal values from the Coombs test and the evaluation of schistocytes should reported in the CRF

12. Section 13.1 Sample Size

Description of Change:

Specified that subjects enrolling in the on-demand cohort and moving to the prophylaxis cohort will not count towards the 40 patient cap on the prophylaxis cohort

13. Section 13.4 Methods of Analysis

Description of Change:

Clarified how efficacy analysis will be conducted for subjects who switch from the on-demand to the prophylaxis cohorts

14. Section 13.4.2.1 Secondary Outcome Measures

Description of Change:

Clarified secondary outcome measures

15. Section 17.2 Study Documentation and Case Report

Description of Change:

Case report forms will be provided in electronic format

16. Section 20.4 Schedule of Study Procedures and Assessments for Subjects on Prophylaxis Cohort: Table 7

Description of Change:

Removed all information for the on-demand cohort (and created Table 8)

Specified a 14-21 day period between PK infusions and study periods

Specified that all assumptions are based on Q2Week dosing

17. Section 20.4 Schedule of Study Procedures and Assessments for Subjects on On-Demand Cohort: Table 8

Description of Change:

Created table to specify procedures and assessments for subjects in the on-demand cohort

18. Section 20.4 Clinical Laboratory Assessments: Prophylaxis Treatment (Prophylaxis Cohort), Table 9

Description of Change:

Removed all information for the on-demand cohort (and created Table 10)

Added an ADAMTS13 post-infusion assessment for acute event and interval study visits

Clarified assessments to occur as part of acute event dosing visits

Added a Coombs test during acute event dosing visits

Added the evaluation of schistocytes as part of acute event visits

Changed blood group assessments to the local lab

Added a comblete blood count and pre-infusion ADAMTS13 activity assessments to prophylactic dosing visits

Added complete blood count, clinical chemistry, immunogenicity, and pregnancy tests assessments to the study completion visit

Specified a ± 2 day window for PK infusions

Specified that all assumptions are based on Q2Week dosing

19. Section 20.4 Clinical Laboratory Assessments: Acute Treatment (On-Demand Cohort): Table 10

Description of Change:

Created table to specify assessments for subjects in the on-demand cohort

22. SUMMARY OF CHANGES

Protocol 281102: Amendment 1 2017 MAR 15

Replaces: Original: 2017 FEB 13

In this section, changes from the previous version of the Protocol, dated 2017 FEB 13, are described and their rationale is given.

1. **Throughout Document**

   Description of Change:
   hTTP replaced with cTTP

   Purpose for Changes: Consistency with published guidance on standardization of terminology. (Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, Lämmle B, Matsumoto M, Pavenshi K, Sadler E, Sarode R, Wu H, on behalf of the international working group for Thrombotic thrombocytopenic purpura (TTP). Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost 2017;15:312-322)

2. **Section 20.1 Study Flow Chart, Figure 1**

   Description of Change:
   Adapted PK infusion numbers.
   Adapted language in footnote 3.

   Purpose for Changes: Clarification of PK infusion dates.

3. **Section 20.3 Schedule of Study Procedures and Assessments, Table 7**

   Description of Change:

   PK Infusion #1*:*
   "Day 2, 4, 6, 7, 8, 9, 10, 11, 12" changed to "Day 2, 3, 5, 8, 9, 10, 11, 12, 13".

   PK Infusion #2*:*
   "Day 26" changed to "Day 15".
   "Day 27, 29, 30, 32, 33, 34, 35, 36" changed to "Day 16, 17, 19, 22, 23, 24, 25, 26, 27".

Period 1:
"V 21-45" changed to "V 21-32" to reflect 2x a month visit schedules for 6 months.
"Day 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191" changed to "Day 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183"

Period 2
"V 46-70" changed to "V 33-44"
"Day 205, 219, 233, 247, 261, 275, 289, 303, 317, 331, 345, 359" change to "Day 197, 211, 225, 239, 253, 267, 281, 295, 309, 323, 337, 351".

Period 3
"V 71-85" changed to "V 45-56" for the same reasons as in Periods 1&2.
"Day 373, 387, 401, 415, 429, 443, 457, 485, 499, 513, 527" changed to "Day 365, 379, 393, 407, 421, 435, 449, 463, 477, 491, 505, 519".

PK Infusion #3:
"V 86" changed to "V 57".
"Day 336" changed to "Day 533".
"V 87-95" changed to "V 58-66".
"Day 337, 338, 340, 341, 343, 344, 345, 346, 347, 348" changed to "Day 534, 535, 537, 540, 541, 542, 543, 544, 545"

Footnotes:
The following was added to ensure clarity in the timing between periods:
"*There is a 14-21 day period between PK Infusion # 1, PK Infusion # 2, Period 1, Period 2, Period 3, and PK Infusion # 3."

Purpose for Changes: Clarification of study visit dates post-adjustment.

4. Section 20.4 Clinical Laboratory Assessments, Table 9

Description of Change:

Removed PK test from dosing visits. ADAMTS13 trough measures will be measured.

Added footnotes "n", "o" and "p".

Deleted footnote f under the SoC PK Infusion column and PK tests row.

Purpose for Changes: Clarification of PK test dates post-adjustment.