Efficacy and safety of hytrombopag ethanolamine tablets in the treatment of thrombocytopenia in patients scheduled for elective surgery

Drug Name: Hytrombopag Ethanolamine Tablets

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Leading site: Chengdu City Third People's Hospital

Version Number: 3.1

Version Date: 30 December 2023

protocol summary

study title	Efficacy and safety of hytrombopag ethanolamine tablets in the treatment of thrombocytopenia in patients scheduled for elective surgery
protocol version No.	3.1
protocol version date	December 30, 2023
Type of clinical study	Non-registration clinical trials
Clinical Study Registry	Investigator-Initiated Trial (IIT)
Clinical Research Unit	Chengdu City Third People's Hospital
study drug	Hytrombopag Ethanolamine Tablets
subject population	Patients with immune thrombocytopenia scheduled for elective surgery
research purposes	To observe the efficacy and safety of hytrombopag ethanolamine tablets in the treatment of thrombocytopenia in patients scheduled for elective surgery
study design	This is an investigator-initiated, single-arm, prospective clinical study to evaluate the efficacy and safety of hytrombopag in the treatment of thrombocytopenia occurring prior to scheduled surgery.[9]After signing the informed consent form, the patients will enter the screening period (up to 7 days) and receive oral treatment with hytrombopag after screening. The specific dosage regimen is: 7.5 mg, once daily, orally before bed on an empty stomach, lasting for up to 14 days,PLT≥100×10^9/L. During oral

	administration of hytrombopag, when PLT≥200×10^9/L, the administration was suspended, and the hemogram was monitored weekly until PLT<100×10^9/L. During the treatment period, blood routine was monitored once every 7 days,PLT≤30×10^9/L or ≥300×10^9/L. Patients will have an end-of-treatment visit within 7 days of treatment discontinuation, followed by a 30-day safety follow-up period.
study endpoints	**primary study endpoint:** Proportion of patients achieving perioperative platelet count goals (≥80×10 μg/L for major surgery and ≥50×10 μg/L for minor surgery) without rescue therapy **Secondary endpoints:** 1. Median time to platelet count target; 2. Subject platelet count ≥50×10^9/L maximum duration; 3. Subject platelet count ≥80×10^9/L maximum duration; 4. Proportion of patients with surgical delay due to thrombocytopenia; 5. Proportion of patients undergoing surgery on schedule; 6. Incidence and severity of bleeding in patients; 7. Proportion of patients receiving emergency treatment; 8. Safety: Adverse events (AEs): include type, incidence, severity, duration, and relationship to study drug.
enrollment criteria **(All must comply)**	1. Subjects ≥18 years of age, regardless of gender; definite diagnosis of immune thrombocytopenia. 2. Platelet ≤75×10 prior to scheduled elective surgery^9/L, Surgery is defined by the treating surgeon and hematologist as major or minor surgery based on the duration and complexity of the procedure and the patient's risk of bleeding. 3. Voluntary participation in clinical research and signing of informed consent form.
exclusion	1.History of allergy to TPO-RA drugs;

criteria **(Excluded if one of them is met)**	2. Severe bleeding symptoms, such as upper gastrointestinal bleeding, bleeding of important organs, intracranial hemorrhage, etc.; 3. thrombotic diseases such as pulmonary embolism, arterial thrombosis and disseminated intravascular coagulation (DIC); 4. Anti-human immunodeficiency virus antibody or anti-Treponema pallidum specific antibody positive; 5. Congestive heart failure New York Heart Association (NYHA) class 3 or 4; 6. History of angina pectoris, myocardial infarction or cerebral infarction within 6 months prior to screening; 7. Active infections that are difficult to control; 8. Pregnant or lactating women; 9. Other circumstances judged by the investigator to be unsuitable for inclusion in the study
Study Early Termination Criteria	1. Death; 2. Unanticipated and unacceptable adverse drug reactions occur; 3. Withdrawal from the study requested by the subject or his/her legal representative; 4. Medical or ethical reasons affect the continuation of the study; 5. The circumstances in which withdrawal from the study is deemed necessary by the investigator in the best interests of the subject; 6. Subject lost to follow-up; 7. Serious violations of the protocol (including serious violations of study enrollment conditions); 8. Untolerable toxicity occurred during the study and could not be recovered after dose adjustment; 9. Other circumstances necessitating withdrawal from the study in the opinion of the investigator.
Sample Size Estimation and Data	The study was designed as a single-arm exploratory design. Based on previous relevant data reports, the estimated proportion of patients meeting platelet targets was 65%. Using NCSS PASS 15 (LLC. Kaysville, Utah, USA,

Analysis and Statistical Methods	ncss.com/software/pass) software, the two-sided 95% confidence interval (Clopper-Pearson method) for enrollment of approximately 50 subjects was (50.2%, 77.9%), and the confidence interval width was 27.7%.

1 Background

1.1 Significance and Necessity of the Study

Perioperative bleeding is a thorny problem in surgical operation, and it is also an important reason for rapid recovery after operation.[1]Platelet is a blood cell directly involved in clot formation and inflammation regulation, its main function is to participate in the body's coagulation and hemostasis. Thrombocytopenia leads to a greatly increased risk of bleeding and transfusion. Thrombocytopenia is very common in perioperative period,Li [2]A retrospective study conducted by et al showed that patients with cirrhosis and severe thrombocytopenia (PLT≤50×10 μ g/L) had a

higher incidence of major bleeding events after invasive procedures (4.9% VS 1.6%, P = 0.008). Perioperative thrombocytopenia may increase bleeding risk, prolong hospital stay, lead to organ damage, increase medical costs, and in severe cases, lead to death.[3, 4]The most important perioperative issue in patients with thrombocytopenia is the risk of bleeding.

Several retrospective studies examined the incidence and prognostic impact of preoperative thrombocytopenia in different surgical settings, analyzing prospectively collected data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. The largest and most comprehensive of these studies was an analysis of 3884400 adult patients who underwent noncardiac surgery between 2006 and 2016.[5]The incidence of asymptomatic thrombocytopenia was 8.1% in patients undergoing elective surgery. After propensity matching, perioperative transfusions in all patients with thrombocytopenia However, unlike a similar analysis that did not perform propensity matching, there was no increase in the incidence of other complications. Odds ratio and 95% CI for receiving red blood cell transfusions for mild thrombocytopenia (100-149 $\times 10^9$/L) patients were 1.2, 1.1-1.2, for moderate thrombocytopenia (75-99 $\times$ 10^9/L) patients were 1.4, 1.3-1.5, for severe thrombocytopenia (50-74 $\times$ 10^9/L) patients were 1.5, 1.2 -1.7 and severe thrombocytopenia (<50 $\times 10^9$Odds ratios and 95% CIs for mortality ranged from 1.2, 1.1 - 1.3 for mild thrombocytopenia, 1.6, 1.3 - 1.8 for moderate thrombocytopenia, 1.6, 1.2 - 2.1 for severe thrombocytopenia, and 1.9, 1.4 - 2.5 for severe thrombocytopenia.

Thrombocytopenia can be caused by many factors during perioperative period, including patient's disease factors, operation type, cardiopulmonary bypass device, drugs, etc.^{9}/L is associated with an increased risk of bleeding, and current clinical practice recommends using different cut-off values prior to invasive surgery. The minimum platelet count required for different surgical procedures varies. Therefore, it is recommended that platelet counts>50 $\times$ 10 be used prior to major general surgery.^{9}/L, platelet count>100$\times$10 in neurosurgery and posterior eye interventions^9/L. At present, there is no official standardized process for clinical management of perioperative thrombocytopenia. In March 2023, Guangdong Province Pharmaceutical

Association issued the Consensus of Medical Experts on Perioperative Thrombocytopenia Management.[6]The principle of treatment is to remove or control the predisposing factors and primary diseases of thrombocytopenia as soon as possible, and give symptomatic treatment if necessary according to the perioperative platelet count requirements. Patients with thrombocytopenia are recommended to control their platelets above the reference threshold of the operation or operation performed to reduce the risk of bleeding during the operation and ensure the smooth operation.

The optimal drug regimen for increasing platelet count in perioperative pat ients preparing for invasive procedures should take into account the patient's u nderlying disease. The patient's underlying disease is an immune disease such a s ITP, and corticosteroids or immunoglobulin may be given first.[7]Recombinant human thrombopoietin (rh-TPO), TPO receptor agonist (TPO-RA), etc. can be used to treat thrombocytopenia associated with liver disease.[8]At present, there are not many drug-related studies on perioperative platelet count increase, and TPO-RA has more evidence-based evidence, among which avatrombopag is also the only one approved by China National Drug Administration. The National Medical Products Administration (NMPA) approves platelet-raising drugs for pat ients with thrombocytopenia associated with chronic liver disease who are sche duled for diagnostic procedures or surgery. Immunoglobulins can be used when rapid platelet elevation is needed, such as emergency surgery, especially in pati ents before pregnancy or delivery.

1.2 research status at home and abroad

In Lancet Hematology, Donald et al.[9]Two methods, intravenous immunoglobulin and eltrombopag, were compared to achieve perioperative platelet count goals By intention-to-treat analysis, 30 of 38 patients (79%) treated with eltrombopag and 22 of 36 patients (61%) treated with intravenous immunoglobulin met perioperative platelet targets (absolute risk difference 17.8%, 95% CI lower bound 0.4%; noninferiority =0.005).

Hani et al.[10]A single-center, retrospective study of perioperative thrombopoietin receptor agonist romistine in patients with thrombocytopenia was conducted. Patient

characteristics, patient use, procedure, and safety outcomes were collected and analyzed (bleeding, thrombosis, transfusion). 47 patients underwent 51 surgical procedures Causes of thrombocytopenia include immune thrombocytopenia, chronic liver disease, hematologic malignancies, drug-related thrombocytopenia, and hereditary thrombocytopenia. Median (range) platelet count improved. From 47 ×10 μ g/L(9-120×10 μ g/L) to 164×10 μ g/L(28-603×10 μ g/L) at the time of surgery (P<0.0001). Twice-weekly doses of 3μg/kg increased platelet counts to>100× 10 μ g/L within 14 days in 79% of patients. In 96% of cases, surgery was performed as scheduled without delay or cancellation.

Thrombopoietin receptor agonist (TPO-RA) activates tyrosine kinase/signal transducer and activator of transcription (JAK/STAT) by acting on the transmembrane domain of human TPO receptor, induces megakaryocyte survival, proliferation and differentiation, stimulates platelet production, and is not resistant to drug resistance.

As a novel oral thrombopoietin receptor agonist, hytrombopag has been structurally optimized to achieve synergistic and attenuated therapeutic effects, especially in terms of safety, and its effect on bilirubin metabolism is superior to eltrombopag. In a clinical trial to explore the efficacy and safety of hytrombopag in ITP patients, 424 patients were enrolled in a 4:4:1: 1Randomization to treatment with 2.5 mg or 5mg of Hatrombopag and two dose-matched placebo groups. A 10-week double-blind treatment phase followed by a 14-week open-label extension phase. The primary endpoint was platelet response (PLT≥50×10) at 8 weeks of treatment.[9]Results After 8 weeks of treatment, 58.9% and 64.3% of patients in the 2.5 mg and 5mg groups achieved platelet response, respectively, which was much higher than that in the placebo group (5.9%).

Based on the above results, we intend to conduct a study on the efficacy and safety of hytrombopag in the treatment of patients with preoperative thrombocytopenia.

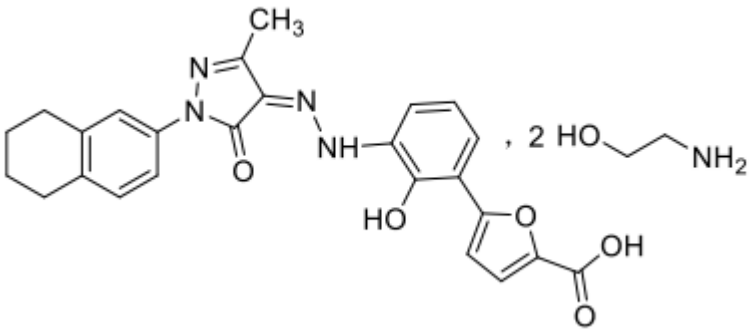
1.2 Investigational Product Description

1.2.1 Drug name, molecular structure and pharmaceutical properties

Generic Name: Hytrombopag Ethanolamine Tablets

Chemical name: (Z)-5-(2-hydroxy-3-(2-(3-methyl-5-oxo-1-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazole-4 (5H)-ylidene) hydrazino) phenyl) furan-2-carboxylic acid ethanolamine salt (1:2)

Chemical formula:



Molecular Formula: $C_{25}H_{22}N_4O_5 \cdot 2C_2H_7NO$

Molecular weight: 580.64

Appearance: This product is a film-coated tablet, light brown to brown after removing the coating

Formulation: Tablet

Strength: 2.5 mg

Route of Administration: Oral

1.2.2 Nonclinical pharmacology studies

In vitro studies showed that hytrombopag ethanolamine significantly promoted the proliferation of thrombopoietin (TPO) receptor positive cell line 32D-MPL with EC50 of 0.4 nM, which was significantly stronger than that of eltrombopag (about 34 times), and also significantly promoted the proliferation and differentiation of human umbilical cord blood CD34 + cells in vitro with EC50 of 2.3 nM and 4.5 nM, which were

significantly stronger than that of eltrombopag.(about 38 and 20 times); In the experiments of promoting cell cycle, resisting apoptosis and activating TPO receptor-dependent STAT and MAPK signal transduction pathways, the activity of hytrombopag ethanolamine was stronger than that of eltrombopag. By using the hollow fiber evaluation model established in nude mice, it was found that hytrombopag ethanolamine was effective (the drug effect lasted for 3 days), and it specifically promoted the proliferation of 32D-MPL cells in vivo and the activation of downstream STAT/MAPK signal transduction pathway. In addition, M1, a metabolite of hytrombopag ethanolamine, promoted the proliferation of 32D-MPL cells and the activation of STAT/MAPK signal in a dose-dependent manner, but its activity was significantly weaker than that of hytrombopag ethanolamine.

1.2.3 pharmacokinetic study

The pharmacokinetics of hytrombopag administered orally to healthy subjects and patients with chronic ITP for 10 consecutive days at doses ranging from 2.5 mg to 7.5 mg were evaluated. The results were similar to those of single-dose trials. The plasma concentration-time curve showed a double-peak phenomenon, i.e., the first peak occurred at 1-2 h after administration, indicating a rapid absorption process, and the second peak occurred at 7-10 h after administration.(Zheng et al., 2017). After oral administration of 2.5~7.5 mg of hitrombopag in patients with chronic ITP on an empty stomach, the plasma concentration increased with the increase of dose. Once daily, the plasma concentration reached its peak at 2-5 h after administration, and the plasma concentration reached steady state on about the 10th day after continuous administration. After absorption, hitrombopag was extensively metabolized, and the main excretion route was feces. The elimination half-life of hatrombopag in plasma was estimated to be 11.9- 40.1 h.

1.2.4 pharmacodynamic studies

After 10 consecutive days of oral administration of 2.5-7.5 mg dose range of

hetrombopag to healthy subjects, platelet count (PLT) showed a continuous increase from the sixth day of continuous administration, and reached the peak at about 12~14 days (2~4 days after discontinuation). The average maximum increase percentage of PLT compared with baseline in 2.5 mg, 5 mg and 7.5 mg groups was 34.1%, 69.9% and 98.2%, respectively. PLT basically returned to baseline in the 2.5 mg group on D28 after drug withdrawal, while platelet growth remained 18.8% and 32.2% in the 5 mg and 7.5 mg groups. Patients with chronic ITP received oral doses ranging from 2.5 mg to 7.5 mg for 14 consecutive days. The results showed that PLT≥50×10 in 12.5%, 58.3% and 66.7% of patients in the 2.5 mg, 5 mg and 7.5 mg groups, respectively, on D28 (14 days after drug withdrawal).^{9}/L.

1.2.5 clinical efficacy studies

1.2.5.1 A Phase III Clinical Study of Hytrombopag in Primary Immune Thrombocytopenia

In a multicenter, randomized phase III clinical study of hetrombopag in primary immune thrombocytopenia, 424 patients (PLT<30×10 at 48 hours prior to enrollment) with at least 6 months of history of primary ITP who had failed or relapsed to at least one line of ITP therapy[9]After 10 weeks of treatment, the patients entered the 14-week open-label phase. The treatment group continued to receive the dose adjusted in the previous phase, while the placebo group received the positive control drug eltrombopag (initial dose 25 mg/d) and maintained PLT(50-150)×10^{9}/L. The results showed that after 8 weeks of treatment, hetrombopag achieved therapeutic response (PLT≥50×10^{9}/L) was significantly higher than placebo (Hytrombopag 2.5 mg vs. Hytrombopag 5 mg vs. placebo: 58.9% vs. 64.3% vs. 5.9%, P <0.0001), and the onset of action was rapid, with a median of 21 days for the 2.5 mg group, respectively (95CI: 15-25),5mg group 14 days (95%CI: 8-14). 24 weeks of treatment with hitrombopag produced a sustained platelet response, with 44.8% of subjects having platelet counts ≥50×10^{9}/L times greater than 75% of total detection times, platelet count ≥50×10^{9}The median (minimum, maximum) maximum duration of/L was 64(6,168) days and the median total duration

was 103(6,168) days.

1.2.5.2 A Phase II Clinical Study of Hytrombopag in Severe Aplastic Anemia with Poor Response to IST

In a multicenter, single-arm, open-label phase II study of severe aplastic anemia with poor response to IST, 55 SAA patients who had a poor response to IST and were not transplant candidates/unwilling received hetrombopag at a starting dose of 7.5 mg.[9]The results showed that 23 patients (41.8%) achieved hematological response at week 18 and 24 patients (43.6%) achieved hematological response at week 24. For those patients who achieved hematologic response during the study, the median remission time was not reached due to the small number of relapses, and the relapse-free survival rates at 9 and 12 months were 82.2%(95% CI: 62.2%, 92.2%).

2 Purpose of the study

To observe the efficacy and safety of hytrombopag ethanolamine tablets in the treatment of thrombocytopenia in patients undergoing elective surgery.

3 Study endpoints

3.1 primary study endpoint

Proportion of patients achieving perioperative platelet count goals ($\geqslant 80\times10$ μ g/ L for major surgery and $\geqslant 50\times10$ μ g/L for minor surgery) without rescue therapy

3.2 secondary study endpoints

1)Median time to platelet count target;

2)Subject platelet count $\geqslant 50\times10^9$/L maximum duration;

3)Subject platelet count ⩾80×10^9/L maximum duration;

4)Proportion of patients with surgical delay due to thrombocytopenia;

5)Proportion of patients undergoing surgery on schedule;

6)Incidence and severity of bleeding in patients;

7)Proportion of patients receiving emergency treatment;

8)Safety: Adverse events (AEs): include type, incidence, severity, duration, and relationship to study drug.

4 Experimental design

This is an investigator-initiated, single-arm, prospective clinical study to evaluate the efficacy and safety of hytrombopag in the treatment of thrombocytopenia occurring prior to scheduled surgery.[9]After signing the informed consent form, the patients will enter the screening period (up to 7 days) and receive oral treatment with hytrombopag after screening. The specific dosage regimen is: 7.5 mg, once daily, orally before bed on an empty stomach, lasting for up to 14 days,PLT⩾100×10^9/L. During oral administration of hytrombopag, when PLT⩾200×10^9/L, the administration was suspended and the hemogram was monitored every 7 days until PLT<100×10.^{9}/L. During the treatment period, blood routine was monitored once every 3 days,PLT≤30×10^9/L or ≥300×10^9/L. Patients will have an end-of-treatment visit within 7 days of treatment discontinuation, followed by a 30-day safety follow-up period.

5 Management of Subjects

5.1 Inclusion criteria (all must be met)

1)Subjects ⩾18 years old, regardless of gender;The diagnosis was immune thrombocytopenia.

2)Platelet ⩽75×10 prior to scheduled elective surgery^9/L, Surgery Major or minor surgery is defined by the treating surgeon and hematologist based on the duration

and complexity of the procedure and the risk of bleeding for the patient;

3)Willing to participate in clinical study and sign informed consent form.

5.2 Exclusion criteria (one of which is excluded)

1) History of allergy to TPO-RA drugs;
2) Severe bleeding symptoms, such as upper gastrointestinal bleeding, bleeding of important organs, intracranial hemorrhage, etc.;
3) thrombotic diseases such as pulmonary embolism, arterial thrombosis and disseminated intravascular coagulation (DIC);
4) Anti-human immunodeficiency virus antibody or anti-Treponema pallidum specific antibody positive;
5) Congestive heart failure New York Heart Association (NYHA) class 3 or 4;
6) History of angina pectoris, myocardial infarction or cerebral infarction within 6 months prior to screening;
7) Active infections that are difficult to control;
8) Pregnant or lactating women;
9) Other circumstances deemed unsuitable for inclusion in the study by the investigator.

6 Dosing Regimen

Subjects must take the drug on an empty stomach every morning (overnight fasting for at least 8 hours), breakfast must not be eaten for 2 hours after dosing, and subjects are required to take all trial drugs of the day once a day, swallow the trial drugs whole, and do not chew, divide or crush them.

7. Concomitant Medications/Concomitant Therapy

The investigator has the right to decide at any time whether to give the following supportive treatment to the subject: transfusion supportive treatment (such as red blood cells and platelets). During this trial, except for the basic treatment and drugs used for

treatment or prevention of adverse events that have been taken stably before the trial, any other drugs are prohibited in principle. Any drugs used during the trial other than the trial drugs should be recorded in detail in the eCRF, and the records should include: drug name, dose, date of administration and indication for use.

8 Test observation methods

During the treatment period, blood routine was monitored once every 7 days,PLT≤50×10^9/L or ≥300×10^9/L. Patients will have an end-of-treatment visit within 7 days of treatment discontinuation, followed by a 30-day safety follow-up period.

9 Adverse events and evaluations

9.1 adverse event definitions

Adverse Event (AE) refers to any adverse medical event occurring in this trial from the time the subject signs the informed consent form until 28 days after the last dose, regardless of whether it is causally related to the trial drug. All adverse events should be followed up by the investigator until the event has been resolved, or recovered to baseline level, or the investigator judges that the event has turned to "stable" without further follow-up, or the subject is lost to follow-up, or the subject dies.

Adverse events include the following:

1)Worsening of pre-existing (before entering clinical trial) medical condition/disease (including symptoms, signs, laboratory abnormalities);

2)Any new adverse event: any new adverse medical condition (including symptoms, signs, newly diagnosed diseases);

3)Abnormal clinically significant laboratory values or results indicating a new disease or organ toxicity worse than baseline.

4)Decreases in platelet values were not recorded as AEs unless they were accompanied by new bleeding symptoms or worsening of existing bleeding symptoms from baseline,

or required urgent treatment.

The investigator should record any adverse event occurred by the subject in detail, including: description of adverse event and all related symptoms, onset time, severity, cause of adverse event, correlation with investigational drug, duration, measures taken, final results and outcome.

9.2 Obtaining adverse event information

Investigators should report all adverse events directly observed or spontaneously reported by subjects in concise language. In addition, subjects should be asked regularly about adverse events after the start of the trial.

9.3 adverse event record

During the trial, the adverse event record form should be truthfully filled in, including the occurrence time, severity, duration, measures taken and outcome of adverse events. Adverse events should be recorded in the adverse event form of the designated case report form.

9.4 Criteria for severity of adverse reactions

When completing the Adverse Event Form in the eCRF, the investigator will describe the severity of the adverse event using mild, moderate, and severe. For uniform criteria, the severity of the event will be graded as follows:

- **Grade 1 (mild)**: usually transient, generally does not interfere with activities of daily living, does not require medication or may require minimal treatment;

- **Grade 2 (moderate)**: Subject feels unwell, activities of daily living are affected, treatment is usually required to alleviate, but there is no risk of major or permanent harm to the subject;

- **Grade 3 (severe)**: The activities of daily living of the subject are interrupted, or the clinical condition is seriously affected, and intensive treatment and intervention are

required;

Severe is used only to describe degree. For example, headache may appear severe in degree but cannot be classified as a serious adverse event (SAE) unless it meets the criteria for an SAE.

9.5 Criteria for determining the relationship between adverse events and investigational drug

Adverse events include all unexpected clinical manifestations. As long as these events occur after signing the informed consent form, regardless of whether they are related to the investigational drug, they should be reported as adverse events. Any discomfort complained by patients or abnormal changes in objective laboratory test indicators during treatment should be recorded truthfully, and the severity, duration, treatment measures and outcome of adverse events should be indicated. Clinicians should also comprehensively judge the relationship between adverse events and the investigational drug. The possible association between adverse events and the investigational drug was evaluated according to the five-level classification method of "definitely related, possibly related, possibly unrelated, definitely unrelated and undeterminable.""definitely related,""possibly related" and "undeterminable" were all listed as adverse drug reactions. The total of these three factors was taken as numerator when calculating the incidence rate of adverse events, and the number of all subjects used for safety evaluation was taken as denominator. The judgment criteria were as follows:

grading	judgment standard
definitely related	The type of adverse event has been identified as a known reaction type to the drug and cannot be explained by other reasons (e.g. concomitant medications and concomitant diseases). The timing of the event strongly suggests a causal relationship (e.g. withdrawal and re-administration of the drug).
possibly related	The occurrence of adverse events was in a reasonable time sequence with the administration of the investigational drug. The occurrence of adverse events may be caused by the investigational drug. It cannot be ruled out whether other factors may be caused, such as concomitant drugs or concomitant diseases. The drug was not

	withdrawn or unclear.
unlikely related	There was no evidence of a causal relationship between the occurrence of the event and the trial drug. The occurrence of the adverse event was more likely related to other factors, such as concomitant medications or concomitant diseases. However, an association between the two could not be ruled out.
not related	Adverse events are not related to the use of the investigational drug.
Unable to assess	There is insufficient information to determine the causal relationship between the event and trial medication. The investigator may change her/his causality assessment based on subsequent follow-up information and modify the AE/SAE report accordingly.

9.6 the definition of serious adverse event

Serious adverse events refer to medical events that require hospitalization or prolongation of hospitalization, disability affecting work ability, life-threatening or death, congenital malformation, etc. during the clinical trial, including the following unexpected medical events:

- Death;
- Life-threatening (defined as the subject being at immediate risk of death at the time of the event);
- Requires hospitalization or prolongation of hospitalization;
- Persistent or significant disability/loss of function;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that harm the patient or require intervention to prevent any of the above).

Hospitalization does not include the following:

- rehabilitation institutions
- sanatorium
- Regular emergency room admissions
- same-day surgery (eg outpatient/same-day/ambulatory surgery)

Hospitalization or prolongation of hospitalization not associated with worsening of an AE is not an SAE per se. Example:

- Admissions due to pre-existing diseases, no new adverse events, and no exacerbation of pre-existing diseases (e.g., to check for laboratory abnormalities that persist from pre-trial to present);
- Manage the cause of hospitalization (e.g. annual routine check-up);
- protocol-specified hospitalizations during the clinical trial (e.g., performed as per protocol requirements);
- Elective hospitalizations unrelated to worsening of adverse events (e.g. elective surgery);
- Scheduled treatments or surgical procedures should be documented throughout the trial protocol and/or in the subject's individual baseline profile;
- Admitted to hospital solely for blood product use.

9.7 reporting of serious adverse events

Any serious adverse event occurring during the clinical study and after drug discontinuation must be immediately reported to the monitor of the sponsor, the principal investigator of the clinical study site and the ethics committee of the clinical study site. Meanwhile, the investigator must fill in the serious adverse event report form (SAE), describe in detail the time of occurrence, severity, relationship with the investigational drug and measures taken, and sign the report.

Follow-up reports should be submitted immediately if the intensity of an ongoing SAE or its relationship to the study drug changes. If the investigator believes that the information previously reported for an SAE is false, a correction, withdrawal, or downgrade can be made in the follow-up report and reported according to SAE reporting procedures.

9.8 contraceptive

All subjects who are considered by the investigator to be sexually active and capable of conceiving or impregnating a partner must agree to use an effective method of contraception throughout the duration of the study (from 2 weeks prior to the first

dose of trial product to at least 30 days after the last dose).

9.9 pregnancy report

If a female subject becomes pregnant during the clinical trial, the subject withdraws from the trial, and if a male subject's partner becomes pregnant, the subject may continue the clinical trial. Pregnancy itself is not considered an SAE, but any negative pregnancy outcome (e.g. stillbirth, spontaneous abortion, fetal malformation) is considered an SAE and needs to be reported according to the time limit of SAE. If the subject also experiences an SAE during pregnancy, the SAE Report Form should be completed and reported according to the SAE Reporting Procedure.

10 Statistical analysis

10.1 statistical analysis plan

Statistical analysis will be performed using SAS statistical analysis software. Detailed statistical analysis details will be provided in the formal statistical analysis plan (SAP).

10.2 statistical hypothesis

10.3 statistical methods

10.3.1 Statistical Analysis Data Sets

1)Safety analysis set (SAS): including subjects who have used the investigational drug at least once;
2)FAS (full analysis set): including all subjects who were randomized into the study group, who used the investigational drug at least once, and who had efficacy indicators after randomization at least once;
3)PPS (per-protocol set): subset of FAS, excluding subjects with serious protocol violations;

10.3.2 Primary Efficacy Analysis

Logistic regression was used for the primary efficacy measure, with treatment as the variable analyzed and baseline platelet count as the covariate. The primary analysis was based on FAS, and the secondary analysis was based on PPS. Baseline platelet count was defined as the most recent measurement before dosing.

10.3.3 Secondary Efficacy Analyses

10.3.4 Safety analysis

Adverse events occurring during the trial will be coded using MedDRA dictionary based on safety analysis set. Frequency and incidence of adverse events will be described according to system organ class (SOC) and preferred term (PT). Correlation and seriousness of adverse events will be further tabulated. Other safety indicators will be summarized by descriptive statistics. Adverse events, adverse reactions, adverse events leading to withdrawal from the trial, adverse events leading to death, Incidence rate of serious adverse events; incidence rate calculated by subsystem and symptoms/signs (count of cases: number of subjects who have experienced at least one adverse event); severity of adverse events and adverse reactions: the same adverse event occurs multiple times in the same subject, and the most serious adverse event is included in the analysis; different adverse events occur in the same subject, and the most serious adverse event is included in the analysis.

Laboratory test parameters: Descriptive summaries of laboratory test values focused on outliers.

Vital signs: Mean, maximum, minimum, median, standard deviation are used to describe the measured values and changes at each visit.

Physical examination, 12-lead ECG, etc. were analyzed descriptively.

10.3.5 Missing Data Handling

For the primary efficacy measure, if a patient has no measurement at a time point

and thereafter, the platelet count at that time point and thereafter is counted as not reaching ≥50×10^9/L.

10.4 sample size

The study was designed as a single-arm exploratory design. Based on previous relevant data reports, the estimated proportion of patients meeting platelet targets was 65%. Using NCSS PASS 15 (LLC. Kaysville, Utah, USA, ncss.com/software/pass) software, the two-sided 95% confidence interval (Clopper-Pearson method) for enrollment of approximately 50 subjects was (50.2%, 77.9%), and the confidence interval width was 27.7%.

11 Research Management

11.1 ethical requirements

·Ethics Committee

Prior to the start of the clinical trial, the clinical trial protocol shall be reviewed and approved by the Ethics Committee and approved by the Ethics Committee before implementation. During the clinical trial, major amendments to the clinical trial protocol, such as new impact on the safety of subjects, or amendments to the informed consent form, shall be approved by the Ethics Committee before implementation.

·Protection of rights and interests of subjects in clinical trials

The clinical investigator must explain to the subject that participation in the clinical trial is voluntary and that he/she has the right to withdraw from the trial at any time during any stage of the trial without discrimination, that his/her medical treatment and rights will not be affected in any way, and that he/she can continue to receive other effective treatment. The subject must be informed that participation in the trial and personal data in the trial are confidential. The subject must also be informed of the nature of the clinical trial, the purpose of the trial, the expected possible benefits and

the possible risks and inconveniences that may occur. Subjects were informed of alternative treatment options and their rights and obligations in accordance with the Declaration of Helsinki, so that they had sufficient time to consider participation in the trial and sign the informed consent form.

11.2 information requirements

- Protocol: read carefully, sign the study director after consent is confirmed, and implement the protocol strictly. Protocol revision can only be carried out after the investigators discuss and reach agreement. Any protocol revision, if it causes new impact on the safety of subjects, or requires revision of informed consent form, needs to be approved by the Ethics Committee.
- Clinical trial data: All kinds of original data of clinical trial shall be recorded timely, truthfully, accurately and completely, and copies of laboratory test sheets shall be kept for 5 years after the end of the trial.

12 References

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