Research protocol

Version: 3.0 | Date: 2026.02.12

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

Applicant: Shanghai Tongji Hospital

Responsible department: Intensive Care Unit

Principal Investigator: Wu Qian

Group leader unit: Shanghai Tongji Hospital

Participating institution: Tongren Hospital Affiliated to Shanghai Jiao Tong University, The First People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Researcher's Statement and Protocol Signing Page

As the principal investigator of this research project, I will adhere to the ethical principles outlined in the Ministry of Health's "Ethical Review Measures for Biomedical Research Involving Human Subjects" (2016), the WMA's "Helsinki Declaration" (2013), the CIOMS "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (2002), and Good Clinical Practice (GCP). Guided by the Good Clinical Practice (GCP) framework, I will implement the protocol approved by the ethics committee and conduct the study in accordance with the protocol requirements to ensure scientific rigor and protect the health and rights of participants.

Name: _____

Signature: _____

Date: _____

scenario summary

Plan Title	Multicenter Clinical Study of Romiplostim N01 in the Treatment of Sepsis-Related Thrombocytopenia
Version number/Version date	3.0 2026.02.12
Sponsor and Participating Organizations	Shanghai Tongji Hospital, Tongren Hospital Affiliated to Shanghai Jiao Tong University The First People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine
Principal Investigator	Wu Qian
Nature of study	RCT
purpose of research	To evaluate the efficacy, advantages, and social value of Romiplostim N01 in the treatment of sepsis-associated thrombocytopenia.
sample capacity	280
study population	Patients with sepsis-associated thrombocytopenia
research technique	Prospective, single-blind, superiority, randomized, positive-controlled clinical study
Inclusion criteria	Patients meeting the diagnostic criteria for sepsis-associated thrombocytopenia
Exclusion criteria	Does not meet the diagnostic criteria for sepsis-associated thrombocytopenia or has other factors affecting the trial study
End-of-Test Criteria	Observation after 28 days or until subject death
Dropout/Exclusion Criteria	Failure to complete the treatment course and observation period specified in this protocol due to certain reasons
Early exit criteria	Subjects declined to continue participating in the clinical trial during the study period.
dosage regimen	Treatment group: Ropivastine therapy 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 <50×109/L, the starting dose was

	adjusted according to the package insert to 4 μg/kg), with administration on day 1. Placebo saline was administered as a placebo 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 ≥100×10^9/L. For patients with PLT levels ≤10×10^9/L or significant bleeding tendency, platelet transfusion and enhanced hemostatic therapy were provided.
Primary efficacy endpoint	Effective rate of platelet-raising therapy after day 7
Secondary efficacy endpoints	Platelet counts on day 3, day 7, day 9, and day 14; time to initial recovery of platelet count to ≥100×10^9/L
Safety indicators	Liver function (ALT, AST, γ-GT, ALP, TBIL), renal function (Scr, BUN), blood cell morphology, coagulation function, thrombotic complications, spleen morphology
Research Progress Plan	January 2026 – February 2026: Passed project ethics review, collected patient data February 2026-February 2027: Collect patient data, conduct preliminary analysis of research findings, and promptly adjust the study protocol. March 2027 – December 2027: Analyze research data, prepare the final report, and preliminarily draft relevant papers.
Statistical analysis methods	Inter-group comparisons of changes in primary efficacy indicators before and after treatment were conducted using superiority testing. Group comparisons were performed using the χ^2 test (including CMH-χ^2 test) or Fisher's exact probability method. Measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± s). For comparisons of means in multi-sample grouped designs, one-way ANOVA was employed, while inter-group comparisons were analyzed using the least

	significant difference method (LSD-t test).
Research publication formats	research paper
Research Period and Visit Schedule	Administration was administered for 7 days, with survival rates assessed on days 14 and 28 of enrollment.

一、 purpose of research

This study aims to randomly assign SAT patients admitted to the ICU into a ropristine N01 treatment group and a recombinant human thrombopoietin control group. The therapeutic efficacy of ropristine N01 will be evaluated by monitoring platelet counts in SAT patients. Additionally, the study will assess the advantages and social value of ropristine N01 treatment for SAT through patient APACHE II scores, improvements in platelet parameters, 28-day mortality rate, incidence of adverse reactions, ICU length of stay, and hospitalization costs.

二、 Research Background

Sepsis refers to life-threatening organ dysfunction caused by host immune dysregulation due to infection. Septic shock in sepsis denotes severe circulatory, cellular, and metabolic disturbances associated with sepsis, exhibiting a higher mortality risk compared to uncomplicated sepsis. The global incidence of sepsis continues to rise, with approximately 48 million cases annually, and its treatment-related costs are substantial. It remains one of the leading causes of infection-related mortality and a major public health challenge worldwide.

Thrombocytopenia is a common condition in ICU patients, with an incidence rate exceeding 55% in sepsis patients and even higher in septic shock patients. Existing studies indicate that the severity of thrombocytopenia is positively correlated with mortality in sepsis patients. Severe thrombocytopenia ($<50 \times 10^9$/L) can significantly increase the 28-day mortality rate, prolong organ support duration, and reduce survival rates in sepsis patients. Sepsis-associated thrombocytopenia (SAT) is a clinical syndrome

characterized by multifactorially mediated thrombocytopenia (typically <100 × 10^9/L or a 50% decline from baseline) during sepsis progression, though its exact pathogenesis remains unclear. Current mechanisms are summarized into three subtypes: reduced platelet production, increased platelet consumption, and enhanced platelet destruction. (1) Reduced platelet production: A multicenter trial involving 301 ICU sepsis patients yielded bone marrow smears from 238 thrombocytopenic cases, revealing thrombocytopenia in 17 patients (7.1%). These findings suggest that some SAT cases may result from bone marrow suppression. It is evident that during severe infections, direct inhibitory effects of pathogenic microorganisms and their toxin products on bone marrow lead to diminished responsiveness of bone marrow to TPO, impaired megakaryocyte function, or destruction of newly synthesized platelets in bone marrow, ultimately resulting in reduced platelet production. (2) Increased platelet consumption: Elevated platelet consumption is considered the primary mechanism of septic amebic thrombophlebitis (SAT). Under the direct or indirect effects of various damage factors released by pathogens, excessive activation of inflammatory responses leads to widespread endothelial cell damage and compromised vascular wall integrity. (3) Increased platelet destruction: SAT is also associated with enhanced platelet destruction. Shortened platelet lifespan results from autoimmune mechanisms. Through innate and acquired immune responses, activated platelets and their products mediate lymphocyte dysfunction, activation, and proliferation, leading to excessive cytokine production and hemophagocytosis. This is recognized as one of the causes of thrombocytopenia in septic states. Treatment of SAT requires first identifying the underlying etiology and controlling infections accordingly, followed by measures to restore platelet counts. Currently, the most commonly used clinical approach is platelet transfusion, supplemented by pharmacological interventions such as recombinant human thrombopoietin (rhTPO), interleukin-11 (IL-11), and intravenous immunoglobulin (IVIG) [6]. Thrombopoietin receptor agonists (TPO-RAs) are drugs that act on thrombopoietin (TPO) receptors to promote megakaryocyte growth, differentiation, and platelet production. rhTPO can modulate the damage of inflammatory mediators to endothelial cells in sepsis, reduce excessive platelet aggregation, and indirectly correct

the reduction in platelet count (PLT), thereby contributing to the improvement of pathological processes in sepsis patients. A retrospective study on elderly sepsis patients demonstrated that rhTPO could increase PLT levels, decrease bleeding events, and restore tissue and organ function. rhTPO achieved rapid PLT recovery within 5 days in 76.32% of patients with thrombocytopenia, reduced the frequency of PLT transfusions in perioperative abdominal infection patients, and decreased the 28-day mortality rate.

Ropivastatin is the world's first second-generation long-acting TPO receptor agonist (TPO-RA) and has been widely used in patients with immune thrombocytopenia and aplastic anemia who have shown poor response to previous treatments. Ropivastatin N01 belongs to the class of TPO receptor agonists, which bind to TPO receptors on megakaryocyte precursors in the bone marrow via its TPO peptide segment and activate them, triggering a series of intracellular signaling pathways including JAK2/STAT5, PI3K/Akt, MEK/ERK, and p38, ultimately leading to gene transcription and increased proliferation and differentiation of megakaryocytes. However, no reports have been published on the use of TPO-RA in the treatment of sepsis. A safety and efficacy study of romipivastatin in patients with primary immune thrombocytopenia who underwent splenectomy or remained non-splenectomized demonstrated that some post-splenectomy patients developed infections, regardless of whether they had undergone splenectomy prior to romipivastatin therapy, indicating favorable safety profiles. Long-term use of romipivastatin maintained platelet counts within target ranges in both splenectomized and non-splenectomized patients without emerging new safety signals. Moreover, compared to the placebo group, romipivastatin did not increase the risk of thromboembolic events in splenectomized patients. Additionally, studies suggest that TPO and MP1 receptor binding function may be dysregulated in sepsis patients, and recombinant human thrombopoietin (rhTPO) has been shown to effectively increase platelet counts in septic acute thrombocytopenia (SAT) patients. Currently, the efficacy evidence of ropivastatin N01 in SAT patients remains insufficient.

三、 Test basis

Current research status at home and abroad: Severe acute thrombocytopenia associated with sepsis (SAT) is a clinical syndrome characterized by multifactorially mediated thrombocytopenia during sepsis (typically <100 × 10^9/L or a 50% decline from baseline), with its pathogenesis remaining unclear. During sepsis, abnormal megakaryocyte function can lead to impaired platelet production, while platelet surface receptors (such as glycoprotein receptors, Toll-like receptors, crystallizable fragment γ receptor IIa, and complement receptors) mediate inflammatory signaling and immune regulation, resulting in abnormal platelet activation and clearance as well as immune thrombosis formation. In addition to conventional platelet transfusion, novel therapeutic agents such as recombinant human thrombopoietin, intravenous immunoglobulin, and TLR-4 inhibitors have demonstrated potential in treating SAT by modulating platelet production, immune function, and inflammatory signaling pathways. The timing and efficacy of conventional platelet transfusion remain controversial. Emerging therapies including receptor antagonists, intravenous immunoglobulin, and recombinant human thrombopoietin offer promising options for promoting platelet production and reducing platelet destruction, providing new treatment alternatives for SAT. Platelet transfusion therapy is widely used for thrombocytopenia and bleeding episodes induced by antiplatelet agents. However, due to the lack of prospective randomized trial evidence, there remains significant uncertainty regarding the optimal transfusion threshold for prophylactic platelet transfusion in ICU-hospitalized thrombocytopenic patients. The European Society of Intensive Care Medicine recommends considering platelet transfusion when platelet counts fall below 10 × 10^9/L. However, the latest cohort study showed that the median pre-transfusion platelet count in patients hospitalized in the ICU who received

prophylactic platelet transfusion was 15 × 10^9/L. Some studies have also found that platelet transfusion increases the risk of patient mortality and does not significantly shorten the hospital stay of ICU patients. Therefore, for SAT patients, when to implement platelet transfusion therapy appropriately remains to be further investigated. Thrombopoietin (TPO) can regulate megakaryocyte formation and increase platelet counts. Recombinant human TPO (rhTPO) is a fully glycosylated TPO produced by China hamster ovary cells, exhibiting biological functions similar to endogenous TPO. ZHANG et al. found that rhTPO could increase platelet counts on day 7 of hospitalization and reduce the demand for blood products during the hospital stay of SAT patients. The network meta-analysis results by CHEN et al. further supported the efficacy of rhTPO: a dose of 300 U/(kg·d) may be the optimal choice for reducing the 28-day mortality rate in SAT patients; a dose of 15,000 U/d may be the best regimen for shortening ICU hospital stays and improving platelet levels on day 7 post-treatment. Recent studies indicate that rhTPO can also modulate the release of inflammatory mediators in sepsis patients, attenuate inflammatory responses, and thereby reduce mortality rates in sepsis patients.

Ropivacaine can stimulate megakaryocyte proliferation and differentiation, rapidly promote platelet production, and simultaneously exhibit immunomodulatory functions by reducing platelet antibody levels, thereby improving regulatory T cell function and decreasing the release of inflammatory cytokines. A meta-analysis demonstrated that ropivacaine can reduce the incidence of grade 3 or higher thrombocytopenia. Soff et al. found that solid tumor patients with chemotherapy-induced platelet counts below 100×10^9/L persisting for more than 4 weeks could maintain normal chemotherapy regimens and achieve platelet counts corrected to $(100-200) \times 10^9$/L with weekly ropivacaine therapy in 93% of cases, compared to only 12.5% (1/8) in patients not treated with ropivacaine. At the 2024 ASCO

meeting, results from a randomized controlled trial on ropivacaine N01 for the prevention and treatment of chemotherapy-induced thrombocytopenia in phase II/III cancer therapies were presented, showing an efficacy rate of 90% (18/20) in the ropivacaine N01 treatment group.

A study on the safety and efficacy of romiprost in patients with primary immune thrombocytopenia who underwent splenectomy versus non-splenectomy demonstrated that some post-splenectomy patients experienced infections. The drug exhibited favorable safety characteristics regardless of whether patients had undergone splenectomy prior to romiprost treatment. Long-term romiprost therapy maintained platelet counts within target ranges in both splenectomized and non-splenectomized patients without emerging new safety signals. Moreover, romiprost did not increase the risk of thromboembolic events in splenectomized patients compared to the placebo group. Additionally, studies suggest potential dysregulation of TPO and MP1 receptor binding function in sepsis patients. While rhTPO has been proven effective in elevating platelet counts in septic acute thrombocytopenia (SAT) patients, current evidence for romiprost N01 efficacy in SAT patients remains insufficient.

Prior research foundation: In a clinical pilot study, our research team observed 20 patients with SAT (Splenomegaly Associated with Thrombocytopenia) treated with either ropustinib N01 or recombinant human thrombopoietin (10 cases in each group). The pilot study revealed that compared to the recombinant human thrombopoietin control group, the ropustinib N01 treatment group exhibited a significant increase in platelet count as early as the first 3 days of therapy, with some patients even achieving normalization of platelet counts. Within 1 week, the effective rates of platelet count improvement were 70% in the treatment group and 50% in the control group. Additionally, compared to the control group, the treatment group demonstrated a reduction in ICU hospitalization duration by approximately 2.7 days and incurred lower hospitalization costs.

Table 1 Comparison of clinical efficacy between the two groups of patients

	valid	of no avail
Lopinastine N01	7（70%）	3（30%）
Recombinant human platelet growth factor	5（50%）	5（50%）

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四、 research contents

1. Trial population

A total of 280 patients with sepsis-associated thrombocytopenia admitted to the Department of Critical Care Medicine at Tongji Hospital in Shanghai from February 2026 to February 2028 were selected, meeting the inclusion criteria: 1) Age ≥ 18 years, with no gender restriction; 2) Meeting the diagnostic criteria for sepsis 3.0, i.e., a) presence of confirmed or suspected infection; b) Infection-induced organ dysfunction, defined as a sequential organ failure

assessment (SOFA) score ≥ 2 points. If pre-existing organ dysfunction (i.e., SOFA score>0 points) was known prior to infection, an increase in SOFA score by ≥2 points after infection was required. 3) Platelet count $\leq 50 \times 10^9$/L. 4) Participants must fully understand and comply with the study protocol requirements, and voluntarily sign an informed consent form. Exclusion criteria were applied: failure to meet the diagnostic criteria for sepsis-associated thrombocytopenia or presence of other factors affecting the study (see exclusion criteria below). The enrolled subjects were randomly divided into a control group and an experimental group, with 140 cases in each group.

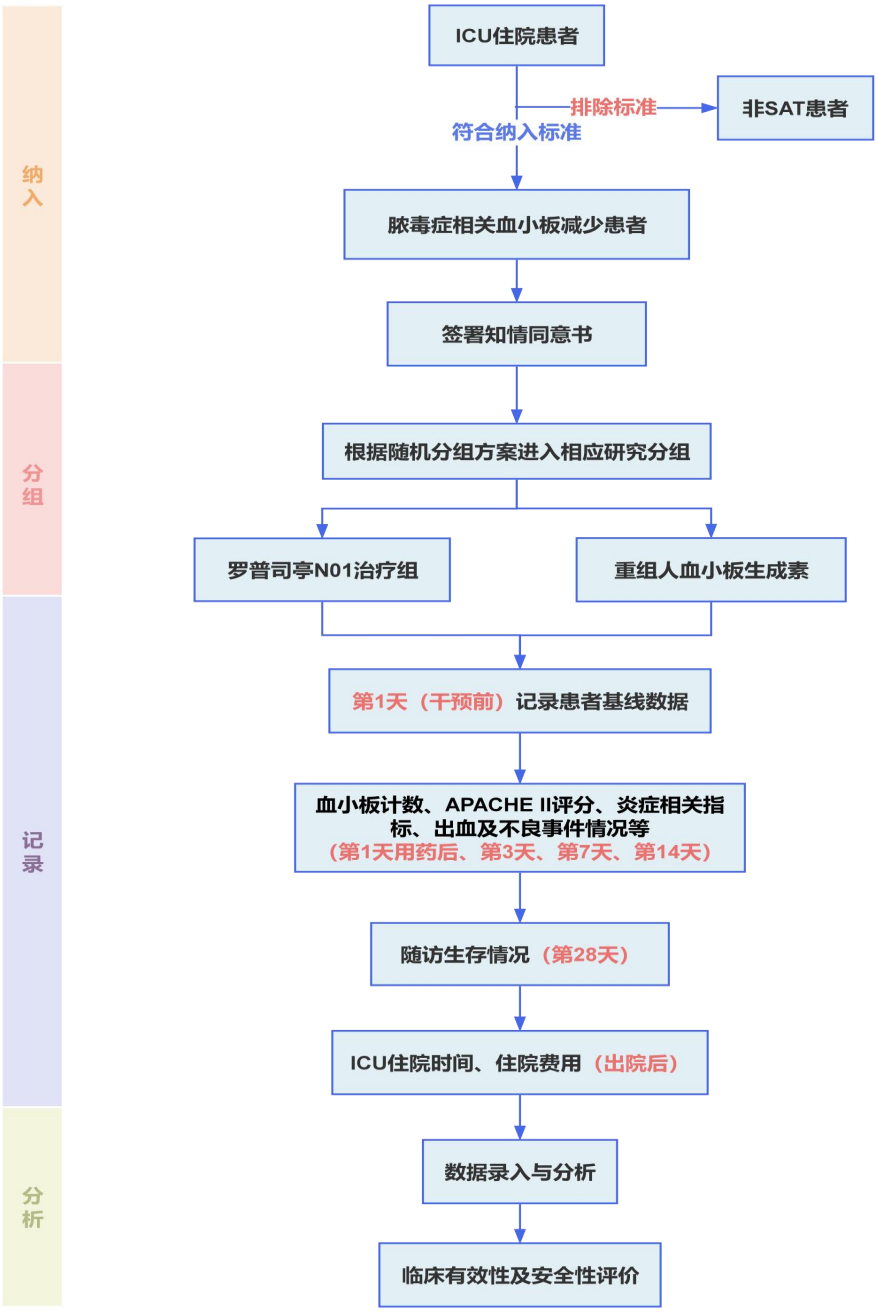

Figure 1 Technical Roadmap

2. Sample size calculation

The patient sample size was 280 cases, with the treatment group receiving ropusitinib N01 and the control group receiving recombinant human thrombopoietin. The observed outcome indicator was the platelet-raising efficacy rate after 7 days. Based on pre $n = \frac{2\bar{p}\bar{q}(Z_\alpha + Z_\beta)^2}{(p_1 - p_2)^2}$ -trial results, the

$n = \frac{2\bar{p}\bar{q}(Z_\alpha + Z_\beta)^2}{(p_1 - p_2)^2}$ relevant data showed an efficacy rate of 70% in the treatment group and 50% in the control group. According to the sample size estimation $\bar{p}$ $\bar{p}$ for rate comparison $\bar{q}$ between $\bar{q}$ two groups, the calculation $\bar{p}$ $\bar{p}$ $\bar{q}$ $\bar{q}$ formula was as follows $= \frac{2*0.6*0.4*(1.96+1.28)^2}{(0.7-0.5)^2} = \frac{2*0.6*0.4*(1.96+1.28)^2}{(0.7-0.5)^2}$: setting α =0.05 and β=0.1 (power=1-0.1=0.90), with two-tailed tests $Z\alpha$=Z0.05=1.96 and $Z\beta$=Z0.1=1.28. p1 and p2 represented the efficacy rates of the treatment group and control group, respectively. In this case, p1=0.7 and p2=0.5. The mean values of p1 and p2 were calculated as 1-p1 and 1-p2, respectively. The sample sizes were n1=n2=125.97 $\approx$ 126. Therefore, the treatment group had 126 cases and the control group had 126 cases. Considering a 10% dropout rate, the adjusted sample size was calculated as 126/0.9=140.

In conclusion, at least 140 subjects each were required for the experimental group and control group, totaling no fewer than 280 study participants.

3. Specific research content

This study was a prospective, single-blind, superiority, randomized, positive-controlled clinical trial. Through clinical randomized controlled trials, the following outcomes were evaluated: (1) the efficacy rate of platelet-raising therapy after 7 days of two intervention measures; (2) the improvement in platelet count on days 3, 7, 9, and 14 of treatment, as well as the time to first recovery of platelet count $\geq 100 \times 10^9$/L; (3) APACHE II (Acute Physiology and Chronic Health Evaluation System) scores at 14 days of treatment and 28-day post-treatment mortality rate to assess clinical efficacy in the treatment group; (4) post-treatment ICU hospitalization duration, hospitalization costs, incidence of bleeding or thrombotic events, and adverse event rates to evaluate

the economic and social value of the drug.

五、 research technique

1. Enrollment criteria (diagnostic criteria, inclusion criteria, exclusion criteria)

Inclusion criteria:

Participants must meet all the following criteria to be eligible for inclusion:

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 ≤50×10^9/L.

4) Participants must fully understand and comply with the requirements of the study protocol, and voluntarily sign the informed consent form.

Exclusion criteria:

Subjects meeting any of the following criteria were not eligible to participate in this study:

(1). Subjects with hypersensitivity to ropustinib N01 or thrombopoietin, or those who have previously received ropustinib N01 or thrombopoietin therapy without efficacy.

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

(3). History of thrombosis or embolic events within 12 months prior to the first dose, or accompanied by extensive severe bleeding (e.g., hemoptysis, massive upper gastrointestinal bleeding, intracranial hemorrhage, etc.), or other abnormal bleeding conditions.

(4). Participation in any other investigational drug study (including vaccines) or exposure to other investigational drugs within 4 weeks prior to the first dose administration or 5 half-lives (whichever is longer).

(5). Use of anticoagulants or any drugs with antiplatelet effects (e.g., aspirin, clopidogrel, etc.) within 3 weeks prior to the first dose.

(6). Received emergency thrombocytopenia treatment within 2 weeks prior to the first dose (e.g., methylprednisolone, platelet transfusion, intravenous immunoglobulin, or TPO-like antirheumatic drugs).

(7). Received prior treatment with azathioprine, danazol, cyclosporine A, tacrolimus, or sirolimus within 4 weeks before the first dose (or received prior treatment with cyclophosphamide or vincristine within 6 months before the first dose).

(8). Spleenectomy was performed within 6 months prior to the first administration.

(9). Diagnosed with myelodysplastic syndrome; or the subject had a history of malignancy within 5 years prior to the first dose administration and during the screening period (excluding complete cure of cervical carcinoma in situ, non-metastatic squamous cell carcinoma, or cutaneous basal cell carcinoma).

(10). Subjects with a history of allogeneic stem cell transplantation or organ transplantation.

(11). Subjects with a history of major clinical diseases that investigators consider potentially posing safety risks to study participants, or whose disease/condition deterioration during the study period may affect safety or efficacy assessment (e.g., circulatory system abnormalities, endocrine system abnormalities, neurological disorders, hematologic diseases, immune system disorders, psychiatric conditions, and unstable metabolic disturbances), specifically including: 1) Cardiovascular diseases: History of acute myocardial infarction (AMI) or unstable angina within 6 months prior to screening, severe arrhythmias (multifocal frequent ventricular premature beats, ventricular tachycardia, ventricular fibrillation), etc.; New York Heart Association (NYHA) cardiac

function class III-IV; 2) Subjects with known moderate-to-severe persistent asthma or chronic obstructive pulmonary disease (COPD) within 5 years prior to screening, or those with currently poorly controlled conditions.

(12). Patients who were transferred out or died within 24 hours of admission (or ICU admission).

(13). Known or suspected history of immunosuppression, including invasive opportunistic infections (such as histoplasmosis, listeriosis, coccidioidomycosis, pulmonary sporotrichosis, and aspergillosis); or infections deemed by the investigator to be abnormally frequent, recurrent, or chronic.

(14). Women currently in pregnancy or lactation, or planning to become pregnant or breastfeed during the study period; and male partners planning to become pregnant during the study period.

(15). The investigator determined that the subject had any other conditions unsuitable for participation in this study.

If any of the items (1) to (15) above is marked as 'Yes', the participant cannot be included in the study.

2. Subject Grouping

Grouping method: Random numbers were generated using SPSS, and the study subjects were randomly divided into a treatment group (n=140) and a control group (n=140) by the random number method. The specific procedure is as follows:

① Numbering: Assign sequential numbers from 01 to 280 based on the order of study subject enrollment; ② Random number generation: Use a random number generator software to assign a unique random number to each subject sequentially, totaling 280 random numbers; ③ Grouping: Assign subjects with random numbers ending in odd digits to the treatment group, while those with even or zero digits are assigned to the control group to ensure balanced sample sizes; ④ Envelope packaging: Prepare random assignment cards containing serial numbers, group assignments, random numbers, and treatment

protocols, and seal them in lightproof envelopes. The envelope numbers must match the card serial numbers. Eligible subjects are assigned treatment according to the envelope's specified grouping method upon enrollment.

3. test of cure

Treatment group: Ropivastine therapy was administered. Ropivastine for Injection N01 (Specification: 250 μg/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 × 109/L, the starting dose was adjusted according to the package insert to 4 μg/kg), with administration on day 1. Placebo saline was administered as a placebo 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 ≥100× 10^9/L.

For patients with PLT ≤10×10^9/L or those with significant bleeding tendency, both groups received platelet transfusion via blood collection machines, with alternative platelet-raising agents substituted when necessary and enhanced hemostatic therapy implemented.

(Note: Both groups of patients were informed about the frequency and administration method of medication.)

Table 2 Administration Schedule for Both Groups

Day / divide		1	2	3	4	5	6	7	8	9	10	11	12	13	14
test team	N01	√							√						
	NS		√	√	√	√	√	√		√	√	√	√	√	√
control group	TPO	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Effectiveness evaluation indicators:

General record items

Trial medication code, first letter of the participant's name in pinyin, hospitalization number, and trial start date

Observation indicators

(1) Biological indicators

Demographic characteristics: Gender, Age

Life signs: body temperature, heart rate, respiration, blood pressure

(2) Diagnostic indicators: body temperature, heart rate, respiratory rate, blood gas analysis, complete blood count

(3) Therapeutic efficacy indicators

1) Primary efficacy endpoint: Effective rate of platelet-raising therapy after day 7

2) Secondary efficacy endpoints: Platelet count on days 3, 7, 9, and 14; Time to first recovery of platelet count $\geq 100\times10^9$/L;

3) Other efficacy indicators: APACHE II score at 14 days of treatment; 28-day mortality rate after treatment; ICU length of stay, hospitalization costs, incidence of post-treatment bleeding events, and incidence of adverse events.

Evaluation criteria for efficacy and related definitions

The hematological response to treatment was primarily assessed through peripheral blood platelet response. The efficacy criteria were defined as follows: ① Markedly effective: PLT> 75×10^9/L; ② Moderately effective: initial PLT <25×10^9/L, with post-treatment levels at least twice the baseline platelet count, and the patient achieving cessation of transfusion dependence; ③ Improvement: PLT elevation from baseline PLT <10×10^9/L to post-treatment PLT> 20×10^9/L, or from baseline PLT <20×10^9/L to post-treatment PLT $\geq 30\times10^9$/L; ④ Ineffective: no change in PLT levels or even a decline, or presence of bleeding symptoms; ⑤ Relapse was defined as a return to decreased peripheral blood PLT levels after normalization, with values <25×10^9/L or significant bleeding symptoms; ⑥ Transfusion

dependence was defined as weekly platelet transfusions ≥ 1 therapeutic unit; ⑦ Time to achieve cessation of platelet transfusion was defined as the period from treatment initiation to PLT ≥ 30×10^9/L; ⑧ Non-transfusion dependence was defined as no platelet transfusions for ≥ 4 consecutive weeks. The overall efficacy rate was calculated as (markedly effective + moderately effective) cases/total cases × 100%.

(4) Safety observation

Liver function (ALT, AST, γ-GT, ALP, TBIL), renal function (Scr, BUN). Blood cell morphology, coagulation function, thrombotic complications, spleen morphology.

(5) Trial evaluation indicators

Concomitant medications (e.g., antibiotics, vasoactive drugs, etc.).

Detachment and exclusion; Compliance.

Observation time point

(1) General physical examination items, diagnostic indicators, and therapeutic efficacy indicators are assessed prior to treatment;

(2) Therapeutic efficacy indicators: Platelet count was assessed before treatment (Day 1) and after treatment (Days 3, 7, 9, and 14).

(3) Liver function (ALT, AST, γ-GT, AKP, TBIL), renal function (Scr, BUN), blood cell morphology, coagulation function, thrombotic complications, and spleen morphology. Examinations on the first day of initial diagnosis and after drug administration completion (days 7 and 14).

4. Criteria for early withdrawal/termination of the trial by subjects

Termination of trial cases

1. Cases of severe adverse events where the physician determines that the clinical trial should be discontinued for that patient.

2. Cases where the condition worsens during the course of the disease, or where other clinical manifestations affecting trial observation occur during the trial, and the physician determines that the clinical trial should be discontinued. Such cases shall be treated as invalid.

3. Significant deviations occurred during the implementation of the clinical trial protocol, such as poor compliance, making it difficult to evaluate drug efficacy.

4. Subjects who are unwilling to continue participating in the clinical trial during the trial process and submit a request to the attending physician for withdrawal from the clinical trial.

Case dropout and management

1. Criteria for dropout: Subjects who underwent informed consent and were eligible for randomization but failed to complete the prescribed treatment course and observation period specified in this protocol due to certain reasons were classified as dropout cases.

2. Management of fallen cases

(1) After the subject discharges, contact them through home visits, scheduled appointments, telephone calls, or letters to inquire about the reasons for discontinuation, record the last medication administration time, and complete all available assessment items.

(2) For cases withdrawing from the trial due to allergic reactions, other adverse reactions, or ineffective treatment, investigators should implement appropriate therapeutic measures based on the actual condition of the subjects.

(3) All cases of data dropout should have relevant trial data properly preserved for both archival purposes and statistical analysis of the full dataset. No additional supplementation is required for patients who were excluded.

Case exclusion

1. The case selection did not meet the inclusion criteria but met the exclusion criteria.

2. No prior use of trial medications.

3. No data was available after randomization.

Prior to statistical analysis of data, statistical personnel and principal investigators discussed and determined whether cases should be excluded.

六、 experimental sequence

1. Subject Management

1) Subject recruitment method: When department physicians or investigators participating in the study deem patients eligible for the study, they invite the patients to join the research.

2) Informed consent process

After screening qualified volunteers, investigators must provide detailed information about the clinical trial, including its objectives, procedures, potential benefits and risks, as well as the rights and obligations of participants. This ensures that subjects fully understand the trial and have sufficient time to consider their options. Consent can only be obtained after all questions are satisfactorily addressed and the informed consent form is signed. When each patient signs the informed consent form, the physician must provide their contact information to facilitate immediate communication in case of any medical changes.

2. Risk Control and Management Procedures

Benefits and Risks: Subjects may derive benefits from this clinical trial, including access to a clinically proven therapeutic regimen effective for treating the disease.

Potential risks for participants in this clinical trial include the possibility that the control drug may cause diarrhea as a side effect. Medical countermeasures have been established for known adverse effects or side reactions, including the authority of investigators to terminate the clinical trial for individual cases based on their professional judgment.

Follow-up schedule: On day 28 of treatment, contact subjects through home visits, scheduled appointments, telephone calls, or letters to inquire about their health status and complete all feasible assessment items.

3. Visit Requirements

1) Screening period: Due to the acute onset and rapid progression of sepsis, if the diagnosis meets the inclusion criteria, enrollment begins on the same day (starting from day 0).

2) Treatment period: Immediate treatment was administered upon enrollment, with a treatment cycle of 7 days.

3) Post-treatment visits: Safety follow-up visits and survival follow-up were conducted on days 14 and 28 after enrollment.

七、 Start and End of the Trial

Subjects meeting diagnostic criteria. After screening, enrollment was initiated, marking the commencement of the trial. Enrollment was terminated on day

28 or upon occurrence of subject death and study completion.

八、 Clinical criteria for early termination of trials

1. Cases of severe adverse events where the physician determines that the clinical trial should be discontinued for that patient.

2. Cases where the condition worsens during the course of the disease, or where other clinical manifestations affecting trial observation occur during the trial, and the physician determines that the clinical trial should be discontinued. Such cases shall be treated as invalid.

3. Significant deviations occurred during the implementation of the clinical trial protocol, such as poor compliance, making it difficult to evaluate drug efficacy.

4. Subjects who are unwilling to continue participating in the clinical trial during the trial process and submit a request to the attending physician for withdrawal from the clinical trial.

九、 Data Security and Monitoring Plan

Study medical records (CRF form)

1. Given that outpatient medical records in Chinese hospitals are predominantly self-reported by patients, a dedicated "study medical record" was designed to comprehensively preserve first-hand clinical trial data.

2. Research medical records serve as source documents for clinical trial subjects and should be retained in hospitals. These records constitute the medical documentation for outpatient subjects, which together with inpatient medical records form the complete medical records for hospitalized subjects.

data logging

1. Requirements for research medical record documentation: ① Investigators must document research medical records concurrently with the diagnosis and treatment of subjects to ensure timely, complete, accurate, and truthful data recording. ② Any evidence-based corrections to research medical records shall only be made by underlining, with revised data annotated in marginal notes, signed by the investigator, and dated; original records must not be erased or overwritten. ③ Original laboratory test reports for outpatients shall be attached to research medical records, while those for inpatients shall be attached to inpatient medical records. Laboratory test results for both outpatients and inpatients must be recorded on the "Physical and Chemical

Examination Result Report Form" within the research medical records.

2. Review of study medical records: After the observation period for each subject concludes, the investigator shall submit the "study medical records," "informed consent form," and "patient medication record card" to the principal investigator of the institution for review within 3 working days. Study medical records (CRF form)

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Data Security Monitoring Program

A designated personnel is responsible for data monitoring. In case of abnormal data occurrences, a discussion meeting shall be convened to evaluate whether further

research or protocol optimization is warranted, and progress reports shall be submitted to the ethics committee for review.

十、 Compliance with ethical principles and relevant regulations

Ethical considerations

1. Ethical Review: The clinical trial protocol is formulated by the principal investigator and implemented after approval by the ethics committee. If revisions are made to the protocol during the clinical trial implementation, they must be resubmitted to the ethics committee for approval before implementation. If significant new data related to the trial medication is identified, the informed consent form must be amended in writing and resubmitted to the ethics committee for approval, followed by obtaining the participants' consent again.

All clinical trial centers agreed that this research project would undergo review by the ethics committee of the lead institution prior to trial initiation, with documentation filed with the ethics committees of each center. When necessary (e.g., in the event of serious adverse events), the ethics committees of each center shall promptly convene meetings for review and communicate the conclusions to the ethics committees of other centers.

2. Medical care and protection of subjects: Investigators at each trial site are responsible for the medical care of subjects, make clinical trial-related medical decisions, and ensure that subjects receive appropriate treatment in the event of adverse events during the trial period.

Researchers should promptly investigate any serious adverse events occurring during the study, take necessary measures to ensure the safety and rights of participants, and simultaneously notify other investigators involved in the clinical trial of the adverse event.

Participants will receive the investigational drug free of charge during the clinical trial period and undergo free physicochemical testing. In the event of adverse events related to the investigational drug, they will also receive free medical care.

3. Protection of subject privacy: Only researchers participating in scientific clinical trials may access the personal medical records of subjects, and they will sign the "Researcher Statement" or "Confidentiality Agreement" which includes confidentiality clauses. Data processing will employ "data anonymization" methods to omit information that could identify individual subjects.

Does not involve human genetic resources.

十一、 Statistical Analysis Plan

(1) General Principles

All statistical tests were performed as one-sided tests, with $P \leq 0.05$ considered to indicate statistically significant differences.

Quantitative indicators will be described by calculating mean and standard deviation, maximum value, minimum value, and median. Categorical indicators will be described by presenting the number of cases and percentages for each category. Statistical analysis was performed using SPSS professional statistical software.

(2) Statistical analysis methods

For categorical data, the $\chi 2$ test (including CMH-$\chi 2$ test) or Fisher's exact probability method was employed for intergroup comparisons. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). For mean comparisons among multiple samples in grouped designs, one-way ANOVA was used, while intergroup comparisons were conducted using the least significant difference method (LSD-t test).

(3) Shedding analysis

The comparison of total dropout rates and dropout rates due to adverse events across groups will be conducted using the $\chi 2$ test or Fisher's exact probability method.

(4) Analysis of baseline value balance

Pairwise t-tests or $\chi 2$ tests were employed to compare demographic data and other baseline indicators such as vital signs, medical history, and baseline treatment regimens, to assess group balance.

(5) Adherence analysis

Compliance was categorized as good or poor to calculate the adherence status of each group and conduct comparative analysis. Good compliance was defined as 80% ≤ actual medication dosage/required medication dosage ≤ 120%, while poor compliance was defined as actual medication dosage/required medication dosage <80% or> 120%.

(6) Validity Analysis

The primary time point for efficacy evaluation was day 7 of treatment.

The between-group comparison of changes in primary efficacy endpoints before and after treatment was performed using the superiority test. Kaplan-Meier survival curves were plotted to analyze survival data, and the Log-rank test was employed to compare differences in survival rates between groups. Multivariate analysis was conducted using the Cox proportional hazards regression model.

Other observation indicators were tested for normal distribution using the Shapiro-Wilk $\bar{\chi}$ $\bar{\chi}$ test. Measurement data conforming to normal distribution were described using mean ± standard deviation (±s), and comparisons were performed using t-tests. Categorical variables were calculated as percentages, and comparisons were conducted using χ^2 tests or Fisher's exact test. The significance level was set at α=0.025. A P-value <0.05 was considered statistically significant.

(7) Safety Analysis

The incidence rates of adverse events were compared among groups using the χ2 test, and adverse events occurring during this trial were described in tabular form. Changes in laboratory test results from normal to abnormal before and after the trial, as well as the relationship between abnormal changes and the investigational drug, were analyzed.

十二、 Publication format and timing of research findings

Expected outcomes (at the end of the research project): 1) Publish at least one academic paper; 2) Apply for a higher-level clinical study.

Research process

time / project	Screening period	Dry expectation			
	0	D1	D3	D7	D14
Review admission criteria					
Sign the informed consent form					

AD					
anamnesis					
Types of antibiotics and duration of treatment					
Height, weight, and BMI					
vital sign					
SOFA grade					
Apache II					
Platelet count (109/L)					
liver function					
renal function					
coagulation function					
Blood specimen collection					
vasoactive agent					
Hemorrhagic event					
Embolism event					
ICU length of stay					
ICU hospitalization costs					
Adverse Event Record					
ICU hospital mortality					
28-day survival rate					