Trial Title

An Open-Label, Multicenter, Phase I/II Clinical Trial to Evaluate the Safety, Tolerability, Efficacy, and PK/PD Characteristics of SR604 Injection in Patients with Hemophilia A/B and Congenital Coagulation Factor VII Deficiency

Investigational Medicinal Product

SR604 Injection

Protocol Number

LS-SR604-I01

Version Number/Date

Ver 3.1 / 13 January 2026

Sponsor

Shanghai RAAS Blood Products Co., Ltd.

Trial Sites

It is planned to select 6 sites as clinical trial institutions

Trial Phase

Phase I/II

Trial Population

Patients with Hemophilia A/B and congenital coagulation Factor VII deficiency

Trial Objectives

Part A:

Primary objective: To evaluate the safety, tolerability, and immunogenicity of SR604 following a single administration in patients with Hemophilia A/B;

Secondary objective: To evaluate the pharmacokinetic characteristics of SR604 following a single administration in patients with Hemophilia A/B;

Exploratory objective: To explore the pharmacodynamic characteristics of SR604 following a single administration in patients with Hemophilia A/B.

Part B / Part C:

Primary objective: To evaluate the efficacy of SR604 following multiple administrations in patients with Hemophilia A/B and congenital coagulation Factor VII deficiency.

Secondary objectives: To evaluate the pharmacokinetic characteristics of SR604 following multiple administrations in patients with Hemophilia A/B and congenital coagulation Factor VII deficiency; to evaluate the safety and additional efficacy endpoints of SR604 following multiple administrations in patients with Hemophilia A/B and congenital coagulation Factor VII deficiency.

Exploratory objective: To explore the pharmacodynamic characteristics of SR604 following multiple administrations in patients with Hemophilia A/B and congenital coagulation Factor VII deficiency.

Trial Endpoints

Part A:

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

Secondary endpoints: Single-dose PK parameters: t1/2z, Cmax, Tmax, AUC0-t, AUC0-∞, CLz/F, Vz/F, MRT, etc.;

Exploratory endpoints (PD parameters): Protac-APTT (Protac-induced protein C-activated APTT assay), protein C, prothrombin time (PT), thrombin generation assay (TGA).

Part B / Part C:

Primary endpoint: Treatment-based annualized bleeding rate (ABR).

Secondary endpoints (PK parameters): Multiple-dose PK parameters: Tmax,ss, Cmax,ss, AUC0-t, CLss/F, Cmin,ss, Cav,ss, AUC0-τ,ss, and degree of fluctuation at steady state (DF), etc.; if data permit, parameters such as t1/2z, AUC0-∞, Vz/F, MRT, and λz will be calculated;

Secondary endpoints (other efficacy): Treatment-based annualized spontaneous bleeding rate, treatment-based annualized total joint bleeding rate; treatment-based annualized menorrhagia bleeding rate (applicable only to female patients of childbearing age with menstruation who have congenital coagulation Factor VII deficiency). Change from baseline in the Hemophilia Joint Health Score (HJHS) (Hemophilia A and B patients); change from baseline in the EuroQol-5 Dimension-5 Level (EQ-5D-5L) questionnaire.

Secondary endpoints (safety and immunogenicity parameters): Same as Part A.

Exploratory endpoints (PD parameters): Protac-APTT (Protac-induced protein C-activated APTT assay), protein C, prothrombin time (PT), thrombin generation assay (TGA), pro-inflammatory cytokines (IL-1β, IL-6, TNF-α).

Trial Design

This trial consists of three parts: Part A, Part B, and Part C. Part A is an open-label, single-dose, dose-escalation Phase I trial. Part B is a two-dose, open-label, multiple-dose efficacy-exploratory Phase IIa trial for prophylactic treatment. Part C is a randomized, open-label, multiple-dose efficacy-exploratory Phase IIb trial for prophylactic treatment.

Part A:

This part employs a combined approach of accelerated titration and a "3+3" design for dose escalation.

Six dose cohorts are designed: 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg. Starting from Cohort 1 (0.025 mg/kg, starting dose), the safety, tolerability, pharmacokinetic, and pharmacodynamic characteristics of each dose cohort will be evaluated sequentially.

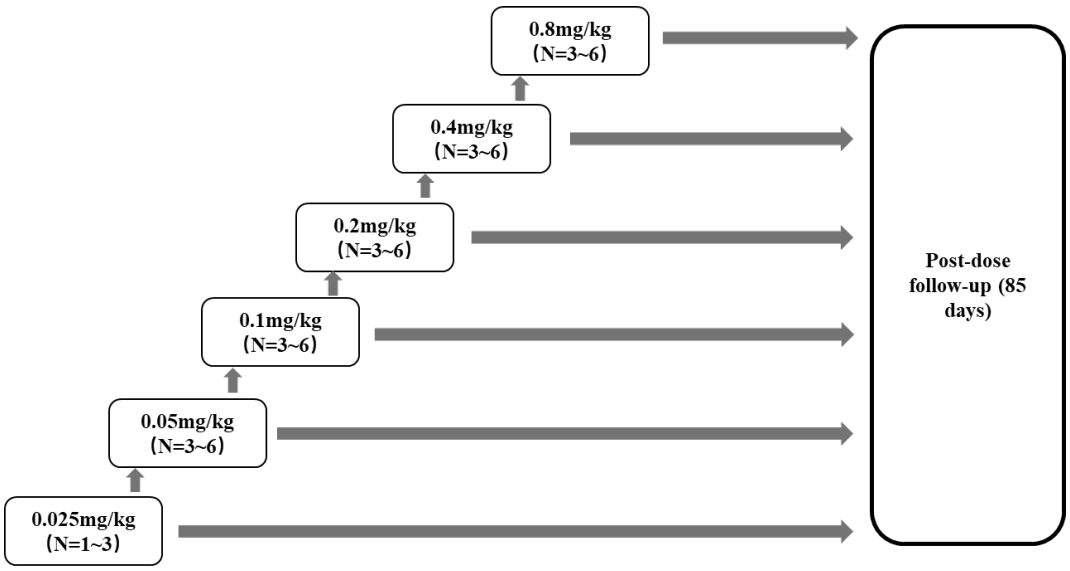

Figure 3-1: Schematic Diagram of Dose Escalation Plan (Part A)

Subjects enrolled in Cohort 3 and subsequent dose cohorts, after completion of the Day 29 safety data review and assessment following dosing, will continue follow-up to Day 85 post-dose for immunogenicity and relevant safety assessments and PK/PD sample collection before exiting the trial. Subjects in Cohort 1, after completing the 29-day follow-up, will continue follow-up per the amended protocol (Ver 1.1) to Day 57 post-dose. Subjects in Cohort 2, after completing the 57-day follow-up per the protocol (Ver 1.1), will continue follow-up per the amended protocol (Ver 1.2) to Day 85 post-dose.

Part B:

This part is a two-dose, open-label, multiple-dose efficacy-exploratory Phase IIa trial for prophylactic treatment. Two dose groups will be selected: 0.05 mg/kg (with a loading dose of 0.1 mg/kg for the first injection) and 0.1 mg/kg (with a loading dose of 0.2 mg/kg for the first injection), with 12 subjects enrolled per dose group.

Eligible patients will enter a 3-month (12-week) treatment period, with dosing every 2 weeks for a total of 6 doses, along with PK/PD blood sample collection. After 12 weeks, subjects may enter a 3-month (12-week) extension treatment period, with dosing every 2 weeks for a total of 6 doses, along with PK/PD blood sample collection, and will exit the trial after completion of a 56-day safety assessment following the last dose.

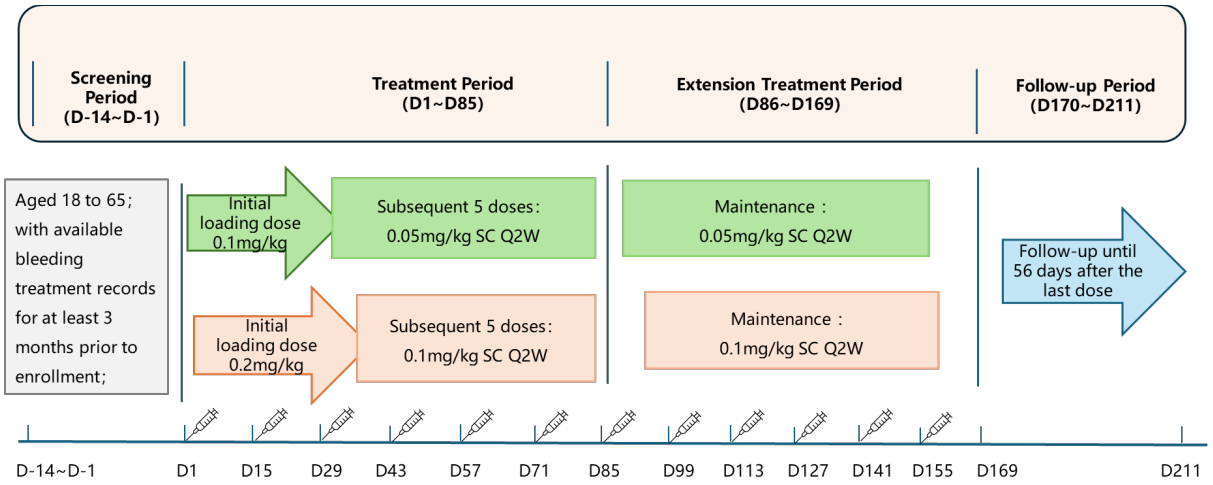

Figure 3-2: Schematic Diagram of Trial Design (Part B)

Part C:

This part is a randomized, open-label, multiple-dose efficacy-exploratory Phase IIb trial for prophylactic treatment. Three groups (A, B, C) will be selected, each enrolling 12 subjects, with the following dosing regimens:

Group A: Dose 0.4 mg/kg, Dosing frequency once every 4 weeks (Q4W)

Group B: Dose 0.4 mg/kg, Dosing frequency once every 6 weeks (Q6W)

Group C: Dose 0.4 mg/kg, Dosing frequency once every 8 weeks (Q8W)

Eligible patients will be randomized in a 1:1:1 ratio to Group A (0.4 mg/kg Q4W), Group B (0.4 mg/kg Q6W), or Group C (0.4 mg/kg Q8W), and will then enter a 6-month (24-week) treatment period. During the treatment period, Groups A, B, and C will receive 6, 4, and 3 doses, respectively. After the treatment period, subjects may enter an extension treatment period of up to 6 months (24 weeks). During the extension treatment period, Groups A, B, and C will receive up to 6, 4, and 3 additional doses, respectively. Efficacy endpoints will be collected at 28 days (Group A), 42 days (Group B), or 56 days (Group C) after the last dose, completing the final visit of the extension treatment period. The follow-up period extends to 84 days after the last dose. See Figure 3-3 for trial design details.

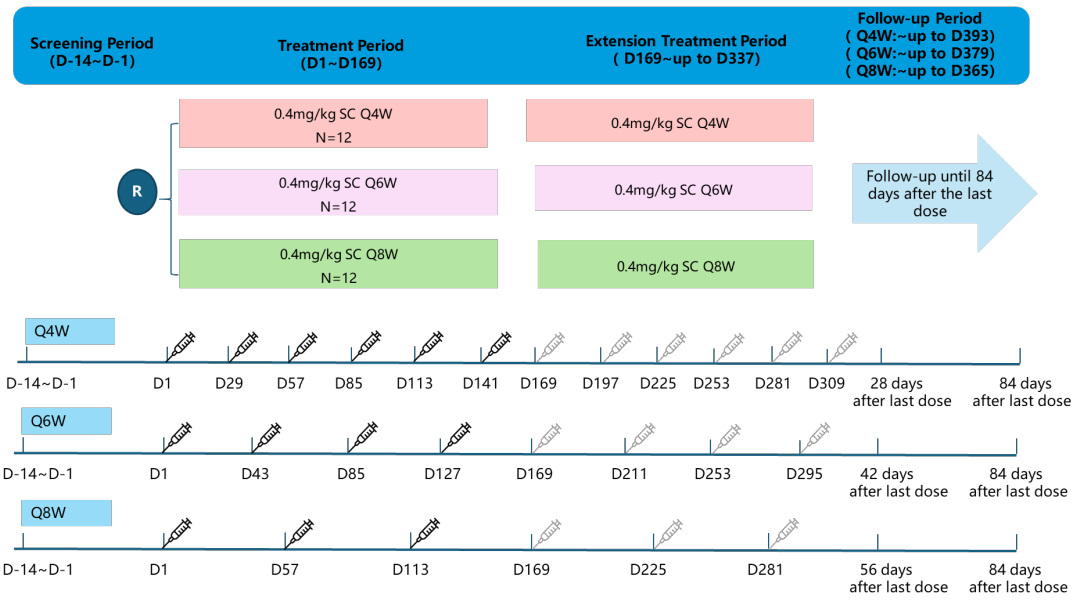

Figure 3-3: Schematic Diagram of Trial Design (Part C)

Sample Size

Part A: For the Hemophilia A/B indication, 6 dose cohorts are prespecified, with approximately 16–33 evaluable subjects planned. Cohort 1 will enroll 1–3 subjects, and each subsequent cohort will enroll 3–6 subjects.

Part B: Two dose groups are planned, with 12 subjects per group, for a total enrollment of 24 subjects, including patients with Hemophilia A/B and congenital coagulation Factor VII deficiency.

Part C: Three groups are planned, with 12 subjects per group, for a total enrollment of 36 subjects, including patients with Hemophilia A/B and congenital coagulation Factor VII deficiency.

Trial Duration

Part A: From screening of the first subject to the last visit of the last subject, the estimated trial duration is 11 months.

Part B: From screening of the first subject to the last visit of the last subject, the estimated trial duration is 15 months.

Part C: From screening of the first subject to the last visit of the last subject, the estimated trial duration is 21 months.

Subject Duration

Part A: For each subject from signing informed consent through completion of all protocol-specified visits, the expected maximum duration is approximately 115 days.

Part B: For each subject from signing informed consent through completion of all protocol-specified visits, the expected maximum duration is approximately 241 days. Among these, female patients with congenital coagulation Factor VII deficiency have an expected maximum duration of approximately 255 days.

Part C: For subjects in Group A, from signing informed consent through completion of all protocol-specified visits, the expected maximum duration is approximately 424 days. Among these, female patients with congenital coagulation Factor VII deficiency have an expected maximum duration of approximately 438 days. For subjects in Group B, the expected maximum duration is approximately 410 days. Among these, female patients with congenital coagulation Factor VII deficiency have an expected maximum duration of approximately 424 days. For subjects in Group C, the expected maximum duration is approximately 396 days. Among these, female patients with congenital coagulation Factor VII deficiency have an expected maximum duration of approximately 410 days.

Subject Selection

Inclusion Criteria:

1. Age ≥18 years and ≤65 years at the time of signing informed consent, regardless of sex;
2. Clinically diagnosed with Hemophilia A or B or congenital coagulation Factor VII deficiency, and must meet the following criteria:

a. Hemophilia A or B patients with historical or screening FVIII activity level <1% or FIX activity level ≤2%;

Note: Hemophilia A or B patients with or without inhibitors may be enrolled. For patients without inhibitors (inhibitor titer <0.6 BU/mL), they must have previously received coagulation factor treatment with exposure days (EDs) >50 days.

b. Congenital coagulation Factor VII deficiency patients with historical or screening FVII activity <10%;

3. Part A only: Received on-demand treatment with FVIII, FIX, recombinant human coagulation Factor VIIa (rFVIIa), or PCC for bleeding events within 1 month prior to screening;
4. Part B/Part C only: Accessible bleeding and treatment records (factor replacement or bypassing agent therapy) for at least 3 months prior to enrollment. Hemophilia A or

B patients must have received on-demand treatment with ≥3 treated de novo bleeding episodes within 3 months prior to enrollment. Congenital coagulation Factor VII deficiency patients must have ≥2 treated de novo bleeding episodes within 3 months prior to enrollment;

5. No active bleeding symptoms prior to first dosing;
6. The subject or a legally acceptable representative has a full understanding of and can comply with the protocol requirements, has the willingness to complete the study as planned, and voluntarily agrees to provide biological samples for testing as required by the protocol;
7. The subject is able to understand the procedures and methods of this clinical trial, has been fully informed, and voluntarily participates in the trial by personally signing the informed consent form.

Exclusion Criteria:

1. Subjects with a known history of hypersensitivity to the investigational medicinal product or any of its components;
2. Intolerance to subcutaneous injection or presence of other local skin abnormalities or dermatological conditions that may affect administration and safety assessment;
3. Subjects meeting any of the following criteria at screening:

a. Hemoglobin <60 g/L;

b. Platelet count <100 × 10^9/L;

c. Hepatic or renal impairment: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 × upper limit of normal (ULN), or total bilirubin ≥1.5 × ULN; or serum creatinine (Cr) ≥1.5 × ULN;

4. Positive result(s) for hepatitis B virus surface antigen (HBsAg), anti-human immunodeficiency virus (HIV) antibody, and/or Treponema pallidum-specific antibody;
5. Clinically diagnosed with active hepatitis C;
6. Any other bleeding disorder or any other disease causing significant coagulation abnormalities (e.g., platelet disorders, vitamin K deficiency, etc.) other than Hemophilia A or B and congenital coagulation Factor VII deficiency;
7. Protein C deficiency or protein S deficiency;
8. History of or current thrombosis, family history of thrombosis, or history of thrombophilia prior to signing informed consent;
9. Intracranial hemorrhage due to Hemophilia A or B or congenital coagulation Factor VII deficiency within 2 years prior to screening;
10. Severe cardiac disease, such as unstable angina, congestive heart failure (New York Heart Association Class ≥III), severe arrhythmia (QTc interval >450 ms,

corrected by Fridericia's formula), or uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg);

11. Received recombinant human coagulation Factor VIIa (rFVIIa) within 48 hours prior to first dosing; received any FVIII-containing product within 72 hours prior to first dosing; received any FIX-containing product within 96 hours prior to first dosing; long-acting products of the above have not completed a washout of 5 half-lives;
12. Used or requires use of any anticoagulant, antifibrinolytic agent, or chemical drug, biological product, or traditional Chinese medicine affecting platelet function, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, within 1 week prior to first dosing or during the trial;
13. Received whole blood or plasma therapy within 2 weeks prior to first dosing;
14. Received emicizumab treatment within 6 months prior to first dosing;
15. Received or planned to receive vaccination within 4 weeks prior to first dosing or during the trial;
16. Underwent major surgery (e.g., orthopedic surgery, abdominal surgery) within 1 month prior to first dosing, or planned to undergo surgery during the study;
17. Enrolled in another clinical trial within 1 month prior to first dosing;
18. History of drug abuse or alcoholism (alcoholism criteria: long-term drinking history exceeding 5 years, equivalent to ethanol intake ≥40 g/day, or heavy drinking within 2 weeks, equivalent to ethanol intake >80 g/day. Ethanol amount (g) conversion formula = alcohol volume (mL) × ethanol content (%) × 0.8);
19. Psychiatric illness or significant mental impairment, or incapacity or lack of cognitive ability due to other reasons;
20. Plans to have children or donate sperm during the entire trial period up to 6 months after the last dose, or unwilling to use effective physical contraceptive measures (e.g., condoms);
21. Subjects with clinically significant disease or other conditions that the investigator considers unsuitable for participation in the clinical trial (e.g., the patient cannot benefit from the clinical trial);
22. Subjects deemed by the investigator to have poor compliance, rendering efficacy evaluation impossible or with low likelihood of completing the planned treatment course and follow-up.

Dose Selection and Rationale

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

In tail-clip bleeding studies in PROC+/+F8-/- and PROC+/+F9-/- mice, subcutaneous administration of SR604 at doses of 0.05, 0.1, and 0.2 mg/kg significantly reduced tail-clip bleeding in humanized protein C hemophilia A and B model mice. At the 0.2 mg/kg dose, SR604 completely achieved a prophylactic bleeding prevention effect.

In a standalone pharmacokinetic study in PROC+/+F8-/- mice, SR604 concentrations at 24 h after subcutaneous injection of 0.05 and 0.2 mg/kg were 0.506 μg/mL and 1.36 μg/mL, respectively. A concentration of 0.506 μg/mL associated with the 0.05 mg/kg dose in mice was considered the minimum relevant trough level of SR604 to provide a clinically relevant pharmacodynamic response in humans.

To determine the efficacy of SR604 on intra-articular bleeding, a knee joint injury experiment simulating intra-articular bleeding was conducted in PROC+/+;F8-/- or PROC+/+;F9-/- mice. The results showed that in PROC+/+;F8-/- or PROC+/+;F9-/- mice, the reduction in knee joint swelling after SR604 pretreatment was comparable to that after FVIII or PCC pretreatment. SR604 pretreatment significantly reduced inflammation and hyperplasia in the synovium and matrix lining of PROC+/+;F8-/- or PROC+/+;F9-/- mice. To evaluate the cytoprotective and endothelial barrier functions of APC in humanized protein C hemophilia mice treated with SR604, assessment was performed in a lipopolysaccharide (LPS)-induced systemic inflammation model. The results showed that SR604 not only did not exacerbate the sublethal LPS response in PROC+/+;F8-/- or PROC+/+;F9-/- mice, but H&E staining images and pan-inflammatory cell marker (CD45) immunostaining also showed that SR604 could reduce LPS-induced inflammatory cell infiltration in lung tissue sections of PROC+/+;F8-/- or PROC+/+;F9-/- mice.

Additionally, studies have shown that histones are associated with various pathologies, including inflammation, cell death, and organ failure, while activated protein C (APC) can cleave histones, thereby reducing histone-induced inflammatory or cytotoxic responses. Some of our in vitro studies showed that SR604 only affected and inhibited the anticoagulant function of APC, while maintaining the cytoprotective and endothelial barrier functions of APC, and it was also found that in the presence of SR604, the histone-cleaving activity of APC was enhanced.

A single-dose toxicity study in cynomolgus monkeys showed: After intravenous administration at 0.3 mg/kg and subcutaneous administration at 0.06, 0.3, and 1.5 mg/kg, the Cmax following subcutaneous administration at the same dose was approximately 0.5 times that of intravenous administration, and the exposure was approximately 0.84 times that of intravenous administration. Based on a modified Protac-APTT coagulation assay, the estimated in vivo effective concentrations of SR604 for 90%, 80%, and 50% target inhibition were 1.21, 0.641, and 0.225 μg/mL, respectively.

Based on the above nonclinical pharmacodynamic study results and nonclinical pharmacokinetic PK data, the minimum pharmacodynamic concentration of SR604 was

set at 0.506 μg/mL (close to the in vitro 90% inhibition concentration). Through modeling and simulation, it was predicted that a single subcutaneous injection of 0.05 mg/kg in hemophilia patients would achieve a peak concentration reaching the predicted minimum effective concentration; a single subcutaneous injection of 0.1 mg/kg would maintain concentrations at or above the minimum effective concentration for approximately 16 days; and a single subcutaneous injection of 0.2 mg/kg would maintain concentrations at or above the minimum effective concentration for approximately 29 days.

In a single-dose toxicity study in mice, the maximum tolerated dose was 100 mg/kg (NOAEL). Referring to relevant guidelines and guidance documents, calculated for an adult body weight of 60 kg, the human equivalent dose (HED) is 8.13 mg/kg (100/12.3). Considering safety factors of 10 or 5, the corresponding maximum recommended starting dose (MRSD) is 0.813 mg/kg or 1.626 mg/kg, respectively.

In a single-dose intravenous and subcutaneous pharmacokinetic study in cynomolgus monkeys, doses of 0.3 mg/kg IV and 0.06, 0.3, and 1.5 mg/kg SC were administered. At the 1.5 mg/kg dose, one animal was euthanized due to moribund condition, and multi-organ thrombosis was considered the likely cause. The moribund condition of this animal was considered possibly related to the test article. In a repeat-dose toxicity study in healthy cynomolgus monkeys, subcutaneous injections were administered at 0.1, 0.3, and 1.5 mg/kg every 2 weeks for 4 weeks, for a total of 3 doses. In the 1.5 mg/kg dose group, two animals developed tail ulceration prior to dosing, and the pharmacological effect of the test article exacerbated distal tissue abnormalities post-dosing, ultimately resulting in moribund condition/euthanasia. In the 0.1 and 0.3 mg/kg groups, apart from tissue injury caused by pharmacological exacerbation of ulceration/scabbing, no other significant abnormalities were observed. Therefore, the NOAEL was established at 0.3 mg/kg. Referring to relevant guidelines and guidance documents, calculated for an adult body weight of 60 kg, the HED is 0.097 mg/kg (0.3/3.1). Given that the preclinical toxicity studies were conducted in healthy cynomolgus monkeys, while the clinical trial will be conducted in a patient population, a safety factor of 5 was considered, resulting in an MRSD of 0.019 mg/kg.

In a 14-week repeat subcutaneous and intravenous toxicity study in cynomolgus monkeys (with an 8-week recovery period), SR604 was administered subcutaneously at 0.03, 0.1, and 0.3 mg/kg every 2 weeks for 14 weeks, for a total of 8 doses, followed by an 8-week recovery period. No mortality or moribund condition was observed in animals of any dose group. Clinical observations included tail ulceration/scabbing, with distal tail necrosis due to pharmacological exacerbation of injury. Transient slight elevation of IL-6 was observed in individual animals. At the end of the 8-week recovery period, the above changes were reversible. No other systemic toxicological changes were observed. No significant abnormalities were observed in safety pharmacology parameters of the central nervous system, cardiovascular system, respiratory system, or other organs and tissues (including male and female reproductive organs) in any dose group. SR604 was

administered intravenously at 0.3 mg/kg every 2 weeks for 14 weeks, for a total of 8 doses, followed by an 8-week recovery period. At this dose, clinical observations included tail ulceration/scabbing, and post-dosing observations showed pharmacologically exacerbated swelling and necrosis of the proximal/middle/distal tail, secondary clinical pathology abnormalities (prolonged APTT, elevated FIB, decreased RBC, HGB, HCT, slight increase in Retic), and transient elevation of IL-6. No abnormalities were observed in the central nervous system or other organs and tissues (including male and female reproductive organs). At the end of the 8-week recovery period, the above changes were reversible. SR604 was administered subcutaneously at concentrations of 0.2, 0.67, and 2 mg/mL (doses of 0.03, 0.1, and 0.3 mg/kg) and intravenously at 2 mg/mL (dose of 0.3 mg/kg) every 2 weeks for 14 weeks, for a total of 8 doses. No local irritation reactions were observed at the injection sites in any subcutaneous or intravenous administration group.

Based on the comprehensive results of nonclinical pharmacodynamic, pharmacokinetic, and toxicity studies, the starting dose for the clinical trial is proposed to be 0.025 mg/kg. This dose is 12-fold lower than the NOAEL in monkeys (0.3 mg/kg) and 4,000-fold lower than the well-tolerated 100 mg/kg single SC dose in PROC+/+F8-/- and PROC+/+F9-/- mice (see Table 3-1). Subsequent dose escalation will proceed at 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg.

Based on preliminary statistical results from the completed Phase I dose-escalation trial, a total of 13 patients in the 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg dose groups demonstrated good safety within 29 days post-dosing. No injection site reactions, adverse drug reactions, hypersensitivity/allergic reactions, or thrombotic events occurred. In the 0.025 mg/kg group, 1 patient was enrolled with 1 Grade 1 AE, deemed unrelated to the investigational product, with outcome of recovery. In the 0.05 mg/kg group, 3 patients were enrolled; 1 patient experienced 1 AE (Grade 2), deemed unrelated to the investigational product, with outcome of recovery. In the 0.1 mg/kg group, 3 patients were enrolled; 2 patients experienced 2 AEs (both Grade 2), deemed possibly unrelated and unrelated to the investigational product, both with outcome of recovery. In the 0.2 mg/kg group, 3 patients were enrolled; 1 patient experienced 1 AE (Grade 1), deemed possibly unrelated to the investigational product, with outcome of recovery. In the 0.4 mg/kg group, 3 patients were enrolled; 1 patient experienced 1 AE (Grade 1), deemed possibly unrelated to the investigational product, with outcome of ongoing.

A preliminary summary of bleeding events within 29 days post-dosing for the 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg dose groups (13 patients total) showed: In the 0.025 mg/kg group, 1 patient was enrolled with 4 spontaneous bleeding events, averaging 2 bleeds per month. In the 0.05 mg/kg group, 3 patients were enrolled, with an average of 1.3 spontaneous bleeding events per subject per month. In the 0.1 mg/kg group, 3 patients were enrolled, with an average of 0.67 spontaneous bleeding events per subject per month. In the 0.2 mg/kg group, 3 patients were enrolled,

with an average of 0.67 spontaneous bleeding events per subject per month. In the 0.4 mg/kg group, 3 patients were enrolled, with no spontaneous bleeding events.

Based on preliminary PK analysis of SR604 plasma concentrations from 1 patient at 0.025 mg/kg, 3 patients at 0.05 mg/kg, and 3 patients at 0.1 mg/kg: The Tmax for 0.025 mg/kg was 168 h post-dose, with a half-life of 7.8 days. The Tmax for 0.05 mg/kg was 120–240 h post-dose, with a mean half-life of 13.49 days. The Tmax for 0.1 mg/kg was 168–240 h post-dose, with a mean half-life of 12.77 days.

Based on comprehensive evaluation, the Phase II trial (Part B) selected 0.05 mg/kg (with a loading dose of 0.1 mg/kg for the first injection) and 0.1 mg/kg (with a loading dose of 0.2 mg/kg for the first injection).

As of May 2025, enrollment and first dosing of 24 subjects in Part B have been completed. To further explore the efficacy and safety of additional dosing regimens and frequencies, a Phase IIb clinical trial (Part C) is planned. This part will include three groups: Group A (0.4 mg/kg Q4W), Group B (0.4 mg/kg Q6W), and Group C (0.4 mg/kg Q8W).

Hemophilia patients develop hemophilic arthropathy due to recurrent joint bleeding. Joint bleeding triggers synovial proliferation, leading to synovial hyperplasia and villus formation. Inflammation is another characteristic manifestation of synovial damage caused by bleeding. Among the numerous compounds involved in the inflammatory process that induces hemophilic arthropathy pathogenesis, cytokines play a dominant role. To explore the effect of SR604 on inflammatory cytokine levels in hemophilia patients, PD parameters for pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) have been added to Part B and Part C.

Dose Escalation Principles (Part A)

To explore the safety and tolerability of single-dose administration, Part A will employ 6 sequentially escalating dose cohorts (0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg).

This part employs a combined approach of accelerated titration and a "3+3" design for dose escalation.

To minimize the number of subjects exposed to ineffective doses, Cohort 1 (0.025 mg/kg, starting dose) will initially enroll 1 subject for accelerated titration. If the subject does not experience Grade 2 or higher investigational product-related adverse reactions within 29 days post-dose, this dose cohort will be concluded, and escalation to Cohort 2 (0.05 mg/kg) will proceed. If the subject experiences Grade 2 or higher investigational

product-related adverse reactions, 2 additional subjects will be enrolled in Cohort 1. If the first subject or any subject in Cohort 1 experiences Grade 3 or higher investigational product-related adverse reactions within 29 days post-dose, or if ≥2 of the 3 subjects in Cohort 1 experience Grade 2 or higher investigational product-related adverse reactions within 29 days post-dose, a Scientific Review Committee (SRC) composed of the principal investigator, sponsor, and other professionals will comprehensively evaluate whether to continue the trial.

After completion of Cohort 1 (0.025 mg/kg, starting dose), all subsequent dose cohorts will transition to a "3+3" dose escalation model. The safety monitoring timepoint (Dn) for dose escalation in subsequent cohorts may be adjusted as necessary based on previously obtained study results.

For each dose cohort, after completing the Day Dn safety visit for 3 evaluable subjects, the SRC will review and assess the safety data. If the dose escalation stopping criteria are not met, the current dose cohort will be concluded, and escalation to the next dose cohort will proceed. If ≥1 of the initial 3 evaluable subjects in a dose cohort experiences Grade 3 or higher investigational product-related adverse reactions within Dn days post-dose, or ≥2 subjects experience Grade 2 or higher investigational product-related adverse reactions within Dn days post-dose, 3 additional evaluable subjects will be enrolled. If ≥2 of the 6 evaluable subjects experience Grade 3 or higher investigational product-related adverse reactions within Dn days post-dose, or ≥4 subjects experience Grade 2 or higher investigational product-related adverse reactions within Dn days post-dose, that dose group will be terminated or dose reduction will be pursued for further exploration. Otherwise, the current dose cohort will be concluded, and escalation to the next dose cohort will proceed.

If one investigational product-related thromboembolic event of Grade 2 or higher occurs in any dose cohort, the SRC will conduct risk analysis and evaluation before determining whether to enroll new subjects and continue the trial.

All adverse events and laboratory abnormalities will be assessed for safety outcomes according to the baseline criteria of the NCI-CTCAE Version 5.0.

Investigational Medicinal Product

Name: SR604 Injection

Strength: 30 mg (1 mL)/vial

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

Storage conditions: Store and transport protected from light at 2–8°C.

Supplying entity: Shanghai RAAS Blood Products Co., Ltd.

Dosing Regimen

Route of Administration:

Administered by slow subcutaneous injection according to the labeled amount, completed within 5 minutes, at the subject's comfort. Injection sites may include the thigh (mid-anterior aspect), abdomen (excluding a 5 cm radius around the navel), or the lateral aspect of the upper arm. Within 1 month, each injection should be administered at a different site, with at least 2.5 cm separation from the previous injection area.

Part A is a single-dose dose-escalation trial; Part B/Part C are multiple-dose trials. Administration in the abdominal region is recommended for all.

Dosage:

Part A: The dose is calculated based on the subject's body weight and the assigned dose cohort. Dose (mg) = dose cohort (mg/kg) × body weight (kg). Subcutaneous injection, single administration only.

Part B: The dose is calculated based on the subject's body weight and the assigned dose group. Dose (mg) = dose group (mg/kg) × body weight (kg). Subcutaneous injection, once every 2 weeks.

Part C: The dose is calculated based on the subject's body weight and the assigned group. Dose (mg) = dose group (mg/kg) × body weight (kg). Subcutaneous injection, Group A once every 4 weeks, Group B once every 6 weeks, Group C once every 8 weeks.

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

Trial Procedures

This trial consists of three parts: Part A, Part B, and Part C.

Part A: Consists of a screening period and a PK/PD study period (including safety follow-up).

Screening Period:

Subjects enter the screening period after signing the informed consent form. Screening assessments and evaluations will be completed per the visit schedule. The screening period shall not exceed 2 weeks (if subjects use rFVIIa, FVIII, FIX, or PCC for on-demand treatment of bleeding events prior to planned dosing, or due to epidemic control measures, or other force majeure factors, the screening period may be extended, but not to exceed 4 weeks). Subjects who meet all inclusion criteria and none of the exclusion criteria will enter the trial.

PK/PD Study Period:

Initially, 1 subject from Cohort 1 (0.025 mg/kg, starting dose) will be enrolled for the PK/PD study. On the day of dosing during the PK/PD study period, the subject will receive a single subcutaneous injection of 0.025 mg/kg SR604. PK biological samples will be collected at 15 time points: within 1 h predose, and at 2 h, 6 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, 168 h (D8), 240 h (D11), 336 h (D15), 504 h (D22), and 672 h (D29) postdose. PD biological samples [Protac-APTT (Protac-induced protein C-activated APTT assay), protein C, thrombin generation assay (TGA)] will be collected at 12 time points: within 1 h predose, and at 2 h, 6 h, 24 h, 36 h, 48 h, 72 h, 120 h, 168 h (D8), 336 h (D15), 504 h (D22), and 672 h (D29) postdose. After completing the 29-day follow-up, subjects in Cohort 1 will continue follow-up per the amended protocol (Ver 1.1) to Day 57 post-dose for PK/PD blood collection and corresponding assessments.

Based on preliminary safety monitoring results and PK/PD characteristics obtained from Cohort 1 (0.025 mg/kg, starting dose), the PK/PD biological sample collection timepoints will be adjusted, and all subjects in Cohort 2 will be studied using the adjusted timepoints per the dose escalation requirements. PK biological samples for Cohort 2 subjects will be collected at 15 timepoints: within 1 h predose, and at 2 h, 8 h, 24 h (D2), 48 h (D3), 96 h (D5), 120 h (D6), 168 h (D8), 240 h (D11), 336 h (D15), 504 h (D22), 672 h (D29), 840 h (D36), 1008 h (D43), and 1344 h (D57) postdose. PD biological samples [Protac-APTT, protein C, TGA] will be collected at 13 timepoints: within 1 h predose, and at 2 h, 8 h, 24 h (D2), 48 h (D3), 120 h (D6), 168 h (D8), 240 h (D11), 336 h (D15), 504 h (D22), 672 h (D29), 1008 h (D43), and 1344 h (D57) postdose. After completing the 57-day follow-up per the protocol (Ver 1.1), subjects in Cohort 2 will continue follow-up per the amended protocol (Ver 1.2) to Day 85 post-dose for PK/PD blood collection and corresponding assessments.

Based on preliminary safety monitoring results and PK/PD characteristics obtained from Cohort 1 and Cohort 2 subjects, the PK/PD biological sample collection timepoints will be adjusted. For subjects in Cohort 3 and subsequent dose cohorts, PK biological samples will be collected at 17 timepoints: within 1 h predose, and at 2 h, 8 h, 24 h (D2), 48 h (D3), 96 h (D5), 120 h (D6), 168 h (D8), 240 h (D11), 336 h (D15), 504 h (D22), 672 h (D29), 840 h (D36), 1008 h (D43), 1344 h (D57), D71 (1680 h), and D85 (2016 h) postdose. PD biological samples [Protac-APTT, protein C, TGA] will be collected at 14 timepoints: within 1 h predose, and at 2 h, 8 h, 24 h (D2), 48 h (D3), 120 h (D6), 168 h (D8), 240 h (D11), 336 h (D15), 504 h (D22), 672 h (D29), 1008 h (D43), 1344 h (D57),

and D85 (2016 h) postdose. The PK/PD biological sample collection timepoints may be appropriately adjusted as necessary based on the obtained PK/PD results.

During the PK/PD blood collection period for subjects in Cohort 3 and subsequent dose cohorts, vital signs will be monitored at the following timepoints: within 1 h predose, and at 2 h (±15 min), 8 h (±15 min), D2, D3, D5, D6, D8, D11, D15, D22, D29, D36, D43, D57, D71, D85/post-early withdrawal postdose. Coagulation function [PT results will also be used for PD parameter analysis] will be monitored at: within 1 h predose, and at 2 h (±5 min), 8 h (±10 min), D2, D5, D8, D15, D29, D43, D57, D85/post-early withdrawal postdose. Electrocardiograms will be monitored at: within 2 h predose, and at 8 h (±1 h), D2, D5, D8, D15, D29, D43, D57, D85/post-early withdrawal postdose. Other safety and tolerability parameters will also be observed.

At 672 h (D29) postdose, the investigator will perform safety assessments including vital signs, physical examination, adverse event assessment, laboratory tests (complete blood count, urinalysis, and blood biochemistry), coagulation function, FDP, 12-lead ECG, anti-SR604 antibodies (ADA), and neutralizing antibodies. Combined with safety parameter monitoring results during the PK/PD blood collection period, the SRC will conduct a comprehensive safety review of the dose cohort (whether dose escalation stopping criteria have been met) and assess the feasibility of proceeding to the next dose cohort (or dose adjustment). After completing the 29-day follow-up, subjects in Cohort 1 will continue follow-up per the amended protocol (Ver 1.1) to Day 57 post-dose for PK/PD blood collection and corresponding assessments. Subjects in Cohort 2, Cohort 3, and subsequent dose cohorts will continue follow-up to D85 for PK/PD blood collection and corresponding assessments.

If a subject withdraws or exits the trial early at any time during the trial, safety assessments including body weight, vital signs, physical examination, laboratory tests (including complete blood count, urinalysis, and blood biochemistry), coagulation function, FDP, 12-lead ECG, anti-SR604 antibodies (ADA), and neutralizing antibodies must be performed. Bleeding events and their treatment, adverse events, and concomitant medications/treatments will be recorded. If safety evaluation parameters are abnormal, follow-up must continue until values return to normal, are deemed not clinically significant, are stable, or return to baseline.

Part B: Consists of a screening period, treatment period, extension treatment period, and follow-up period.

Screening Period: Subjects enter the screening period after signing the informed consent form. Screening assessments and evaluations will be completed per the visit schedule. The screening period shall not exceed 2 weeks (if subjects use rFVIIa, FVIII, FIX, or PCC for on-demand treatment of bleeding events prior to planned dosing, or due to epidemic control measures, or other force majeure factors, the screening period may be extended, but not to exceed 4 weeks; for patients with congenital coagulation Factor

VII deficiency, it may be extended to D-42 at most). Subjects who meet all inclusion criteria and none of the exclusion criteria will enter the trial.

Treatment Period: Eligible patients will enter a 3-month (12-week) treatment period, with dosing every 2 weeks for a total of 6 doses. Specific dosing details are provided in the dosage and administration section. Patients will complete efficacy and safety assessments per the visit schedule, along with PK/PD blood sample collection.

Extension Treatment Period: After completing the treatment period, subjects will enter a 3-month (12-week) extension treatment period, with dosing every 2 weeks for a total of 6 doses. Specific dosing details are provided in the dosage and administration section. Patients will complete efficacy and safety assessments per the visit schedule, along with PK/PD blood sample collection.

When patients experience breakthrough bleeding requiring treatment, the occurrence and treatment of bleeding events will be collected. The investigator will select appropriate therapeutic agents and measures based on the patient's condition. Commercially available human coagulation Factor VIII/IX (plasma-derived or recombinant), recombinant human coagulation Factor VIIa (rFVIIa), or PCC may be used for bleeding treatment. Recommended treatment regimens are provided in Table 6-1. The specific dose and treatment course may be determined by the investigator based on the bleeding site, severity, and hemostatic response.

Follow-up Period: After completing the D169 efficacy and safety assessment, subjects will continue PK/PD blood sample collection until D211/early withdrawal. At D211/early withdrawal, safety assessments including vital signs, physical examination, laboratory tests (including complete blood count, urinalysis, and blood biochemistry), coagulation function, FDP, 12-lead ECG, anti-SR604 antibodies (ADA), and neutralizing antibodies will be performed. Bleeding events and their treatment, adverse events, and concomitant medications/treatments will be recorded. If safety evaluation parameters are abnormal, follow-up must continue until values return to normal, are deemed not clinically significant, are stable, or return to baseline.

PK/PD Study: PK biological samples will be collected at 20 timepoints: D1 (predose), D2 (24 h ±20 min post-first dose), D3 (48 h ±20 min post-first dose), D5 (96 h ±1 h post-first dose), D8 (168 h ±4 h post-first dose), D11 (240 h ±4 h post-first dose), D15 (predose, before 2nd dose), D57 (predose, before 5th dose), D71 (predose, before 6th dose), D72 (24 h ±20 min post-6th dose), D73 (48 h ±20 min post-6th dose), D75 (96 h ±1 h post-6th dose), D78 (168 h ±4 h post-6th dose), D81 (240 h ±4 h post-6th dose), D85 (336 h post-6th dose, predose before 7th dose), D127 (predose, before 10th dose), D169 (336 h–4 days post-last dose), D183 (672 h ±1 day post-last dose), D197 (1008 h ±2 days post-last dose), and D211 (1344 h ±2 days post-last dose). PD biological

samples [Protac-APTT, protein C, TGA, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)] will be collected at 17 timepoints: D1 (predose), D2 (24 h ±20 min post-first dose), D3 (48 h ±20 min post-first dose), D8 (168 h ±4 h post-first dose), D11 (240 h ±4 h post-first dose), D15 (predose, before 2nd dose), D57 (predose, before 5th dose), D71 (predose, before 6th dose), D72 (24 h ±20 min post-6th dose), D73 (48 h ±20 min post-6th dose), D78 (168 h ±4 h post-6th dose), D81 (240 h ±4 h post-6th dose), D85 (336 h post-6th dose, predose before 7th dose), D127 (predose, before 10th dose), D169 (336 h–4 days post-last dose), D183 (672 h ±1 day post-last dose), and D211 (1344 h ±2 days post-last dose). Specific PD parameters corresponding to each collection timepoint are detailed in Section 8.1.22. "Predose" refers to within 12 h before dosing.

Part C: Consists of a screening period, treatment period, extension treatment period, and follow-up period.

Screening Period: Same as Part B.

Treatment Period: Eligible patients will enter a 6-month (24-week) treatment period. Group A will be dosed once every 4 weeks for a total of 6 doses; Group B will be dosed once every 6 weeks for a total of 4 doses; Group C will be dosed once every 8 weeks for a total of 3 doses. Specific dosing details are provided in the dosage and administration section. Patients will complete efficacy and safety assessments per the visit schedule, along with PK/PD blood sample collection.

Extension Treatment Period: After completing the treatment period, subjects will enter an extension treatment period of up to 6 months (24 weeks). Group A will be dosed once every 4 weeks for up to 6 additional doses; Group B will be dosed once every 6 weeks for up to 4 additional doses; Group C will be dosed once every 8 weeks for up to 3 additional doses. Patients will complete efficacy and safety assessments per the visit schedule, along with PK/PD blood sample collection.

Follow-up Period: At 84 days after the last dose/early withdrawal, safety assessments including vital signs, physical examination, laboratory tests (including complete blood count, urinalysis, and blood biochemistry), coagulation function, FDP, 12-lead ECG, anti-SR604 antibodies (ADA), and neutralizing antibodies will be performed. Bleeding events and their treatment, adverse events, and concomitant medications/treatments will be recorded. If safety evaluation parameters are abnormal, follow-up must continue until values return to normal, are deemed not clinically significant, are stable, or return to baseline.

Pharmacokinetics/Pharmacodynamics (PK/PD)

Biological Sample Collection:

All subjects participating in this trial will have biological samples collected at designated timepoints for PK/PD analysis, following the initially proposed sampling schedule. During the trial, based on the PK/PD data and analysis results obtained from completed dose cohorts, the PK/PD biological sample collection timepoints for subjects in subsequent dose cohorts may be appropriately adjusted as necessary.

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

Table 8-2 PK/PD Sampling Timepoints and Time Windows (Part A)

Collection Timepoint	PK Sample	PD Sample	Tolerance Window
Predose (0h)	▲	▲	Within 1 h predose
2 h postdose	▲	▲	±5 min
8 h postdose	▲	▲	±10 min
D2 (24 h postdose)	▲	▲	±20 min
D3 (48 h postdose)	▲	▲	±20 min
D5 (96 h postdose)	▲		±1 h
D6 (120 h postdose)	▲	▲	±1 h
D8 (168 h postdose)	▲	▲	±4 h
D11 (240 h postdose)	▲	▲	±4 h
D15 (336 h postdose)	▲	▲	±4 h
D22 (504 h postdose)	▲	▲	±1 d
D29 (672 h postdose)	▲	▲	±1 d
D36 (840 h postdose)	▲		±1 d
D43 (1008 h postdose)	▲	▲	±2 d
D57 (1344 h postdose)	▲	▲	±2 d
D71 (1680 h postdose)	▲		±2 d
D85 (2016 h postdose)	▲	▲	±2 d

PD parameters assessed in Part A: protac-APTT, protein C, prothrombin time (PT), and thrombin generation assay (TGA).

Table 8-3 PK/PD Sampling Timepoints and Time Windows (Part B)

Collection Timepoint	PK Sample	PD Sample			Tolerance Window
	SR604	Protac-APTT	Protein C, TGA	Pro-inflammatory	/

					Cytokines	
First Dose	Predose	▲	▲	▲	▲	Predose
	D2 (24 h post-first dose)	▲	▲	▲		± 20min
	D3 (48 h post-first dose)	▲	▲			± 20min
	D5 (96 h post-first dose)	▲				±1h
	D8 (168 h post-first dose)	▲	▲	▲		±4h
	D11 (240 h post-first dose)	▲	▲	▲		±4h
2nd Dose	D15 (predose, before 2nd dose)	▲	▲	▲	▲	Predose
5th Dose	D57 (predose, before 5th dose)	▲	▲	▲		Predose
6th Dose	D71 (predose, before 6th dose)	▲	▲	▲		Predose
	D72 (24 h post-6th dose)	▲	▲	▲		± 20min
	D73 (48 h post-6th dose)	▲	▲			± 20min
	D75 (96 h post-6th dose)	▲				±1h
	D78 (168 h post-6th dose)	▲	▲	▲		±4h
	D81 (240 h post-6th dose)	▲	▲	▲		±4h
	D85 (336 h post-6th dose)	▲	▲		▲	Predose (before 7th dose)
10th Dose	D127 (predose, before 10th dose)	▲	▲	▲		Predose
Last Dose	D169 (336 h-4 d post-last dose)	▲	▲		▲	-4d
	D183 (672 h post-last dose)	▲	▲	▲		±1d
	D197 (1008 h post-last dose)	▲				±2d
	D211 (1344 h post-last dose)	▲	▲	▲	▲	±2d

Table8-4 PK/PD Sampling Timepoints and Time Windows (Part C) (Q4W)

Collection Timepoint	PK Sample	PD Sample	Tolerance Window

		SR604	Protac-APTT, Protein C, TGA)	(Pro-inflammatory Cytokines	/
First Dose	D1(predose)		▲	▲	Predose
	D11 (240 h post-first dose)	▲	▲		±4h
2nd Dose	D29 (predose, before 2nd dose)	▲	▲		Predose
3rd Dose	D57 (predose, before 3rd dose)	▲	▲		Predose
4th Dose	D85 (predose, before 4th dose)	▲	▲	▲	Predose
5th Dose	D113 (predose, before 5th dose)	▲	▲		Predose
6th Dose	D141 (predose, before 6th dose)	▲	▲		Predose
7th Dose ※	D169 (predose, before 7th dose)	▲	▲	▲	Predose
8th Dose ※	D197 (predose, before 8th dose)	▲	▲		Predose
9th Dose ※	D225 (predose, before 9th dose)	▲	▲		Predose
10th Dose ※	D253 (predose, before 10th dose)	▲	▲		Predose
11th Dose ※	D281 (predose, before 11th dose)	▲	▲		Predose
Last Dose	Predose	▲	▲		Predose
	240 h post-last dose	▲	▲	▲	±4h

Note: ※Collected based on actual dosing duration. #Added PD parameter: pro-inflammatory cytokines (IL-1beta, IL-6, TNF-alpha). If duplicate blood collection timepoints occur, collect only once.

Table 8-5 PK/PD Sampling Timepoints and Time Windows（Part C） (Q6W)

Collection Timepoint		PK Sample	PD Sample			Tolerance Window
		SR604	Protac-APTT	Protein C, TGA	Pro-inflammatory Cytokines	/
First Dose	D1（24 h pre-first dose）	▲	▲	▲	▲	Predose
	D2（24 h post-first dose）	▲	▲	▲		±20min
	D3（48 h post-first dose）	▲	▲			±20min
	D5（96 h post-first dose)）	▲				±1h
	D8（168 h post-first dose)）	▲	▲	▲		±4h

	D11（240 h post-first dose）	▲	▲	▲		±4h
	D15（336 h post-first dose）	▲	▲			±4h
	D29（672 h post-first dose）	▲	▲	▲		±1d
2nd Dose	D43 (predose)	▲	▲	▲		Predose
3rd Dose	D85 (predose)	▲	▲	▲	▲	Predose
4th Dose	D127 (predose, before 4th dose)	▲	▲	▲		Predose
	D128 (24 h post-4th dose)	▲	▲	▲		±20min
	D129 (48 h post-4th dose)	▲	▲			±20min
	D131 (96 h post-4th dose)	▲				±1h
	D134 (168 h post-4th dose)	▲	▲	▲		±4h
	D137 (240 h post-4th dose)	▲	▲	▲		±4h
	D141 (336 h post-4th dose)	▲	▲			±4h
	D155 (672 h post-4th dose)	▲	▲	▲		±1d
5th Dose※	D169 (predose, before 5th dose)	▲	▲	▲	▲	Predose
6th Dose※	D211 (predose, before 6th dose)	▲	▲	▲		Predose
7th Dose※	D253 (predose, before 7th dose)	▲	▲	▲		Predose
Last Dose	672 h post-last dose	▲	▲	▲		±1d
	1008 h post-last dose	▲	▲	▲	▲	±2d
	1344 h post-last dose	▲	▲	▲		±2d
	1680 h post-last dose	▲				±2d
	2016 h post-last dose	▲	▲	▲		±3d

※Collected based on actual dosing duration. Added PD parameter: pro-inflammatory cytokines (IL-1beta, IL-6, TNF-alpha). If duplicate blood collection timepoints occur, collect only once.

Table8-6 PK/PD Sampling Timepoints and Time Windows（Part C） (Q8W)

Collection Timepoint		PK Sample	PD Sample		Tolerance Window
		SR604	Protac-APTT, Protein C, TGA)	Pro-inflammatory Cytokines	/
First Dose	D1 (predose)		▲	▲	Predose
	D11 (240 h post-first dose)	▲	▲		±4h

2nd Dose	D57 (predose, before 2nd dose)	▲	▲		Predose
3rd Dose	D113 (predose, before 3rd dose)	▲	▲		Predose
4th Dose※	D169 (predose, before 4th dose)	▲	▲	▲	Predose
5th Dose※	D225 (predose, before 5th dose)	▲	▲		Predose
Last Dose	Last Dose	▲	▲		Predose
	240 h post-last dose	▲	▲	▲	±4h

※Note: Collected based on actual dosing duration. Added PD parameter: pro-inflammatory cytokines (IL-1beta, IL-6, TNF-alpha). If duplicate blood collection timepoints occur, collect only once

Collected blood samples will be centrifuged and stored frozen at –60°C or below. Test samples will be transported by a specialized cold chain logistics company to the central laboratory for analysis. Backup samples will be stored frozen at –60°C or below at the clinical trial institution or transported by a specialized cold chain logistics company to a sponsor-designated third party after trial completion.

Biological Sample Analysis:

All PK/PD biological samples collected from subjects will be transported to the central laboratory. Specific requirements will be executed according to the relevant standard operating procedures and testing requirements established by the central laboratory.

Safety and Immunogenicity Evaluation Parameters

Safety parameters: Incidence of AEs/SAEs/AESIs assessed through clinical signs and symptoms, vital signs, physical examination, laboratory tests (complete blood count, urinalysis, and blood biochemistry), coagulation function [PT, TT, INR, FIB, 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 subjects with anti-drug antibodies (ADA) and neutralizing antibodies.

Immunogenicity parameters: Number and incidence of subjects with anti-drug antibodies (ADA) and neutralizing antibodies.

Efficacy Parameters (Part B)

Primary efficacy parameters:

At 12 weeks and 24 weeks of treatment, treatment-based annualized bleeding rate (ABR).

The ABR at 12 weeks of treatment can be calculated using the following formula: Total number of treated bleeding episodes from first dose to within 14 days after the 6th dose / [(date of 6th dose – date of first dose + 14) / 365.25]. The ABR at 24 weeks of treatment can be calculated using the following formula: Total number of treated bleeding episodes from first dose to within 14 days after the last dose / [(date of last dose – date of first dose + 14) / 365.25].

Note: Total bleeding includes spontaneous and traumatic bleeding. A treated bleeding episode refers to a bleeding event for which factor replacement or bypassing agent therapy was administered.

Secondary efficacy parameters:

1. At 12 weeks and 24 weeks of treatment, treatment-based annualized spontaneous bleeding rate;
2. At 12 weeks and 24 weeks of treatment, treatment-based annualized total joint bleeding rate (AJBR);
3. At 12 weeks and 24 weeks of treatment, treatment-based annualized menorrhagia bleeding rate (applicable only to female patients of childbearing age with menstruation who have congenital coagulation Factor VII deficiency);
4. At 12 weeks and 24 weeks of treatment, change from baseline in the Hemophilia Joint Health Score (HJHS) (Hemophilia A and B patients);
5. At 12 weeks and 24 weeks of treatment, change from baseline in the EuroQol-5 Dimension-5 Level (EQ-5D-5L) questionnaire.

Efficacy Parameters (Part C)

Primary efficacy parameters:

At 24 weeks of treatment and during the treatment period (including treatment and extension treatment periods), treatment-based annualized bleeding rate (ABR).

The following formulas can be used for calculation:

ABR at 24 weeks = (Number of treated bleeding episodes within the dosing interval after the last dose during the 24-week treatment period x 365.25) / (Date of last dose during the 24-week treatment period - Date of first dose + dosing interval)

ABR during the treatment period (including treatment period and extension treatment period) = (Number of treated bleeding episodes within the dosing interval after the last dose x 365.25) / (Date of last dose - Date of first dose + dosing interval)

Note: Total bleeding includes spontaneous and traumatic bleeding. A treated bleeding episode refers to a bleeding event for which factor replacement or bypassing agent therapy was administered.

The 'dosing interval' for the Q4W group is 28 days; for Q6W it is 42 days; for Q8W it is 56 days.

Secondary efficacy parameters:

1. At 24 weeks of treatment and during the treatment period (including treatment and extension treatment periods), treatment-based annualized spontaneous bleeding rate;
2. At 24 weeks of treatment and during the treatment period (including treatment and extension treatment periods), treatment-based annualized total joint bleeding rate (AJBR);
3. At 24 weeks of treatment and during the treatment period (including treatment and extension treatment periods), treatment-based annualized menorrhagia bleeding rate (applicable only to female patients of childbearing age with menstruation who have congenital coagulation Factor VII deficiency);
4. At 24 weeks of treatment and during the treatment period (including treatment and extension treatment periods), change from baseline in the Hemophilia Joint Health Score (HJHS) (Hemophilia A and B patients);
5. At 24 weeks of treatment and during the treatment period (including treatment and extension treatment periods), change from baseline in the EuroQol-5 Dimension-5 Level (EQ-5D-5L) questionnaire.

Pharmacokinetic Evaluation Parameters

Single-dose PK parameters: Tmax, Cmax, t1/2z, AUC0-t, AUC0-∞, CLz/F, Vz/F, MRT, λz, etc.

Multiple-dose PK parameters: Tmax,ss, Cmax,ss, AUC0-t, CLss/F, Cmin,ss, Cav,ss, AUC0-τ,ss, and degree of fluctuation at steady state (DF), etc. If data permit, parameters such as t1/2z, AUC0-∞, Vz/F, MRT, and λz will be calculated.

Exploratory Parameters

To explore the effect of the investigational drug on PD parameters: Protac-APTT (Protac-induced protein C-activated APTT assay), protein C, prothrombin time (PT), thrombin generation assay (TGA), and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α).

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 later); all other analyses will be performed using SAS software (Version 9.4 or later).