

Protocol Summary (English Translation)

SR604 Injection — A Single-Arm, Multicenter Phase III Clinical Trial of Prophylactic Treatment in Hemophilia A/B Patients with or without Inhibitors: Evaluation of Efficacy and Safety

Protocol Synopsis

Study Title

A Single-Arm, Multicenter Phase III Clinical Trial to Evaluate the Efficacy and Safety of SR604 Injection for Prophylactic Treatment in Patients with Hemophilia A or B with or without Inhibitors

Investigational Product

SR604 Injection

Protocol Number

LS-SR604-AB-III01

Version/Date

Ver1.0/September 14, 2026

Sponsor

Shanghai RAAS Blood Products Co., Ltd.

Study Sites

Approximately 16 sites are planned to be selected as clinical trial centers.

Phase

Phase III

Study Population

Patients with hemophilia A or B with or without inhibitors

Study Objectives

Primary objective: To evaluate the efficacy of SR604 Injection for prophylactic treatment in patients with hemophilia A or B with or without inhibitors.

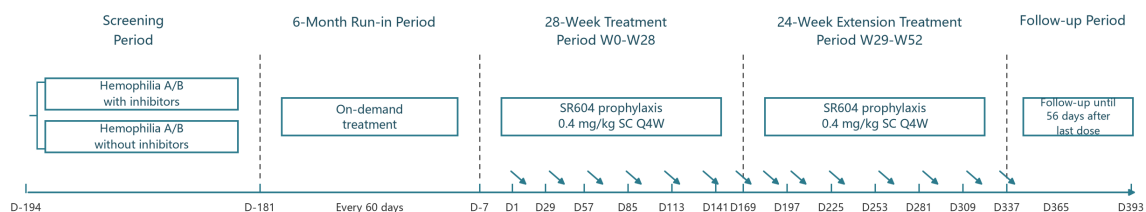
Secondary objectives: To evaluate the safety, immunogenicity, and pharmacokinetic/pharmacodynamic (PK/PD) characteristics of SR604 Injection for prophylactic treatment in patients with hemophilia A or B with or without inhibitors.

Study Design

This is a single-arm, multicenter Phase III clinical trial designed to evaluate the efficacy, safety, immunogenicity, and pharmacokinetic/pharmacodynamic (PK/PD) characteristics of SR604 Injection for prophylactic treatment in patients with hemophilia A or B with or without inhibitors.

Eligible study participants with or without inhibitors who pass screening will enter a 6-month (180-day) run-in period. During the run-in period, participants without inhibitors will receive on-demand treatment with plasma-derived or recombinant FVIII/FIX and PCC, and participants with inhibitors will receive on-demand treatment with recombinant activated factor VII (rFVIIa) and PCC. Bleeding events and their treatments will be recorded. Participants who have ≥ 6 bleeding events requiring treatment with coagulation factor replacement or bypassing agents during the run-in period will be considered qualified from the run-in and eligible to enter the treatment period. The treatment period lasts 28 weeks, during which study participants will receive SR604 Injection prophylactic treatment 7 times at a dose and frequency of 0.4 mg/kg Q4W. After completion of the treatment period, study participants may enter a 24-week extension treatment period and receive SR604 Injection prophylactic treatment 6 times at the same dose and frequency as in the treatment period. The final visit of the extension treatment period will take place 4 weeks after the last dose, followed by a 4-week follow-up period.

The study design is illustrated in Figure 3-1.



Sample Size

The trial plans to enroll 90 study participants, including patients with hemophilia A or B with or without inhibitors. The analysis of the primary efficacy endpoint will be based on negative binomial regression; therefore, the sample size calculation is based on simulation using a negative binomial distribution. The target value is set at 5, i.e., the one-sided 97.5% upper limit of the post-prophylaxis ABR must be less than 5 for the trial to be considered to have achieved the expected result. Assuming an annualized rate of 3.3 events/subject/year for prophylactic treatment after enrollment, an overdispersion coefficient $ODC=6$ (variance/mean), simulation was performed using SAS software with $\alpha=0.025$ (one-sided), distribution function negbin, link function ID, seed number 20241231, and 1000 simulation replicates. The simulation results showed that 72 evaluable subjects would provide more than 85% power. Taking into account the impact of dropouts and intercurrent events, 90 study participants are planned to be enrolled based on the 72 evaluable subjects.

Since study participants with or without inhibitors of hemophilia A or B all receive on-demand treatment, after the target value test is completed, superiority analyses will also be performed separately for study participants with and without inhibitors to analyze the superiority of prophylactic treatment versus on-demand treatment. The superiority margin is set at 0.5[1], i.e., superiority is considered achieved when the one-sided 97.5% upper limit of the ratio of post-prophylaxis ABR to on-demand treatment ABR is less than 0.5.

Assuming an annualized on-demand treatment ABR of 32 events/subject/year[2] in patients with inhibitors, an annualized rate of 3.8 events/subject/year for prophylactic treatment after enrollment, an overdispersion coefficient $ODC=6$ (variance/mean), a correlation coefficient of 0.2 for ABR before and after treatment within the same study participant, simulation was performed using SAS software with $\alpha=0.025$ (one-sided), distribution function negbin, link function log, seed number 20241231, and 1000 simulation replicates. The simulation results showed that no fewer than 30 evaluable subjects would provide more than 99% power.

Assuming an annualized on-demand treatment ABR of 32 events/subject/year[2] in patients without inhibitors, an annualized rate of 3 events/subject/year for prophylactic treatment after enrollment, an overdispersion coefficient $ODC=6$ (variance/mean), a correlation coefficient of 0.2 for ABR before and after treatment within the same study participant, simulation was performed using SAS software with $\alpha=0.025$ (one-sided), distribution function negbin, link function log, seed number 20241231, and 1000 simulation replicates. The simulation results showed that no fewer than 30 evaluable subjects would provide more than 99% power.

In summary, enrolling 90 study participants (with no fewer than 30 study participants each for those with or without inhibitors) will satisfy both the target value test and the superiority design. Therefore, the final planned enrollment for this trial is 90 study

participants. According to the Chinese Guidelines for the Diagnosis and Treatment of Coagulation Factor VIII/IX Inhibitors (2018 Edition)[3], the inhibitor incidence rate is approximately 30% in patients with severe hemophilia A, 3%–13% in non-severe patients, and 1%–6% in patients with hemophilia B. Taking into account the population proportion of patients with inhibitors, combined with the actual conditions of this project, this trial plans to enroll 30 study participants with inhibitors and 60 study participants without inhibitors. Hemophilia epidemiology shows that among all hemophilia patients, hemophilia A accounts for approximately 80%–85% and hemophilia B accounts for 15%–20%[4]. According to the Chinese Hemophilia B Registry Study[5], as of 2021, 44 patients with FIX inhibitors were identified among 4,485 patients with hemophilia B, with a registry proportion of only 0.98%. Considering the rarity of hemophilia B patients with inhibitors, the hemophilia type is not restricted for study participants with inhibitors, and the enrollment numbers will be determined based on actual conditions. Among study participants without inhibitors, no fewer than 40 should have hemophilia A and no fewer than 10 should have hemophilia B. According to China data from the WFH Annual Global Survey 2022[6], patients aged 14–18 years account for approximately 12%. The planned enrollment of adolescent study participants is approximately 16% of the total, i.e., 15 subjects, including 5 with inhibitors and 10 without inhibitors. See the table below for details:

Hemophilia A/B with inhibitors	30 subjects (including 5 adolescents)	
Hemophilia A with inhibitors	No minimum as long as the total number of subjects with inhibitors is met	Unrestricted
Hemophilia B with inhibitors*	No minimum as long as the total number of subjects with inhibitors is met	Unrestricted
Hemophilia A/B without inhibitors	60 subjects (including 10 adolescents)	
Hemophilia A without inhibitors	≥40 subjects	
Hemophilia B without inhibitors	≥10 subjects	

Total	90 subjects	
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Trial Duration

From screening of the first trial participant to the last visit of the last trial participant, the study is expected to last approximately 28 months.

Visit Duration

From signing the informed consent form (ICF) to completion of all protocol-specified visit procedures, the expected duration for a trial participant is at least approximately 592 days.

Trial Population

Inclusion Criteria

- 1. Patients aged ≥ 12 years and ≤ 65 years at the time of signing the informed consent form (ICF), male or female;
- 2. Patients with hemophilia A with FVIII activity level $< 1\%$ or hemophilia B with FIX activity level $\leq 2\%$, confirmed by testing during the screening period or by prior test results;
- - For patients without inhibitors: FVIII or FIX inhibitor test results during the screening period are negative or below the lower limit of normal (LLN); no bleeding treated with bypassing agents due to inhibitors within at least 6 months prior to screening; no history of immune tolerance induction (ITI) within 3 years prior to screening; and ≥ 150 exposure days (EDs) of clotting factor replacement therapy;
- - For patients with inhibitors: FVIII or FIX inhibitor titer during the screening period is high titer (≥ 5 Bethesda units/mL [BU/mL]), or the inhibitor titer is low titer (0.6 BU/mL or the upper limit of normal $\leq$ inhibitor titer < 5 BU/mL) and treatment with a bypassing agent (rFVIIa or PCC) has already been initiated;
- 3. ≥ 6 bleeds requiring treatment with a clotting factor replacement or bypassing agent within the 6-month run-in period (bleeds related to surgery are not counted);
- 4. No active bleeding symptoms prior to the first administration of SR604 Injection;
- 5. Able to understand the procedures and methods of this clinical trial, with adequate informed consent; the patient voluntarily participates and signs the informed consent form (ICF).

Exclusion Criteria

1. Patients with a known history of hypersensitivity to the investigational product or any of its components;
2. Intolerance to subcutaneous (SC) injection, or presence of other local skin abnormalities or skin diseases that affect dosing and safety assessment;
3. Meeting any of the following criteria during the screening period or prior to enrollment:
 - a) Hemoglobin <60 g/L;
 - b) Platelet count $<100 \times 10^9$ /L;
 - c) Abnormal hepatic or renal function: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 2.5 \times$ the upper limit of normal (ULN), or total bilirubin $\geq 1.5 \times$ ULN; or serum creatinine (Cr) $\geq 1.5 \times$ ULN;
 - d) Positive for anti-human immunodeficiency virus (HIV) antibodies;
4. Markedly abnormal coagulation parameters caused by diseases other than hemophilia A or B (e.g., platelet disorders, vitamin K deficiency, etc.);
5. Patients with protein C deficiency or protein S deficiency;
6. History of thrombosis or family history of thrombosis, or history of thrombophilia;
7. Intracranial hemorrhage due to hemophilia A or B within 2 years prior to signing the informed consent form (ICF);
8. Suffering from severe cardiac disease, such as unstable angina, congestive heart failure (New York Heart Association [NYHA] class $\geq$ III), severe arrhythmia (QTc interval >480 ms, corrected by Fridericia's formula), uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg), etc.;
9. Received any product containing FVIII within 72 hours prior to the first administration of the investigational product; received any product containing FIX within 96 hours prior to the first administration of the investigational product; received recombinant human coagulation factor VIIa (rFVIIa) within 48 hours prior to the first administration of the investigational product; the washout period for long-acting forms of the above medicinal products is less than 5 half-lives;
10. Used within 1 week prior to screening, or requiring during the trial, any anticoagulants, antifibrinolytics, or chemical drugs, biological products, or traditional Chinese medicines that affect platelet function, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin;
11. Received non-factor regular replacement therapy within 6 months prior to signing the informed consent form (ICF), such as emicizumab, marstacimab, Fitusiran injection (fitusiran sodium), etc.;

12. Underwent major surgery (e.g., orthopedic surgery, abdominal surgery) within 1 month prior to signing the informed consent form (ICF), or planned to undergo surgery during the study period;
13. Enrolled in another clinical trial and received drug/medical device treatment within 1 month prior to signing the informed consent form (ICF);
14. Patients with mental illness or significant psychiatric disorders, or incapacity or cognitive impairment due to other causes;
15. Planning to have children or donate sperm during the entire trial period and within 6 months after the last dose, or unwilling to use effective physical contraception (e.g., condoms, etc.);
16. Other conditions considered by the investigator to make the patient unsuitable for enrollment, such as alcohol abuse, anticipated poor compliance of the trial participant that makes it impossible to complete dosing and trial follow-up, poorly controlled other chronic diseases, or presence of severe systemic diseases.

Dose Selection and Rationale

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

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

Based on the above nonclinical pharmacodynamic results and nonclinical PK data, the minimum efficacious concentration of SR604 was set at 0.506 µg/mL (similar to the concentration associated with the 90% inhibition rate in vitro). Through modeling and simulation, it was predicted that in patients with hemophilia, the peak concentration after a single subcutaneous injection of 0.05 mg/kg would reach the predicted minimum effective concentration; a single subcutaneous injection of 0.1 mg/kg would maintain the concentration at or above the minimum effective concentration for approximately 16 days; a single subcutaneous injection of 0.2 mg/kg would maintain the concentration at or above the minimum effective concentration for approximately 29 days.

This product first completed Phase I and Phase IIa clinical trials in patients with hemophilia A/B and congenital coagulation factor VII deficiency, and a Phase IIb trial with 24 weeks of treatment. Based on the clinical trial data, quantitative pharmacology analysis was performed to simulate different doses at different dosing intervals. The results are shown in Figures 3-2 to 3-4.

[Figure 3-2: Simulated SR604 concentration-time profile with Q4W dosing (original figure left blank as requested — not translated)]

[Figure 3-3: Simulated SR604 concentration-time profile with Q6W dosing (original figure left blank as requested — not translated)]

[Figure 3-4: Simulated SR604 concentration-time profile with Q8W dosing (original figure left blank as requested — not translated)]

Preliminary results from the Part C portion (24 weeks of treatment) of an ongoing Phase I/II clinical trial in patients with hemophilia A/B and congenital coagulation factor VII deficiency are as follows:

Three groups were selected in Part C (Phase IIb): Group A: 0.4 mg/kg every 4 weeks (Q4W), Group B: 0.4 mg/kg every 6 weeks (Q6W), and Group C: 0.4 mg/kg every 8 weeks (Q8W), with 12 participants enrolled in each group, for a total of 36 participants. Based on the available data, in patients with hemophilia A/B treated for 24 weeks, the mean treated total annualized bleeding rate (ABR) (95% CI) in the Q4W group was 3.256 (1.712, 6.193), a decrease of 91.3% from baseline; the Q6W and Q8W groups were 7.979 (4.669, 13.634) and 9.421 (5.583, 15.895), representing decreases of 80.5% and 76.8%, respectively. The Q4W group showed statistically significant differences compared with the Q6W and Q8W groups ($P=0.0358$ and $P=0.0120$). The treated ABR at 0.4 mg/kg Q4W was statistically different from that at 0.4 mg/kg Q6W and 0.4 mg/kg Q8W, and the treated ABR tended to decrease as the dosing interval was prolonged (Week 0-Week 12: 4.675 → Week 12-Week 24: 1.818). The 0.4 mg/kg Q4W regimen demonstrated the best efficacy.

A population pharmacokinetic (PopPK) model was established based on the interim data from Part A, Part B, and Part C ($N=76$). The PK characteristics of the adolescent population were extrapolated by body weight, and with the steady-state exposure of 0.4 mg/kg Q4W dosing in adults (mean body weight 67.5 kg) as the target, the safe and effective dose for the adolescent population was predicted. By comparing simulated systemic exposure between adolescents (12-18 years, 30-60 kg) and adults, the exposure levels of 0.4 mg Q4W dosing in adolescents were comparable to those of 0.4 mg/kg Q4W dosing in adults.

Based on the Phase II clinical trial results, the three groups in Part C (Phase IIb)--0.4 mg/kg Q4W, 0.4 mg/kg Q6W, and 0.4 mg/kg Q8W--had treated total annualized bleeding rates of 3.256, 7.979, and 9.421, respectively, over 24 weeks of treatment. The 0.4 mg/kg Q4W group had the lowest total annualized bleeding rate and excellent safety. Considering the quantitative pharmacology analysis and the Phase II clinical trial results, the 0.4 mg/kg Q4W dose group was ultimately selected for both adolescents and adults for the Phase III study of prophylactic treatment efficacy, safety, immunogenicity, and pharmacokinetic/pharmacodynamic characteristics.

Investigational Product

Name: SR604 injection

Strength: 30 mg/mL

Composition: SR604; the main excipients include histidine, histidine hydrochloride, trehalose, arginine hydrochloride, and polysorbate 80

Storage conditions: Store and transport at 2-8°C, protected from light

Supplier: Shanghai RAAS Blood Products Co., Ltd.

Dosing Regimen

Administration

Administer by slow subcutaneous injection according to the labeled amount; the injection should be completed within 5 minutes, at a pace comfortable for the participant. The injection site may be the abdomen (excluding the area within a 5-cm radius around the umbilicus), the thigh (middle anterior area), or the outer aspect of the upper arm. Within each month, each injection should be given at a different site, at least 2.5 cm away from the area of the previous injection. Do not select areas that may rub against a belt or waistband. Do not inject into areas with moles, scars, or bruising, or areas where the skin is tender, red, hardened, or broken.

Dose

The dose is calculated based on the participant's body weight: $\text{dose (mg)} = 0.4 \text{ (mg/kg)} \times \text{body weight (kg)}$; administered subcutaneously once every 4 weeks. If the investigational product is not administered within the planned dosing window, it should be given as soon as possible; if no dose has been given for more than 14 days, the dose should be given on the next scheduled dosing day, and the routine dosing schedule should then be resumed.

The administration volume is converted from the labeled amount in the product insert. If the injection volume does not exceed 1 mL, the dosing volume should be accurate to 0.01 mL (rounded). If the injection volume exceeds 1 mL, the dosing volume should be accurate to 0.1 mL (rounded).

Trial Procedures

This trial comprises a screening period, a run-in period, a treatment period, an extended treatment period, and a follow-up period.

Screening period: After signing the informed consent form, participants enter the screening period and complete the screening examinations and assessments according to the visit schedule. The screening period should not exceed 2 weeks. The investigator will review the information collected during the screening period to determine whether the participant is suitable for this trial.

Run-in period: After passing screening, participants enter a 6-month (180-day) run-in period. Participants without inhibitors receive on-demand treatment with plasma-derived or recombinant FVIII/FIX or PCC during the run-in period, while participants with inhibitors receive on-demand treatment with recombinant activated coagulation factor VIIa (rFVIIa) or PCC. Those who have ≥ 6 bleeds requiring treatment with clotting factor replacement or bypassing agents during the run-in period are considered eligible for the run-in and may enter the treatment period. If a participant experiences a bleeding event before the end of the run-in period, the run-in period may be extended for washout of the therapeutic agent; bleeds occurring during the extended run-in period are not used to determine run-in eligibility, but will be included in the calculation of the pre-treatment annualized bleeding rate.

Treatment period: Run-in-eligible participants will be assigned an enrollment number and enter the 28-week treatment period to receive SR604 prophylaxis at a dose of 0.4 mg/kg once every 4 weeks for 7 administrations in total. Refer to the drug usage and dose specifications for details. Participants will complete efficacy, safety, and immunogenicity assessments according to the visit schedule, together with PK/PD blood sampling.

Extended treatment period: After completing the treatment period, participants enter a 24-week extended treatment period and continue to receive SR604 prophylaxis at a dose of 0.4 mg/kg once every 4 weeks for 6 administrations in total. Participants will complete efficacy, safety, and immunogenicity assessments according to the visit schedule, together with PK/PD blood sampling.

At 28 days after the last dose / upon early withdrawal, participants are required to undergo assessments including body weight, vital signs, physical examination, Hemophilia Joint Health Score (HJHS), EQ-5D-5L scale, laboratory tests (complete blood count, urinalysis, coagulation function, blood biochemistry, FDP), 12-lead electrocardiogram, pregnancy test, prothrombin fragment 1+2 (F1+2), anti-SR604 antibody (ADA) and neutralizing antibody (NAb) testing, and PK/PD sample collection; participant diaries are distributed and collected, and bleeding events and their treatment, adverse events, and concomitant medications/non-drug therapies are recorded. If safety evaluation parameters are abnormal, follow-up is required until they return to normal, become abnormal without clinical significance, stabilize, or return to baseline status.

Follow-up period: At 56 days after the last dose, participants are required to complete a telephone visit to collect/record bleeding events and their treatment since the previous visit, adverse events, concomitant medications/non-drug therapies, and to collect participant diaries.

Primary Efficacy Endpoint

Treated total annualized bleeding rate (ABR) over 28 weeks of treatment.

It can be calculated using the following formula: total number of treated bleeds during 28 weeks of treatment / bleeding exposure time over 28 weeks × 365.25.

Note: Total bleeds include spontaneous bleeds and traumatic bleeds. Treated bleeds refer to bleeds for which factor replacement or bypassing agents were used.

Key Secondary Efficacy Endpoint

Treated total annualized bleeding rate (ABR) over 52 weeks of treatment.

It can be calculated using the following formula: total number of treated bleeds during 52 weeks of treatment / bleeding exposure time over 52 weeks × 365.25.

Other Secondary Efficacy Endpoints

Treated and untreated spontaneous annualized bleeding rate

- Treated and untreated spontaneous annualized bleeding rate over 28 weeks and 52 weeks of treatment

Treated and untreated traumatic annualized bleeding rate

- Treated and untreated traumatic annualized bleeding rate over 28 weeks and 52 weeks of treatment

Treated and untreated annualized joint bleeding rate (AJBR)

- Treated and untreated annualized joint bleeding rate (AJBR) over 28 weeks and 52 weeks of treatment

Total annualized bleeding rate, including treated and untreated bleeding events

- Total annualized bleeding rate over 28 weeks and 52 weeks, including treated and untreated bleeding events

Untreated total annualized bleeding rate

- Untreated total annualized bleeding rate over 28 weeks and 52 weeks of treatment

Treated and untreated target joint annualized bleeding rate

- Treated and untreated target joint annualized bleeding rate over 28 weeks and 52 weeks of treatment

Treated total annualized bleeding rate in patients with and without inhibitors

- Treated total annualized bleeding rate over 28 weeks and 52 weeks of treatment in patients with and without inhibitors

Proportion of patients with no treated bleeding events

- Proportion of patients with no treated bleeding events over 28 weeks and 52 weeks of treatment

Change in the number of target joints

- Change in the number of target joints over 28 weeks and 52 weeks of treatment

Change from pre-treatment in Hemophilia Joint Health Score (HJHS)

- Change from pre-treatment in Hemophilia Joint Health Score (HJHS) over 28 weeks and 52 weeks of treatment

Change from pre-treatment in health index scale (EQ-5D-5L)

- Change from pre-treatment in health index scale (EQ-5D-5L) over 28 weeks and 52 weeks of treatment

Safety Endpoints

The incidences of AE/SAE/AESI are assessed through clinical symptoms and signs, 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], prothrombin fragment 1+2 (F1+2), FDP, 12-lead electrocardiogram, injection site reactions, hypersensitivity/allergic reactions, and thromboembolic events; as well as the incidence of treatment-related AE/SAE/AESI.

Immunogenicity Endpoints

Number of participants positive for anti-drug antibody (ADA) and neutralizing antibody (NAb) and their incidence.

Pharmacokinetic Endpoints

All participants will have biological samples collected at protocol-specified time points for the determination of SR604 concentrations in plasma. The plasma drug concentrations of SR604 collected at the specified time points of each visit will be used to establish a population pharmacokinetic (PopPK) model.

Pharmacodynamic Endpoints

Changes from baseline in Protac-APTT (Protac-induced protein C activation APTT assay) and pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α).

Exploratory Endpoints

Change from baseline in protein C.

PK/PD Sample Collection

All participants enrolled in this trial are required to have biological samples collected at the specified time points for PK/PD analysis (see the table below). Biological sample collection will be performed by authorized and trained research personnel in accordance with the requirements of the testing laboratory.

The collected blood samples are centrifuged and stored frozen at -60°C or below.

Samples to be tested are transported by a professional cold-chain transport company to the central laboratory for testing. Backup samples are temporarily stored at the clinical trial site or transported by a professional cold-chain transport company to a third party designated by the sponsor and stored frozen at -60°C or below.

Table 7-2 PK/PD Sampling Time Points and Time Windows

Time point of collection	PK sample	PD sample	Allowable window
First dose: D1 (before first dose)	▲	▲	Before dosing

Dose 4: D85 (before Dose 4)	▲	▲	Before dosing
Dose 6: D141 (before Dose 6)	▲	▲	Before dosing
Dose 8: D197 (before Dose 8)	▲	▲	Before dosing
Dose 11: D281 (before Dose 11)	▲	▲	Before dosing
Dose 13: D365 (28 days after Dose 13)	▲	▲	28 d $\pm$ 3 d after dosing
Early withdrawal	▲	▲	N/A

Statistical Software and General Requirements

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

Pharmacokinetic analyses 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).