

Pharmacokinetics, Safety, and Pharmacodynamics of Romiplostim in Chinese Subjects With Immune Thrombocytopenia: A Phase I/II Trial

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Abstract

Romiplostim is approved for the treatment of immune thrombocytopenia (ITP). This study aimed to evaluate the pharmacokinetics, safety, and pharmacodynamics of romiplostim in Chinese patients with ITP. This multicenter, open-label, dose-escalation phase I/II trial enrolled ITP patients from 5 centers in China between October 2015 and August 2017. There were 2 cohorts: 1 $\mu\text{g}/\text{kg}$ and 3 $\mu\text{g}/\text{kg}$ weekly for 2 weeks. The end points included pharmacokinetics, platelet changes from baseline, hematological indicators, and adverse events (AEs). Sixteen participants, with 8 patients in each cohort, were enrolled. In the 1 $\mu\text{g}/\text{kg}$ cohort, time to maximum concentration was 4.00 (4.00–7.83) hours, maximum serum drug concentration was 52.0 (16.0–228.0) pg/mL , and area under the serum drug concentration–time curve from time 0 to the last detectable time point was 389 (32.0–5400) $\text{pg} \cdot \text{h}/\text{mL}$. In the 3 $\mu\text{g}/\text{kg}$ cohort, time to maximum serum drug concentration was 11.91 (4.00–12.00) hours, maximum serum drug concentration was 105.0 (25.5–313.0) pg/mL , and half-life was 12.7 (8.2–23.6) hours. The absolute change of peak platelet count from baseline was 14 (3–40) and 72 (3–369) $\times 10^9/\text{L}$ in the 1 and 3 $\mu\text{g}/\text{kg}$ cohorts, respectively. Seven (87.5%) and eight (100%) participants had treatment-emergent AEs in 1 $\mu\text{g}/\text{kg}$ cohort and 3 $\mu\text{g}/\text{kg}$ cohort, respectively. No major AEs occurred in the 2 cohorts. Romiplostim (1 and 3 $\mu\text{g}/\text{kg}$) is safe and well tolerated in Chinese patients with ITP.

Keywords

immune thrombocytopenia, pharmacodynamics, pharmacokinetics, phase I/II, romiplostim, safety

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by immune-mediated destruction of otherwise normal platelets.^{1–5} ITP is de-

finied by a platelet count $<100 \times 10^9/\text{L}$ in the absence of other causes of thrombocytopenia.^{1–6} The incidence of ITP varies among countries, from 3.4

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to 23.6 per 100 000 person-years.^{7–11} Primary ITP (80% of cases) is ITP without an obvious initiating or underlying cause, while secondary ITP (20% of cases) is ITP due to an underlying disease or drug exposure, including autoimmune disease, infection, malignancy, or medications.^{1–5,12} In ITP, thrombocytopenia results from immune-mediated clearance of platelets and decreased platelet production due to cross-reactivity of antiplatelet antibodies with megakaryocytes.¹³ Complications include fatal hemorrhage (about 0.02–0.04 cases per patient-year, with older age being associated with increased risk), severe hemorrhage, and paradoxical thrombosis.^{1–6}

Clinically, the treatment for patients with ITP aims to increase the platelet count and maintain it at a safe level and reduce the risk of bleeding and avoid treatment-related adverse events (AEs).^{4,6,14–16} The mainstream first-line drugs for ITP in clinical practice are glucocorticoids or intravenous immunoglobulin. Still, long-term use of glucocorticoids causes significant side effects, and ITP relapses in about one-third of the patients taking the drugs.^{4,6,14–16} Various kinds of immune preparations, thrombopoietin (TPO) receptor (TPO-R) agonists, and splenectomy are the mainstream second-line therapies.^{4,6,14–16}

Romiplostim activates the TPO receptors in megakaryocyte progenitors and promotes thrombopoiesis through intracellular signal transduction.^{17–21} Romiplostim is a peptide mimetic for natural human TPO produced using a recombination technology and is a second-generation TPO-R agonist that shares no homology of amino acid sequence with endogenous TPO.^{17,21,22} Its structure is available.²³ In mice, the estimated half-life of romiplostim at 1000 $\mu\text{g}/\text{kg}$ is 12.5 hours, the volume of distribution and clearance rate are dose dependent, and the clearance mechanisms are multiple, including neonatal Fc receptors, c-Mpl receptors, catabolic degradation, platelets, and the kidney.²⁴ In humans, romiplostim showed nonlinear pharmacokinetics (PK). Increasing the dose from 0.3 to $\mu\text{g}/\text{kg}$ decreases the mean central volume of distribution from 122 to 48.2 mL/kg and the mean time-averaged clearance from 754 to 6.67 mL/h/kg.²⁵

Romiplostim can increase the platelet count in patients with ITP, irrespective of whether they had undergone splenectomy or used adrenocortical hormones.^{18–20} In 2 phase III trials, the patients with ITP not responding to prior treatment were enrolled before and after splenectomy.^{18,19} The participants were randomized into the romiplostim or placebo group to receive the drug for 24 weeks. The starting dose was 1 $\mu\text{g}/\text{kg}$, administered subcutaneously once weekly; the dose was adjusted according to the platelet counts, and the maximum dose was 15 $\mu\text{g}/\text{kg}$, administered once weekly. Both studies showed that the romiplostim

group showed significant improvements in durable platelet response compared to the placebo group.

Romiplostim has been approved for treating chronic ITP in adults and pediatric patients ≥ 1 year of age.^{26,27} Still, its use in adult patients with ITP in China has never been reported. Therefore, before starting the clinical study that would evaluate the efficacy and safety of romiplostim in patients with ITP in China, this first phase I clinical trial was conducted to evaluate the PK, pharmacodynamics (PD), and preliminary safety in Chinese participants.

Methods

Study Design and Participants

This study was a multicenter, open-label, dose-escalation phase I/II trial. Patients with ITP were enrolled from 5 centers in China (Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; West China Hospital of Sichuan University; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences; Henan Cancer Hospital/The Affiliated Cancer Hospital of Zhengzhou University and Wuxi People's Hospital) between October 2015 and August 2017. The study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonization. The ethics committees of each participating center approved the study protocol. Written informed consent was obtained from all subjects before enrollment. The trial was registered on ClinicalTrials.gov (NCT02868060).

The key inclusion criteria were (1) diagnosed with ITP for at least 6 months before participation; (2) 18 to 70 years of age; (3) no response or relapsed after splenectomy, or patients who had not been splenectomized and had completed at least 1 prior treatment for ITP; and (4) signed the written informed consent. The key exclusion criteria were (1) any known history of bone marrow stem cell disorder or any abnormal bone marrow findings other than those typical of ITP; (2) documented diagnosis of arterial thrombosis (eg, cerebral thrombosis, transient ischemic attack, or myocardial infarction) in the previous year, history of or concomitant venous thrombosis (eg, deep vein thrombosis or pulmonary embolism), or receiving anticoagulation therapy or antiplatelet drug before screening; (3) antiphospholipid antibody syndrome, systemic lupus erythematosus, or documented diagnosis of secondary ITP; (4) receiving glucocorticoid therapy (except oral glucocorticoids administered at a constant dose for more than 4 weeks at the first screening visit) within 4 weeks or any other treatment for ITP including emergency treatment within 2 weeks before signing the ICF; (5) splenectomy for any reason within 12 weeks before

study entry; (6) received eltrombopag, recombinant human TPO, or other Mpl receptor agonists; and (7) received hematopoietic growth factors (eg, granulocyte colony-stimulating factor, macrophage colony-stimulating factor, erythropoietin, or interleukin-11) for any reason within 4 weeks prior to study entry.

Intervention

This study included a screening period (2 weeks) and a dosing and observation period (6 weeks, 2 injections of romiplostim). The injection of romiplostim was performed on days 1 and 8. Dose adjustment was not allowed. Before the second dosing, the romiplostim injection was discontinued if the platelet counts were $\geq 400 \times 10^9/L$ and continued if the platelet counts were $< 400 \times 10^9/L$.

Based on the completed clinical trials,¹⁷⁻²⁰ 2 cohorts were designed: 1 $\mu\text{g/kg/wk}$ for 2 weeks, which is the minimum dose in completed clinical trials, and 3 $\mu\text{g/kg/wk}$ for 2 weeks. The 3 $\mu\text{g/kg/wk}$ was not enrolled if any of the following criteria occurred in the 1 $\mu\text{g/kg/wk}$ cohort: (1) ≥ 6 of 8 participants achieved platelet counts $> 300 \times 10^9/L$ on day 15; (2) ≥ 4 of eight participants achieved platelet counts $> 600 \times 10^9/L$ on day 15; (3) ≥ 2 of eight participants achieved platelet counts $> 900 \times 10^9/L$ on day 15; or (4) ≥ 4 of eight participants experienced a romiplostim-related serious AE (SAE).

If subjects showed severe bleeding or investigators judged that treatment was necessary, emergency treatment aimed at increasing platelet count was carried out, including intravenous human immunoglobulin, platelet transfusion, or adrenocorticotrophic hormone. During the emergency treatment, the investigational product could be continued. ITP therapeutic agents aiming at increasing platelet count, but not for emergency treatment (eg, glucocorticoid [except oral glucocorticoid with stable usage and dosage in combination with the test drug], azathioprine, danazol, immunosuppressive drugs, etc) were not allowed.

Assessments

The serum samples for detecting serum romiplostim levels were collected before dosing on day 1, after the first dosing at 4, 8, 12, 24, 36, 48, 72, 96, and 168 hours (before the second dosing), and on days 11 and 15. For determining the platelet counts for PD analysis, the blood samples were collected before dosing on day 1, after the first dosing at 12, 24, 36, 48, 72, 96, and 168 hours (before the second dosing) and on days 11 and 15. Then, the end-of-treatment, follow-up, and end-of-study (EOS) visits were performed on days 15, 29, and 43, respectively. Safety evaluation was performed, and a dose-escalation cohort decision was made in writing by the principal investigator after all subjects completed the end-of-treatment visit in 1 cohort.

For PK assay, the enzyme-linked immunosorbent assay method was used. Rabbit anti-romiplostim antibody was coated onto polystyrene 96-well plates as the capture reagent. Romiplostim in study samples was captured by the immobilized rabbit anti-romiplostim antibody. A biotinylated rabbit anti-romiplostim antibody was added as the detection antibody. After a wash step, streptavidin conjugated to poly-horseradish peroxidase was added to bind the complex. After a final wash step, a tetramethylbenzidine, which is a peroxide substrate, was added. The TMB substrate solution reacts with the peroxide and in the presence of horseradish peroxidase produces a colorimetric signal that is proportional to the amount of romiplostim. The intensity of the color was measured at 450 nm with reference to 650 nm.

For anti-TPO antibody assessment, romiplostim neutralizing antibody and TPO neutralizing antibody use the 32D clone 23 (32Dcl23) cell line, a murine cell line transfected with the human thrombopoietin (TPO) receptor. The 32Dcl23 cell line is dependent on recombinant murine interleukin-3 for routine culturing and growth. The cells respond to TPO and murine interleukin-3 with proliferation, which was measured using the CellTiter-Glo Luminescent Cell Viability Assay (Promega Corp., Madison, Wisconsin). The luminescence signal, detected using the EnVision multilabel plate reader (PerkinElmer, Waltham, Massachusetts) as counts per second, was proportional to the amount of cell proliferation. In the presence of neutralizing antibodies to romiplostim or TPO, cell proliferation was inhibited, resulting in a lower luminescent signal. The antibody testing strategy involved a 2-tiered assay approach consisting of a neutralizing antibody screening assay and a confirmatory assay. In the screening assay, untreated samples were tested in the presence of romiplostim or TPO. In the confirmatory assay, samples underwent treatment with beads coupled to protein G and protein L, which depleted antibodies from serum.

End Points

The end points included the PK data, the platelet changes from baseline, changes in hematological indicators, blood biochemical indicators, changes in vital signs and electrocardiographic findings, romiplostim antibody examination, and anti-TPO antibody examination. The safety end points were the treatment-emergent AEs (TEAEs) and treatment-related AEs (TRAEs).

Statistical Analysis

All below the limit of quantification values of PK were entered as 0. The safety set included all participants who received ≥ 1 dose of romiplostim. The PD set included all participants who received a full dose of romiplostim on day 1 and had at least 1 platelet counting

Table 1. Characteristics of the Participants

Parameter	1 $\mu\text{g}/\text{kg}$ (n = 8)	3 $\mu\text{g}/\text{kg}$ (n = 8)	All (n = 16)
Sex, n (%)			
Female	2 (25.0)	8 (100.0)	10 (62.5)
Male	6 (75.0)	0	6 (37.5)
Age, y			
Median (range)	42.5 (19-69)	42.0 (28-66)	42.0 (19-69)
Mean (SD)	43.0 (18.1)	44.3 (13.4)	43.6 (15.4)
Weight, kg			
Median (range)	74.00 (56.0-84.0)	65.00 (40.0-76.0)	73.00 (40.0-84.0)
Mean (SD)	73.63 (8.48)	63.38 (12.58)	68.50 (11.64)
Baseline platelets ($10^9/\text{L}$)			
Median (range)	11.5 (3-27)	7.0 (3-14)	7.0 (3-27)
Mean (SD)	12.9 (8.6)	7.5 (3.9)	10.2 (7.0)
Splenectomy, n (%)	0	1 (12.5)	1 (6.3)
ITP treatment history, n (%)	8 (100.0)	8 (100.0)	16 (100.0)

ITP, immune thrombocytopenia; SD, standard deviations.

collected after administration. Finally, the PK set included all participants who received a full dose of romiplostim on day 1 and had at least 1 serum romiplostim concentration collected after administration. According to the previous studies,¹⁷⁻²⁰ 8 participants per dose were needed to evaluate the PK changes.

Descriptive statistics were used. All continuous variables are presented as medians (ranges) and means (standard deviations). The categorical and ranked data are presented as n (%). Statistical analyses were performed using the SAS Drug Development 4.5.2 (SAS 9.4; SAS Institute, Cary, North Carolina). Phoenix WinNonlin 7.0 (Certara, Princeton, New Jersey) was used to calculate the PK parameters.

Results

Characteristics of the Participants

All 16 participants were included in the safety set and the PD set. The PK set included 13 participants (1 $\mu\text{g}/\text{kg}$, n = 5; 3 $\mu\text{g}/\text{kg}$, n = 8). Participants were enrolled in 2 cohorts (1 and 3 $\mu\text{g}/\text{kg}$), for a total of 16, eight for each cohort. There were 10 women (62.5%). The participants were 42 (19-69) years of age. Baseline platelets were at 7 (3-27) $\times 10^9/\text{L}$. One (6.3%) participant had a history of splenectomy, 13 (81.3%) had comorbidities, and all (100%) had a history of treatments for ITP (Table 1).

Pharmacokinetics

Figure 1 and Table 2 present the serum romiplostim concentration-time profile and PK parameters of the participants with ITP treated with romiplostim, respectively. In the 1 $\mu\text{g}/\text{kg}$ cohort, the median time to maximum serum drug concentration (t_{max}) was 4.00 hours, maximum serum drug concentration (C_{max})

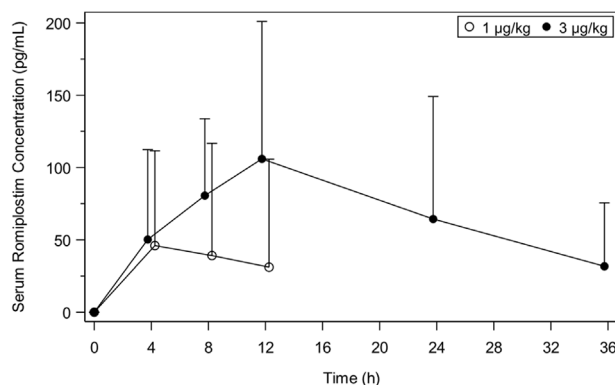


Figure 1. Pharmacokinetics of romiplostim. Mean serum romiplostim concentration (pg/mL), linear plot. The error bars are standard deviations.

was 52.0 pg/mL, and area under the serum drug concentration–time curve from time 0 to the last detectable time point was 389 $\text{pg} \cdot \text{h}/\text{mL}$. In the 3 $\mu\text{g}/\text{kg}$ cohort, t_{max} was 11.91 hours, and C_{max} was 105.0 pg/mL.

Pharmacodynamics

Figure 2 and Table 3 present the PD data. In the 1 $\mu\text{g}/\text{kg}$ cohort, the peak platelet count was $34 \times 10^9/\text{L}$, and the time to peak was 2.5 days. In the 3 $\mu\text{g}/\text{kg}$ cohort, the peak platelet count was $80 \times 10^9/\text{L}$, and the time to peak was 10.5 days. The absolute change of peak platelet count from baseline was 14 and $72 \times 10^9/\text{L}$ in the 1 and 3 $\mu\text{g}/\text{kg}$ cohorts, respectively. The median fold change of peak platelet count from baseline was 2.1 and 9.9 in the 1 and 3 $\mu\text{g}/\text{kg}$ cohorts, respectively.

Safety

Tables 4, 5, and S1 present the adverse events. Seven (87.5%) and 8 (100%) participants had TEAEs in

Table 2. Pharmacokinetic Parameters Obtained After a Single Administration of Romiplostim

Parameter	1 μg/kg	3 μg/kg
t_{max} , h	n = 5	n = 8
Median (range)	4.00 (4.00-7.83)	11.91 (4.00-12.00)
Mean (SD)	4.77 (1.71)	10.42 (2.93)
C_{max} , pg/mL	n = 5	n = 8
Median (range)	52.0 (16.0-228)	105 (25.5-313)
Mean (SD)	80.2 (84.9)	121 (98)
AUC_{0-t} (pg · h/mL)	n = 5	n = 8
Median (range)	389 (32.0-5400)	2280 (48.1-10900)
Mean (SD)	1280 (2310)	2810 (3450)

AUC_{0-t} , area under the serum drug concentration time curve from time 0 to the last detectable time point; C_{max} , maximum serum drug concentration; SD, standard deviation; t_{max} , time to maximum serum drug concentration.

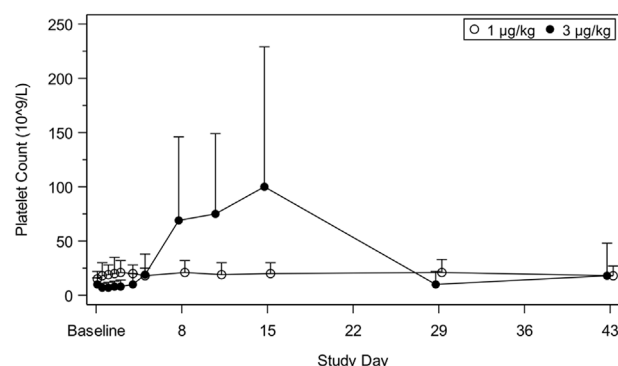


Figure 2. Pharmacodynamics of romiplostim. Mean platelet count-time profiles (linear plot). The error bars are standard deviations.

1 μg/kg cohort and 3 μg/kg cohort, respectively (Table 4). The most common TEAEs in 1 μg/kg cohort were puncture site bruising (n = 3; 37.5%) and petechiae (n = 3; 37.5%). In 3 μg/kg cohort, the most common TEAEs were gastrointestinal disorders (n = 4; 50.0%) and epistaxis (n = 3; 37.5%) (Table 5). Four (50.0%) and 5 (62.5%) had TRAEs in 1 μg/kg cohort and 3 μg/kg cohort, respectively (Tables 4 and S1).

Anti-Romiplostim Antibody and Anti-TPO Antibody

No participants had anti-romiplostim antibodies. At EOS, one participant in the 1 μg/kg cohort developed anti-TPO antibodies. In the 3 μg/kg cohort, 1 patient had anti-TPO antibodies at baseline and shifted negative at EOS.

Discussion

Romiplostim is approved in the United States, European Union, Japan, and many other countries to treat ITP. This study aimed to evaluate the safety, PK, and PD of romiplostim in Chinese patients with ITP. The results suggest that romiplostim (1 and 3 μg/kg) is safe

Table 3. Descriptive Statistics of the Pharmacodynamic Parameters

Parameter	1 μg/kg	3 μg/kg
Peak platelet count (10 ⁹ /L)	n = 8	n = 8
Median (range)	34 (16 to 52)	80 (5 to 389)
Mean (SD)	31 (12)	123 (134)
Time to peak (days)	n = 8	n = 8
Median (range)	2.5 (1.0 to 28.0)	10.5 (1.4 to 14.0)
Mean (SD)	7.3 (9.4)	9.8 (4.9)
Absolute change from baseline to Time to peak (10 ⁹ /L)	n = 8	n = 8
Median (range)	14 (3 to 40)	72 (3 to 369)
Mean (SD)	16 (11)	113 (128)
Day 8	n = 8	n = 8
Median (range)	5 (-5 to 22)	43 (-1 to 224)
Mean (SD)	6 (9)	60 (72)
Day 11	n = 8	n = 8
Median (range)	3 (-4 to 12)	51 (0 to 166)
Mean (SD)	4 (5)	65 (68)
Day 15	n = 7	n = 8
Median (range)	5 (-4 to 14)	52 (-1 to 369)
Mean (SD)	4 (6)	91 (124)
Fold-change from baseline to Time to peak	n = 8	n = 8
Median (range)	2.1 (1.2 to 4.3)	9.9 (2.5 to 19.5)
Mean (SD)	2.4 (1.1)	9.8 (6.4)
Day 8	n = 8	n = 8
Median (range)	1.3 (0.7, 3.2)	5.8 (0.5, 13.4)
Mean (SD)	1.5 (0.8)	6.1 (4.2)
Day 11	n = 8	n = 8
Median (range)	1.3 (0.3 to 2.0)	7.0 (1.0 to 10.2)
Mean (SD)	1.2 (0.5)	6.1 (4.1)
Day 15	n = 7	n = 8
Median (range)	1.3 (0.4 to 2.0)	5.1 (0.5 to 19.5)
Mean (SD)	1.2 (0.5)	7.9 (7.1)

SD, standard deviations.

Table 4. Adverse Events Occurring After a Single Administration of Romiplostim

Parameter	(1 μg/kg) (n = 8)	(3 μg/kg) (n = 8)	All (n = 16)
Subjects with any TEAE	7 (87.5)	8 (100.0)	15 (93.8)
Death	0	0	0
Other serious	0	1 (12.5)	1 (6.3)
Other significant	0	0	0
Subjects with any drug-related TEAE	4 (50.0)	5 (62.5)	9 (56.3)
Death	0	0	0
Other serious	0	0	0
Other significant	0	0	0

TEAE, treatment-emergent adverse event. All data are shown as n (%).

Table 5. TEAEs Occurring After a Single Administration of Romiplostim

Parameter	1 $\mu\text{g}/\text{kg}$ (n = 8)				3 $\mu\text{g}/\text{kg}$ (n = 8)			
	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe
Subjects with any TEAE	7 (87.5)	6 (75.0)	1 (12.5)	0	8 (100.0)	5 (62.5)	3 (37.5)	0
Cardiac disorders	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Palpitations	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Gastrointestinal disorders	1 (12.5)	1 (12.5)	0	0	4 (50.0)	3 (37.5)	1 (12.5)	0
Gingival bleeding	0	0	0	0	2 (25.0)	2 (25.0)	0	0
Mouth hemorrhage	0	0	0	0	2 (25.0)	1 (12.5)	1 (12.5)	0
Angina bullosa haemorrhagica	1 (12.5)	1 (12.5)	0	0	0	0	0	0
General disorders and administration site conditions	3 (37.5)	3 (37.5)	0	0	2 (25.0)	2 (25.0)	0	0
Vessel puncture site bruising	3 (37.5)	3 (37.5)	0	0	1 (12.5)	1 (12.5)	0	0
Injection site hemorrhage	2 (25.0)	2 (25.0)	0	0	0	0	0	0
Chest discomfort	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Infusion site hemorrhage	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Hepatobiliary disorders	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Gallbladder polyp	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Infections and infestations	1 (12.5)	0	1 (12.5)	0	2 (25.0)	1 (12.5)	1 (12.5)	0
Upper respiratory tract infection	1 (12.5)	0	1 (12.5)	0	1 (12.5)	0	1 (12.5)	0
Nasopharyngitis	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Laboratory Investigations	2 (25.0)	2 (25.0)	0	0	3 (37.5)	1 (12.5)	2 (25.0)	0
Alanine aminotransferase increased	0	0	0	0	2 (25.0)	1 (12.5)	1 (12.5)	0
Aspartate aminotransferase increased	0	0	0	0	2 (25.0)	2 (25.0)	0	0
Low-density lipoprotein increased	1 (12.5)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	0	0
Blood calcium decreased	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Blood cholesterol increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Blood triglycerides increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Hematocrit increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Mean cell volume increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Neutrophil count decreased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Neutrophil count increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Platelet count decreased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Reticulocyte count increased	0	0	0	0	1 (12.5)	0	1 (12.5)	0
White blood cell count decreased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
White blood cell count increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Blood phosphorus decreased	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Platelet count increased	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Metabolism and nutrition disorders	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Hypercholesterolemia	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Hypertriglyceridemia	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (12.5)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	0	0
Arthralgia	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Muscular weakness	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Nervous system disorders	2 (25.0)	2 (25.0)	0	0	1 (12.5)	1 (12.5)	0	0
Headache	1 (12.5)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	0	0
Dizziness	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Psychiatric disorders	2 (25.0)	2 (25.0)	0	0	1 (12.5)	1 (12.5)	0	0
Insomnia	2 (25.0)	2 (25.0)	0	0	1 (12.5)	1 (12.5)	0	0
Respiratory, thoracic, and mediastinal disorders	2 (25.0)	2 (25.0)	0	0	4 (50.0)	3 (37.5)	1 (12.5)	0
Epistaxis	2 (25.0)	2 (25.0)	0	0	3 (37.5)	2 (25.0)	1 (12.5)	0
Nasal obstruction	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Oropharyngeal pain	0	0	0	0	1 (12.5)	1 (12.5)	0	0

(Continued)

Table 5. (Continued)

Parameter	1 $\mu\text{g}/\text{kg}$ (n = 8)				3 $\mu\text{g}/\text{kg}$ (n = 8)			
	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe
Skin and subcutaneous tissue disorders	6 (75.0)	6 (75.0)	0	0	3 (37.5)	3 (37.5)	0	0
Purpura	2 (25.0)	2 (25.0)	0	0	2 (25.0)	2 (25.0)	0	0
Ecchymosis	2 (25.0)	2 (25.0)	0	0	1 (12.5)	1 (12.5)	0	0
Petechiae	3 (37.5)	3 (37.5)	0	0	0	0	0	0
Pruritus	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Vascular purpura	0	0	0	0	1 (12.5)	1 (12.5)	0	0
Vascular disorders	1 (12.5)	1 (12.5)	0	0	0	0	0	0
Flushing	1 (12.5)	1 (12.5)	0	0	0	0	0	0

TEAE, treatment-emergent adverse event.

All data are shown as n (%).

and well-tolerated. Platelet response to romiplostim increased with dosage. This multicenter, open-label, phase I study was the first to evaluate the PK, PD, and preliminary safety of ascending doses of romiplostim (1 and 3 $\mu\text{g}/\text{kg}$) in Chinese patients with ITP.

In this study, the serum exposure and platelet counts increased dependently with the dose escalation. The C_{max} and area under the serum drug concentration–time curve from time 0 to the last detectable time point increased in a dose-dependent manner. t_{max} was delayed in the 3 $\mu\text{g}/\text{kg}$ cohort compared with the 1 $\mu\text{g}/\text{kg}$ cohort. The dose proportionality was not observed in this study, which may reflect, at least in part, the high intersubject PK variability. The PK parameters observed here are supported by the results of the previous studies of romiplostim, albeit in different populations and ethnicities^{21,25} and in animal studies.^{24,28}

The pharmacodynamic parameters (peak platelet count, time to peak, absolute changes from baseline, and fold changes from baseline) of the 3 $\mu\text{g}/\text{kg}$ cohort were higher than that of the 1 $\mu\text{g}/\text{kg}$ cohort. The platelet count response to romiplostim increased as the dose increases. As for the PK data, the data are limited because only 2 cohorts were created. Previous studies showed that the PD of romiplostim was dose dependent.^{19,25,29} In the study by Arkam et al,²⁹ the time to platelet peak was 18 days with 1 $\mu\text{g}/\text{kg}$ of romiplostim, which was longer than the median time of 2.5 (range, 1.0–28.0) days observed in this study. Kuter et al¹⁹ compared romiplostim vs standard of care and showed that the platelet response rate was 2.3-fold higher in the romiplostim group than the standard of care, indicating the efficacy of romiplostim; this could not be verified here because this study did not include a control group. Previous phase II and III studies of romiplostim were performed in other countries,^{15,17,19,20,25,29,30} and that is why this study fo-

cused on the PK and PD of romiplostim in Chinese subjects.

This study showed that romiplostim 1 and 3 $\mu\text{g}/\text{kg}$ was safe and well tolerated. TEAEs were similar between 1 and 3 $\mu\text{g}/\text{kg}$ in types, incidence, and severity. The most frequently occurring TEAE was epistaxis, insomnia, purpura, ecchymosis, and petechiae. Even though nearly all subjects reported TEAEs, all of the TEAEs reported were of mild or moderate intensity during the study. One SAE of oral hemorrhage was observed, contradicting Kuter et al,¹⁹ who reported SAEs in 23% of the patients on romiplostim. The TRAEs were also similar between the 2 groups. There were no subjects who developed antibodies against romiplostim or TPO after treatment. In a previous phase II double-blind study, eligible patients (with criteria similar to those of the present study) were randomly assigned to receive romiplostim 1, 3, or 6 $\mu\text{g}/\text{kg}$ or placebo once weekly for 6 weeks.²³ The most frequently reported AEs were contusions, ecchymosis, and epistaxis. None of their patients had a positive test for antibodies against romiplostim or TPO. The most common AEs (incidence of $\geq 5\%$ and occurring more often romiplostim than with the placebo) include joint pain, dizziness, insomnia, myalgia, limb pain, abdominal pain, shoulder pain, dyspepsia, and paresthesia; headache is most often reported. Hence, the present study did not identify new safety signals.^{31–33}

This study has limitations. Only the 1 and 3 $\mu\text{g}/\text{kg}$ doses of romiplostim were evaluated in the study, limiting the evaluation of the dose-dependent effects. Indeed, the 6 $\mu\text{g}/\text{kg}$ cohort was abandoned under the communication with the Center for Drug Evaluation in China. Nevertheless, removing the 6 $\mu\text{g}/\text{kg}$ cohort did not influence the assessment of the safety and PD. In addition, some parameters (such as area under the serum drug concentration–time curve from time 0

to infinity [$AUC_{0-\infty}$], apparent volume of distribution [V_z/F], apparent clearance [CL/F], and $t_{1/2}$) could not be analyzed in the 1 and 3 $\mu\text{g}/\text{kg}$ cohorts because elimination phases were identified in few subjects in this study. Indeed, as seen in Figure 1, it can be seen that the sampling duration was not long enough to determine the $t_{1/2}$ for the 1- $\mu\text{g}/\text{kg}$ dose. For the 3- $\mu\text{g}/\text{kg}$ dose, the $t_{1/2}$ could be estimated in only 4 of 8 subjects, thereby causing the median or mean values of $t_{1/2}$, $AUC_{0-\infty}$, CL/F , and V_z/F to have little meaning. Given these limitations, $t_{1/2}$, $AUC_{0-\infty}$, CL/F , and V_z/F cannot be reported. It can also be noted from Figure 1 and from the ranges in Table 2 that the variability is huge, probably due to the factors presented above.

In conclusion, romiplostim (1 and 3 $\mu\text{g}/\text{kg}$) is safe and well tolerated in Chinese patients with ITP. Platelet response to romiplostim increased with dosage. No new safety signals were identified. These results warrant further investigation of romiplostim with the starting dose of 1 $\mu\text{g}/\text{kg}$ in a phase III study in the Chinese population.

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Conflicts of Interest

All authors declare that they have no competing interests.

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Data Sharing

The data sets generated and/or analyzed during the study sponsored by Kyowa Kirin will be available in the Vivli repository (<https://vivli.org/ourmember/kyowa-kirin/>) as long as conditions of data disclosure specified in the policy section of the Vivli website are satisfied.

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