

Study Title

A Multi-Dose, Randomized, Multicenter Phase II Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetic Profile of SR604 Injection in Patients with von Willebrand Disease

Investigational Drug

SR604 Injection

Protocol Number

LS-SR604-VWD-II01

Version Number/Date

Ver 1.0 / 05 November 2025

Sponsor

Shanghai RAAS Blood Products Co., Ltd.

Study Sites

Approximately 9 centers are planned to serve as clinical trial institutions

Study Phase

Phase II

Study Population

Patients with von Willebrand Disease (VWD)

Study Objectives

Primary Objective:

To evaluate the efficacy of SR604 in patients with von Willebrand disease.

Secondary Objectives:

1. To evaluate the safety of SR604 in patients with von Willebrand disease;
2. To evaluate additional efficacy parameters of SR604 in patients with von Willebrand disease;
3. To evaluate the pharmacokinetic profile of SR604 in patients with von Willebrand disease.

Exploratory Objectives:

1. To explore the pharmacodynamic profile (Protac-APTT, protein C, PT) of SR604 in patients with von Willebrand disease.
2. To explore the effect of SR604 on menstruation in female patients with von Willebrand disease (PBAC score and annualized menorrhagia bleeding rate).
3. To explore the utilization of replacement therapies in patients with von Willebrand disease before and after SR604 treatment (types of replacement therapeutic agents).

Study Design

This study is a multi-dose, randomized, multicenter Phase II clinical trial.

Sample Size

This study plans to enroll 24 patients, randomized into 4 groups of 6 patients each.

Study Duration

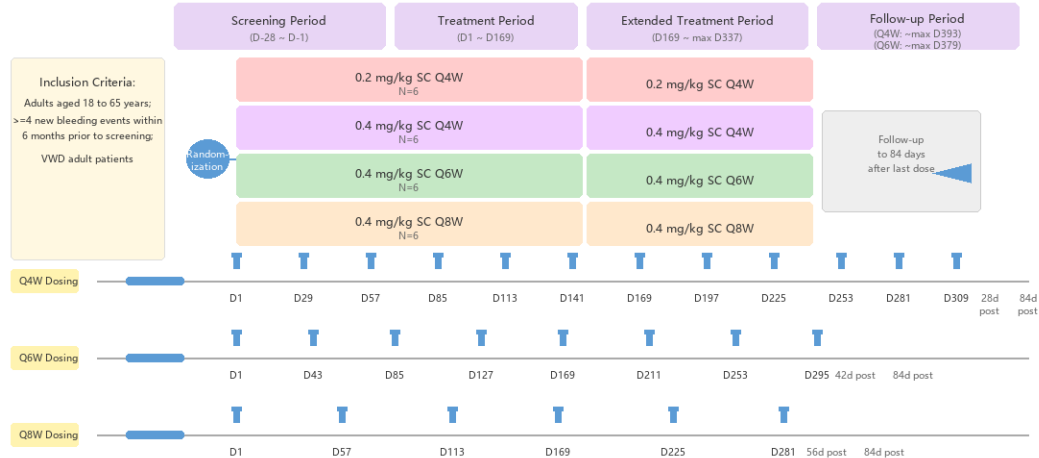
From the screening of the first patient to the last visit of the last patient, the study is expected to last approximately 22 months.

Visit Duration

From the signing of informed consent to completion of all protocol-specified visits, the expected maximum duration per patient is approximately 438 days.

Overall Design

This study is a multi-dose, randomized, open-label clinical trial to evaluate the efficacy, safety, and PK/PD profile of SR604 in patients with von Willebrand disease. The screening period is 28 days, extendable up to 42 days. The study includes 4 groups: 0.2 mg/kg Q4W, 0.4 mg/kg Q4W, 0.4 mg/kg Q6W, and 0.4 mg/kg Q8W, with a planned enrollment of 6 patients per group, totaling 24 patients. The treatment period is 24 weeks, with Q4W, Q6W, and Q8W dosing intervals corresponding to 6, 4, and 3 doses, respectively. The extended treatment period is no longer than 24 weeks, with Q4W, Q6W, and Q8W dosing intervals allowing a maximum of 6, 4, and 3 additional doses, respectively. The last visit of the extended treatment period is completed at 28, 42, or 56 days after the last dose for Q4W, Q6W, and Q8W dosing intervals, respectively. The follow-up period for Q4W, Q6W, and Q8W dosing intervals extends to 84 days after the last dose.



Inclusion Criteria:

Patients must meet ALL of the following inclusion criteria to be enrolled:

1. Age ≥ 18 years and ≤ 65 years at the time of signing informed consent, regardless of sex;
2. At screening, patients with a confirmed diagnosis of von Willebrand disease (VWD) with documented evidence and a defined VWD subtype;
3. At least 4 new bleeding episodes within 6 months prior to screening;
4. No active bleeding symptoms prior to the first dose;
5. The subject or impartial witness fully understands and is able to comply with the protocol requirements, is willing to complete the study as planned, and voluntarily agrees to provide biological samples for testing as required by the protocol; is able to understand the procedures and methods of this clinical trial, provides voluntary participation after full informed consent, and personally signs the informed consent form.

Exclusion Criteria:

Patients meeting ANY of the following exclusion criteria will not be enrolled:

1. Known history of hypersensitivity to the investigational drug formulation or any of its components;
2. Intolerance to subcutaneous injection or presence of other local skin abnormalities or dermatological conditions that may affect drug administration and safety assessment;
3. Meeting any of the following criteria at screening:
 - a. Hemoglobin < 60 g/L;
 - b. Platelet count $< 80 \times 10^9$ /L;
 - c. Hepatic or renal dysfunction: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 x upper limit of normal (ULN), or total bilirubin ≥ 1.5 x ULN; or serum creatinine (Cr) ≥ 1.5 x ULN;
4. Positive for anti-human immunodeficiency virus (HIV) antibody;
5. Presence of any bleeding disorder other than von Willebrand disease [hemophilia A or B, congenital coagulation factor VII deficiency, acquired von Willebrand disease (AVWS), platelet-type VWD, inherited platelet disorders, etc.]; or significantly abnormal coagulation parameters due to diseases other than von Willebrand disease (e.g., platelet disorders, vitamin K deficiency, etc.);
6. Presence of protein C deficiency or protein S deficiency;
7. History of thrombosis or family history of thrombosis prior to signing informed consent or currently, or history of thrombophilia;
8. Severe bleeding due to VWD within 2 years prior to screening, such as intracranial hemorrhage, esophageal variceal bleeding, etc.;

9. Severe cardiac disease, such as unstable angina, congestive heart failure (New York Heart Association class \geq III), severe arrhythmia (QTc interval > 500 ms, corrected by Fridericia formula), uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg), etc.;
10. Female patients with menstrual abnormalities due to organic gynecological diseases (e.g., uterine fibroids, endometriosis, adenomyosis, etc.);
11. Previous or current life-threatening malignant neoplasms or end-stage liver disease;
12. Use of DDAVP or plasma-derived VWF-containing factor VIII concentrate, plasma-derived/recombinant VWF preparations, or antifibrinolytic therapy within 1 week prior to the first dose;
13. Use of antithrombotic agents within 1 week prior to the first dose;
14. Receipt of fresh blood/plasma or cryoprecipitate therapy within 2 weeks prior to the first dose;
15. Receipt of vaccination within 1 month prior to the first dose or planned vaccination during the study period;
16. Major surgery (major surgery defined as Grade III and IV surgeries) within 1 month prior to the first dose, or planned surgery during the study period;
17. Enrollment in other clinical trials within 1 month prior to the first dose;
18. History of drug abuse or alcohol dependence (alcohol dependence criteria: long-term drinking history exceeding 5 years, equivalent ethanol intake ≥ 40 g/day, or heavy drinking within 2 weeks, equivalent ethanol intake > 80 g/day. Ethanol amount (g) conversion formula = alcohol consumption (mL) x alcohol content (%) x 0.8);
19. Presence of psychiatric disease or significant mental disorder, or other reasons resulting in incapacity or lack of cognitive ability;
20. Plans for procreation or sperm donation throughout the study period up to 3 months after the last dose, or unwillingness to use effective physical contraceptive measures (e.g., condoms);
21. Presence of clinically significant disease or other reasons rendering the patient unsuitable for clinical trial participation in the investigator's opinion (e.g., patient unlikely to benefit from the clinical trial);
22. Patients whom the investigator considers to have poor compliance, rendering efficacy evaluation difficult or likelihood of completing the planned treatment course and follow-up low.

Dose Selection and Rationale

In vitro inhibition studies showed that at concentrations of 0.303-0.445 ug/mL in human coagulation factor-deficient plasma, and at concentrations of 0.455 ug/mL and 0.439 ug/mL in normal monkey plasma and human plasma, respectively, the inhibition rate of Protac-APTT reached approximately 90%.

In a standalone pharmacokinetic study conducted in PROC+/+F8-/- mice, SR604 concentrations at 24 h following subcutaneous administration of 0.05 and 0.2 mg/kg were 0.506 ug/mL and 1.36 ug/mL, respectively. The SR604 concentration of 0.506 ug/mL associated with the 0.05 mg/kg dose in mice is considered the minimum relevant SR604 trough level required to provide a clinically relevant pharmacodynamic response in humans.

Based on the above nonclinical pharmacodynamic study results and nonclinical pharmacokinetic (PK) data, the minimum effective concentration of SR604 was set at 0.506 ug/mL (similar to the 90% inhibition concentration in vitro). Modeling and simulation predicted that in hemophilia patients, a single subcutaneous dose of 0.05 mg/kg would achieve a peak concentration reaching the predicted minimum effective concentration; a single subcutaneous dose of 0.1 mg/kg would maintain concentrations at or above the minimum effective concentration for approximately 16 days; and a single subcutaneous dose of 0.2 mg/kg would maintain concentrations at or above the minimum effective concentration for approximately 29 days.

An ongoing Phase I/II clinical trial of this product in patients with hemophilia A/B and congenital coagulation factor VII deficiency has provided data for quantitative pharmacology analysis. Simulations were performed for different doses and dosing intervals; results are shown in Figures 3-2 to 3-5. Based on the simulation results and a conservative selection approach, the present study ultimately selected 4 dose groups -- 0.2 mg/kg Q4W, 0.4 mg/kg Q4W, 0.4 mg/kg Q6W, and 0.4 mg/kg Q8W -- to evaluate the efficacy and safety of prophylaxis in patients with VWD.

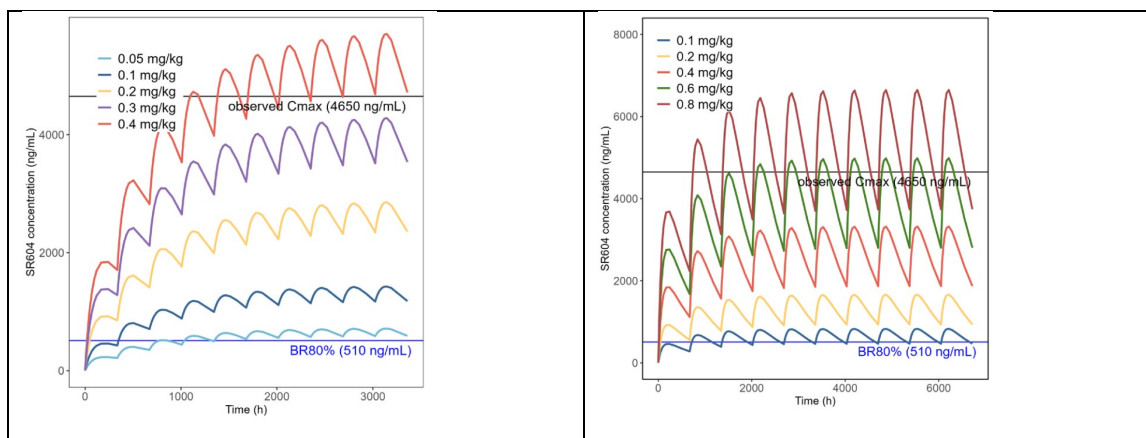


Figure 1 Simulated concentration-time curve of SR604 after Q2W administration

Figure 2 Simulated concentration-time curve of SR604 after Q4W administration

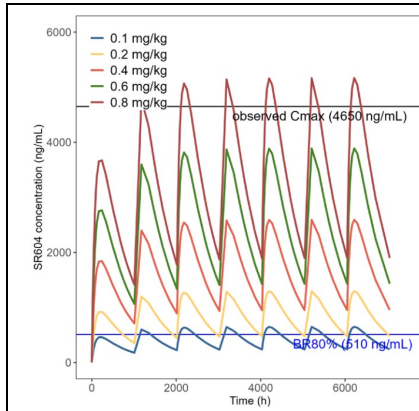


Figure 3 Simulated concentration-time curve of SR604 after Q6W administration

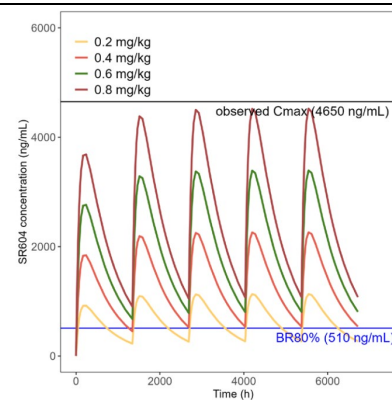


Figure 4 Simulated concentration-time curve of SR604 after Q8W administration Investigational Product

Investigational Drug

Name: SR604 Injection

Strength: 30 mg (1 mL)/vial

Composition: Each vial contains SR604 30.0 mg. Excipients include: histidine, histidine hydrochloride, trehalose, arginine hydrochloride, polysorbate 80.

Storage Conditions: Store and transport at 2-8 degrees C, protected from light.

Supplier: Shanghai RAAS Blood Products Co., Ltd.

Dosing Regimen

Administration:

Administer by slow subcutaneous injection according to the labeled volume, completing the injection within 5 minutes, adjusting to patient comfort. Injection sites may include the thigh (mid-anterior aspect), abdomen (excluding the 5 cm radius area around the navel), or the lateral aspect of the upper arm (abdominal administration is recommended). A different injection site should be selected for each injection within a 1-month period, with

at least 2.5 cm distance from the previous injection area. Do not inject into areas that may rub against belts or waistbands. Do not inject into areas with moles, scars, or bruises. Do not inject into areas with skin tenderness, redness, induration, or broken skin.

Dosage:

Two dose levels are used in this study: 0.2 mg/kg or 0.4 mg/kg. The dose is calculated based on the patient's body weight and assigned dose group: $\text{Dose (mg)} = \text{Dose Level (mg/kg)} \times \text{Body Weight (kg)}$. Administered subcutaneously once every 4 weeks, 6 weeks, or 8 weeks, for a continuous treatment duration not exceeding 48 weeks.

The injection volume is calculated based on the labeled product specification. For injection volumes not exceeding 1 mL, the volume should be precise to 0.01 mL (rounded). For injection volumes exceeding 1 mL, the volume should be precise to 0.1 mL (rounded). For injection volumes exceeding 2.5 mL, the dose should be administered as divided injections.

Study Procedures

This study includes a screening period, treatment period, extended treatment period, and follow-up period.

Screening Period:

Patients enter the screening period after signing the informed consent form. Screening assessments and evaluations will be completed according to the visit schedule. The screening period shall not exceed 28 days (may be extended if the patient receives medication for a bleeding event, or if the 28-day screening period does not encompass one menstrual cycle for female patients of reproductive potential; however, the maximum extension shall not exceed 42 days). Patients meeting all inclusion criteria and none of the exclusion criteria will enter the study.

Treatment Period and Extended Treatment Period:

Eligible patients enter a 6-month treatment period and an extended treatment period of no more than 6 months. Dosing occurs every 4 weeks, 6 weeks, or 8 weeks according to the assigned dose group, with a total of 6, 4, or 3 doses administered during the

treatment period, and a maximum of 6, 4, or 3 additional doses administered during the extended treatment period, respectively. Specific dosing details are described in the dosage and administration section. Patients will undergo efficacy and safety assessments according to the visit schedule, along with PK/PD blood sample collection.

When bleeding occurs during the treatment period requiring treatment, the occurrence and management of bleeding events will be documented.

The investigator will select appropriate treatment medications and measures based on the patient's specific condition, including desmopressin (DDAVP), plasma-derived VWF-containing factor VIII concentrate or plasma-derived/recombinant VWF preparations, cryoprecipitate or fresh plasma, antifibrinolytic agents, sex hormones, and topical thrombin or fibrin glue for bleeding management, or other hemostatic agents as deemed appropriate for the patient's condition.

Follow-up Period:

From the last dose until study exit, if bleeding events occur, the investigator will select appropriate treatment medications and measures based on the patient's specific condition, including desmopressin (DDAVP), plasma-derived VWF-containing factor VIII concentrate or plasma-derived/recombinant VWF preparations, etc.

At Day 84 after the last dose or upon early withdrawal at any time, the investigator will perform safety assessments including vital signs, physical examination, adverse event assessment, laboratory tests (complete blood count, urinalysis, and blood chemistry), coagulation function, FDP, 12-lead ECG, anti-SR604 antibodies (ADA), and neutralizing antibodies. Bleeding events and their treatment, adverse events, and concomitant medications/non-drug therapies will also be recorded. If safety evaluation parameters are abnormal, follow-up must continue until values return to normal, become abnormal but not clinically significant, stabilize, or return to baseline.

Pharmacokinetics/Pharmacodynamics (PK/PD)

Biological Sample Collection:

All patients participating in this study are required to provide biological samples at designated time points for PK/PD analysis, according to the planned sampling time points (see tables below).

Biological sample collection will be performed by authorized or trained medical personnel according to the requirements of the testing facility.

Table 7-2 PK/PD Sampling Time Points and Time Windows for 0.2 mg/kg Q4W

Collection Time Point	Time Label	PK Sample	PD Sample	Tolerance Window
First Dose	D1 (predose)	▲	▲	Within 1 h predose
	D2 (24 h postdose)	▲	▲	± 4 h
	D3 (48 h postdose)	▲	▲	± 4 h
	D5 (96 h postdose)	▲	▲	± 4 h
	D8 (168 h postdose)	▲	▲	± 4 h
	D11 (240 h postdose)	▲	▲	± 4 h
	D15 (336 h postdose)	▲	▲	± 4 h
2nd Dose	D29 ± 2 d (672 h after first dose)	▲	▲	Within 1 h predose
3rd Dose	D57 ± 2 d (within 1 h predose)	▲	▲	Within 1 h predose
4th Dose	D85 ± 2 d (within 1 h predose)	▲	▲	Within 1 h predose
	24 h postdose	▲	▲	± 4 h
	48 h postdose	▲	▲	± 4 h
	96 h postdose	▲	▲	± 4 h
	168 h postdose	▲	▲	± 4 h
	240 h postdose	▲	▲	± 4 h
	336 h postdose	▲	▲	± 4 h
5th Dose	D113 ± 2 d (672 h after 4th dose)	▲	▲	Within 1 h predose
6th Dose	D141 ± 2 d (predose)	▲	▲	Within 1 h predose
7th Dose*	D169 ± 2 d (predose)	▲	▲	Within 1 h predose
8th Dose*	D197 ± 2 d (predose)	▲	▲	Within 1 h predose
9th Dose*	D225 ± 2 d (predose)	▲	▲	Within 1 h predose
10th Dose*	D253 ± 2 d (predose)	▲	▲	Within 1 h predose
11th Dose*	D281 ± 2 d (predose)	▲	▲	Within 1 h predose
Last Dose	672 h postdose	▲	▲	± 2 d
	1008 h postdose	▲	▲	± 2 d
	1344 h postdose	▲	▲	± 2 d
	1680 h postdose	▲	▲	± 2 d
	2016 h postdose	▲	▲	± 3 d

* Collected depending on actual duration of treatment.

If duplicate blood collection time points occur, collect only once.

Table 7-3 PK/PD Sampling Time Points and Time Windows for 0.4 mg/kg Q4W

Collection Time Point	Time Label	PK Sample	PD Sample	Tolerance Window
First Dose	D1 (Pre-dose)	▲	▲	Within 1h pre-dose
	D11 (240h post-dose)	▲	▲	±4h
2nd Dose	D29±2d (Pre-dose)	▲	▲	Within 1h pre-dose
3rd Dose	D57±2d (Pre-dose)	▲	▲	Within 1h pre-dose
4th Dose	D85±2d (Pre-dose)	▲	▲	Within 1h pre-dose
5th Dose	D113±2d (Pre-dose)	▲	▲	Within 1h pre-dose
6th Dose	D141±2d (Pre-dose)	▲	▲	Within 1h pre-dose
7th Dose※	D169±2d (Pre-dose)	▲	▲	Within 1h pre-dose
8th Dose※	D197±2d (Pre-dose)	▲	▲	Within 1h pre-dose
9th Dose※	D225±2d (Pre-dose)	▲	▲	Within 1h pre-dose
10th Dose※	D253±2d (Pre-dose)	▲	▲	Within 1h pre-dose
11th Dose※	D281±2d (Pre-dose)	▲	▲	Within 1h pre-dose
Last Dose	Pre-dose	▲	▲	Within 1h pre-dose
	240h post-dose	▲	▲	±4h

※ Collected based on actual dosing duration.

If duplicate sampling points exist, collect only once.

Table 7-4 PK/PD Sampling Time Points and Time Windows for 0.4 mg/kg Q6W

Collection Time Point	Time Label	PK Sample	PD Sample	Tolerance Window
First Dose	D1 (Pre-dose)	▲	▲	Within 1h pre-dose
	D11 (240h post-dose)	▲	▲	±4h
2nd Dose	D43±2d (Pre-dose)	▲	▲	Within 1h pre-dose
3rd Dose	D85±2d (Pre-dose)	▲	▲	Within 1h pre-dose
4th Dose	D127±2d (Pre-dose)	▲	▲	Within 1h pre-dose
5th Dose※	D169±2d (Pre-dose)	▲	▲	Within 1h pre-dose
6th Dose※	D211±2d (Pre-dose)	▲	▲	Within 1h pre-dose
7th Dose※	D253±2d (Pre-dose)	▲	▲	Within 1h pre-dose
Last Dose	Pre-dose	▲	▲	Within 1h pre-dose
	240h post-dose	▲	▲	±4h

※ Collected based on actual dosing duration.

If duplicate sampling points exist, collect only once.

Table 7-5 PK/PD Sampling Time Points and Time Windows for 0.4 mg/kg Q8W

Collection Time Point	Time Label	PK Sample	PD Sample	Tolerance Window
First Dose	D1 (Pre-dose)	▲	▲	Within 1h pre-dose
	D2 (24h post-dose)	▲	▲	±4h
	D3 (48h post-dose)	▲	▲	±4h
	D5 (96h post-dose)	▲	▲	±4h
	D8 (168h post-dose)	▲	▲	±4h
	D11 (240h post-dose)	▲	▲	±4h
	D15 (336h post-dose)	▲	▲	±4h
	D29 (672h post-dose)	▲	▲	±2d
	D43 (1008h post-dose)	▲	▲	±2d
	D57±2d (1344h post-first dose)	▲	▲	Within 1h pre-dose
3rd Dose	D113±2d (Pre-dose)	▲	▲	Within 1h pre-dose
	24h post-dose	▲	▲	±4h
	48h post-dose	▲	▲	±4h
	96h post-dose	▲	▲	±4h
	168h post-dose	▲	▲	±4h
	240h post-dose	▲	▲	±4h
	336h post-dose	▲	▲	±4h
	672h post-dose	▲	▲	±2d
	1008h post-dose	▲	▲	±2d
4th Dose※	D169±2d (1344h post-3rd dose)	▲	▲	Within 1h pre-dose
5th Dose※	D225±2d (Pre-dose)	▲	▲	Within 1h pre-dose
Last Dose	672h post-dose	▲	▲	±2d
	1008h post-dose	▲	▲	±2d
	1344h post-dose	▲	▲	±2d
	1680h post-dose	▲	▲	±2d
	2016h post-dose	▲	▲	±3d

※ Collected based on actual dosing duration.

If duplicate sampling points exist, collect only once.

Note: Sampling points may be adjusted based on newly acquired data.

Note: Blood collection time points may be adjusted based on newly obtained data results.

Collected blood samples will be centrifuged and stored frozen at -60 degrees C or below. Test samples will be transported by a professional cold-chain logistics company to the central laboratory for analysis. Backup samples will be stored frozen at -60 degrees C or below at the clinical trial institution or transported by a professional cold-

chain logistics company to a third party designated by the sponsor after study completion.

Biological Sample Testing:

PK/PD biological samples collected from all patients will be shipped to the central laboratory. Specific requirements will follow the relevant standard operating procedures and testing requirements established by the central laboratory.

Efficacy Endpoints

Primary Efficacy Endpoint:

Treated total annualized bleeding rate (TABR) at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period).

The treated annualized bleeding rate (ABR) at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period) shall be calculated using the following formulas:

Treated ABR at Week 24

$$= \frac{(\text{Number of treated bleeding episodes within the dosing interval after the last dose during the 24-week period}) \times 365.25}{(\text{Date of last dose within the 24-week period} - \text{Date of first dose} + \text{Dosing interval})}$$

Treated ABR over the total treatment period (including treatment period and extended treatment period)

$$= \frac{((\text{Number of treated bleeding episodes within the dosing interval after the last dose}) \times 365.25)}{((\text{Date of last dose} - \text{Date of first dose} + \text{Dosing interval}))}$$

Note: Total bleeding includes spontaneous bleeding and traumatic bleeding. Treated bleeding refers to bleeding episodes managed with corresponding pharmacotherapy.

Note: For the Q4W group, the dosing interval is 28 days; for the Q6W group, the dosing interval is 42 days; for the Q8W group, the dosing interval is 56 days.

Secondary Efficacy Endpoints:

1. Treated spontaneous annualized bleeding rate (SABR) at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period);

2. Treated traumatic annualized bleeding rate at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period);

3. Treated total, spontaneous, and traumatic annualized bleeding rates by bleeding site at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period);

4. Total annualized bleeding rate (TABR) at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period).

The total annualized bleeding rate (ABR) at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period) shall be calculated using the following formulas:

ABR at Week 24

$$= \frac{((\text{Number of bleeding episodes within the dosing interval after the last dose during the 24 – week period}) \times 365.25)}{(\text{Date of last dose within the 24 – week period} - \text{Date of first dose} + \text{Dosing interval}))}$$

ABR over the total treatment period (including treatment period and extended treatment period)

$$= \frac{((\text{Number of bleeding episodes within the dosing interval after the last dose}) \times 365.25)}{((\text{Date of last dose} - \text{Date of first dose} + \text{Dosing interval}))}$$

Note: Total bleeding includes spontaneous bleeding and traumatic bleeding.

Note: For the Q4W group, the dosing interval is 28 days; for the Q6W group, the dosing interval is 42 days; for the Q8W group, the dosing interval is 56 days.

5. EQ-5D-5L health questionnaire utility scores at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period);

6. Change from baseline in EQ-VAS score at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period).

Exploratory Efficacy Endpoints:

1. Change from baseline in PBAC score at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period) (females with menstruation only);

2. Annualized menorrhagia bleeding rate at Week 24 of treatment and over the total treatment period (including treatment period and extended treatment period) (females with menstruation only);

3. Categorization of replacement therapeutic agents prior to investigational product administration, at Week 24 of treatment, and over the total treatment period (including treatment period and extended treatment period).

Safety Endpoints

Incidence of AEs/SAEs/AESIs assessed through clinical signs and symptoms, vital signs, physical examination, laboratory tests (complete blood count, urinalysis, and blood chemistry), coagulation function [prothrombin time (PT), thrombin time (TT), international normalized ratio (INR), fibrinogen (FIB), activated partial thromboplastin time (APTT), D-dimer], FDP, 12-lead ECG, injection site reactions, hypersensitivity/allergic reactions, thrombotic events, etc.; incidence of drug-related AEs/SAEs/AESIs; number and incidence of patients with anti-drug antibodies (ADA) and neutralizing antibodies.

Pharmacokinetic Parameters

Single-dose PK parameters:

Tmax, Cmax, AUC0-t, etc. If data permit, $t_{1/2z}$, AUC0-infinity, CLz/F, Vz/F, MRT, lambda-z, etc., will be calculated.

Multiple-dose PK parameters:

Tmax,ss, Cmax,ss, AUC0-t, CLss/F, Cmin,ss, Cav,ss, AUC0-tau,ss, and degree of fluctuation (DF) at steady state, etc. If data permit, $t_{1/2z}$, AUC0-infinity, Vz/F, MRT, lambda-z, etc., will be calculated.

If necessary, parameters such as AUC0-t will be normalized for the dosing interval.

Pharmacodynamic Parameters

Protac-APTT (APTT assay based on Protac-induced protein C activation), protein C, prothrombin time (PT).

Statistical Software and General Requirements

Detailed statistical methods will be provided in the Statistical Analysis Plan.

Pharmacokinetic analysis will be performed using Phoenix WinNonlin (Version 8.3 or higher); all other analyses will be performed using SAS software (Version 9.4 or higher).