Efficacy and Safety of Romiplostim vs. rhTPO in Promoting Platelet Engraftment after Allo-HSCT in Patients with MDS and AA

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Responsible Department: Department of Hematology

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Protocol Version: V1.0 **Version Date:** 2025-12-24

Ethics and Compliance Statement

This study protocol will be submitted to the Ethics Committee of The First Affiliated Hospital of Soochow University for review and approval, and will be registered with the Chinese Clinical Trial Registry. The study will be conducted in strict compliance with the Good Clinical Practice (GCP) guidelines, the World Medical Association Declaration of Helsinki (2013), and relevant Chinese laws and regulations, ensuring the protection of subjects' rights and safety.

Investigator Statement and Signature Page

As the principal investigator of this study, I will adhere to the ethical principles of the National Health Commission's "Measures for Ethical Review of Biomedical Research Involving Humans" (2016), the World Medical Association Declaration of Helsinki (2013), and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans (2016). Under the guidance of Good Clinical Practice (GCP), I will strictly follow the protocol approved by the Ethics Committee to conduct the study, ensuring scientific integrity and protecting the health and rights of subjects.

Protocol Synopsis

Study Objectives	**Primary Objectives:** To preliminarily evaluate the efficacy of romiplostim in promoting platelet engraftment after allo-HSCT (parameter estimation) and to assess its safety (incidence of ≥ Grade 3 AEs within 100 days). **Secondary Objectives:** To compare platelet engraftment time, 60-day engraftment rate, platelet transfusion requirements, and survival differences (OS, PFS, NRM) between the two groups.
Sample Size	Total of 66 evaluable subjects, randomized 1:1 (33 in romiplostim group, 33 in rhTPO group). Considering dropout rate, approximately 74 subjects planned for enrollment.
Study Population	Patients aged 18-65 years, diagnosed with MDS or severe/very severe AA (SAA/VSAA) and eligible for allo-HSCT.
Study Design	Prospective, single-center, randomized, open-label, parallel-controlled Phase II clinical trial.
Inclusion Criteria	Key criteria: Age 18-65 years; diagnosed with MDS or SAA/VSAA; planned for allo-HSCT; platelet count $<20\times10^9$/L with transfusion dependence between day +4 and +10 post-transplant; ECOG performance status 0-2; signed informed consent.
Exclusion Criteria	Key criteria: Uncontrolled active infection; specific history of thrombosis; active TA-TMA; bone marrow fibrosis ≥ MF-2 grade; allergy to study drugs; pregnancy/lactation, etc.
Intervention	**Experimental Group:** Romiplostim, starting dose 5.0 μg/kg, subcutaneous injection, once weekly, with dose adjustment based on platelet counts. **Control Group:** rhTPO, 15000 U, subcutaneous injection, once daily. **Treatment Duration:** Starting from day +4 post-transplant, until platelet count $\geq50\times10^9$/L sustained for 7 days, or until day +60, maximum 8 weeks.
Primary Endpoints	1. Platelet engraftment time (first achievement of $\geq20\times10^9$/L without platelet transfusion for 7 consecutive days) 2. Incidence of ≥ Grade 3 adverse events (AEs) within 100 days post-transplant
Secondary Endpoints	60-day platelet engraftment rate ($\geq50\times10^9$/L), total platelet transfusion units (days 0-60), overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM).

Study Timeline	Screening period (pre-transplant), treatment period (day +4 to day +60), primary follow-up period (to day +100), long-term follow-up period (to 2 years post-transplant).
Statistical Methods	Primary endpoints: Engraftment time analyzed using Kaplan-Meier method and Log-rank test; incidence of ≥ Grade 3 AEs analyzed using Fisher's exact test. Secondary endpoints: Categorical variables analyzed using Fisher's exact test or χ^2 test; continuous variables using Wilcoxon rank-sum test; survival analysis using Kaplan-Meier method. Full Analysis Set (FAS) as primary analysis set.
Publication Plan	Results will be published in peer-reviewed international scientific journals and presented at relevant academic conferences.

1. Study Background

Myelodysplastic syndrome (MDS) and aplastic anemia (AA) are two important categories of hematopoietic failure disorders. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective and potentially curative treatment for intermediate/high-risk MDS and severe AA patients who have failed or relapsed after immunosuppressive therapy (IST). Approximately 5% to 37% of patients may experience delayed platelet engraftment (DPE) or secondary thrombocytopenia, leading to increased non-relapse mortality and significantly reduced overall survival. This not only significantly increases bleeding risk, transplant-related mortality (TRM), and healthcare costs, but also severely impacts patients' quality of life and overall survival (OS).

Studies have shown that 69% of patients receiving myeloablative conditioning achieve platelet recovery within 60 days. Platelet and immune function recovery are closely related to treatment-related mortality and overall survival (OS). However, there is currently a lack of reliable and effective methods to improve platelet recovery and prevent DPE. Intravenous immunoglobulin, corticosteroids, repeated platelet transfusions, and rituximab remain important treatment approaches, mostly based on small-scale studies or case reports, lacking high-level evidence support. These methods are associated with higher costs and infection risks and may affect patients' quality of life.

Thrombopoietin (TPO) is the most critical cytokine regulating megakaryocyte differentiation and platelet production. In China, it has been widely used clinically, particularly in AA and chemotherapy-induced thrombocytopenia (CIT). Some studies have shown that it can promote platelet recovery and reduce transfusion requirements after allogeneic transplantation (such as haploidentical or cord blood transplantation). However, its efficacy remains controversial, especially in the autologous transplantation setting, where some studies have shown that it did not significantly accelerate platelet engraftment and instead increased medical costs. Its daily or every-other-day injection regimen also poses inconvenience for post-transplant outpatient management.

Unique Advantages of Romiplostim:

1. **Mechanism of Action:** Romiplostim is a peptide body molecule with no sequence homology to endogenous TPO. It binds to different epitopes of the TPO receptor transmembrane region, activating downstream signaling pathways, theoretically allowing synergistic or additive effects with rhTPO.
2. **Pharmacokinetic Advantage:** Long-acting formulation requiring only once-weekly subcutaneous injection, greatly improving dosing convenience and patient compliance, particularly suitable for long-term management of post-transplant discharged patients.
3. **Preliminary Evidence:** Proven effective in immune thrombocytopenia (ITP) and chemotherapy-induced thrombocytopenia (CIT). Preliminary studies by Scordo et al. (2023) showed that while romiplostim did not shorten platelet engraftment time after autologous transplantation, it significantly increased post-engraftment platelet counts, demonstrating good biological activity and safety.

This study selects MDS patients requiring allo-HSCT (covering different risk groups) and AA patients who have failed first-line non-transplant therapy as the study population, based on the following considerations:

1. **Clear Clinical Need:** This population has a high incidence of post-transplant DPE, and there is currently a lack of unified, effective preventive or treatment measures, representing a clear unmet clinical need.
2. **Disease Biology and Risk Balance:** Both MDS and AA share pathophysiological backgrounds of hematopoietic stem cell defects and bone marrow failure, posing significant challenges for post-transplant hematopoietic reconstitution. This study will control potential impacts of different disease subtypes on outcomes through strict inclusion/exclusion criteria (such as excluding patients with severe pre-transplant bone marrow fibrosis) and stratified randomization. Simultaneously, the potential risk of TPO-RA stimulating clonal evolution will be carefully assessed as an important safety monitoring point across the entire MDS population, not limited to low-risk groups, which will provide more comprehensive safety evidence for this class of drugs.
3. **Treatment Convenience Need:** Post-transplant management is complex, and the long-acting dosing regimen of romiplostim has significant potential in improving patient compliance and simplifying outpatient management.

Although TPO-RAs show promising application prospects, there is currently a lack of prospective, controlled study data on romiplostim in allogeneic hematopoietic stem cell transplantation, particularly in MDS and AA patients. Its safety, especially potential impacts on graft-versus-host disease (GVHD) occurrence and development (due to its possible modulation of immune cell function), and whether it increases thrombotic event risks are key questions that this study needs to address.

Therefore, this study aims to evaluate the efficacy and safety of romiplostim compared with rhTPO in promoting platelet engraftment after allo-HSCT in MDS and AA patients through a prospective, single-center, randomized controlled clinical trial,

with the goal of providing a new, potentially superior treatment option for clinical practice.

2. Study Objectives

Primary Objectives

1. **Preliminary Efficacy Estimation:** To preliminarily evaluate the efficacy of romiplostim in promoting platelet engraftment, providing parameter estimation for subsequent studies.
2. **Safety:** To assess the incidence of ≥ Grade 3 adverse events (AEs) within 100 days, including: GVHD (graded according to NIH criteria), thrombotic events (TA-TMA, deep vein thrombosis, etc.).

Secondary Objectives

1. To compare differences between the two groups in platelet engraftment time (first achievement of $\geq 20\times10^9$/L without platelet transfusion for 7 consecutive days), 60-day platelet engraftment rate ($\geq 50\times10^9$/L), and platelet transfusion requirements (total units from day 0 to day 60).
2. To evaluate differences between the two groups in overall survival (OS), progression-free survival (PFS), and non-relapse mortality (NRM).

Exploratory Objectives

- Immune reconstitution (lymphocyte subsets, such as CD4+/CD8+ T cells, NK cells, B cell counts)
- Megakaryocyte-related biomarkers (total megakaryocyte count CD41+/CD61+, maturity CD41+/CD61+/CD36+, TPO levels at post-transplant day +14, +28, or when platelet recovery is delayed)
- Pharmacoeconomic evaluation (comparison of total hospitalization costs, drug costs, and cost-effectiveness between the two groups)

3. Study Rationale

3.1 Research Foundation

Mechanistic Studies: Romiplostim is a peptide body TPO receptor agonist with no sequence homology to endogenous TPO. It promotes megakaryocyte differentiation and platelet production by activating TPO receptor downstream signaling pathways, with its mechanism validated in preclinical models.

Preclinical and Clinical Literature: Multiple studies have shown that rhTPO can promote platelet engraftment after allo-HSCT (e.g., Han et al., 2015; Wang et al., 2017). Romiplostim has been proven effective in immune thrombocytopenia (ITP)

and chemotherapy-induced thrombocytopenia (CIT) (Scordo et al., 2023), but its application in allo-HSCT still lacks prospective controlled studies.

3.2 Subject Selection

Disease Background: MDS and AA patients have a high incidence of delayed platelet engraftment (DPE) after transplantation (5%-37%), and there is currently a lack of unified effective interventions, representing a clear clinical need.

Pathophysiological Commonality: Both involve hematopoietic stem cell defects and bone marrow failure, with similar challenges for post-transplant hematopoietic reconstitution.

Risk Control: Exclusion of patients with bone marrow fibrosis ≥ MF-2 grade before transplantation to reduce disease heterogeneity impact. Stratified randomization by disease type (MDS vs. AA) to control prognostic factors. Inclusion of MDS patients across different risk groups to comprehensively assess potential clonal evolution risks of TPO-RAs.

3.3 Dose and Administration

Romiplostim Dose: Starting dose of 5.0 μg/kg (once weekly) is based on its common dosing in ITP and CIT and exploratory studies by Scordo et al. (2023) in post-transplant patients.

Dose adjustment is based on dynamic platelet counts, aiming to maintain platelets within a safe range (≥20×10^9/L) while avoiding excessive elevation that could trigger thrombotic risks.

rhTPO Dose: 15000 U per dose once daily is the standard clinical practice in China, consistent with the drug label and previous transplantation study protocols.

Administration Timing: Starting from day +4 post-transplant, covering the critical period for platelet engraftment, continuing until platelet count ≥50×10^9/L or for a maximum of 8 weeks.

3.4 Endpoint Selection

Primary Endpoints:

- Incidence of ≥ Grade 3 AEs within 100 days: Focuses on safety assessment, particularly transplant-related complications such as GVHD and thrombotic events.
- Platelet engraftment time: Directly reflects the drug's efficacy in promoting platelet recovery.

Secondary Endpoints:

- 60-day platelet engraftment rate, transfusion requirements: Assess short-term efficacy and clinical burden.
- OS, PFS, NRM: Assess impact on long-term prognosis.

Exploratory Endpoints: Include immune reconstitution, biomarkers, pharmacoeconomics, providing preliminary data for mechanism and health economics research.

3.5 Risk-Benefit Assessment

Risks:

- Clonal evolution risk: TPO-RAs may stimulate malignant clone proliferation, particularly requiring close monitoring in MDS patients.
- Thrombotic risk: Excessive platelet elevation may increase thrombotic events.
- GVHD risk: TPO-RAs may affect immune function, requiring monitoring of GVHD occurrence and development.
- Other AEs: Such as allergic reactions, hepatic/renal function effects, etc.

Risk Control Measures:

- Weekly monitoring of platelets, D-dimer, GVHD biomarkers.
- Establishment of discontinuation criteria (e.g., new onset of Grade II or higher aGVHD, thrombotic events, bone marrow fibrosis progression).

Benefits:

- Potential acceleration of platelet engraftment, reduced transfusion dependence, decreased bleeding risks and medical costs.
- Long-acting formulation (once weekly) improves patient compliance, suitable for post-transplant outpatient management.
- If effective, could provide a new treatment option for this patient population, filling a clinical gap.

4. Study Design

4.1 Sample Size Calculation

This is an exploratory Phase II clinical trial aimed at obtaining preliminary efficacy and safety data. A total of 66 subjects are planned to be enrolled, randomly allocated 1:1 to the experimental group (n=33) and rhTPO control group (n=33).

Calculation Basis: Based on consideration of estimation precision for efficacy indicators rather than traditional superiority/non-inferiority hypothesis testing. Referring to recent literature, rhTPO achieves platelet engraftment rates of approximately 90% in post-transplant patients. This study conservatively estimates the romiplostim group engraftment rate at 85%.

Under this assumption, calculations show that including 33 evaluable patients per group would control the 95% confidence interval width for the romiplostim group platelet engraftment rate at approximately ±12% (i.e., 95% CI: 73% - 97%). This precision level can provide a valuable preliminary estimate of romiplostim's efficacy.

Note: Considering an approximately 10% dropout rate, approximately 74 subjects are planned for enrollment to ensure 66 subjects ultimately complete primary endpoint assessment.

4.2 Study Population Selection

Inclusion Criteria

1. Aged 18-65 years (inclusive).
2. Diagnosed with myelodysplastic syndrome (MDS) according to WHO criteria, or severe/very severe aplastic anemia (SAA/VSAA) according to Camitta criteria, and assessed as eligible for allogeneic hematopoietic stem cell transplantation (allo-HSCT).
3. Planned to receive allo-HSCT from matched sibling, haploidentical, or unrelated donors (including cord blood).
4. Eastern Cooperative Oncology Group (ECOG) performance status score 0-2.
5. During days +4 to +10 post-transplant, persistent platelet count $<20\times10^9$/L with platelet transfusion dependence (defined as platelet count not doubling within 24-48 hours post-transfusion or still requiring prophylactic transfusion).
6. Cardiac, hepatic, and renal functions meeting transplantation standards (specific indicators assessed by investigators).
7. Voluntary participation in this study with signed written informed consent after full understanding.

Exclusion Criteria

1. Presence of active, uncontrolled bacterial, fungal, or viral infection.
2. History of arterial thrombosis, or venous thromboembolism within the past 6 months (unless cured or stable for over 6 months).
3. Active transplant-associated thrombotic microangiopathy (TA-TMA).
4. Pre-transplant bone marrow biopsy confirming bone marrow fibrosis grade ≥ MF-2 (according to WHO criteria).
5. Known allergy to romiplostim, recombinant human thrombopoietin (rhTPO), or any of their excipient components.
6. Pregnant or lactating women, or women/men of childbearing potential planning pregnancy during the study period or within 3 months after last dose, unwilling to use effective contraception.
7. Any other condition considered by the investigator as unsuitable for study participation.

Withdrawal Criteria

Subjects meeting any of the following criteria should discontinue study treatment:

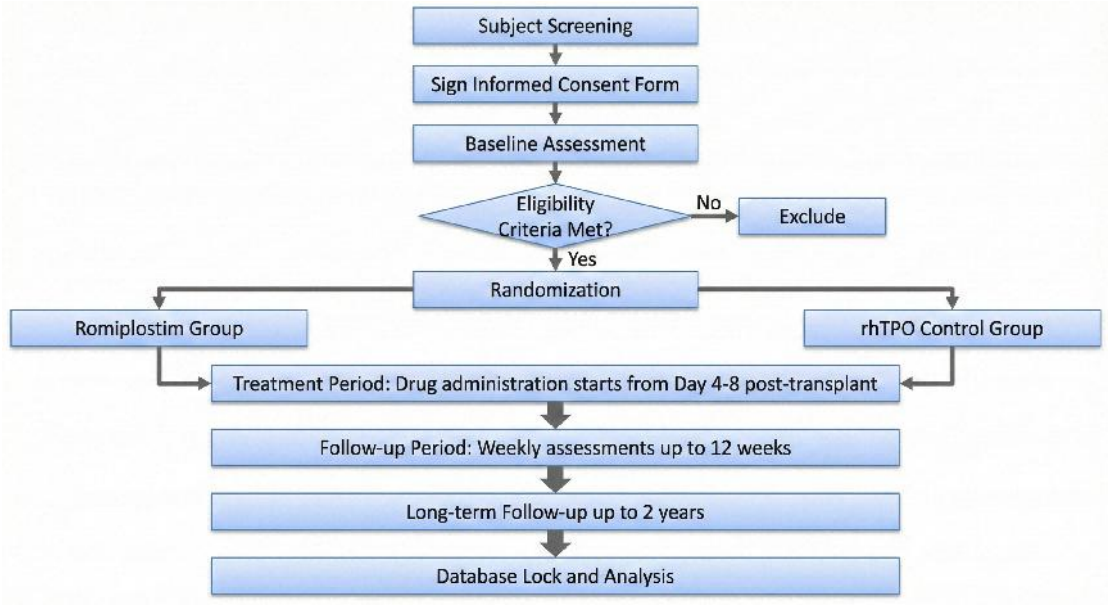
1. Occurrence of ≥ Grade 3 non-hematological toxicity (according to CTCAE v5.0 criteria), and investigator judges as possibly related to study drug.
2. Occurrence of ≥ Grade 4 hematological toxicity.
3. Occurrence of intolerable ≥ Grade 2 non-hematological toxicity, judged by investigator to require study withdrawal.
4. Occurrence of serious adverse event (SAE), judged by investigator or sponsor as possibly related to study drug.
5. Pregnancy.
6. Investigator considers that continued study participation may pose unacceptable risk to subject.

Termination Criteria

Subjects may terminate the study for the following reasons, considered as sample dropout:

1. Subject or legal representative actively withdraws informed consent.
2. Subject requests withdrawal from treatment or refuses continued follow-up for any reason (e.g., perceived insufficient efficacy, personal reasons).
3. Study cannot continue due to force majeure (e.g., severe natural disasters) or unexpected events.
4. Lost to follow-up (defined as consecutive failure to contact subject through any reserved means).

4.3 Study Flow Diagram



4.4 Subject Grouping and Interventions

Grouping Method

Web-based central randomization system, using stratified block randomization (1:1). Stratification factor: disease type (MDS vs. AA).

Interventions

- **Experimental Group:** Romiplostim. Starting dose 5.0 μg/kg, subcutaneous injection, administered on days +4 and +11 post-transplant. From day +18, dose adjustment based on weekly platelet counts.
- **Control Group:** rhTPO. Fixed dose 15000 U, once daily subcutaneous injection.

Off-Label Use Statement

The Informed Consent Form must clearly and prominently state that romiplostim is used as "off-label" in this study, with detailed explanation of its rationale, potential benefits, and risks.

Concomitant Medications

All patients receive unified standard transplant treatment. Prohibition of other platelet-promoting drugs (e.g., eltrombopag, lusutrombopag). Drugs affecting platelet function or counts should be used cautiously and recorded in detail.

Rescue Therapy

In case of serious adverse events, immediately suspend study drug administration and provide corresponding symptomatic supportive treatment (e.g., platelet transfusion, anticoagulation, escalated immunosuppression).

5. Study Procedures

5.1 Subject Management

Includes recruitment, informed consent, screening, randomization, compliance management.

5.2 Safety Evaluation and Risk Control Procedures

Establish comprehensive monitoring system including AE/SAE handling, predefined discontinuation criteria.

5.3 Efficacy Measurement Procedures

Detailed description of measurement methods and timing for primary and secondary efficacy indicators.

5.4 Discontinuation/Withdrawal Procedures

Standardized handling procedures for subject discontinuation or withdrawal from study.

5.5 Blinding and Bias Control

Reiterates open-label design, key endpoints assessed by independent review committee under blinded conditions.

5.6 Visit Schedule

- **Screening Period (Pre-transplant)**
- **Treatment Period (Day +4 to Day +60)**
- **Primary Follow-up Period (Day +100)**
- **Long-term Follow-up Period (Up to 2 Years Post-transplant)**

6. Safety Monitoring and Adverse Event Management

Original content is complete and can be retained. It is recommended to add a **"Independent Data Safety Monitoring Committee (DSMB)"** section, describing its composition by hematology, transplantation, and statistics experts not involved in the study, responsible for regularly reviewing cumulative safety data and providing recommendations to the principal investigator and ethics committee regarding trial continuation.

6.1 Safety Monitoring System

Routine Monitoring

Monitoring frequency: During treatment period (post-transplant to day +60), once weekly; from day +60 to day +100, according to visit schedule.

Targeted Monitoring

For known or potential risks, such as thrombotic events, GVHD, clonal evolution/bone marrow fibrosis risk, immunomodulatory risk, etc.

6.2 Adverse Event (AE) and Serious Adverse Event (SAE) Management Plan

Includes definitions and grading, management procedures, reporting requirements, etc.

6.3 Predefined Discontinuation and Intervention Criteria

To control specific risks, study drug must be suspended or permanently discontinued when the following situations occur:

- Graft-versus-host disease (GVHD): New onset of Grade II or higher acute GVHD

- Thrombotic events: D-dimer persistently > 5 times upper limit of normal or imaging-confirmed diagnosis
- Bone marrow fibrosis progression: Bone marrow biopsy confirmation of progression to MF-1 grade or higher compared to baseline
- Other severe toxicities

7. Data Management and Statistical Analysis

7.1 Data Management

Validated electronic data capture (EDC) system will be used for data collection. Implementation of "independent double data entry" and logical checks, with data query forms (DQF) to resolve data inconsistencies. All study documents will be kept strictly confidential, preserved for at least 5 years after study completion as required by regulations.

7.2 Statistical Analysis Plan

Analysis Sets

- **Full Analysis Set (FAS):** All subjects randomized who received at least one dose of study drug and have at least one efficacy evaluation, analyzed using intention-to-treat (ITT) principle.
- **Per Protocol Set (PPS):** Subjects who strictly followed protocol and completed main phase treatment, used for supportive analysis.
- **Safety Set (SS):** All subjects who received at least one dose of study drug.

Missing Data Handling

For primary endpoint (platelet engraftment time), if subject withdraws before reaching endpoint, data will be treated as censored. For other continuous variables, appropriate imputation methods or sensitivity analyses will be selected based on missing data mechanism.

Statistical Methods

- **Primary Endpoints:** Platelet engraftment time estimated using Kaplan-Meier method, between-group comparison using Log-rank test. Incidence of ≥ Grade 3 AEs within 100 days compared using Fisher's exact test.
- **Secondary Endpoints:** Categorical variables analyzed using Fisher's exact test or χ^2 test; continuous variables (e.g., transfusion volume) using Wilcoxon rank-sum test; survival data (OS, PFS) using Kaplan-Meier method and Log-rank test.
- **Statistical Software and Significance Level:** Using SPSS (v26.0 or higher) or R (v4.0 or higher) software. All tests are two-sided, with P value <0.05 considered statistically significant.

8. Quality Control and Quality Assurance

The sponsor/principal investigator will designate monitors to regularly monitor the study site, checking protocol compliance, informed consent process, data recording accuracy and completeness. Audits may be conducted when necessary. All research personnel must receive protocol and GCP training.

9. References

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