# Safety and efficacy of hetrombopag in patients with chronic immune thrombocytopenia: a single-arm, open-label, multi-center phase 1 study

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**Background:** Thrombopoietin receptor agonists (TPO-RAs) are promising therapeutic strategy for patients with immune thrombocytopenia (ITP). We conducted this phase 1 trial (NCT02614846) to evaluate the preliminary efficacy and safety of hetrombopag (a TPO-RA) in patients with ITP.

**Methods:** Patients with ITP who had an insufficient response or had progressed on at least one standard treatment for ITP were given hetrombopag orally at an initial dose of 5 mg once daily for up to 6 weeks. The primary endpoint was the proportion of patients who achieved platelet counts of $\geq 50\times10^9$/L at week 6.

**Results:** A total of 37 eligible patients received hetrombopag treatment. This study met its primary endpoint, 22 (59.5%, 95% CI: 42.1–75.3) patients responded to hetrombopag, achieving platelet counts $\geq 50\times10^9$/L at week 6. Of the 29 (78.4%, 95% CI: 61.8–90.2%) patients who responded at least once during the study, the median time from treatment initiation to first response was 2.1 weeks (95% CI: 1.3–4.1 weeks). The median accumulative response duration was 3.1 weeks [interquartile range (IQR), 2.1–4.1 weeks]. The incidence of bleeding was reduced with hetrombopag treatment compared to the baseline. Adverse events (AEs) occurred in 32 (86.5%) patients and treatment-related AEs occurred in 13 (35.1%) patients. Two (5.4%) serious AEs were reported, but neither were treatment related. The dose was modified in one (2.7%) patient due to an AE. There were no incidences of treatment discontinuation/interruption or death.

**Conclusions:** Hetrombopag showed preliminary activity in elevating platelet counts and reducing bleeding in patients with chronic ITP who had received at least one standard therapy. It was well-tolerated.

**Keywords:** Hetrombopag; immune thrombocytopenia (ITP); thrombopoietin receptor; hematologic response; clinical trial

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## Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder which the immune system attacks and destroys platelets, leading to the destruction and impaired production of platelets (1,2). ITP is characterized by thrombocytopenia which results in an increased risk of bleeding (3). Some patients with ITP have no symptoms or only slight bruising; however, others may experience life-threatening bleeding (3). The aim of managing chronic ITP is to maintain a target platelet level of $>30\times10^9$/L, since a platelet level below $30\times10^9$/L indicates an increased risk of bleeding (4-6). Corticosteroids and intravenous immunoglobulins (IVIGs) are the standard first-line therapy for patients with ITP, and have a response rate of 70–90% (7).

For ITP patients who relapsed or refractory to first-line standard therapy, splenectomy has been the most commonly used second-line treatment for a few decades (7,8). However, as splenectomy may be associated with poor clinical outcomes and adverse events (AEs), such as post-operative morbidity and an increased risk of infections, its clinical application is decreasing (9-11). The stimulation of platelet production by thrombopoietin receptor agonists (TPO-RAs) provides a promising therapeutic option for patients with ITP (8). The development of eltrombopag and avatrombopag [both of which are small-molecule TPO-RAs that bind to the transmembrane site of the thrombopoietin receptor (TPO-R)], and romiplostim (a peptibody that binds directly and competitively to the TPO binding site), revolutionized the clinical management of ITP patients (12-16). A recombinant human TPO (rhTPO) has also been licensed in China in adults and children with ITP (17-19). These drugs are effective in increasing platelet counts and reducing bleeding, but safety concerns still hamper their use in clinical practice (8).

Hetrombopag is a novel orally bioavailable small-molecule TPO-RA that was developed to increase platelet counts (20-22). It is produced by structural modifications to eltrombopag to enhance potency and minimize toxicity. Preclinical studies have shown that hetrombopag has a similar mechanism of action as eltrombopag, but its pharmacological performance *in vivo* (nude mice) is superior to that of eltrombopag (23). In the first-in-patient study, hetrombopag was found to be well-tolerated and have preliminary efficacy in ITP patients (24). Thus, we conducted this phase 1 trial (NCT02614846) to further assess the activity and safety of hetrombopag in ITP patients who had an insufficient response or had progressed on a previous standard ITP treatment. We present the following article in accordance with the TREND reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-4361/rc).

## Methods

### *Study design and participants*

A single-arm, open-label, multi-center, phase 1 study was conducted. Patients were enrolled in this study between August 12, 2015 and November 11, 2016 from 8 sites in China (see Table S1). Patients were considered eligible to participate in this study if they were aged 18–65 years, had been diagnosed with chronic ITP (not including myelodysplastic syndrome, systemic lupus erythematosus, early aplastic anemia, atypical aplastic anemia, thrombotic thrombocytopenic purpura, or pseudothrombocytopenia), had a baseline platelet count $<30\times10^9$/L, and had an insufficient response or had progressed on at least one previous treatment for ITP (including but not limited to corticosteroids, intravenous gamma globulin or anti-D IVIG, azathioprine, danazol, cyclophosphamide, immunomodulators, or splenectomy). Further, previous rescue treatment for ITP had to have been completed at least 2 weeks before enrollment. Immunosuppressive maintenance therapy was permitted provided the doses were stable for at least 4 weeks before enrollment.

Patients were excluded from the study if they had received eltrombopag or any other TPO-RA treatment within 30 days before enrollment, had arterial or venous thrombosis, malignant disease, or cardiac disease, had participated in other clinical trials, were pregnant or nursing, had undergone rituximab treatment or splenectomy within 6 months before the study, had human immunodeficiency virus infection, or hepatitis B or C virus infection (Appendix 1).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Good Clinical Practice Guidelines. The protocol and all amendments were approved by the institutional review board or independent ethics committee at each study site (see Table S1). All patients provided written informed consent. This trial is registered with ClinicalTrials.gov (identifier NCT02614846).

### *Procedures*

All eligible patients were given hetrombopag orally at an initial dose of 5 mg once daily after overnight fasting (>8 hours of fasting) and at least 2 hours before a meal (21,25). The hetrombopag treatment lasted 6 weeks. Platelet counts were evaluated twice per week. The dose of hetrombopag could be modified (to 2.5, 3.75, 5, or 7.5 mg once daily) on the basis of the platelet count of patients after 2 weeks of administration. The dose modification scheme is presented in Table S2. If the platelet count fluctuated sharply within the first 2 weeks, the dose could be modified ahead of schedule. Doses could also be modified according to the investigator's judgement.

Patients were allowed to receive concomitant ITP treatment, including but not limited to corticosteroids, azathioprine, danazol, cyclosporin A, or mycophenolate mofetil. Rescue treatment for ITP was permitted on the basis of investigator judgement, which referred to treatments for increasing platelet count, including drug, platelet transfusion, splenectomy, or dose increase of baseline combination therapy for ITP.

From the first administration of hetrombopag, the researchers compared the returned hetrombopag with the dose information recorded by the patients and the prescription at each visit (except the follow-up visit) to assess compliance. If a patient failed to take hetrombopag or failed to follow the investigator's prescription for >5 consecutive days or ≥20% of the total days, the patient was recorded as having deviated from protocol.

### *Assessment*

Patients were assessed for safety and efficacy weekly during the 6-week treatment period. Safety was followed up within 2 weeks after the last dose of hetrombopag, and any AE within 4 weeks was recorded. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v.4.0). The severity of bleeding symptoms was graded according to the World Health Organization (WHO) bleeding scale (grade 0: no bleeding; grade 1: petechiae; grade 2: mild blood loss; grade 3, gross blood loss; grade 4: debilitating blood loss).

### *Outcomes*

The primary endpoint was the proportion of patients who achieved platelet counts ≥$50\times10^9$/L at week 6 after the initiation of hetrombopag treatment. The secondary endpoints included the proportion of patients with a platelet count ≥$50\times10^9$/L at least once, the proportion of patients with a platelet count ≥$30\times10^9$/L and at least twice the baseline amount, the time from treatment initiation to the first occurrence of a platelet count ≥$50\times10^9$/L, the total duration of a platelet count ≥$50\times10^9$/L, the incidence and severity of bleeding, and safety.

### *Statistical analysis*

We estimated that 60% of patients would respond to hetrombopag (i.e., have a platelet count ≥$50\times10^9$/L at week 6) (26). The null hypothesis defined in this study was that 30% of patients would respond to hetrombopag. Thus, a sample size of 23 patients was needed to provide 80% power at a type I error of 0.025 (1-sided) using the exact method. Allowing for a 20% dropout rate, 29 patients had to be enrolled.

Both full analysis set (FAS) and safety set (SS) included all patients who received at least one dose of hetrombopag. The FAS was used as the primary population for the efficacy analysis, and the SS was used for the safety analysis. Descriptive statistics were used to summarize the baseline demographic and clinical characteristics of the patients, the duration of platelet counts ≥$50\times10^9$/L, and safety data. Proportions in the primary and secondary endpoints were reported with their exact 95% CIs calculated using Clopper-Pearson methods. The median time from treatment initiation to the first occurrence of a platelet count ≥$50\times10^9$/L was estimated and presented with the accompanying 95% CI. The primary endpoint was analyzed using the last-observation-carried-forward imputation in which the last platelet count after the baseline was used in the subsequent analysis for any patient with a missing follow-up visit value. All the analyses were conducted with SAS software, version 9.4.

## Results

### *Patient baseline characteristics*

From August 12, 2015 to November 11, 2016, 47 patients were screened, and 37 eligible patients received hetrombopag treatment. All 37 patients completed the 6-week treatment regimen, and were included in the FAS and SS. Patients' baseline demographic and clinical characteristics are presented in *Table 1*. Patients had a

**Table 1** Baseline characteristics

| Characteristics | Data |
|---|---|
| Age (years) | 40.0 (28.0–53.0) |
| Gender | |
| Male | 12 (32.4%) |
| Female | 25 (67.6%) |
| Body mass index (kg/m$^2$) | 24.0 (21.3–25.1) |
| Platelet counts (×10$^9$/L) | 14.0 (11.0–22.0) |
| Bleeding (WHO bleeding scale) | |
| Total | 18 (48.7%) |
| Grade 1 | 17 (45.9%) |
| Grade 2 | 1 (2.7%) |
| Grade 3 | 0 |
| Grade 4 | 0 |
| Time from diagnosis of ITP (years) | 3.1 (1.9–9.0) |
| Prior treatment for ITP | |
| Corticosteroid | 37 (100.0%) |
| Immunosuppressant | 13 (35.1%) |
| Splenectomy | 3 (8.1%) |

Data are presented as n (%) or median (IQR). ITP, immune thrombocytopenia.

median age of 40.0 years [interquartile range (IQR), 28.0–53.0), and 12 (32.4%) patients were male. The median baseline platelet counts were 14×10$^9$/L (IQR, 11×10$^9$–22×10$^9$). The median time from diagnosis of ITP to study enrollment was 3.1 years (IQR, 1.9–9.0 years), and 3 (8.1%) patients had received prior splenectomy.

### *Efficacy*

This study reached its primary endpoint, with 22 (59.5%, 95% CI: 42.1–75.3%) patients achieved a response (i.e., a platelet count ≥50×10$^9$/L) at week 6 after the initiation of treatment (see *Table 2*). During the 6-week treatment period, 29 (78.4%, 95% CI: 61.8–90.2%) patients had a platelet count ≥50×10$^9$/L at least once. The median platelet count increased from 14×10$^9$/L (IQR, 11×10$^9$–22×10$^9$) at baseline to 55×10$^9$/L (IQR, 26×10$^9$–150×10$^9$) at week 2, and remained several-fold higher than that of baseline thereafter (see *Figure 1*). For the 29 responders, the median time from treatment initiation to the first response was 2.1 weeks (95% CI: 1.3–4.1). The median accumulative response duration was 3.1 weeks (IQR 2.1–4.1). Sixteen (43.2%) patients had an accumulative response duration ≥3 weeks and 8 (21.6%) patients had an accumulative response duration ≥4 weeks. Thirty-three (89.2%, 95% CI: 74.6–97.0%) patients met both criteria of reaching a platelet count ≥30×10$^9$/L and at least twice the baseline amount during 6-week treatment period.

Grade 1–4 bleeding symptoms occurred in 18 (48.7%) of the 37 patients at the time of baseline visit, but only occurred in 6 (16.2%) patients at week 6 after hetrombopag treatment. Throughout the treatment period, 15 patients experienced grade 1–4 bleeding, and 5 patients experienced grade 2–4 bleeding (see *Figure 2*). An obvious decrease in the incidence of bleeding occurred rapidly after treatment, and this decrease continued to be maintained from weeks 3–6. This reduction was mainly driven by a decrease in grade 1 bleeding. The trend of decreased bleeding incidence was in line with that of increased platelet counts throughout the treatment period.

### *Safety*

The median compliance rate was 100.0% in the 37 patients receiving hetrombopag treatment. The final dose was 2.5 mg once every other day in 1 (2.7%) patient, 2.5 mg once daily in 4 (10.8%) patients, 3.75 mg once daily in 4 (10.8%) patients, 5 mg once daily in 9 (24.3%) patients, and 7.5 mg once daily in 19 (51.4%) patients (see Table S3).

AEs occurred in 32 (86.5%) patients, the most common ones being upper respiratory tract infection (12 patients, 32.4%), increased alanine aminotransferase (8 patients, 21.6%), increased blood lactate dehydrogenase (6 patients, 16.2%), and skin hemorrhage (5 patients, 13.5%) (see *Tables 3*,*4*). Treatment-related AEs were reported in 13 (35.1%) patients. The common treatment-related AEs were increased blood lactate dehydrogenase (5 patients, 13.5%), increased alanine aminotransferase (4 patients, 10.8%), increased aspartate aminotransferase (2 patients, 5.4%), and increased blood uric acid (2 patients, 5.4%) (see Table S4). Four (10.8%) patients experienced grade 3 or 4 AEs. Among these patients, 2 (5.4%) AEs were considered treatment related (1 patient had increased alanine aminotransferase and 1 had hyperuricemia). One patient experienced dose reduction due to peripheral and facial edema, and this AE was considered treatment related. No patient discontinued or interrupted treatment due to AEs. Serious AEs occurred in 2 (5.4%) patients, including 1 patient with a decreased

**Table 2** Efficacy outcomes

| Outcomes | Data |
|---|---|
| Proportion of patients achieving platelet counts ≥50×10$^9$/L at week 6 | 22 (59.5%, 42.1–75.3%) |
| Proportion of patients achieving platelet counts ≥50×10$^9$/L at least once | 29 (78.4%, 61.8–90.2%) |
| Duration from treatment initiation to the first response | |
| n | 29 |
| Median (95% CI), weeks | 2.1 (1.3–4.1) |
| Duration of accumulative response | |
| n | 29 |
| Median (IQR), weeks | 3.1 (2.1–4.1) |
| ≥3 weeks | 16 (43.2%) |
| ≥4 weeks | 8 (21.6%) |
| Proportion of patients meeting both criteria of reaching platelet count ≥30×10$^9$/L and at least twice the baseline amount during 6-week treatment period | 33 (89.2%, 74.6–97.0%) |
| Bleeding throughout the treatment period (WHO bleeding scale) | |
| Total | 15 (40.5%) |
| Grade 1 | 10 (27.0%) |
| Grade 2 | 5 (13.5%) |
| Grade 3 | 0 |
| Grade 4 | 0 |

Data are presented as n (%), n (%, 95% CI), median (95% CI), or median (IQR).

platelet count and 1 with gingival bleeding, but neither of these AEs were related to hetrombopag treatment. No deaths were reported.

## Discussion

In this study, we evaluated the efficacy and safety of hetrombopag in patients who had undergone at least one previous treatment for ITP. This study reached its primary endpoint; that is, 59.5% (95% CI: 42.1–75.3%, 22/37) of patients achieved a platelet count of ≥50×10$^9$/L at week 6 following the initiation of hetrombopag treatment. The accumulative response duration was 3.1 weeks (IQR, 2.1–4.1 weeks). Hetrombopag had a tolerable and manageable safety profile in patients with ITP.

As the first oral TPO-RA, eltrombopag had a response rate (achieving a platelet count of ≥50×10$^9$/L after 6 weeks treatment) of 57.7% (60/104) in patients with ITP in a Chinese study (27), 60% (9/15) in a Japanese study (28), and 59% (43/73) and 79% (106/135) in two international phase 3 studies (26,29). We found that hetrombopag had a similar response rate (59.5%) to that of eltrombopag after 6 weeks of treatment. Patients' platelet counts rapidly increased after treatment, and were maintained thereafter during the hetrombopag treatment period. Cross-trial comparisons should be interpreted with caution due to different patient populations included; however, these results indicate that hetrombopag shows promise in upregulating platelet counts.

The main goal of treatment of chronic ITP is to prevent bleeding symptoms. In this study, the bleeding status of patients during the screening and trial period was evaluated according to the WHO bleeding scale. The results showed that the bleeding symptoms of patients were clinically improved after hetrombopag treatment. The incidence of bleeding decreased with the increase of platelet counts after hetrombopag treatment, a phenomenon that has also been observed in previous eltrombopag studies (26-28). No uncontrolled bleeding occurred.

The safety of hetrombopag was manageable. During the treatment period, most patients (29, 78.4%) only

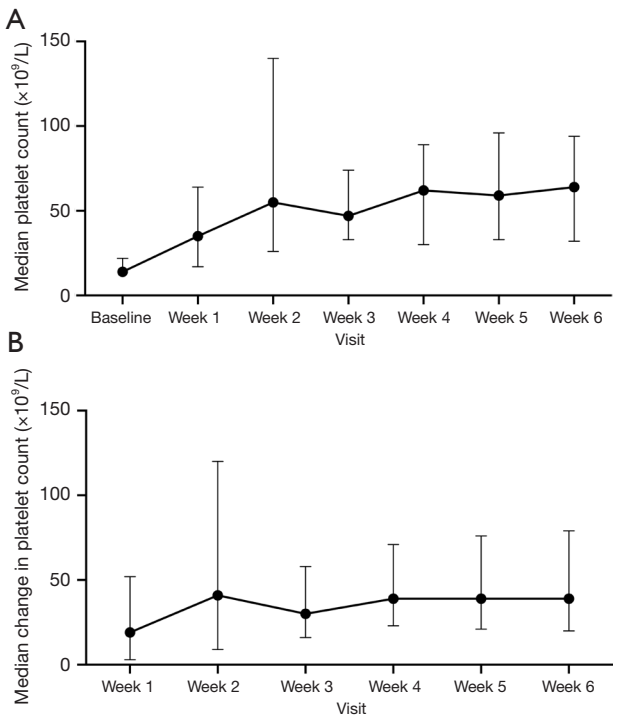


**Figure 1** Median platelet counts (A) and median changes in platelet counts (B) at each visit.

**Table 3** Adverse events

| Adverse events | Data |
|---|---|
| Adverse events of any cause | 32 (86.5%) |
| Grade 3 or higher | 4 (10.8%) |
| Serious | 2 (5.4%) |
| Leading to dose reduction/treatment interruption | 1 (2.7%) |
| Leading to treatment discontinuation | 0 |
| Leading to death | 0 |
| Treatment-related adverse events* | 13 (35.1%) |
| Grade 3 or higher | 2 (5.4%) |
| Serious | 0 |
| Leading to dose reduction/treatment interruption | 1 (2.7%) |
| Leading to treatment discontinuation | 0 |
| Leading to death | 0 |

Data are presented as n (%). *, the treatment-related adverse events refers to the correlation of the adverse events with study treatment was "definitely related", "possibly related", or "unassessable", as judged by investigators.

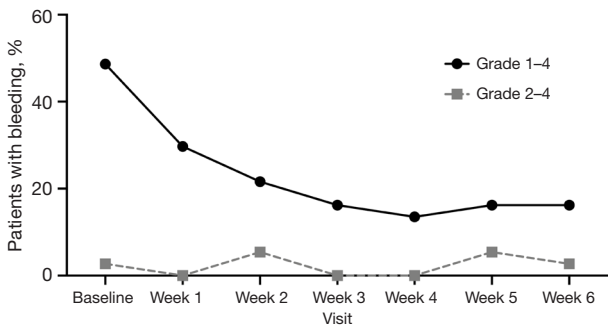


**Figure 2** Proportion of patients with bleeding during hetrombopag treatment.

required a dose modification once or twice. Two patients had >5 dose modifications, and 2 patients did not require dose modification. After dose adjustment, the changes of platelet count were stable and the toxicities of hetrombopag were tolerable. We found the mean dose of hetrombopag was 5.5 mg but the final dose in most patients was 7.5 mg, which may indicate that the dose demand for patients with chronic ITP is a little bit high. Only one patient's dose of hetrombopag was modified due to an AE. Liver toxicity in this study was not a new safety signal since it had been observed in a previous first-in-patient trial of hetrombopag in ITP patients (24). In the current study, most of the treatment-related increased transaminases were grades 1–2, and only 1 patient had grade 3 increased alanine aminotransferase. The increased alanine aminotransferase in all patients returned to normal after appropriate liver-protection treatment, and did not lead to dose reduction, or treatment interruption or discontinuation. A thromboembolic event was an eltrombopag-related AE, which was reported in patients on day 42 after eltrombopag treatment (12). In the present hetrombopag study, no thromboemboli were observed.

Cataracts have been observed in rodent studies of eltrombopag (30). In our study, no cataracts were reported, but 1 patient reported visual impairment. That patient had optic atrophy at the baseline and had more serious optic atrophy at his last scheduled visit for the study. This patient was given vitamin B1 and mecobalamin tablets, and his optic atrophy was relieved 1 week later. The aggravation of his optic atrophy was considered treatment related. It should be noted that the limited follow-up duration of this study may not be enough to detect AEs such as cataract. Results

**Table 4** Adverse events occurring in ≥5% of patients

| Adverse events | Any grade | Grade 3–4 |
|---|---|---|
| Upper respiratory tract infection | 12 (32.4%) | 0 |
| Alanine aminotransferase increased | 8 (21.6%) | 1 (2.7%) |
| Blood lactate dehydrogenase increased | 6 (16.2%) | 0 |
| Skin hemorrhage | 5 (13.5%) | 0 |
| Dizziness | 4 (10.8%) | 0 |
| Lymphocyte morphology abnormal | 3 (8.1%) | 0 |
| Aspartate aminotransferase increased | 3 (8.1%) | 0 |
| Gingival bleeding | 3 (8.1%) | 1 (2.7%) |
| Hyperuricemia | 3 (8.1%) | 1 (2.7%) |
| Asthenia | 3 (8.1%) | 0 |
| Occult blood positive | 2 (5.4%) | 0 |
| Blood uric acid increased | 2 (5.4%) | 0 |
| Blood glucose increased | 2 (5.4%) | 0 |
| Nausea | 2 (5.4%) | 0 |
| Headache | 2 (5.4%) | 0 |
| Alopecia | 2 (5.4%) | 0 |
| Hypokalemia | 2 (5.4%) | 0 |
| Arthralgia | 2 (5.4%) | 0 |
| Epistaxis | 2 (5.4%) | 0 |
| Platelet count decreased | 2 (5.4%) | 2 (5.4%) |

Data are presented as n (%).

with longer follow-ups can be found in the phase 3 trial in patients with ITP (31). In that study, 1 of 339 patients developed cataract during the 24 weeks of hetrombopag treatment.

It should be noted that the recommended dose of eltrombopag varies according to the characteristics of different ethnic groups. The recommended initial dose of eltrombopag for ITP is 50 mg once daily in American patients, 12.5 mg once daily in Japanese patients, and 25 mg once daily in Chinese patients (26-28,30). Thus, different starting doses need to be considered when extrapolating the use of hetrombopag to populations in other parts of the world.

Despite these promising results, our study had several limitations. First, this was a single-arm phase 1 study and the sample size was small. Second, as the treatment duration was only 6 weeks, no evidence was gathered about the long-term efficacy and safety of hetrombopag. Third, the results of other studies on eltrombopag have shown that the platelet count level cannot be maintained after treatment discontinuation (26-28). In our study, the observation period was short (only 2 weeks after drug discontinuation); thus, it is unknown whether all patients' platelet counts returned to the baseline after hetrombopag discontinuation as occurs with eltrombopag. The above unanswered questions will be further explored in a randomized phase 3 study (NCT03222843).

TPO-RAs including eltrombopag, avatrombopag, and romiplostim have been approved for treating ITP; however, developing new drugs that have a similar mechanism of action to pre-existing drugs is still valuable, as these follow-on drugs may provide more therapeutic choices (32). In our study, hetrombopag showed preliminary activity in elevating platelet levels and reducing bleeding symptoms in ITP

 

patients who had an insufficient response or had progressed on at least one previous treatment for ITP. The toxicity of hetrombopag was tolerable, and no new safety signals were identified. A placebo-controlled phase 3 confirmatory study is currently underway to further assess the safety and efficacy of hetrombopag in ITP patients.

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## Footnote

*Reporting Checklist:* The authors have completed the TREND reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-4361/rc

*Data Sharing Statement:* Available at https://atm.amegroups.com/article/view/10.21037/atm-21-4361/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-4361/coif). YT, JX, and JZ report that they are employees of Jiangsu Hengrui Pharmaceuticals Co., Ltd. All other authors report that this study was funded by Jiangsu Hengrui Pharmaceuticals Co., Ltd. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was done in accordance with Declaration of Helsinki (as revised in 2013) and the Good Clinical Practice Guideline. The protocol and all amendments were approved by the institutional review board or independent ethics committee of each study site. All patients provided written informed consent.



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