Study on avatrombopag for the promotion of platelet engraftment after allo-HSCT

(Scheme No. SKX-2009)

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Sponsor: The First Affiliated Hospital of Soochow University

Version 1.0

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CONFIDENTIALITY STATEMENT

a clinical observation for the sponsor. The investigator can disclose the contents of the plan to trial participants, institutional review board, independent ethics committee or pharmacy administration committee for the same purpose on the basis of meeting the following conditions. The content of the protocol cannot be used in other clinical observations, nor can the content be disclosed to any other individual or group without the written permission of the sponsor. Although this condition does not apply to the disclosure required by government regulations, the investigator must promptly notify the sponsor. In addition, any information added to the protocol is also confidential and owned by the sponsor. The confidentiality principle is the same as the content of the plan.

The protocol should keep confidential and be used only for matters authorized by the sponsor, and shall not be disclosed to any other person without prior written permission. If you are in possession of the protocol without prior authorization, please contact the study sponsor in a timely manner and return the protocol and a copy of it to the sponsor.

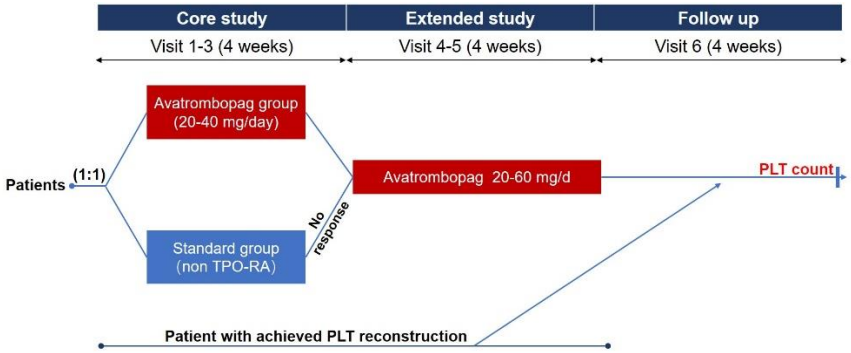
PROTOCOL SYNOPSIS

Title	Study on avatrombopag for the promotion of platelet engraftment after allo-HSCT

Version	1.0
Population	Patients with thrombocytopenia after allogenic hematopoietic stem cell transplantation (Allo-HSCT)
Objective	To evaluate the efficacy and safety of avatrombopag in the treatment of thrombocytopenia after Allo-HSCT, and provide evidence-based instruction of avatrombopag in promoting hematopoietic function reconstruction and reducing PLT transfusion for patients with delayed PLT reconstruction after Allo-HSCT in clinical practice
Design	Single, prospective, randomized controlled trial
Subject Number	78 participants
Eligibility Criteria	**Inclusion criteria** Each participant must meet all of the following criteria: 1. Male or female, aged between 18-60 years; 2. PLT has not been reconstructed 14 days after Allo-HSCT (PLT reconstruction was defined as the status of peripheral PLT count > $20*10^9$/L for consecutive 7 days without the need for PLT transfusion); 3. Expected survival time > 3 months; 4. ECOG performance status 0-2; 5. Agree to receive the treatment of avatrombopag after Allo-HSCT and must sign the informed consent form. **Exclusion criteria** Participant meets any of the following criteria will be excluded from this study: 1. Pregnant or lactating; 2. With severe and uncontrollable infection; 3. With graft-versus-host disease (GVHD) with steroid

	resistance; 4. With thrombotic microangiopathy; 5. With active thromboembolism requiring anticoagulation 6. With detected disease recurrence due to chimerism by flow cytometry; 7. With chronic active hepatitis B and C virus infection; 8. With secondary or multiple transplantation, or multiple organ transplantation; 9. With severe heart disease, lung disease, diabetes and metabolic diseases; 10. HIV positive; 11. With a history of PLT dysfunction or bleeding disorders 12. With the active hepatic venous occlusion disease, or a history of clinically significant hepatic venous occlusion disease (The disease was defined as the abnormal condition of painful hepatomegaly after transplantation with bilirubin ≥ 6.0 mg/dL); 13. With progressive solid tumor; 14. With severe bleeding requiring transfusion of more than 2 units of red blood cells, or sudden drop of blood cell volume ≥10% within 7 days prior to screening; 15. With any other clinical trial of investigational product or device within 30 days prior to the baseline visit, except for observational study; 16. With treatment of thrombopoietin receptor agonist (TPO-RA) one month before enrollment; 17. Deemed unsuitable for enrollment by the investigator. **Withdrawal criteria** 1. PLT remains less than $20*10^9$/L after two weeks' treatment of avatrombopag in a maximum dose of 60

	mg/d (Solution: receive other treatment after withdrawal from the study); 2. The participant or his legal guardian requests a withdrawal ; 3. c poor compliance(medicine taken less than 80% of the prescribed amount or more than 120% of the prescribed amount); 4. With requirement of a medicine that is prohibited in the study; 5. With adverse events that discontinues the study; 6. With some unexplained serious complications; 7. Be pregnant during treatment; 8. Deemed unsuitable for further study by the investigator. **Trial Termination** 1. Sponsor decides to stop the trial for safety reasons; 2. Independent ethics committee decides to stop the trial; 3. Principal investigator decides to stop the trial.
Investigational Product	• Name: avatrombopag; • Dosage form: tablet; • Specification: 20 mg/tablet.
Treatment Design	• The whole study is divided into two stages, including 4-weeks' core study and 4-weeks' extended study; • During the core study, participants are randomly assigned into the avatrombopag group and the rhTPO treatment group(standard group) with 1:1 ratio. The initial dose of avatrombopag is 20 mg/d. If the patient's PLT count remains less than $20*10^9$/L after one week, the maximum dose was increased to 40 mg/d. Avatrombopag will be taken orally with food. The rhTPO

	will be subcutaneously injected with dosage of 300 U/kg/d; • After the end of the core study, participants in the avatrombopag group who does not meet the withdrawal indication can be enrolled in the extended study and continue the avatrombopag treatment with a maximum dose of 60 mg/d. Participants who does not respond to treatment in the rhTPO group (PLT< $20*10^9$/L) can also be enrolled in the extended study to receive avatrombopag treatment, by titrating avatrombopag in the dose of 20-60 mg/d according to the participants' condition; • Patients who achieved PLT reconstruction during the core study and the extended study period are followed up to 4 weeks after investigational product withdrawal, and PLT count is measured for one time during the follow up; • Adjustment Indication: When PLT ≥$50*10^9$/L excluding the factor of blood transfusion, the dosage of avatrombopag and rhTPO will be eventually decreased and stopped according to clinicians. 
Outcome Measure	**Primary outcome measures** • Percentage of participants whose PLT reaches ≥

	$20*10^9$/L without the need for PLT transfusion for consecutive 7 days during core study **Secondary outcome measures** • Percentage of participants whose PLT reaches ≥ $20*10^9$/L without the need for PLT transfusion for consecutive 7 days during extended study; • Percentage of participants without PLT response in the standard group but with PLT reconstruction after receiving avatrombopag; • Percentage of participants with PLT≥ $50*10^9$/L without the need of PLT transfusion for consecutive 7 days during the core and extended study; • The time to achieve PLT ≥ $20*10^9$/L without the need of PLT transfusion for consecutive 7 days in both group; • Proportion of participants achieving platelet reconstitution after 4 weeks of drug withdrawal; • Volume of PLT transfusion; • Hematopoietic reconstruction condition (absolute neutrophils, hemoglobin) PLT reconstruction is defined as the status of PLT ≥ $20*10^9$/L without the need of PLT transfusion for consecutive 7 days.
pSafety Measure	1. Liver and renal functions; 2. Occurrence and severity of transplantation-related complications; 3. Bleeding risk (WHO bleeding assessment scale); 4. Adverse events.
Study	**Screening stage (Day 10~14 after Allo-HSCT)**

process	1. Informed consent; 2. Subject's demographic information and basic information; 3. Medical history, current treatment, concomitant medication; 4. Vital signs, physical examination; 5. Transplantation mode and preprocessing scheme; 6. Blood test: blood routine, blood biochemical (including liver and renal functions), virus infection; 7. Pregnancy tests (women of childbearing age); 8. Eligibility criteria review. **Visit 1(Day 15 after Allo-HSCT, Initial treatment)** 1. Blood test: blood routine, blood biochemical (including liver and renal functions); 2. Vital signs, physical examination; 3. Concomitant medication, including PLT transfusion; 4. Adverse events. **Visit 2-9 (one visit per 1~2 weeks. Visit 2, day 21±2; visit 3, day 28±2; visit 4, day 35±2; visit 5, day 42±2; visit 6, day 49±2; visit 7, day 56±2; visit 8, day 62±2; visit 9, day 70±2 after Allo-HSCT)** 1. Blood test: blood routine, blood biochemical (including liver and renal functions); 2. Vital signs, physical examination; 3. Concomitant medication, including PLT transfusion; 4. Adverse events; (Participants who achieved PLT reconstruction during the core and extended study period directly enter the follow up period; Participants who do not respond to the standard

	treatment can enter the extended study after visit 3 to receive avatrombopag treatment) **Visit 10 (day 28±5 after achieved PLT reconstruction)** 1. Vital signs, physical examination; 2. Blood test: blood routine, blood biochemical (including liver and renal functions). **Long-term follow up is recommended.** **Adverse events are closely observed and concomitant medication is recorded in detail during the study.**
Concomitant Treatment	1. PLT transfusion is allowed according to the bleeding situation: PLT transfusion is given to participant when PLT account < $20*10^9$/L, or between 21-60 $*10^9$/L with active bleeding; 2. G-CSF treatment (subcutaneous injection of G-CSF at 5 μg/kg/d from the first day after transplantation until the neutrophils count (ANC) recovered to ≥ $1*10^9$/L); 3. Cyclosporine A, short courses of mycophenolate mofetil and methotrexate are allowed to use for the prevention of GVHD; 4. For medications that have been used before the trial, try to maintain the same dose during the trial; 5. Other TPO-RA (such as Eltrombopag and Romiplostim) should be prohibited during the study period; 6. Participants are allowed to take concomitant medications that are not specified as prohibited during the study period; Medications used one month prior to screening will be recorded on the case report form. All

	prescription medicines, herbal medicines, nutritional supplements (including vitamins), and over-the-counter medicines should be recorded, as well as any changes in medication taken, including the dose. CYP2C9 or CYP3A4/5 medium or strong inducers may affect the exposure level of avatrombopag in vivo, and medication regimen should be comprehensively assessed by the investigator; 7. Observation of adverse events and concomitant medication assessment are conducted for all participants at each visit from the signing of informed consent to the end of the study; 8. All concomitant medications should be recorded and described in the corresponding section of the case report form (CRF).
Statistical Analysis	• The sponsor will utilize appropriately qualified individuals to supervise the conduct of the trial to make sure the data collection, entry and management are in accordance with good clinical practice (GCP); • Corresponding database will be established and source data will be input independently; • Data administrator uses Epidata software to compile data entry program and carry out following process. Two data administrators will independently enter and proofread the data in double copies to ensure the accuracy. **Sample size estimation** • 78 participants Based on the known literature, 35% of patients in the control group and 60% of patient in the trial group were

	estimated to achieve the primary endpoint. Under the condition of the number ratio of control to trial group 1:1, α=0.05 (bilateral) and 1-β=0.9, the number of participants in the control group and the test group was 79 and 79 respectively, calculated by the pros and cons test method of the clinical controlled study with PASS software. Further taking into account a 20% shedding rate per group, 95 cases per group were actually needed, for a total of 190 cases **Statistical analysis data set** • **Full analysis set (FAS):** All subjects who were enrolled and had at least one dose of investigation product along with efficacy evaluation were included in FAS as per the intention-to-treat (ITT) principles. FAS contributes to the main population for efficacy evaluation in this study. • **Per-protocol set (PPS):** PPS includes all subjects who have fulfilled the protocol-required treatment or have not seriously violated the protocol. The exact definition of serious violation will be finalized during data review, which includes but not limited to the following conditions: fails to meet the main inclusion criteria, experiences the treatment that significantly interferes with efficacy evaluation after enrollment, poor compliance, poor follow-up record that significantly beyond the time window. PPS contributes to the secondary population for efficacy evaluation in this study. However, if the analysis results of PPS are inconsistent with the FAS, detailed analysis of the inconsistent results is required.

	• **Safety set (SS):** SS is defined as the data that collected from subjects receiving at least one dose of investigation product. **Statistical analysis method** • PLT and other mean variation trends were processed by repeated measurement data analysis of variance; Kaplan-Meier survival analysis was used to estimate the recovery of PLT count, cumulative predicted survival rate, cumulative recurrence rate of malignant hematologic disease, cumulative mortality associated with transplantation, and cumulative incidence of GVHD, and log-rank test was performed. Independent sample nonparametric test was used to analyze the accumulative demand of PLT suspension. The statistical process and graph were all run on SPSS 13.0 software. All tests were bilateral, and P≤0.05 was considered to be significant. The PLT recovery time, granulocyte implantation time and PLT infusion number were compared by one-way analysis of variance. OS and DFS are estimated by Kaplan-Meier method. Risk factor analysis: variables: age, sex, HLA match, CD34+ cell number, incidence of GVHD within 100 days after transplantation, CMV infection rate. Multivariate Cox regression analysis was performed on the factors with significant differences (P<0.05) by one-way analysis of variance. **Safety analysis** • Safety and tolerance evaluation consist of adverse events and changes in laboratory values. Adverse

	events were statistically described and listed in terms of occurrence, endurance, severity, relationship to the investigation product and outcome. Abnormalities in laboratory values were summarized in toxicity grade as per CTC AE 5.0. At the same time, the statistical description of the changes of the assessment values was carried out.
Study Duration	1.5 years

Subject No. :

Version: 1.0

Final version: May 28, 2021

Informed consent for biomedical research

Study on avatrombopag for the promotion of platelet engraftment after allo-HSCT.

Dear Madam/Sir,

We are considering inviting you to participate in a "study on avatrombopag for the promotion of platelet engraftment after allo-HSCT". It is important that you understand the details of the study before agreeing to participate. Please read this document carefully and ask questions. This study has been approved by the ethics committee of the medical institution. It is up to you to participate in this study.

1. Research purpose

To observe the efficacy and safety of Avatripolpa in the treatment of thrombocytopenia after allogeneic hematopoietic stem cell transplantation, and to provide evidence-based evidence for promoting hematopoietic reconstruction and reducing platelet transfusion after avatripolpa in patients

with delayed platelet recovery in clinical practice.

2. background

Persistent thrombocytopenia is one of the common complications after allogeneic hematopoietic stem cell transplantation, including primary thrombocytopenia and secondary thrombocytopenia. Persistent thrombocytopenia after allogeneic hematopoietic stem cell transplantation often leads to fatal bleeding, resulting in transplant-related mortality, and seriously affecting the quality of life of patients.

Now after allogeneic hematopoietic stem cell transplantation, no standard for the treatment of persistent thrombocytopenia, commonly used treatment with glucocorticoid, human recombinant platelet hormone, human recombinant interleukin - 11, intravenous immunoglobulin of choose and employ persons, but the above treatment response rate between patients with heterogeneity, and once the treatment is invalid, patients with poor prognosis. In order to prevent bleeding, most patients need platelet infusion, but platelet infusion may also lead to many adverse reactions, such as acute lung injury, heart failure, viral infection, etc., and invalid infusion may also occur in some patients. Therefore, platelet infusion cannot be used as a means of long-term prevention of bleeding. For patients with thrombocytopenia after allogeneic hematopoietic stem cell transplantation, it is urgent to find new therapeutic methods to improve the efficacy.

Avatrombopag is a novel oral thrombopoietin receptor agonist that mimics the biological effects of thrombopoietin in vitro and in vivo.Avatrombopag stimulates megakaryocytes through binding and activation of thrombogenietin receptors, thereby promoting platelet production.

Avatrombopag has been approved in the United States, the European Union and China for the treatment of thrombocytopenia associated with chronic liver disease in adults undergoing elective diagnostic operations or surgery, and in the United States in June 2019 and the European Union in January 2021 for the treatment of immune thrombocytopenia (ITP) with

excellent efficacy.

3. Approximate number of subjects and expected duration of study participation

Eight patients with thrombocytopenia following allogeneic hematopoietic stem cell transplantation are planned to be enrolled in the study.The total duration of the study is estimated to be 3 months, and your participation is expected to be 1 month.

4. The research process

After you sign the informed consent, you will be screened and treated with Avatrombopag if you are eligible for inclusion. The duration of the study was 4 weeks. The initial dose of avatrombopag was 20 mg/d, and if your platelet count was still below 20×109/L after 1 week, the maximum dose was 40 mg/d until the platelet count reached 50×109 /L and the drug was gradually discontinued.

You will be followed up once a week for blood sampling during the study period.The specific follow-up time can follow the clinician's arrangement.

5. Possible risks and discomfort of participating in the study

Reference adverse reactions of Avatrombopaglpa in a global multicenter Phase iii clinical trial in the treatment of immune thrombocytopenia:

During the 6-month core phase, three patients in the Avatrombopag group developed thrombosis, two of whom had multiple risk factors for thrombotic disease, and one of whom was considered by the investigator to be unrelated to treatment.One patient had abnormal liver function test, including fatty liver, hepatitis C, obesity, and gallstones. He had abnormal liver function in the past and was drinking alcohol at the time of abnormal liver function. The researcher believed that this event had nothing to do with treatment drugs. Other common adverse reactions are headache, bruising, upper respiratory tract infection, arthralgia, epistaxis, fatigue, bleeding gums, stasis, thrombocytopenia, pharyngitis, hypertension, and nasopharyngitis.After adjustment for exposure, the incidence of various adverse events in the

avatrombopag group was comparable to that in the placebo group.

6. Possible benefits

For patients undergoing hematopoietic stem cell transplantation, avatrombopag offers a novel therapeutic option with the potential to shorten platelet transplantation in these patients.

7. Expenses and Compensation

You may use avatrombopag free of charge during the study period.In addition, you will receive a free insurance policy to cover the treatment costs and corresponding financial compensation for subjects who experience serious adverse reactions related to the study.

Clinical diagnosis and treatment related examination and treatment and other expenses shall be borne by you.

8. Confidentiality and privacy authorization

The investigator is responsible for handling your study data in accordance with applicable data protection regulations.However, the ethics committee and higher administrative departments can inspect the data.The results may all be published in medical journals/conferences, but your personal information will not be made public.

By signing this informed consent form, you consent to the collection, use and sharing of your health information data by the research physician and the staff of the research center.Your authorization to use your health information remains valid until the study is completed and the results are available.But you can withdraw the informed consent at any time through the study of the doctor in charge.

9. Voluntary participation/complete or partial withdrawal from the study

Participation in this study is entirely of your own free will.You can choose not to participate in this study, or you can withdraw at any time, and your medical treatment and rights will not be affected, nor will you be discriminated against by medical staff.

10. Questions and Information

All study group members will answer all your questions before you sign this consent form.If you still have questions, suggestions or comments after signing this consent form, you can also communicate with the researcher.You can know the information and progress of this study at any time.

Researcher and Contact Number:

11. Informed consent

I have been orally informed about this study by the doctor in charge of the study or relevant researchers, and I have also read the above written information.

I was given ample opportunity to discuss and ask questions about the study.I agree to participate in this study with the understanding that my participation in this study is entirely voluntary. I understand that I can withdraw from the study at any time and that my withdrawal will not affect my future medical treatment. By signing this informed consent, I agree that my personal information data, including my medical information data, will be used in the manner described above. I know I'm gonna get a copy of this informed consent.

Signed by the patient or his/her legal representative: year month day

Researchers state:

I will strictly perform the obligations stipulated in Article 22 of the Law of the People's Republic of China on Professional Doctors; Abide by laws, regulations and technical operation specifications;Set up professional dedication, abide by professional ethics, due diligence for the patient service; Care for, cherish, respect patients, protect patients' privacy;Strive to study business, update knowledge, improve professional and technical level;Disseminate knowledge of health care and educate patients about health.

Investigator signed: year month day