A Single-arm, Open-label, Single-dose, Phase I Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Recombinant Human Thrombopoietin for Injection (rhTPO) in Healthy Caucasian Volunteers

Sponsor	**3SBIO AU PTY LTD**
Study Number	**rhTPO-101-AUS**
Version	**2.0**
Version date	**6 Sep 2024**

Approved by the Applicant

Signature of the Sponsor

The undersigned confirms that the following protocol has been agreed and accepted.

Sponsor Signatory:

Signature:

..... Date: ...../...../.....
Printed Name:

SONG Weifeng, MD
Director of Medical Department

Principal Investigator Signature Page

The undersigned confirms that the following protocol has been agreed upon and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in ICH Good Clinical Practice (GCP), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Principal Investigator:

Signature:

..... Date: ...../...../.....
Printed Name:

Dr. Sam Francis

Protocol Amendment Summary

Document	Date	Description of Change
Original Protocol (Version 1.0)	13 Aug 2024	NA
Version 2.0	6 Sep 2024	• Replaced “PD sampling” with “Hematology/PD sampling” for clarification in Table 3. • Added “Plateletcrit and platelet distribution width are adjunctive pharmacodynamic parameters and they will not be reviewed as part of clinical safety laboratory results” in Section 1.3 and 8.4.4 because plateletcrit and platelet distribution width are not standard haematology parameters in Australia. • Added study stopping rules in Section 5.6. • Modified ISR definition in Section 8.4.9. • Modified SAP related description and removed statistical analysis report in Section 9. • Modified statistical analysis details in Section 9. • Modified a few wordings, but did not change the original intent.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transferase
AUC	Area Under the Curve
AUC_{0-t}	Area under the serum concentration-time curve from time zero to the last measurable serum concentration time t
$AUC_{0-\infty}$	Area under the curve extrapolated from zero to time of infinity
$AUC_{\_\%Extrap}$	Area ratio under extrapolated concentration-time curve
BMI	Body Mass Index
BP	Blood Pressure
BQL	Below Quantitation Limit
C_{max}	Peak Concentration
CHO	Chinese Hamster Ovary
CIT	Chemotherapy-Induced Thrombocytopenia
CLD-TCP	Chronic Liver Disease - Thrombocytopenia
CL/F	Apparent Clearance
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Clinical Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DM	Data Manager
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen

Abbreviation or special term	Explanation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IP	Investigational Product
ISR	Injection Site Reaction
ITP	Immune Thrombocytopenia
IUD	Intrauterine Device
Ke	Terminal Elimination Rate Constant
LLOQ	Lower Limit of Quantification
MRT	Mean Residence Time
MPV	Mean Platelet Volume
NC	Non-Computable
ND	Not Quantifiable
NQ	Non-Quantifiable
rhTPO	Recombinant Human Thrombopoietin
PD	Pharmacodynamic
PDW	Platelet Distribution Width
PK	Pharmacokinetic
PLT	Platelet Count
QTcF	Corrected QT Interval (Fridericia)
RSI	Reference Safety Information
RT-PCR	Real-Time Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDV	Source Data Verification
SoA	Schedule of Activities
SUSAR	Suspected and Unexpected Serious Adverse Reaction
$t_{1/2}$	Elimination Half-life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Peak Drug Concentration
Vd/F	Apparent Volume of Distribution
WOCBP	Women of Childbearing Potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Single-arm, Open-label, Single-dose, Phase I Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Recombinant Human Thrombopoietin for Injection (rhTPO) in Healthy Caucasian Volunteers

Rationale:

Thrombocytopenia is a common clinical problem, with approximately 8 million units of platelets transfusions administered each year in the United States to reduce severe bleeding in patients. However, this is not an ideal therapy, as at least 30% of patients experience transfusion-related complications. Repeated platelet transfusions are required in 15 to 25 percent of patients, which often lead to HLA-related immune response.

TPO can significantly stimulate platelet production, increase peripheral blood platelet count, and has no significant impacts on platelet morphology and functionality, thus it is an effective thrombopoiesis stimulating factor. A large number of studies have shown that recombinant human thrombopoietin (rhTPO) can effectively increase the platelet level both in terms of the mechanism of action and clinical practice, and has demonstrated a favourable safety profile.

Recombinant human thrombopoietin (rhTPO, trade name TPIAO®), developed by Shenyang Sunshine Pharmaceutical Co., Ltd. (3SBio Inc.), is a full-length glycosylated rhTPO expressed in Chinese hamster ovary (CHO) cells and purified via conventional gene recombination technology. There are two (2) formulations of rhTPO drug product, namely injection (TPIAO®) and lyophilized powder for injection. Both rhTPO formulations are given by subcutaneous injection, and they have consistent pharmacokinetic (PK) profile in a single dose PK study of cynomolgus monkeys. TPIAO® has been launched in China for chemotherapy-induced thrombocytopenia (CIT) in 2005 and for adult immune thrombocytopenia (ITP) in2010. It was further approved in 2024 for the treatment of pediatric ITP in children over six years old. In addition, TPIAO® has been approved for marketing in the nine other countries, including Thailand, Philippines, Sri Lanka, Cambodia, Dominica, Paraguay, Costa Rica, Uzbekistan and Ukraine. Completed clinical trials have demonstrated that rhTPO could significantly increase platelet levels in patients with CIT and ITP, with mild adverse reactions and favourable safety.

This study is designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD) and safety profile of rhTPO in healthy Caucasian volunteers.

Objectives and Endpoints:

Objectives	Endpoints
Primary	

Objectives	Endpoints
To evaluate the PK profile following a single dose of rhTPO in healthy Caucasian	PK concentration-time profile and PK parameters: T_{max}, C_{max}, $t_{1/2}$, MRT, AUC_{0-t}, $AUC_{0-\infty}$, Vd/F, Ke, CL/F, $AUC_{\_\%Extrap}$
Secondary	
To evaluate the PD profile following a single dose of rhTPO in healthy Caucasian	PLT counts and changes in PLT over time.
To evaluate the safety and tolerability following a single dose of rhTPO in healthy Caucasian	Incidence and severity of AEs and SAEs, physical examination, vital sign, clinical laboratory test, ECG, ISR
To evaluate the immunogenicity profile following a single dose of rhTPO in healthy Caucasian	Incidence of the development of ADAs and NAb (if applicable) to rhTPO.

Overall Design:

This is a single-center, single-arm, open-label, single-dose phase I clinical study to evaluate pharmacokinetics, pharmacodynamics, safety and tolerability of Recombinant Human Thrombopoietin for Injection (rhTPO) in healthy Caucasian participants. Approximately 22 healthy Caucasian participants will be enrolled for this study.

One dose level is planned in this study, and participants will receive a single abdominal subcutaneous injection at a dose of 300U/kg after entering the study.

Participants will undergo screening, admission (baseline), administration and follow-up observation period. Participants will sign an informed consent form before any study procedures are performed. During screening, all participants will be screened for study eligibility within 28 days prior to administration. Eligible participants will be admitted to the clinical study ward no later than one day prior to dosing (D-1). Participants need to fast for at least 10 hours prior to dosing and 4 hours after dosing. Single abdominal subcutaneous injection of the study drug will be given on D1. The administration and follow-up observation period will be 29 days (D1~D29). Participants may be discharged at D7 at the judgment of the investigator. PK blood samples will be collected from D-1 to D14, tolerance and safety will be observed from D1 to D29, and blood samples for PD and anti-drug antibody (ADA) will be collected from screening to D29. After completion of relevant assessments on D29, participants will be considered as having completed this study.

Design of PK study

PK study is required for all participants in this study. PK blood samples will be collected at the following specified time points: D-1, before administration (D1), 2 h, 5 h, 8 h, 10 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 216 h, 264 h and 312 h after administration.

Design of PD study

PD blood samples will be collected from participants in this study at specified time points: D-28 ~ D-2, D-1, D4, D8, D10, D14, D22 and D29; PD blood samples will be collected in the early morning for hematology, in which platelet count will be taken as PD indicator.

Design of immunogenicity study

Immunogenicity blood samples will be collected from participants in this study at specified time points: D-1, D14, and D29. Samples may be further characterized to determine the titer and the presence of neutralizing antibodies (NAb) if positive for ADA.

Data Monitoring / Other Committee: No

Statistical methods:

Unless otherwise specified, all statistical analyses will be performed using SAS 9.4 software (or above). In general, continuous variables will be described statistically using number of cases, mean, standard deviation, median, quartile, minimum, and maximum etc; categorical and rank variables will be described statistically using frequencies and percentages for each category or rank; missing values will not be included in the calculation of percentages unless otherwise specified. This is a Phase I exploratory clinical study of single-arm, single-dose administration. Descriptive statistical analysis will be mainly used without statistical inferences.

Demographic data and other baseline characteristics

Demographic data and other baseline characteristics will be summarized using descriptive statistics.

PK parameter analysis

Pharmacokinetic parameters will be calculated using Phoenix WinNonlin 7.0 software (or above) for fitting with noncompartmental analysis. The following pharmacokinetic parameters will be calculated based on the Pharmacokinetics Parameter Sets (PKPS): time to peak drug concentration (T_{max}), peak concentration (C_{max}), mean residence time (MRT), terminal elimination rate constant (Ke), area under serum concentration-time curve (AUC), apparent clearance (CL/F), apparent volume of distribution (V_d/F), elimination half-life ($t_{1/2}$), area ratio under extrapolated concentration-time curve ($AUC_{\_\% Extrap}$), etc. Descriptive statistics will be performed for pharmacokinetic parameters, such as number of observations, arithmetic mean, standard deviation, coefficient of variation (CV%), median, quartiles (Q1 and Q3), minimum, maximum, geometric mean, geometric standard deviation and geometric CV%. For T_{max}, only the number of observations, median, minimum, and maximum will be listed.

PD indicator analysis

All analyses of pharmacodynamics will be based on the Pharmacodynamic Analysis Set (PDS).

Platelet count (PLT) at each time point and its change from baseline will be statistically described, and the number of observations, mean, standard deviation, coefficient of variation, median, quartiles (Q1 and Q3), minimum and maximum will be provided. Maximum platelet count change from baseline (E_{max}) and time to peak platelet count (ET_{max}) will be calculated , and descriptive statistics will be performed. In addition, ET_{max} will be only presented as median, minimum and maximum values. A line graph with mean and SD will be generated. Line plots of the changes in platelet count by visit for each participant will also be displayed.

Immunogenicity Analysis

ADAS will be used to summarize the immunogenicity data of the participants at different time points. According to the planned timepoints, the number and percentage of ADA positive will be summarized and listed. If possible, the titers and NAb for ADA-positive will be further analyzed and summarized.

Safety and tolerability analysis

The analysis of safety data (adverse event [AE], treatment emergent adverse event [TEAE], serious adverse event [SAE], clinical laboratory parameters, electrocardiogram [ECG] parameters, vital signs, and physical examinations) will be descriptive and performed on the safety population. The adverse events incidence, overall and per Common Terminology Criteria for Adverse Events (CTCAE) grade, will be presented. The attribution to the test drugs, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be reported.

1.2 Schema

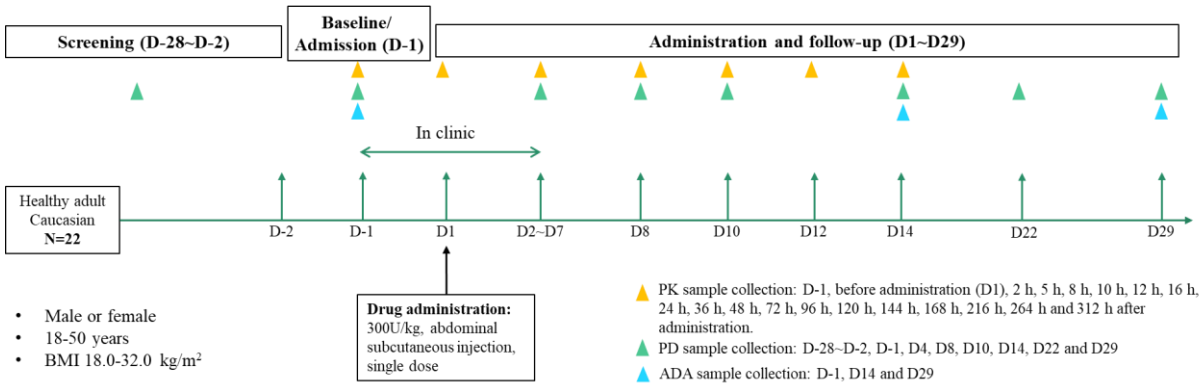

Figure 1 Study design and process

1.3 Schedule of Activities

The procedures for this study are presented in the schedule of activities (SoA) (Table 1).

Table 1 Schedule of Activities

Item	Screening	Baseline	Administration	Follow-up observation period							
	D-28~D-2	D-1	D1	D2~D6	D7	D8	D10	D12	D14	D22	D29/Early withdrawal
Visit Window	/	/	/	/	/	/	/	/	/	±2d	±2d
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographic information[1]	X										
Prior therapy[2]	X	X									
Smoking history	X										
Medical history[3]	X	X									
Single dose administration			X								
Admission		X									
Discharge[4]					X						
Safety Assessments											
Injection site examination		X									
Injection site reaction			X[5]	X (D2, D3)	X				X		X
Physical examination[6]	X	X		X (D4 only)		X					X
Height, weight, body mass index	X	X[7]									
Vital signs[8,17]	X	X	X[8]	X (daily)	X	X	X	X	X	X	X
12-lead ECG[9,17]	X	X	X[9]						X		X
Adverse events[10]	X	X									
Concomitant medication/therapy	X		X								
Laboratory Assessments[11,17]											

Item	Screening	Baseline	Administration	Follow-up observation period							
	D-28~D-2	D-1	D1	D2~D6	D7	D8	D10	D12	D14	D22	D29/Early withdrawal
Visit Window	/	/	/	/	/	/	/	/	/	±2d	±2d
Hematology/PD blood collection[12]	X	X		X (see Table 3)					X	X	X
Urinalysis[12]	X	X									X
Clinical chemistry[12]	X	X		X (D4 only)		X			X	X	X
Coagulation[12]	X	X		X (D4 only)		X			X	X	X
Serum virology test[13]	X										
RT-PCR test for COVID-19[14]	X	X									
Pregnancy test[15]	X	X									X
Drug Abuse and Alcohol Testing[16]	X	X									
PK sample collection		X	X (see Table 2)								
ADA sample collection		X							X		X

Notes:

1 Demographic data will include age or year of birth, gender, and race/ethnicity.

2 Prior therapy includes medications used by the participant within 28 days prior to study drug administration.

3 Medical history related to the inclusion and exclusion criteria, other medical history of clinically significant disease starting within 3 months before signing the ICF, surgery history, reproductive status (i.e., no childbearing potential or childbearing potential), and allergy history will be collected.

4 Participant s may be discharged at D7 at the judgment of the investigator.

5 For D1, injection site assessment (ISR) will be performed at pre-dose, 0.5h, 1h±10min, 3h±15min, 6h±15min, 9h±15min, 12h±15min post-dose.

6 A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/lymphatic, and neurological systems.

7 Weight only will be tested at D-1.

8 Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, body temperature, and respiratory rate, see section 8.4.1. For D1, vital signs will be performed at pre-dose, 6h±15min, 12h±15min post-dose. Allow a single repeat for vital signs at screening or baseline per the Investigator's discretion for the purpose of further determining eligibility.

9 Allow a single repeat for ECG at screening or baseline per the Investigator's discretion for the purpose of further determining eligibility. See section 8.4.3. ECG on D1 will be performed at 10 h ± 15 min post-dose (before blood sample collection).

10 Adverse medical events occurring after the participant has signed the ICF and prior to the first dose are recorded in the eCRF as history/concomitant illnesses and are not recorded as AEs unless one of the following is met: injury/damage resulting from the operation of any clinical laboratory test (AEs related to study operating procedures); AEs resulting from discontinuation of medication related to the study protocol; AEs meet SAE severity criteria.

11 Any abnormal laboratory parameter(s) results outside of the reference range at screening or baseline may be repeated once per the Investigator's discretion for the purpose of further determining eligibility. Plateletcrit and platelet distribution width are adjunctive pharmacodynamic parameters and they will not be reviewed as part of clinical safety laboratory results.

12 Unscheduled blood sample is required as soon as possible for hematology in the presence of venous thrombosis. Additional samples may be collected if clinically significantly abnormal at the discretion of the investigator. Participants will abstain from all food at least 8 h prior to any safety laboratory evaluations (minimum of 12 h for lipid profile at screening).

13 Serum virology tests include:

- HBsAg, HBsAb, HBeAg, HBeAb, HBcAb
- HCV antibody (In the case of positive HCV antibody, the test of HCV RNA will be followed)
- HIV antibody
- Syphilis (treponema pallidum particle assay, TPPA)

14 Nasopharyngeal or oropharyngeal swab will be collected for Coronavirus Disease 2019 (COVID-19) real-time reverse transcription polymerase chain reaction (RT-PCR) test.

15 Pregnancy test on urine or blood sample will be performed for female Participants of childbearing potential (see section 5.3.3). The serum pregnancy test will be performed at the screening visit, and the urine pregnancy test will be performed on Day-1 and afterwards. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

16 Urine drug test includes at minimum: Amphetamines (AMP), Methamphetamines (MET), Methadone (MTD), Barbiturates (BAR), Benzodiazepines (BZO), Cocaine (COC), Opiates (OPI), Methyl enedioxy methamphetamine (MDMA), Phencyclidine (PCP), Tetrahydrocannabinol (THC). Allow a single repeat for drug of abuse urine test in the event of a false positive.

17 If assessments are scheduled at the same time, the order will be ECG > Vital signs> bloods sample.

Table 2 Pharmacokinetic blood sampling

Study day	D-1	D1							D2		D3	D4	D5	D6	D7	D8	D10	D12	D14
Hours post start time of administration	Pre-dose	Pre-dose	2	5	8	10	12	16	24	36	48	72	96	120	144	168	216	264	312
Window Period	/	/	±10min	±15 min						±1 h					±2 h		±8 h		
☆PK sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: For PK sample marked with "☆", the samples should be sent to a third-party testing organization for testing.

Table 3 Pharmacodynamics and immunogenicity blood sampling

Study day	D-28~-2	D-1	D4	D8	D10	D14	D22	D29
Window Period	/	/	/	/	/	/	±2d	±2d
Hematology/PD sampling	X	X	X	X	X	X	X	X
☆ADA sampling		X				X		X

Note:

a. For ADA sample marked with "☆", the samples should be sent to a third-party testing organization for testing. Samples may be further characterized to determine the titer and the presence of neutralizing antibodies (NAb) if positive for ADA.

b. All PD samples will be collected in the early morning for hematology test, in which platelet count will be used as an index of PD.

2 INTRODUCTION

2.1 Study Rationale

Thrombocytopenia is a common clinical problem, with approximately 8 million units of platelets transfusions administered each year in the United States to reduce severe bleeding in patients. However, this is not an ideal therapy, as at least 30% of patients experience transfusion-related complications. Repeated platelet transfusions are required in 15 to 25 percent of patients, which often lead to human leukocyte antigen (HLA)-related immune response. TPO can significantly stimulate platelet production, increase peripheral blood platelet count, and has no significant impacts on platelet morphology and functionality, thus it is an effective thrombopoiesis stimulating factor. A large number of studies have shown that recombinant human thrombopoietin (rhTPO) can effectively increase the platelet level both in terms of the mechanism of action and clinical practice, and has demonstrated a favourable safety profile.

Recombinant human thrombopoietin (rhTPO, trade name: TPIAO®), developed by Shenyang Sunshine Pharmaceutical Co., Ltd. (3SBio Inc.), is a full-length glycosylated rhTPO expressed in Chinese hamster ovary (CHO) cells and purified via conventional gene recombination technology. There are two (2) formulations of rhTPO drug product, namely injection (TPIAO®) and lyophilized powder for injection. Both rhTPO formulations are given by subcutaneous injection, and they have basically consistent pharmacokinetic (PK) profile in a single dose PK study of cynomolgus monkeys. TPIAO® has been launched in China for chemotherapy-induced thrombocytopenia (CIT) in 2005 and for adult immune thrombocytopenia (ITP) in 2010. It was further approved in 2024 for the treatment of pediatric ITP in children over six years old. In addition, TPIAO® has been approved for marketing in the nine other countries, including Thailand, Philippines, Sri Lanka, Cambodia, Dominica, Paraguay, Costa Rica, Uzbekistan and Ukraine. Completed clinical trials have demonstrated that rhTPO could significantly increase platelet levels in patients with CIT and ITP, with mild adverse reactions and favourable safety.

This study is designed to evaluate the pharmacokinetic (PK), pharmacodynamic (PD) and safety profile of rhTPO in healthy Caucasian volunteers.

2.2 Background

2.2.1 Thrombopoietin and Recombinant Human Thrombopoietin (rhTPO)

Thrombopoietin (TPO) is an endogenous cytokine that stimulates the growth and differentiation of megakaryocytes, mainly produced by the liver, and produces biological effects by binding to its specific receptor c-mpl, i.e., it regulates megakaryocyte proliferation, differentiation, maturation, and splitting to form functional platelets. In vivo tests have shown that TPO can significantly stimulate platelet production and increase platelet count in peripheral blood[1][2][3] . TPO also acts on early stem cells and expands the pool of targeted megakaryotic progenitor

cells[4] . TPO also works synergistically with erythropoietin, stem cell factor, interleukin-3, granulocyte colony-stimulating factor, etc., to promote proliferation of erythroid and granulocytic progenitor cells, and to facilitate the entry of stem cells into the proliferative cycle[5].

Recombinant human thrombopoietin, developed by 3SBio Inc., is a full-length glycosylated TPO expressed in CHO cells and purified, with a half-life of approximately 40 hours. rhTPO, which has a similar platelet-raising pharmacology to endogenous thrombopoietin, was approved for the treatment of CIT for solid tumors in 2005, and gained a second indication for the treatment of adult ITP in 2010. It was further approved in 2024 for the treatment of pediatric ITP in children over six years old. In addition, TPIAO® has been approved for marketing in the 9 other countries.

2.2.2 Overview of Nonclinical Studies

Nonclinical studies have indicated that rhTPO exhibited pharmacological effects of increasing platelets like endogenous TPO: rhTPO stimulated the proliferation and differentiation of bone marrow megakaryocytic cell lines and promoted the recovery of peripheral blood platelets. In terms of toxicology and safety pharmacology, rhTPO was well tolerated and had no influence on the nervous system, cardiovascular and respiratory systems of animal model after administration.

2.2.3 Overview of Clinical Studies

A total of 14 clinical studies sponsored by 3SBio Inc. were conducted, including 7 Phase I clinical studies, 1 Phase II clinical study, 4 Phase III clinical studies and 2 Phase IV clinical studies (Table 4).

Currently, numerous clinical studies have shown that rhTPO was effective in increasing platelet levels in ITP patients and demonstrated favorable effects in CIT patients with solid tumors, including increasing platelet count, shortening the duration of thrombocytopenia, and reducing the need for platelet transfusions. For patients with CLD-TCP undergoing invasive surgery, rhTPO represented a potential alternative to platelet transfusion.

Completed clinical studies have shown that the overall incidence of adverse reactions in healthy subjects, CIT patients and ITP patients is low and mild, and most of them do not require special treatment and improve on their own, with no obvious effects on liver and kidney function, coagulation system and hematology, demonstrating a good safety profile of rhTPO.

See more detailed information in the Investigator’s Brochure.

Table 4 List of Clinical Studies

Study No.	Study phase	Study design	Dosage and administration	Sample size	Target population	Duration of treatment
001	I	Self-controlled	0.25, 0.5, 1.0, 2.0μg/kg; s.c	27	Healthy subjects	Up to 14 days
002	I	Self-controlled	1.0μg/kg; q.d.s.c	7	CIT patients receiving chemotherapy	7-14 days
003	I	Pharmacokinetic study	0.5, 1, 2 μg/kg; s.c	24	Healthy subjects	Single dose
004	I	Pharmacokinetic study	1.0 μg/kg; q.d × 14 doses or q.o.d ×7 doses	8	Patients with malignancy, ITP or aplastic anemia	7 or 14 days
005	Ia	Single dose pharmacokinetic study	Cohort A: 300 U/kg Cohort B: 300 U/kg Cohort C: 150 U/kg, 300 U/kg, 450 U/kg	A:10 B:12 C:0	Patients with hepatic impairment	Single dose
006	Ia	Single dose pharmacokinetic study	300U/kg	10	Healthy volunteers	Single dose
007	Ib	Multiple-dose pharmacokinetic study	Fixed dose 15000U once daily	54	Patients with hepatic impairment	7 days
008	II	Randomized crossover self-controlled	1.0μg/kg; q.d., s.c	62	CIT patients receiving chemotherapy	14 days
009	III	Randomized, crossover, self-controlled; non-randomized, self-controlled; uncontrolled, open-label	1.0μg/kg; q.d., s.c	229	CIT patients receiving chemotherapy	14 days
				82	ITP patients	
010	III	Multicenter, randomized, open-label, blank controlled	1.0μg/kg; q.d., s.c	140	ITP patients refractory to glucocorticoids	14 days

011	III	Open-label, randomized, crossover, self-blank controlled	1.0μg/kg; q.d., s.c	59	Patients with CIT	14 days
012	IV	Open-label, multicenter post-marketing non-interventional clinical study	300U/kg; q.d., s.c	2000 planned, 1153 currently enrolled	CIT Patients for solid tumors	≤ 14 days
013	IV	Ongoing			ITP patients	
014	III	Multi center, randomized, double-blind, parallel, placebo-controlled clinical study	Fixed dose 15000U once daily	120	Patients with chronic liver disease-related thrombocytopenia (CLDT)	≤ 5 days or 7 days

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the PK profile following a single dose of rhTPO in healthy Caucasian	PK concentration-time profile and PK parameters: T_{max}, C_{max}, $t_{1/2}$, MRT, AUC_{0-t}, $AUC_{0-\infty}$, V_d/F, Ke, CL/F, $AUC\_{\%Extrap}$.
Secondary	
To evaluate the PD profile following a single dose of rhTPO in healthy Caucasian	PLT counts and changes in PLT over time.
To evaluate the safety and tolerability following a single dose of rhTPO in healthy Caucasian	Incidence and severity of AEs and SAEs, physical examination, vital sign, clinical laboratory test, ECG, ISR
To evaluate the immunogenicity profile following a single dose of rhTPO in healthy Caucasian	Incidence of the development of ADAs and NAb (if applicable) to rhTPO

4 STUDY DESIGN

4.1 Overall Design

This is a single-center, single-arm, open-label, single-dose phase I clinical study to evaluate pharmacokinetics, pharmacodynamics, safety and tolerability of Recombinant Human Thrombopoietin for Injection (rhTPO) in healthy Caucasian volunteers. Approximately 22 healthy Caucasian participants will be enrolled for this study.

One dose level is planned in this study, and participants will receive a single abdominal subcutaneous injection at a dose of 300U/kg after entering the study.

Participants will undergo screening, admission (baseline), administration and follow-up observation period. Participants will sign an informed consent form before any study procedures are performed. During screening, all participants will be screened for study eligibility within 28 days prior to administration. Eligible participants will be admitted to the clinical study ward no later than one day prior to dosing (D-1). Participants need to fast for at least 10 hours prior to dosing and 4 hours after dosing. Single abdominal subcutaneous injection of the study drug will be given on Day 1 (D1). The administration and follow-up observation period will be 29 days (D1~D29). Participants may be discharged at D7 at the judgment of the investigator. PK blood samples will be collected from D-1 to D14, tolerance and safety will be observed from D1 to D29, and blood samples for PD and ADA will be collected from screening to D29. After completion of relevant assessments on D29, participants will be considered as having completed this study.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Population

As the PK, PD, and safety profile of rhTPO in Caucasian populations have not been determined, the target population for this study is healthy participants from the Caucasian population. The data obtained from this healthy Caucasian participant study could provide theoretical support for the subsequent bridging data from domestic and international clinical studies.

4.3 Justification for Dose

In a single subcutaneous injection of rhTPO (0.25 μg/kg ~ 2.0 μg/kg) in Chinese healthy subjects conducted by the sponsor in 2001, a total of 27 subjects were enrolled in the study. The results showed that: only one subject's body temperature rose to 37.4℃ 6 hours after the administration of rhTPO, and then fell back to normal 2 hours later; one subject experienced mild fatigue, poor appetite and drowsiness on the second day after the administration of rhTPO; no other uncomfortable reactions or abnormal signs were observed during the period of observation. In addition, in this study, 21 days after single subcutaneous administration of rhTPO, there were no significant changes in peripheral blood red blood cell and haemoglobin,

and no significant changes in white blood cell counts and classifications; platelet counts increased dose-dependently, and platelet counts increased gradually after administration of rhTPO, reaching a peak on the 10th to 14th day after administration of rhTPO. The PLT counts of the rhTPO 2.0 μg/kg group increased from (209±40) × 10^9/L to (317±54) × 10^9/L on 14th day after administration of rhTPO, and decreased to (262±64) × 10^9/L on 21st day after administration of rhTPO. There were no significant changes in mean platelet volume (MPV) and platelet distribution width (PDW) before and after the administration of rhTPO 2.0 μg/kg in the study.

In the single subcutaneous injection of rhTPO (300 U/kg) tolerance study in healthy Chinese subjects conducted in 2020, a total of 10 subjects were enrolled, and the results showed that: a total of 7 (70%) subjects experienced treatment emergent adverse event (TEAE), and all of the TEAEs were grade 1; 3 (30%) subjects experienced TEAE related to the investigational drug, and no medical intervention was given, and all of them recovered to normal by the completion date of the study. No serious adverse even (SAEs) and no TEAEs leading to withdrawal from the study occurred in this study.

Taken together, the above information suggests that rhTPO is expected to be safe for a single subcutaneous injection of 300U/kg (about 1.0 μg/kg) in healthy participants.

4.4 End of Study Definition

End of study (End of trial): The end of the study is defined as the date of the last visit of the last participant in the study.

End of Study (Individual participant): A participant who has completed all phases of the study will be considered to have completed this study.

5 STUDY POPULATION

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Healthy **Caucasian** adult male and female participants aged 18-50 years (inclusive) at the time of informed consent. Caucasian is defined as of European, Middle Eastern, or North African descent.
2. Male participants weighing no less than 50 kg. Female participants should not weigh less than 45 kg.
3. Body mass index (BMI) within the range 18.0 to 32.0 kg/m^2 (inclusive).
   Note: BMI = weight [kg] / (height [m])^2

4. Participants are in good general health as determined by the investigator, based on a medical evaluation including medical history, vital signs, physical examination, 12-lead electrocardiogram, clinical safety laboratory tests;

   Note: Any results outside of the reference range at screening or baseline may be repeated once per the Investigator's discretion for the purpose of further determining eligibility.

5. Platelet counts must be within the normal range; measurements can repeat once for verification, if necessary.
6. Women of childbearing potential (WOCBP, see section 5.3.3) must have a negative serum or urine pregnancy test prior to the start of study drug and must not be breastfeeding, lactating or planning pregnancy during the study period. WOCBP who are not exclusively in same-sex relationships and males with partners of child-bearing potential must agree to use adequate contraception from signing the informed consent until 3 months after completion of the study. In addition, females must not donate ova (eggs) and males must not donate sperm from signing the informed consent until 3 months after completion of the study;
7. Negative for COVID-19 based on the nasopharyngeal or oropharyngeal swab with the method of real-time reverse transcription-polymerase chain reaction (RT-PCR) at Screening and Day-1.
8. Volunteer to participate in this study, be able to understand and comply with the clinical study protocol requirements, and sign the informed consent form in writing.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1 History of hypersensitivity to components of study drug or analogs; history of anaphylaxis or other significant allergy in opinion of the investigators.

2 Known allergy to heparin or history of heparin-induced thrombocytopenia;

3 Received a platelet transfusion within 2 weeks or platelet-boosting medication within 4 weeks prior to dosing;

4 History of hospitalization or surgical procedure within 3 months prior to dosing, or bleeding from trauma or internal bleeding greater than 100 mL, or donating more than 100 mL of blood;

5 History or presence of autoimmune disease, malignancy, thromboembolic disease, bleeding disorders, cardiovascular, hepatic, renal, muscular, hematopoietic, respiratory, neurological, or psychiatric disorders capable of significantly altering the absorption, metabolism, or elimination of drugs, constituting a risk to the participant when taking the study drug; or interfering with the interpretation of data judged by the investigator;

   Note: Uncomplicated cholecystectomy and appendectomy are permitted; History of fully resolved childhood asthma is **not** permitted.

6 History or presence of chronic diseases such as hypertension and diabetes (including type 1 and type 2 diabetes);

7 History of malignancy with the exception of successfully treated basal cell or squamous cell skin cancer with no evidence of recurrence for 5 years.

8 History of platelet clumping that prevents reliable measurement of platelet counts;

9 Positive for Hepatitis B surface antigen (HBsAg), Hepatitis C Virus (HCV) antibody and Human Immunodeficiency Virus (HIV) antibody, Syphilis antibody;

Note: Participants with positive hepatitis C antibody can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.

10 Immunization with a COVID-19 vaccine 14 days prior to dosing or planned vaccination within 30 days after dosing

11 Use of prescription medication within 14 days prior to dosing and 7 days prior to dosing for over the counter medication/vitamins/herbal supplements (with the exception of contraception, occasional paracetamol < 2g/day, and standard dose of multivitamins).

12 Consuption of alcohol, caffeinated products (coffee, tea, cola, chocolate), grapefruit fruits, or products containing grapefruit within 48 hours prior to dosing;

13 Consuption of any poppy seeds (e.g., orange and poppy seed muffin, poppy seed bread) within 48 hours prior to screening and admission.

14 History of drug abuse within 2 years prior to dosing; or positive alcohol/urine drug screen prior to dosing; Regular alcohol consumption within 6 months prior to dosing, i.e., on average more than 14 units of alcohol per week (1 unit = 360mL of beer or 45mL of spirits at 40% alcohol by volume or 150mL of wine);

15 Use of tobacco or nicotine products equivalent to more than 2 cigarettes a day on average within 3 months prior to dosing;

16 Have special dietary requirements and are unable to comply with the diet offered and the corresponding regulations;

17 Pregnant or breastfeeding female, or positive pregnancy test;

18 Individuals who cannot tolerate venipuncture or who suffer from needle and bloodsickness;

19 Participation in another clinical study of investigational drug within 3 months prior to dosing;

20 Other participants judged by the investigator to be unsuitable for participation.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will be admitted to the site the day before dosing (D-1) and will be uniformly fed a standard meal.

Participants will abstain from alcohol, tobacco- or nicotine-containing products, caffeine- or xanthine-containing products (e.g., coffee, tea, cola, chocolate, etc), grapefruit-containing

products for 48 h prior to dosing and until collection of the final PK sample, as well as 24 h prior to subsequent outpatient visits.

Participants will abstain from any poppy seeds (e.g., orange and poppy seed muffin, poppy seed bread) within 48 hours prior to screening and admission.

Participants will abstain from all food at least 8 h prior to any safety laboratory evaluations (minimum of 12 h for lipid profile at screening).

5.3.2 Activity Restrictions

Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

5.3.3 Contraception requirements

WOCBP are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) at least 6 weeks before screening and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in the absence of other biological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause. Male participants with potentially postmenopausal partners who are under the age of 55 years must use condoms unless their partner's postmenopausal status has been confirmed by FSH level.

WOCBP who are not exclusively in same-sex relationships and males with partners of child-bearing potential must use adequate contraception from signing the informed consent until 3 months after completion of the study. In addition, females must not donate ova (eggs) and males must not donate sperm from signing the informed consent until 3 months after completion of the study.

Males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing as per protocol.

Investigators will counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators will advise on the use of an adequate methods of contraception, which is defined as use of a condom by the male partner **combined with** use of a highly effective method of contraception by the female partner. A highly effective method of contraception is one that has a failure rate of < 1% when used consistently and correctly. Male participants must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

Highly effective methods of contraception are listed below:

- Hormonal methods of contraception including oral contraceptives containing combined estrogen and progesterone, a vaginal ring, injectable and implantable hormonal contraceptives, intrauterine hormone-releasing system (e.g. Mirena) and progestogen-only hormonal contraception associated with inhibition of ovulation
- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomised participant/partner with documented azoospermia 90 days after procedure, if that partner is the sole sexual partner.

For female participants, contraception (required to be a highly effective method as described above) should begin at least 1 month prior to screening to ensure contraceptive is in full effect.

Complete abstinence, defined as the complete avoidance of heterosexual intercourse - is an acceptable form of contraception if used consistently throughout the duration of study and for the durations after dosing specified for males and females above. It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP who choose complete abstinence must continue to have pregnancy tests as per protocol. The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

5.4 Screen Failures

For participants who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before the single dose of study drug is administered, study site personnel should document the screen failure in the participant's source documents. A minimum set of screen failure information is required to be entered into the Electronic Data Capture (EDC) Systems, including demographics, screen failure details (e.g., failed eligibility criteria), any AEs, any SAEs and any related concomitant medications that occurred during the Screening Period.

Participants who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened once. Rescreened participants will be re-consented and assigned a new screening number. All screening assessments must be repeated during re-screening unless some screening assessments are considered valid by the investigator.

5.5 Participant Number

Participants will be given a screening number after signing the informed consent form, which consists of S + three Arabic numerals, with the 1st screened participant having a screening number of S001, and so on.

Participants who were screened and qualified for entry into this study will be given an enrolment

number, which consists of R + three Arabic numerals, starting with R001, and assigned to participants in the order of screening.

When a participant is replaced, the enrolment number of the replacement participant will be increased by "100" to distinguish it from other participants. For example, if the dislodged participant's entry number is "R006", the replacement participant's entry number is "R106". If the replacement participant is dislodged again, add an additional "100" to the entry number of the replacement participant and therefore a second replacement would be R206, and so on.

5.6 Study Stopping Rules

After the first group participants (ten or more) dosing, and before the second group dosing, the study will stop enrollment when two or more participants have ≥ grade 3 drug-related adverse events. The already enrolled participants will be still required to complete the subsequent visits. If all 22 participants are dosed, no stopping rules will be set.

6 STUDY INTERVENTION(s) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term study drug may be used synonymously with study intervention.

6.1 Study Intervention(s) Administered

Table 6 Study drug

Generic Name	Recombinant Human Thrombopoietin for Injection (rhTPO)
Type	Drug
Dose Formulation	Lyophilized powder for injection
Unit Dose Strength(s)	15000 U/1mL/vial
Auxiliary materials	D(-)-Mannitol 40mg, α,α-trehalose dihydrate 20mg, polysorbate 20 (Tween 20) 0.05mg, sodium dihydrogen phosphate monohydrate 0.85mg, and di-sodium hydrogen phosphate dihydrate 0.6mg
Dosage Level(s)	300 U/kg
Route of Administration	Abdominal subcutaneous injection
Use	Experimental
Dosing Instructions	A single dose of 300U/kg will be administered through abdominal subcutaneous injection. For reconstitution, add 1.1 mL of sterile water for injection, sterile powder will quickly dissolve into a clear liquid. After reconstitution, this product can be stored at 2-8°C for 72

	h and at 20-25°C for 24 h (excursions may be permitted between 15-25℃), protected from light. It is recommended to use it as soon as possible upon reconstitution. Please refer to the Pharmacy Manual for details.
Storage conditions:	2～8℃, protect from light
China Marketing Authorization Approval number:	State Pharmaceutical Code S20050048
Sourcing	Shenyang Sunshine Pharmaceutical Co., Ltd.

6.2 Preparation, Handling, Storage, and Accountability

rhTPO For Injection required for this clinical study is managed in accordance with the regulations for the management of study drugs in clinical research organizations. The sponsor supplies study drugs according to the number of cases of participants in the clinical study unit. All investigational drugs are kept in a safe and compliant storage place, and a person is responsible for managing the registration and record of investigational drugs. The drug administrator records the dosage form, specification, quantity, batch number and expiry date of the study drug received from the sponsor.

Clinical research institutions accepting clinical research drugs must sign a drug receipt form, signed by both the sender and receiver, in duplicate, with one copy for each clinical research unit and applicant unit. The research organization shall store in the secure access Investigational Product (IP) room which is only accessible to site Pharmacy personnel. The dispensing/administration of IP will be documented in a timely manner by 2 team members. At the end of the study, the remaining drugs and boxes can either be handed over to the sponsor or disposed of, and the clinical drugs should not be handed over to any non-clinical study participant or third party.

6.3 Assignment to Study Intervention

This is an open-label, single-arm study. Once participants have signed the informed consent form (ICF) and enrolled at the site they will be assigned study drug according to the agreed participant number (see section 5.5).

6.4 Blinding

Not applicable.

6.5 Study Intervention Compliance

Participants will be administered study drug in a controlled setting directly from the Investigator or designee, under medical supervision. All pertinent/required information on the preparation

and administration of the dose will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.6 Prior and Concomitant Therapy

6.6.1 Prior Therapy

The exclusion criteria (Section 5.2) specify that:

Participants must not have received prescription medication within 14 days prior to dosing and 7 days prior to dosing for over the counter medication/vitamins/herbal supplements (with the exception of contraception, occasional paracetamol < 2g/day, and standard dose of multivitamins).

Participants must not have received a COVID-19 vaccine within 14 days prior to dosing.

Prior therapy includes medications used by the participant within 28 days prior to the single dose of study drug.

6.6.2 Concomitant Therapy

Concomitant procedures are not allowed unless medically indicated. Participants must not receive a COVID-19 vaccine for 30 days after dosing. Multivitamins, contraceptives, and paracetamol (ie, acetaminophen, at doses of ≤ 2 g/day) are permitted for use during the study at the Investigator's discretion. If medical events (such as, severe hypersensitivity) occur during the study period, the participants may receive appropriate medical treatment. Other concomitant medication may be considered on a case-by-case basis by the Investigator if required.

The use of any concomitant therapy (with the exception of medication with no adjunctive therapeutic effect, e.g., solvents [sodium chloride], contrast media, etc.) during the study should be documented in detail in the original record and electronic clinical report form (eCRF).

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose, frequency and route.

Since rhTPO is a protein-based macromolecular drug, it may cause anaphylactic reactions during and after administration. Adequate preventive and first-aid measures should be taken during the study period, e.g., anti-allergic drugs should be prepared at all times. Participants should be closely observed for more than 60 minutes after administration, and qualified physicians and nurses should be on duty during confinement. First-aid equipment and

medication should be available in the study ward. Once a participant is found to have a severe allergic reaction, first aid treatment should be given according to the procedures stipulated by the site.

Investigators should ask participants in detail about previous drug or food allergies during screening and before administration, and participants with a history of drug or food allergy should be enrolled with caution.

6.7 Intervention after the End of the Study

No intervention will be provided to participants at the end of the study.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study protocol non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Participants may discontinue or withdraw from the study for termination of the study by the sponsor or the regulatory authority.

Note: If a participant tests positive for COVID-19 after administration, an AE should be reported and the decision to withdraw from the study should be made based on the AE situation.

For participants who withdraw early, the investigator must record the reason for early withdrawal on the eCRF and carefully complete the final visit record on the eCRF. At the time of discontinuing from the study, if possible, an early withdraw visit should be conducted. See the SoA (Table 1) for assessments to be collected at the time of discontinuation of study.

This study endeavours to ensure that sufficient participants receive the study drug. Participants who withdraw from the study after enrolment, but prior to receiving study drug may be automatically replaced. Participants who withdraw from study after dosing may be replaced at the discretion of sponsor and investigator.

7.2 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- If the participant continues to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1).

8.1 General Procedures

8.1.1 Demographic data

Demographic data will include age or year of birth, gender, and race/ethnicity.

8.1.2 Height and weight

Height and weight will be measured at screening and baseline. BMI will be calculated in the formula: BMI = weight (kg)/height^2 (m^2).

The data of height and weight will be recorded in the eCRF.

8.1.3 Medical History and Prior Therapy

Medical history related to the inclusion and exclusion criteria, other medical history of clinically significant disease starting within 3 months before signing the ICF, surgery history, reproductive status (i.e., no childbearing potential or childbearing potential), and allergy history will be collected.

Prior therapy includes medications used by the participant within 28 days prior to the single dose of study drug.

8.2 Pharmacokinetics and Immunogenicity

Blood samples will be collected to characterize the PK profile and anti-drug antibody (ADA) of rhTPO. Blood sampling for PK and ADA will be collected at the timepoints specified in Table 2 and Table 3.

Samples may be further characterized to determine the titer and the presence of neutralizing antibodies (NAb) if positive for ADA.

Refer to Laboratory Manual for information on the collection, processing, and shipment of samples to the Central Laboratory.

8.3 Pharmacodynamics

Hematology test will be performed by the site, in which platelet count (PLT) will be used as an indicator of PD. Blood sampling for PD will be collected at the timepoints specified in Table 3.

8.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.4.1 Vital Signs

Vital signs include systolic and diastolic blood pressure (mmHg), respiration rate (breaths/min), heart rate (bpm), and body temperature (°C). Blood pressure (BP) and heart rate will be measured after 5 minutes of rest in a supine position in a quiet setting without distractions (e.g., television, cell phones).

Vital signs normal ranges as below:

SBP: 90 mmHg - 140 mmHg

DBP: 40 mmHg - 90 mmHg

Heart rate: 40 - 100 bpm

Respiration Rate: 10 - 22 breaths/min

Temperature: 35.5 - 37.5℃

8.4.2 Physical Examinations

A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/lymphatic, and

neurological systems.

8.4.3 Electrocardiograms

ECG parameters including PR Interval, QRS duration, QT Interval, RR Interval, Corrected QT Interval (Fridericia) (QTcF), and ECG mean heart rate.

QTcF = QT/ (RR^0.33). QT is the QT interval, RR is the standardised heart rate value, obtained by dividing the heart rate by 60.

12-lead ECGs will be obtained after the participant has been rested in a supine position for at least 10 minutes in the absence of environmental distractions (e.g., television, cell phones). The investigator or designated physician will review the 12-lead ECGs. If a participant shows an abnormal ECG, the abnormality will be followed to resolution.

The original ECG traces (per local practice) must be stored in the participant's medical record as source data.

ECG normal ranges as below:

Heart rate: 40-100 bpm

PR Interval: ≥ 120 to ≤ 220 msec

QRSD: < 120 msec

QT: < 500 msec

QTcF ≤ 450 msec both genders

8.4.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis will be performed by local laboratory.

Plateletcrit and platelet distribution width are adjunctive pharmacodynamic parameters and they will not be reviewed as part of clinical safety laboratory results.

Participants will abstain from all food at least 8 h prior to any safety laboratory evaluations (minimum of 12 h for lipid profile at screening).

Samples will be taken at the visits indicated in the SoA (Table 1). Allow repeat once for safety laboratory assessment to confirm initial result and trending. Blood sample is required as soon as possible for hematology in the presence of venous thrombosis. Additional samples may be collected if clinically significantly abnormal at the discretion of the investigator. The date, time

of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The following laboratory variables detailed in Table 7 will be measured.

Table 7 Laboratory Safety Variables

Hematology	Clinical chemistry	Coagulation	Urinalysis
White blood cell count with differential (both absolute count and percentage): • Lymphocyte • Neutrophils • Monocytes • Eosinophil • Basophil Red blood cell count Hematocrit Hemoglobin Reticulocyte count Platelet count mean Platelet volume Plateletcrit Platelet distribution width	Total bilirubin Direct bilirubin Alanine aminotransferase Aspartate aminotransferase Total protein Albumin Lactate dehydrogenase Creatine kinase Troponin Gamma-glutamyl transpeptidase Alkaline phosphatase Renal function tests: • Urea • Creatinine • Uric acid Lipids: • Total cholesterol • Triglycerides Electrolytes: • Potassium • Sodium • Chlorine Glucose	Prothrombin time International normalized ratio Partial thromboplastin time or activated partial thromboplastin time Fibrinogen D-dimer	Specific gravity PH Leukocytes Nitrite Protein Glucose Ketone bodies Urobilinogen Bilirubin Blood Leukocyte microscopy[a] Erythrocyte microscopy [a]

a. If there are any abnormalities considered clinically significant, the urine sample will be sent for microscopic examination.

8.4.5 Virology Test

Blood samples collected at screening will be analysed for the following:

- HBsAg, HBsAb, HBeAg, HBeAb, HBcAb
- HCV antibody (In the case of positive HCV antibody, the test of HCV RNA will be followed)
- HIV antibody
- Syphilis (treponema pallidum particle assay, TPPA)

Nasopharyngeal or oropharyngeal swab will be collected for Coronavirus Disease 2019 (COVID-19) RT-PCR test.

8.4.6 Serum or Urine Pregnancy Test

Pregnancy test on urine or blood sample will be performed for female participants of childbearing potential. Samples for pregnancy testing will also be performed by local laboratory.

The serum pregnancy test will be performed at the screening visit, and the urine pregnancy test will be performed on Day-1 and afterwards. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

8.4.7 Drug Abuse and Alcohol Test

Breath test and urine drug test will be performed at screening. Urine drug test includes at minimum:

- Amphetamines (AMP)
- Methamphetamines (MET)
- Methadone (MTD)
- Barbiturates (BAR)
- Benzodiazepines (BZO)
- Cocaine (COC)
- Opiates (OPI)
- Methyl enedioxy methamphetamine (MDMA)
- Phencyclidine (PCP)
- Tetrahydrocannabinol (THC)

8.4.8 Injection site examination

Injection site examination will be performed at baseline (Day -1) to ensure injection site is suitable prior to dosing.

8.4.9 Injection site reaction

Injection site reaction (ISR) is a type of hypersensitivity reaction that may be immediate, although it usually appears within 24-48 hours after injection. ISR, by definition, includes the

following: erythema, induration, ecchymosis, pain, pruritus, paresthesia, warmth, hemorrhage, swelling, etc. at the injection site. ISR will be assessed based on the CTCAE severity scale.

8.5 Adverse Events and Serious Adverse Events

8.5.1 Definitions

8.5.1.1 Definition of adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to medicinal product.

8.5.1.2 Definition of Serious Adverse Event

A **serious adverse event** is defined as any untoward medical occurrence that at any dose:

1) Resulting in death.

2) Life-threatening*.

3) Results in persistent or significant disability/incapacity.

4) Requires hospitalization or prolonged hospitalization**.

5) Congenital abnormalities/birth defects.

6) Other important medical events***.

* The term "**life-threatening**" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe**. **Hospitalization** means transfer to an inpatient unit or emergency ward (usually meaning at least overnight)/intensive care unit for observation or treatment.

The following are not considered hospitalization:

1) Detention in a doctor's office or outpatient observation room;

2) Treated only in the emergency room not admitted to the hospital;

3) Hospitalization for scheduled surgical or other therapeutic or investigative purposes immediately prior to entry into the study, such as elective surgical hospitalization and no worsening of underlying disease;

4) Program-mandated hospitalization (e.g., program-required procedures);

5) Hospitalization for diagnosis or treatment prior to use of the investigational drug;

6) Any hospitalization not related to an adverse event, e.g., cosmetic surgery, hospitalization for non-medical reasons (e.g., reimbursement, benefits, or convalescence).

7) Hospitalization or prolonged hospitalization due to social, or convenience or administrative reasons (such as annual physical examination, hospitalization for reimbursement reasons, etc.).

Note: If there is a pre-planned hospitalization prior to the start of the study, the investigator will need to document this in the medical record and eCRF.

***Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.5.1.3 Definition of Suspected and Unexpected Serious Adverse Reactions

Suspected and Unexpected Serious Adverse Reaction (SUSAR) means a serious adverse event that meets both of the following conditions:

Relevant (Related)*: there is a reasonable likelihood of correlation between the adverse event and the investigational drug according to the investigator and/or according to the sponsor's evaluation;

Unexpected (Unexpected)**: the nature, severity, consequences, or frequency of the adverse event is inconsistent with the safety reference information in the single safety reference document for the product specified in the protocol (e.g., investigator's brochure or product insert/summary of product characteristics for a marketed product).

*: For the purposes of this protocol, “related” means “definitely related”, “probably

related”, or “possibly related”.

**: For the purposes of this protocol, the drug safety reference information (RSI) for assessing the anticipation of adverse events can be found in: the investigator's brochure for the investigational drug.

8.5.2 Monitoring and Follow-up

8.5.2.1 Monitoring

Adverse event monitoring time period: from the time of participant signing the ICF until the end of the last visit.

Adverse medical events occurring after the participant has signed the ICF and prior to the first dose are recorded in the eCRF as history/concomitant illnesses and are not recorded as AEs unless one of the following is met: injury/damage resulting from the operation of any clinical laboratory test (AEs related to study operating procedures); AEs resulting from discontinuation of medication related to the study protocol; AEs meet SAE severity criteria.

8.5.2.2 Follow-up

The investigator or his/her designee should follow all adverse events occurring during the study, with unrelated adverse events followed until the end of the final visit, and related AEs followed until the adverse event returns to normal or baseline or stabilizes, or the abnormality is deemed by the investigator to be not clinically significant, or is reasonably explained, or the participant is lost to follow-up or dies. All AEs in the study must be treated and documented. Any waivers must be approved by the sponsor's safety contact.

For related adverse events, the investigator should follow up until any of the following is achieved:

- Events resolved or stabilized;
- The event returns the baseline level, if a baseline value is available;
- The investigators conclude that the abnormalities are not clinically significant;
- Events can be attributed to drugs other than the investigational drug or to factors unrelated to the study behavior;
- When more information is unlikely to be available again (patient or healthcare professional refuses to provide more information, or there is evidence that the patient is still missing visits after best efforts have been made).

8.5.3 Adverse Event Recording

The investigator should give detailed instructions to the participant and ask the participant to respond truthfully to changes in condition after administration of the medication. Physicians should avoid inducing questions. While observing the efficacy of the treatment, close attention should be paid to observing the adverse events, analyzing the causes, making judgments, and conducting follow-up observations and records.

All adverse events occurring between the signing of the informed consent and the end of the last visit must be documented in the appropriate section of the CRF (including the name of the adverse event, start/end time, severity, duration, whether it is a serious adverse event, severity criteria (if applicable), measures taken on the test medication as a result of the adverse event, causal relationship between the adverse event and the investigational drug, outcome, etc.) and recorded in detail in the study medical record, whether or not they are study-related, with the exception of participants who have withdrawn Informed consent and/or participants who are unable to be followed up are excluded.

The investigator should assess the possible association between the adverse event and the investigational drug and coadministration of the drug, as categorized in 8.5.4.2 Assessment of Causality. The severity of the adverse event will be graded according to CTCAE version 5.0. For each symptom, when there is a change in severity level, the change in severity level needs to be documented in detail, and any increase or decrease in severity needs to be documented.

Any recurrence, worsening, or exacerbation of an AE after remission or return to baseline condition will be documented as a new AE. All AEs should be documented in standard medical terminology whenever possible. The documented AE should not be an operation (e.g., surgical procedure) or a clinical or laboratory test, but rather reflect a known cause leading to the operation or clinical/laboratory test. If applicable, the AE should be evaluated and documented according to the diagnosis, not the participant's signs and symptoms. However, it may be recorded as the participant's signs and symptoms if a definitive diagnosis is not possible.

All SAEs, whether treatment-related or not, that occur between the time of signing the informed consent and the end of the last visit are to be recorded. SAEs that occur at the end of the trial or after the end of follow-up until the conclusion of the review need to be reported to the sponsor if the investigator considers them to be related to the investigational drug.

8.5.4 Assessment of Adverse Event

8.5.4.1 Severity Classification

Adverse drug events will be determined with reference to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0) criteria for grading adverse events, and parameters not covered by CTCAE 5.0 may be interpreted, at the investigator's judgment, on the basis of the CTCAE Base Guidelines for Severity Grading or in a similar manner. The CTCAE 5.0 Base

Guidelines for Grading are as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no treatment required.
- Grade 2: Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using telephone and managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life (e.g. bathing, dressing and undressing, feeding self, using toilet, and taking medications), but not bedridden.
- Grade 4: Life-threatening; urgent intervention required.
- Grade 5: Death related to AE.

Symptoms and signs should be described using clear, standardized, and recognized professional medical terminology, avoiding colloquial language that is vague and likely to lead to ambiguity.

8.5.4.2 Causality Assessment

- Investigators should use their medical knowledge to consider the circumstances surrounding the event, and evaluate any potential alternative causes prior to making a final causality assessment, i.e., whether there is a reasonable possibility that the study drug caused the adverse event. The Investigator should provide the rationale or evidence to support the causality assessment as needed. The causality will be assessed according to the five-level classification criteria as follows:
- Positively related: The occurrence of AE is determined pharmacologically and is reasonably temporally related to the investigational drug. AE disappears or alleviates after discontinuation or reduction, and reappears after re administration. AE is not related to concomitant medication or non-pharmacological factors (food, participant's own illness, environment, etc.);
- Probably related: The occurrence of AE is reasonably temporally related to the investigational drug. AE disappears or alleviates after discontinuation or reduction. AE is not related to concomitant medication or non-pharmacological factors;
- Possibly related: The occurrence of AE is reasonably temporally related to the investigational drug. Remission of the AE after discontinuation or reduction is unknown or insignificant, and other factors (e.g., participant's own illness, concomitant medication, or non-pharmacological factors) may also contribute to the event;

- Possibly unrelated: The time relationship between the occurrence of AE and investigational drug administration is unclear. AE does not resolve after discontinuation or remission is unknown, and concomitant medication or non-pharmacological factors can explain the AE;
- Definitely unrelated: The occurrence of AE is not reasonably temporally related to the investigational drug and/or evidence exists that the AE is definitely related to concomitant medication or non-pharmacological factors.

Because this study is a single administration and does not involve observation of adverse events through dose reduction/discontinuation/re-use, the investigator should make a comprehensive judgment of relevance based on the metabolic and pharmacodynamic characteristics of the investigational drug and the participant's clinical presentation, as well as the possible presence of non-pharmacological factors. When there is a change in consistency among test individuals, it is more likely to be related to the investigational drug.

In order to minimize risk to the medication-using population and to comply with regulatory requirements, sponsors will address the relevance of the incident in the following manner:

- "Possibly unrelated", "Definitely unrelated", i.e. "unrelated", are categorized as unrelated adverse events;
- "Positively Related", "Probably Related", or "Possibly Related" should be considered "Related" and categorized as related adverse events.

8.5.5 Serious Adverse Event Reporting

8.5.5.1 Serious Adverse Event Reporting

When an investigator is informed of a serious adverse event in a participant during a clinical study, he or she should promptly manage and treat the event, whether or not the serious adverse event is related to the investigational drug. It should also be reported immediately (within 24 hours) to the sponsor or the sponsor's designated representative, and the investigator should complete, sign and date the full Drug Serious Adverse Event Report Form.

For reports involving fatal events, the investigator should provide other required information such as autopsy reports and final medical reports to the sponsor and ethics committee.

8.5.5.2 Serious Adverse Event Notification

The Clinical Supervisor notifies the Program Manager of all serious adverse events occurring in the program species on a quarterly basis, and the Program Manager is responsible for notifying all members of this program team.

8.5.6 Pregnancy

If pregnancy occurs in a participant or the female partner of a male participant in the 3 months after completion of the study, the investigator should fill out a pregnancy report form and report

it to the sponsor or the sponsor's designated representative and the Ethics Committee (if required) within 24 hours of being informed. Female participants should withdraw from the trial immediately after the occurrence of pregnancy.

Cases of pregnancy in the trial should be followed up with regard to the outcome of the pregnancy as well as the condition of the newborn to determine the outcome of the pregnancy (e.g., severe maternal complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomalies, or birth defects). In the case of live births, the newborn should be followed for up to **12 months** following the birth.

Although the pregnancy itself is not an SAE, complications or serious outcomes resulting from the pregnancy that meet the criteria for an SAE must be reported according to the procedures in 8.5.5. Elective abortion to terminate a pregnancy for no medical reason is not considered an AE/SAE.

8.5.7 Medication Error

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength, or noncompliance as described in Section 6.1 and 6.2.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the eCRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the eCRF.

If the associated adverse event fulfils serious criteria, the event should be reported to the Sponsor or delegate immediately (i.e., within 24 hours after learning of the event).

8.5.7.1 Treatment of Overdose

For this study, any dose of study intervention greater than that specified in the protocol will be considered an overdose. Sponsor does not recommend specific treatment for overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose or suspected overdose, the Investigator should：

1. Contact the Sponsor within 24 hours.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a blood sample for PK/PD analysis if requested by the Sponsor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

9 STATISTICAL CONSIDERATIONS

After the study protocol and CRF are completed and finalized, the development of statistical analysis plan will be carried out. The statistician will develop the relevant statistical analysis plan (SAP) according to the study protocol and the content of CRF, including the content of safety statistical analysis and PK, PD, etc. This is an exploratory phase 1 study with no statistical hypothesis by using descriptive statistical method, no additional assessments are needed. If there're protocol/CRF amendment or some additional analysis to be added during the course of study, the SAP will be revised if necessary. And any updates will be tracked with SAP version amendment after the initial SAP is finalized. The SAP will be approved by the sponsor before database locking. After database locking, the statistical analysis plan will not be modified in principle.

9.1 Sample Size Determination

This is an exploratory Phase I clinical study of the pharmacokinetics, pharmacodynamics, safety and tolerability of a single dose of Recombinant Human Thrombopoietin for Injection (rhTPO) in a single-center, single-arm, open-label, single-dose design in healthy volunteers from a Caucasian population. The sample size of this study is not based on statistical hypothesis and the study is planned to enrol approximately 22 healthy Caucasian participants.

9.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 8 Populations for Analysis

Analysis Set	Description
Safety analysis set (SS)	All participants enrolled and receiving the full dose of study drug and have at least one post-dose safety assessment. SS will be used for demographics, baseline characteristics, and safety analyses.
PK concentration set (PKCS)	All participants enrolled and receiving the full dose of study drug with at least one evaluable concentration data during the study. PKCS will be used for PK concentration analysis.
PK parameter sets (PKPS)	All participants enrolled and receiving the full dose of study drug with at least one evaluable PK parameter during the study. Participants whose PK parameter results affected by major protocol violations will be excluded from the PK parameter set. PKPS will be used for PK parameter analysis.
PD analysis set (PDS)	All participants enrolled and receiving the full dose of study drug with at least one evaluable PD data during the study, but participants whose PD e results affected by major protocol violations will be excluded. The PDS will be used for the pharmacodynamic analysis.
Immunogenicity Analysis Set (ADAS)	Participants with at least one immunogenicity result in the safety analysis set. ADAS will be used for immunogenicity analysis.

9.3 Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

There is no statistical hypothesis associated with the study objectives. As such, no statistical tests will be performed. The analyses of safety, efficacy, biomarker and pre-defined subgroups will primarily be descriptive.

9.3.1 General Considerations

- Analysis software: Phoenix WinNonlin 7.0 software (or above) will be used to calculate pharmacokinetic parameters, and all other statistical analyses will be performed using SAS 9.4 software (or above).
- Baseline definition: the most recent measurement prior to the first dose of investigational drug is defined as baseline. If it is missing or cannot be determined then the screening period or baseline visit will be taken as baseline.
- Statistical descriptions: quantitative statistical descriptions include: number of cases (N), mean (Mean), standard deviation (S.D.), coefficient of variation (CV), median, quartiles (Q1/Q3), minimum (Min), maximum (Max), geometric mean, geometric S.D., geometric CV. Qualitative statistical descriptions include: frequency and percentages.

9.3.2 Participant Distribution, Demographics and Baseline Characteristics

The distribution of participants will be analyzed using SS. Number of participants screened, and the number and ratio of participants who failed screening with reasons will be listed. Calculate the number and ratio of participants enrolling, completing the study, and ending the study early and their reasons. Summarize protocol deviations by category and severity. Draw a flow chart of the distribution of participants.

Descriptive demographics and other baseline characteristics will be used.

9.3.3 Pharmacokinetic Analysis

Using PKCS, individual and mean concentration-time (c-t) curves and semi-log c-t curves will be plotted, and descriptive statistics will be used to list the mean, standard deviation, median, quartiles (Q1 and Q3), maximum, minimum, coefficient of variation, geometric mean, geometric standard deviation, and geometric coefficient of variation of the PKconcentrations at the time points.

Pharmacokinetic parameters will be calculated for each participant by non-compartment model using PKPS with Phoenix WinNonlin 7.0 software (or above), including time to peak drug concentration (T_{max}), peak concentration (C_{max}), elimination half-life ($t_{1/2}$), mean residence time (MRT), area under the serum concentration-time curve from time zero to the last measurable serum concentration time t (AUC_{0-t}), area under the curve extrapolated from zero

to time of infinity ($AUC_{0-\infty}$), apparent volume of distribution (Vd/F), terminal elimination rate constant (Ke), apparent clearance (CL/F), and area ratio under extrapolated concentration-time curve ($AUC_{\_\%Extrap}$). When calculating pharmacokinetic parameters, samples with concentrations below the lower limit of quantification (LLOQ) prior to the C_{max} being reached should be treated as zero, and as not quantifiable (ND) for LLOQ samples after the C_{max}. Also, the arithmetic mean, standard deviation, coefficient of variation, median, quartiles (Q1 and Q3), maximum, minimum, geometric mean, geometric standard deviation, and geometric coefficient of variation will be calculated for pharmacokinetic parameters. For T_{max}, only the number of observations, median, minimum, and maximum will be listed. When $AUC_{\_\%Extrap}$ >20%, $AUC_{0-\infty}$, $t_{1/2}$, Ke, and $AUC_{\_\%Extrap}$ will be not analyzed for descriptive statistics but only listed.

Because of the endogenous substance of TPO in this study, there may be cases of non-below quantitation limit (BQL) of concentration in blood samples before administration, if such cases occur, baseline correction is required before calculating the pharmacokinetic parameters, and the concentration value after administration minus the baseline value is used to calculate the PK parameter. If a negative value occurs in the process of calculation, and if the negative value occurs before or after quantifiable data, the negative value will be treated as 0. If the negative value occurs between two quantifiable data, it is treated as missing.

Agreement on out-of-window of key PK data points: deviations exceeding the maximum time range allowed for non-relevance under the protocol will be considered to be out of window, and all PK parameters will be calculated using the actual time of blood sampling, and the actual time of blood sampling will be used in plotting the serum concentration-time curve for each participant.

Phoenix WinNonlin 7.0 software (or above) will be used to calculate pharmacokinetic parameters, and all other statistical analyses will be done using SAS 9.4 software (or above).

9.3.4 Safety Analysis

The analysis of safety data (AE, TEAE, SAE, clinical laboratory parameters, ECG parameters, vital signs, and physical exam) will be descriptive and performed on the safety population. The adverse events incidence, overall and per CTCAE grade, will be presented. The attribution to the test drugs, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be reported.

Events will be reported on per-individual basis, i.e. counting individuals rather than events. This means that even if a patient suffers the same event repeatedly during the follow-up, the event will be counted only once. Repeated events in patients will be summarized according to the following rule: if a patient suffers the same event more than once, the event will be assigned the worst severity, the closest relationship to the drug and the earliest starting date. In the listings, however, all occurrences of the events will be shown.

All AEs reported will be classified using frequency and intensity, with the most recent version of the MedDRA and listed together with information on onset, duration, seriousness, expectedness, relationship, outcome, and countermeasures taken. Serious adverse events will be listed separately.

The absolute and relative frequencies of participants with any AEs will also be listed. Furthermore, the absolute and relative frequencies for participants with AEs will be provided by System Organ Class and Preferred Term according to the MedDRA. Similarly, degrees of intensity, causal relationship with the test drugs, and the countermeasures taken for each AEs will be tabulated for each treatment. The time of onset of AEs after treatment and their duration will be evaluated on a categorical basis.

All clinical laboratory parameters will be analyzed descriptively. Summary statistics for baseline, on-treatment, and change from baseline in laboratory, vital signs, and ECG parameters will be provided by treatment group in table format. Mean change from baseline over time will be plotted with the corresponding standard errors. Values of safety laboratory parameters and urinalysis outside the reference range will be flagged as H (above the reference range) or L (below the reference range) in the listings. A summary will be prepared by counting both the values out of reference range and the number of patients in whom one or more abnormalities occurred after treatment. Shift tables may be provided for the changes with respect to reference range for the following groups of parameters: hematology, clinical chemistry, and urinalysis. For all parameters, these shifts may be tabulated within each treatment and by visit, for the comparison before and after treatment.

Patients with abnormalities for vital signs, ECG, physical exams or clinical laboratory parameters will be tabulated and listed in different tables. Abnormality ranges will be defined for actual values and for changes from reference.

9.3.5 Pharmacodynamics Analysis

All analyses of pharmacodynamics will be based on the Pharmacodynamics Analysis Population (PDS).

Statistical descriptions of PLT and their differences from baseline at each time point will be performed, providing the number of cases, mean, standard deviation, coefficient of variation, median, quartiles, minimum, and maximum values. Calculate the maximum value of the change in platelet count relative to baseline (E_{max}), the time to peak (ET_{max}), and plot a line graph of the mean with standard deviation.

Line graphs of changes in PLT at each visit for each participant.

9.3.6 Immunogenicity Analysis

ADAS will be used to summarize the immunogenicity data of the participants at different time

points. According to the planned timepoints, the number and percentage of ADA positive will be summarized and listed. If possible, the titers and NAb for ADA-positive will be further analyzed and summarized.

9.4 Data Monitor Committee

No.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable Council for Harmonisation (ICH) Good Clinical Practice (GCP)
  - Applicable laws and regulations
- Prior to the commencement of the clinical study, the study protocol, informed consent form and other information provided to the participants are subject to review and approval by the Ethics Committee, and the relevant approvals are provided to the sponsor. Any modifications to the protocol and ICF during the study also need to be reported to the IEC for approval before implementation.

A 2 Informed Consent Process

The investigator or his/her authorized representative must obtain an informed consent form signed by the participants participating in the study and explain to the participants the nature, purpose, potential hazards, and benefits of the study, and must let the participants know that they may withdraw from the study at any time without restriction. If the participant is unable to sign the informed consent form, the participant's legal representative must sign the informed consent form. If the participant or their legal representative is unable to read the informed consent form, an impartial witness must be present throughout the informed consent process. After the participant and his/her legal representative verbally agree to participate in the study, the impartial witness must sign the informed consent form and ensure that the participant and his/her legal representative are fully informed and understand the contents, and that the participant is aware that they may withdraw from the study at any time without restriction. If safety results result in a significant change in the risk/benefit assessment, the informed consent form is reviewed and changed as necessary, and all participants (including those already receiving treatment) must be informed of the updated information and sign the new informed consent form before continuing with the study.

Both “telehealth discussion and signing” and “in-person discussion and signing” are available.

Two copies of the informed consent form should be signed and one should be kept with the participant, and the other copy of the informed consent form should be kept with the study records at the site. The informed consent process should be documented in the participant's medical or other original records.

A 3 Management of Investigational Drug

A 3.1 Packaging and Labeling

All investigational drugs will be provided to the investigator by Shenyang Sunshine Pharmaceutical Co. or its designee. The following information should be stated on the drug label:

- Study/Protocol Number
- Specifications
- Storage instructions
- Expiry/Retest Date
- Lot number
- Description of "Clinical study material - Study Use Only", or similar statement
- Name and address of study sponsor/investigational drug manufacturer

The Investigator or his/her designee shall not provide investigational drugs to any participant not enrolled in the study, or to any physician or scientist not appointed to this study.

A 3.2 Storage

The investigational drug shall be kept in a secure locked cabinet or sealed container with strictly limited access only to the investigator or his/her designated personnel. Neither the investigator nor his/her authorized personnel shall provide the drug to any participant not enrolled in this study protocol.

Investigational drugs should be stored under the conditions specified on the investigational drug label.

A 3.3 Traceability

The investigator, or designee, must maintain a detailed inventory record of receipt, distribution, use, and retrieval in order to provide assurance to the sponsor that the investigational drug has not been distributed to any person other than a participant who meets the deadlines and conditions set forth in this study protocol.

The investigator must securely store the drugs supplied for the conduct of the study. For

investigational drugs sent to the study site, the investigator or designee shall confirm the quantity sent, the date of acceptance, and that the drug supply will be undamaged and uncontaminated in transit, and shall sign and date the appropriate documentation.

All used and unused/unopened medication containers must be carefully inventoried and kept at the site until collected by the sponsor or disposed of.

A 3.4 Restitution

Once the study is nearing completion or termination, all unused and/or partially used study medication can be returned to the sponsor or disposed of.

A 4 Data Management

A 4.1 Data Collection

The Web-based Electronic Data Capture (EDC) Systems will be used to collect, store, and manage clinical data. The EDC database builder will establish the electronic case report form(eCRF) in EDC according the protocol. Before EDC database go live, the eCRF will be approval by Project Managers, Medical Reviewer and Biostatistician etc. The DM will conduct the EDC training and introduce the eCRF completion guideline for project managers, clinical research associates (CRA), investigators etc. After receiving the training, the relevant personnel can log into the EDC system and then enter the data into the eCRF. The EDC system can automatically verify the data in the eCRF and generate corresponding prompt messages. After the investigators modifying and verifying the entered data, the Principal Investigator or his/her authorized Investigators will sign electronically to confirm the data.

A 4.2 Data Review

The CRAs review the data entered into the eCRF by investigators for completeness and authenticity, and if necessary, query message to ask investigators to verify and revise until the data are accurate, complete and clean;

The data manager reviews the data entered into the eCRF by investigators for consistency and accuracy, and if necessary, query message to ask investigators to verify the changes until the data is accurate, complete and clean;

Medical reviewers to review eCRF data from medical expertise, if necessary, a query to ask investigators to verify modifications, until the data are accurate, complete, and clean;

All data issues should be confirmed before the database lock. The audit trails are required for all data changes and related operations.

A 4.3 Database Locking

If there is a data review meeting or other form of data review communication, the principal investigator, medical manager, project manager, data manager, and statistician should confirm any protocol deviation events that occurred in the trial and the impact on the statistical analysis dataset, and confirm that the database is complete and accurate before co-signing the relevant documents to lock the database. In principle, no further changes to the locked database are allowed. Problems found after data locking can be updated in the database or explained in the report after confirmation, and a written record will be kept. In order to ensure the security of the data, unrelated persons are not allowed to approach and modify the data, and the data must be backed up.

A 5 Quality Control

A 5.1 Monitoring

The sponsor's monitor or representative/designee will visit the site prior to enrolment of the first participant at the site and will conduct on-site visits at a planned frequency during the course of the study, as well as periodic telephone and written communications.

After the investigator or clinical research coordinator (CRC) completes data entry, the supervisor conducts online for raw data approval (SDV), and the supervisor, medical staff, and data manager conduct data verification and send data queries online. After the query is sent, the investigator verifies the raw data and resolves the query online.

A 5.1.1 Data Requirements for Supervisor Surveillance

1) Supervisors check for informed consent and screening of participants for inclusion during the study;

2) Verify that all eCRFs are completed correctly and agree with the original information;

3) All errors or omissions have been corrected or noted, signed and dated by the investigator;

4) Dose changes, therapeutic alterations, concomitant, and intercurrent illnesses should be identified and documented for each participant;

5) Verify that both withdrawals and lost visits of enrolled participants should be accounted for in the eCRF;

6) Confirmation that all adverse events have been recorded and that serious adverse events have been reported and recorded;

7) Verify that investigational drugs are supplied, stored, dispensed, and withdrawn in

accordance with the relevant regulations, and record accordingly;

8) The eCRF form is completed by the investigator or his/her authorized personnel and the eCRF must be completed for each enrolled case.

A 5.2 Auditing

Both sponsors and investigators should establish their own quality assurance systems, fulfil their respective responsibilities, and strictly follow the clinical study protocols and adopt the appropriate standard operating procedures to ensure the implementation of quality control and quality assurance systems for clinical study.

The sponsor may conduct audits of the above clinical study process, sample testing process, data, reports and calculations in different categories as needed, taking into account the progress of the study and the results of the verification by the quality controller/supervisor. The investigator shall agree to cooperate with the audit in a reasonable manner and at a reasonable time.

A 6 Study Documentation Management

A 6.1 Study Data Acquisition and Modification

At each follow-up visit of the participant, the investigator participating in the study or his/her designee shall document in the study medical record the content of the visit to the participant, the examination and observations, etc., which shall include, at a minimum:

1) Documentation of the process of obtaining informed consent, including various revised consent forms.

2) Dates and days of follow-up visits and visits equivalent to their follow-up in the study schedule.

3) Overall participant status, including all significant medical findings. The severity, frequency, and duration of various adverse events and the investigator's assessment of their causal relationship with the investigational drug, study manipulation, and other concomitant medications must also be documented.

4) Various changes in concomitant medication or dosage levels.

5) A general reference to the completed operation.

6) Signature and date of the clinical staff member who wrote the chart entry and/or signature and date of the investigator.

In addition, clinically significant information discovered by contacting participants by telephone or other means should also be documented in the study medical record as required by the methodology described above.

Any changes to information in the study chart and other original documents should be initiated and dated on the day of the change by the investigator who authorized the change. Amendments should be made by drawing a single straight line through the incorrect data and clearly documenting the correct data. If the reason for the modification is not obvious, a brief explanation of the modification should be provided by the Investigator on the original documentation. For participants who withdraw early, only the withdrawal follow-up should be completed.

A 6.2 Original Documents

Original documentation is defined as all information contained in the original records necessary for study reconstruction and evaluation in a clinical study, as well as qualified copies of original records of clinical findings, observations, or other items. Original documentation includes progress notes, electronic data, screening records, and recorded data from automated instruments.

All original documents related to this study will be kept by the investigator. The investigator is obliged to allow study-related surveillance, audits by the sponsor or its appointees, reviews by the IEC and inspections by the competent authorities.

A 6.3 Document Management at the Study Site

Investigators are responsible for ensuring that study site documentation is maintained in accordance with GCP guidelines.

A 6.4 Record-keeping at the Study Site

The principal investigator is obliged to keep study records and data for safety information traceability and audit and visual inspection after the study has ended. The primary documentation should be kept until at least 5 years after the completion or discontinuation of the study. However, if required by relevant regulations or if requested by the sponsor, the above documents should be kept for a longer period of time. Samples, documents and computerized records should be kept in a secure area to prevent trespassing, loss or interference.

The investigator may not dispose of any records related to this study without the following permission:

- Written permission from the sponsor.
- Provide opportunities for sponsors to collect such records.

The investigator shall be responsible for maintaining adequate and accurate electronic or paper-based source documentation of all observations and data generated during this study. Such participant documentation is the basis for visual inspection by the sponsor and relevant authorities. If the investigator withdraws from the study (e.g., change of position or retirement), study-related records should be transferred to a mutually agreed upon designee. The sponsor shall be notified in writing of such transfer.

A 6.5 Record-keeping for Sponsors

The sponsor will maintain all essential sponsor-specific documents in accordance with the appropriate regulatory requirements of the regulatory authority. If the sponsor discontinues the clinical development of an investigational drug (i.e., due to any or all of the indications, routes of administration, or dosage forms), the sponsor will maintain essential sponsor-specific documentation until at least 5 years after the formal discontinuation or as required by the relevant regulations.

If the sponsor discontinues clinical development of the investigational drug, the sponsor should notify all investigators/institutions and all relevant authorities.

Important documents that are proprietary to the sponsor should be kept until at least 5 years after the completion or discontinuation of the study. However, these documents should be retained for a longer period of time if required by relevant legislation or if requested by the sponsor.

The sponsor shall notify the investigator/institution in writing of the record (original and/or study base document) retention requirements and shall notify the investigator/institution in writing when records related to the study are no longer required to be maintained.

A 7 Confidentiality

All information generated during the study shall be kept in the highest degree of confidentiality and shall not be disclosed to anyone not directly related to the study without the written permission of the participant. However, direct access may be granted to authorized management, sponsor personnel (or their representatives) and the IEC to inspect and copy these records. Only participants who have signed an informed consent form may be enrolled in this study. All applicable data confidentiality provisions must be fully complied with. All investigational drugs, participant body fluids, and/or other collected materials shall be used exclusively in accordance with the protocol of this study, unless written consent is obtained from the sponsor.

All pages of the eCRF and all reports and correspondence pertaining to participants in the study shall be distinguished only by the participant's abbreviation of name letters (The four spaces of the participant's name abbreviation should be filled in, consisting of the first two letters of the first name and the first two letters of the last name), and by the participant's number. The

investigator should keep a list of the identification codes of the participants in this study. This information shall be kept in the strictest confidence and shall be used only in case of emergency if required.

A 8 Publication Policy

Relevant data about this study will be published only with the consent of the research unit and the sponsoring organization.

11 REFERENCES

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