informed consent

(ICF Template)

Project Name: Multicenter Clinical Study of Romiplostim N01 in the Treatment of Sepsis-Related Thrombocytopenia

Research institution: Tongji Hospital, Shanghai

Principal Investigator: Wu Qian

You will be invited to participate in a clinical study. This informed consent form provides you with information to assist in deciding whether to participate in this clinical study. Please read it carefully, and if you have any questions, please consult the investigator responsible for the study.

This study has been reviewed and approved by the Ethics Review Committee of Tongji Hospital in Shanghai. Tongji Hospital in Shanghai is a tertiary Grade A general hospital and has been accredited by the National Medical Products Administration (NMPA) as a clinical trial institution for pharmaceuticals, with official registration with the NMPA. The principal investigator of this study is Dr. Wu Qian, an attending physician in the Department of Critical Care Medicine.

This study plans to enroll 280 participants, with three hospitals participating in the research, led by Shanghai Tongji Hospital as the principal investigator. Among them, the study institution intends to enroll more than 200 participants.

1. Research objective (Why was this study conducted?): By comparing the platelet-raising effects of Romiplostim N01 with recombinant human thrombopoietin, this study aims to investigate whether Romiplostim N01 can treat sepsis-associated thrombocytopenia with superior efficacy and safety profiles, while also reducing ICU hospitalization duration and medical costs.

2. Research Background and Significance: Sepsis-associated thrombocytopenia is a clinical syndrome characterized by multifactorially mediated thrombocytopenia (typically $<100 \times 10^9$/L or a 50% decline from baseline) during sepsis progression. Its incidence exceeds 55% in sepsis patients and is even higher in septic shock patients, with significantly elevated mortality rates. Traditional platelet transfusion relies on voluntary donations, which face challenges such as short storage duration (only 5 days), strict typing requirements, and contamination risks, making it

difficult to meet patient needs promptly. Ropivastatin N01, the world's first second-generation long-acting TPO-RA, provides a novel therapeutic option for sepsis-associated thrombocytopenia. Studies demonstrate that ropivastatin N01 stimulates megakaryocyte proliferation and differentiation, rapidly promotes platelet production, and exhibits immunomodulatory effects by reducing platelet antibody levels, thereby improving regulatory T cell function and decreasing inflammatory cytokine release. Multiple clinical trials have confirmed ropivastatin N01's efficacy in increasing platelet counts in hematologic disorders. Preliminary small-sample studies showed that compared to recombinant human thrombopoietin, ropivastatin N01 achieves significantly higher short-term platelet elevation with superior efficacy. This randomized controlled trial employed completely randomized assignment (unpredictable group allocation) to ensure identical dosing regimens between trial and control groups. The trial group received weekly administration followed by 6 days of saline placebo, with other treatments remaining identical to those in the control group. The placebo used was sterile saline of equivalent volume, which was safe and non-toxic.

3. Inclusion and exclusion criteria (who is eligible to participate in this study?):

You may participate in this study (inclusion criteria) if you meet the following requirements:

1) Age ≥18 years old, gender unrestricted;
2) Meets the diagnostic criteria for sepsis 3.0, which include: a) presence of confirmed or suspected infection; b) infection-induced organ dysfunction, specifically a sequential organ failure assessment (SOFA) score ≥2 points. If pre-infection organ dysfunction is known (i.e., SOFA score>0 points), an increase in SOFA score by ≥2 points after infection onset is required.
3) Platelet count $\leq 50 \times 10^9$/L.

If you meet the following criteria, you are not eligible to participate in this study (exclusion criteria):

1) Patients with malignant tumors who have a history of chemotherapy or radiotherapy, or patients with advanced malignant tumors;

2) Presence of thrombocytopenia unrelated to sepsis;

3) Received immunomodulatory therapy within 6 months;

4) Patients who have undergone cardiopulmonary resuscitation (CPR) or those with end-stage hepatic or renal failure;

5) Patients who were transferred out or died within 24 hours of admission (or ICU admission);

6) Patients with hematologic disorders leading to thrombocytopenia, or those with other hypercoagulable states, recent history of thrombotic events, or acute active bleeding;

7) Patients with severe cardiovascular and cerebrovascular diseases, severe trauma, major surgery, or other causes of massive hemorrhage;

8) History of antiplatelet drug use within two weeks prior to medication administration, such as platelet membrane glycoprotein antagonists like clopidogrel.

If any of the items ① to ⑧ above is marked as 'Yes', the participant cannot be included in the study.

4. Research process (What is required to participate in this study?):

This study primarily aims to investigate whether ropusitin N01 can treat sepsis-associated thrombocytopenia by comparing its efficacy with recombinant human thrombopoietin in platelet elevation, with the expectation of demonstrating superior therapeutic outcomes and safety profiles. A total of 280 enrolled subjects will be randomly assigned to either the experimental group or control group, with equal probability of assignment to different trial groups. Subjects diagnosed with sepsis-associated thrombocytopenia will receive different pharmacological treatments upon enrollment, with a treatment duration of 7 days. Study observations and follow-ups will be conducted at days 0, 7, 14, and 28.

Treatment group: Ropivastine N01 was administered. Ropivastine for Injection N01 (Specification: 250μg/vial) was administered via subcutaneous injection at a dose of 250μg once weekly (due to the higher bleeding risk in sepsis patients and the inclusion of patients with platelet counts <50×10^9/L, the starting dose was adjusted to 4 μg/kg according to the package insert), with administration on day 1. Placebo was given as normal saline, administered over the last 6 days of the treatment week, with the same injection volume as ropivastine.

Control group: Recombinant human thrombopoietin was administered. Thrombopoietin injection (specification: 15,000 U/mL) was administered subcutaneously at a dose of 15,000 U per dose, once daily, for continuous administration for ≥1 week. Treatment was suspended if PLT levels reached $\geq 100\times10^{9}$/L.

Note: For patients with PLT $\leq 10\times10^{9}$/L or those with significant bleeding tendency, both groups received platelet transfusion and enhanced hemostatic therapy.

If you agree to participate in this study, each participant will be assigned a unique number and a research profile will be established. During the study, your blood samples will be collected by trained professionals, with 3 mL of venous blood drawn from your arm (synchronized with hospital admission examinations, requiring 3 sessions) and 15 mL of fecal samples collected (requiring 2 sessions). For patients receiving ventilator therapy, an additional 20 mL of condensate fluid from the ventilator tubing will be collected (requiring 3 sessions, with no physical harm involved). Additionally, your examination results during ICU admission will be utilized for data analysis in this study. All research data will undergo anonymization and will not be disclosed externally.

5. Potential risks and discomforts associated with trial participation:

Blood sample collection may cause physiological discomfort including pain, localized cyanosis, and bleeding. The procedure will be performed by qualified nurses and specialists in strict accordance with standardized protocols.

If any discomfort, new changes in condition, or unexpected events occur in study participants, regardless of their association with the drug/procedure, the primary physician of the participant should be promptly contacted. The physician will make an assessment and provide appropriate medical intervention. If any discomfort, new changes in condition, or unexpected events occur in study participants, regardless of their association with the drug/procedure, the primary physician of the participant should be promptly contacted. The physician will make an assessment and provide appropriate medical intervention.

6. Potential benefits (What benefits will this study provide me):

(1) Through the collection and analysis of your blood, stool samples, and medical history, this research will facilitate disease diagnosis, provide essential recommendations for your treatment, or offer valuable insights for disease research.

(2) Participation in this study and adherence to the protocol and study instructions for medication administration may lead to symptom relief and disease control. However, this treatment may also be ineffective for you. Your study physician will evaluate and monitor your health status and medication regimen to ensure your safety to the greatest extent possible.

(3) Although participation in this study may not provide you with direct benefits, information related to the clinical study you are involved in may potentially improve current diagnostic and therapeutic approaches in the future, thereby advancing medical science and benefiting other individuals suffering from the same disease as you.

7. Potential additional costs or burdens (Do I need to pay any fees for participating in this study?)

Participation in this research project will not incur additional expenses for you. Examinations related to the study, such as medications, stool samples, and condensation water from exhaled breath, will be covered by the research funding. However, treatments and examinations required for concomitant comorbidities are not included in the free scope.

8. Medical treatment and compensation for injuries (What to do if injured during study participation)

If you experience any injury during the study period or adverse events during medication treatment, please contact your study physician, and you will receive prompt medical attention. For any injuries with a causal relationship to this study or the trial medications, the sponsor will cover medical expenses and provide corresponding economic compensation in accordance with relevant national laws and regulations.

Even if you have signed this informed consent form, you still retain all your statutory rights and interests.

10. As a research subject, you have the following responsibilities:

Provide truthful information regarding your medical history and current physical condition; inform the study physician of any discomfort experienced during the study period; refrain from taking restricted medications or consuming restricted foods; disclose to the study physician

whether you have recently participated in other studies or are currently participating in other research projects.

11.Privacy and Confidentiality:

If you decide to participate in this study, we will make every effort to protect your personal privacy within the limits permitted by law. Any public reports regarding the results of this study will not disclose any of your personal information. Your study physician and researchers will collect your information for use in this study. This may include date of birth, gender, height and weight, health-related information, medical history, diagnoses, and data obtained from collected blood or urine samples and imaging materials (collectively referred to as "personal information," excluding information that has undergone anonymization). Your personal information will be collected, processed, and stored during the study period and after its completion.

Your medical records (including original medical charts, laboratory reports, etc.) will be fully preserved at the hospital where you received treatment. Within the scope permitted by law, monitors, auditors, ethics committee members, and inspectors from drug regulatory authorities are authorized to review your original medical records to verify the clinical trial process and data, without any disclosure of your personal information during this procedure.

As part of this study, the research physician will also record the results of your study-related assessments in your personal medical records. The research physician will also review your personal medical records to obtain health-related information, such as past medical history and recent treatments received.

Your personal information will be stored exclusively at this research center. Any external sharing of information will undergo anonymization processing (your identity information will be represented by your date of birth and participant number). Therefore, your personal information will not be disclosed and is password-protected. This password-protected data is referred to as "study data," with your research physician controlling the password. Your personal information will not be disclosed to any third party unless for your health and benefit, for the health and benefit of other participants, or as required by law. Any public reports regarding the study results will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within legal limits. In accordance with medical research ethics, experimental data will be available for public inquiry and sharing, but such access and sharing will be restricted to web-based electronic databases to ensure no personal privacy information is compromised. If you find any inaccuracies or incomplete information, you have the right to request corrections or supplements from your research physician.

The anonymized information will be conducted and evaluated in accordance with relevant regulatory requirements within China or worldwide based on the protocol. Further research, development, and safety assessment of new products and/or improvements to existing products will be carried out during subsequent development phases, with applications for marketing approval and sales of products anywhere in the world.

The findings of this research project may be published in medical journals, but we will maintain confidentiality of your research records in accordance with legal requirements. No personal information will be disclosed during publication.

If you withdraw your consent, the study physician will no longer use your study data or share it with others. However, study data that you have shared with the sponsor prior to withdrawing consent may still be utilized by the sponsor.

If any of the above requirements regarding the processing and management of your personal information are amended, the study physician will promptly inform you of the changes and obtain your consent again.

During the study period, we will promptly notify you of any significant new developments or medical information related to your health, such as recommendations for your child to undergo certain examinations to confirm these new findings. We will also timely inform you of any new information that may influence your decision to continue participating in the study.

12. Are there currently other treatment methods available, and what are the advantages and disadvantages of the treatment approach adopted in this study?

Participation in the study is not your only treatment option. If you choose not to participate in the study, you will still receive other therapeutic measures and guidance provided by your physician. The physician will develop a tailored treatment plan based on your individual circumstances and inform you of potential benefits and risks. Currently available standard treatments include platelet transfusion and recombinant human thrombopoietin (rHTPG), both of which will be included in this study. Compared to rHTPG, the trial group may demonstrate superior efficacy.

13. Rights of Subjects:

Participation in the study is entirely voluntary. You may decline to participate in this study or withdraw at any time during the research process, and your data will not be included in the study results. This will not affect your relationship with your physician. Your medical treatment and benefits will not be impacted as a result.

If additional treatment is required, if you fail to comply with the study protocol, if study-related injuries occur, or for any other reason, the study physician will promptly notify you and terminate your participation in the study. The study physician will provide recommendations for your next treatment plan based on your health status.

If you withdraw from the study midway, for safety considerations, we will complete all required examinations specified in the final safety follow-up as much as possible, and you have the right to decline. If new information related to your health and rights is discovered after your withdrawal, please promptly inform the study physician, and we will contact you again.

14. Who should I contact if I encounter problems or difficulties?

If you have any questions related to this study, please contact:

Research Physician: Wu Qian, Contact Number: 13535056114 。

If you wish to express any dissatisfaction with the research process or have questions related to your rights and interests, please contact the Secretary of the Ethics Committee at Tongji Hospital, Shanghai. Telephone: 021-66111243; Email: tongjilunli2012@163.com

Informed Consent Form Signature Page

I have read this informed consent form and discussed the study with my physician, raising any questions I may have. The physician has provided me with a detailed explanation of the study objectives, procedures, potential risks and benefits, and has addressed all my inquiries. I am fully aware that participation in this study is voluntary.

I confirm that I have had sufficient time to consider this matter, including the potential risks associated with participating in the study. I am available to consult with my physician for further information at any time and may withdraw from the study without facing discrimination or retaliation. My medical treatment and benefits will not be affected by withdrawal from the study. I am also aware that if I withdraw midway, particularly due to treatment-related reasons, I will promptly inform my physician of any changes in my condition and complete the corresponding physical and biochemical examinations, which will benefit both myself and the entire study. If any additional treatments are required due to changes in my condition, I will consult with my physician in advance or provide truthful information afterward.

I voluntarily participate in this study. I consent to the researchers, sponsors, health administration and supervision departments/pharmaceutical and food regulatory authorities, and ethics committees accessing my research materials. I will receive a signed and dated copy of the informed consent form.

Subject Name (regular script): _____ Subject Signature:

_____

contact number ： _____ date ： _____days_____sun

Guardian's name (regular script):_____Guardian's signature:_____

contact number ： _____Date: _____ _ year _____ month

_____ day

Witness name (regular script):_____Witness signature:_____

contact number ： _____Date: _____ _ year _____ month _____ day

(Note: If the subject is illiterate, a witness signature is required; if the subject lacks legal capacity, a proxy signature is necessary.)

I have accurately informed the subject of this document, and he/she has properly read the informed consent form, with evidence demonstrating that the subject had the opportunity to raise questions. I confirm that the subject provided voluntary consent.

Name of Investigator (regular script): _____ Investigator's Signature: _____

contact number ： _____Date: _____ _ year _____ month _____ day