Multicentre, randomised phase III study of the efficacy and safety of eltrombopag in Chinese patients with chronic immune thrombocytopenia

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Summary

Eltrombopag, a thrombopoietin receptor agonist, raises platelet counts and reduces bleeding in patients with immune thrombocytopenia (ITP). In Chinese patients, eltrombopag was evaluated at an initial dose of 25 mg, vs. 50 mg for non-Asians, because the plasma exposure of eltrombopag is higher in East Asians. A multicentre, double-blind, randomised, placebo-controlled, 8-week, phase III study enrolled 155 patients with chronic, previously treated ITP. Dosage could be adjusted (25–75 mg/day) to maintain platelet counts 50–250 × 109/l. The primary efficacy endpoint was the proportion of patients with a platelet count ≥50 × 109/l after Day 42. Pharmacokinetics and pharmacodynamics of eltrombopag were analysed in an open-label extension. After Day 42, 57.7% of eltrombopag-treated and 6.0% of placebo-treated patients achieved platelet counts ≥50 × 109/l. Odds of achieving a platelet count ≥50 × 109/l were 26.08 times greater with eltrombopag than placebo (P < 0.001). Compared with placebo, time to response and duration of response were better with eltrombopag (P < 0.001) and the odds of any bleeding were reduced by 72% (P = 0.001). Tolerability, pharmacokinetics, and pharmacodynamics were similar to previous findings in East Asian patients. In conclusion, in Chinese patients with chronic ITP, eltrombopag 25 mg once daily, elevated platelet counts to a safe range and reduced bleeding.

Keywords: Asian Continental Ancestry Group, autoimmune thrombocytopenia, blood platelet disorders, platelet count, treatment outcome.

Immune thrombocytopenia (ITP) is characterized by thrombocytopenia due to the destruction of platelets and the suppression of platelet production by autoantibodies and cytotoxic T lymphocytes (Qin et al., 2013). Normal platelet counts in most healthy individuals are 100–150 × 109/l in non-Western ethnic groups (Neunert et al., 2011), and 100–300 × 109/l in Chinese individuals (Wang et al., 2006). Primary ITP is defined as an isolated thrombocytopenic event (platelet count <100 × 109/l) after excluding all other conditions that result in thrombocytopenia, while chronic ITP is thrombocytopenia that lasts for more than 12 months (Neunert et al., 2011).

The aim of ITP treatment is to prevent bleeding and to achieve a platelet count that is associated with adequate haemostasis, rather than a normal platelet count (Arnold & Kelton, 2007). In adults with ITP, treatment is considered when platelet counts fall below 30 × 109/l as this is when most fatal bleeding occurs. First-line treatment includes corticosteroids or intravenous immunoglobulin to reduce the destruction of antibody-coated platelets (Cheng et al., 2011; Neunert et al., 2011; Neunert, 2013). If these agents are unsuccessful, splenectomy, rituximab to target B cells (although this is contraindicated in patients with hepatitis B), more potent immunosuppression or thrombopoietin receptor agonists (eltrombopag or romiplostim) should be considered to stimulate platelet production.

Eltrombopag has shown efficacy in raising platelet counts and reducing bleeding in short- and longer-term studies in
mostly Western (Bussel et al, 2007, 2009; Saleh et al, 2013) or Japanese (Tomiyama et al, 2012; Katsutani et al, 2013) patients with ITP. Asian ITP patients have been included in two previous studies of eltrombopag: the 6-month phase III randomised placebo-controlled ITP RAISE study with eltrombopag (Cheng et al, 2011) and the long-term eltrombopag extended dosing (EXTEND) study, the interim analysis of which included patients that received eltrombopag treatment for up to 3 years (Saleh et al, 2013). Asians accounted for only 17% and 15% of the RAISE and EXTEND study populations, respectively (Cheng et al, 2011; Saleh et al, 2013). These patients received the same initial dose of eltrombopag (50 mg once daily) as patients of other ethnicities, although the European Union and United States labelling for eltrombopag recommend a lower initial dose for East Asian patients because eltrombopag plasma exposure has been shown to be 87% higher in this population (Gibiansky et al, 2011).

Subanalyses of efficacy and safety data from the East Asian patients enrolled in earlier eltrombopag studies were not carried out. Therefore, we conducted this phase III, randomised, multicentre, placebo-controlled study to evaluate the safety and efficacy of eltrombopag at an initial dose of 25 mg once daily in Chinese patients who had chronic ITP that had not responded or had relapsed after previous treatment.

**Methods**

**Patients**

Chinese adults aged ≥18 years previously treated for chronic ITP (diagnosed at least 12 months before randomisation), with insufficient response or relapse after prior ITP treatment and a pretreatment platelet count <30 × 10⁹/l were enrolled into the study. Previous therapy for ITP with immunoglobulins, immunomodulators and cyclophosphamide had to have been completed at least 2 weeks before randomisation. Splenectomy had to have been carried out at least 4 weeks before randomisation. Patients treated with maintenance immunosuppressive therapy (corticosteroids, azathioprine, danazol, ciclosporin A and mycophenolate mofetil) must have received a stable dose for at least 1 month. Patients were excluded if they had any prior history of cardiovascular disease; showed evidence of human immunodeficiency virus or hepatitis B or C infections; or if they consumed aspirin, aspirin-containing compounds, salicylates, anticoagulants, quinine or non-steroidal anti-inflammatory drugs for longer than three consecutive days within 2 weeks. Patients who achieved platelet counts ≥50 × 10⁹/l at least once upon eltrombopag could be resumed at the lower dosage level.

Patients were included if they had any prior history of cardiovascular disease; showed evidence of human immunodeficiency virus or hepatitis B or C infections; or if they consumed aspirin, aspirin-containing compounds, salicylates, anticoagulants, quinine or non-steroidal anti-inflammatory drugs for longer than three consecutive days within 2 weeks before the study started.

This study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, and the ethical principles outlined in the Declaration of Helsinki 2008. The study protocol was approved by the investigational centres’ ethics committees or Institutional Review Boards. Written informed consent was obtained from each patient before any study-specific procedures were carried out.

**Study design, treatment, and outcome measures**

This was a multicentre, double-blind, randomised, placebo-controlled phase III study to evaluate the short-term efficacy and safety of eltrombopag in a double-blind, placebo-controlled manner (Stage I). The pharmacokinetics (PK) and PK/pharmacodynamics (PD) of eltrombopag were evaluated during the 24-week Stage II, during which all patients who completed Stage I received open-label eltrombopag.

All patients randomised into this study were assigned a unique randomisation code by GlaxoSmithKline’s interactive voice response system (GlaxoSmithKline, Brentford, UK), with randomisation stratified by splenectomy status (Yes/No), use of maintenance concomitant ITP therapy at baseline (Yes/No), and baseline platelet counts (≤15 × 10⁹/l or >15 × 10⁹/l). For Stage I, the patients were randomised in a 2:1 ratio to receive treatment for 8 weeks with oral eltrombopag at an initial dose of 25 mg once daily or matching placebo. Patients, caregivers, investigators and outcomes assessors were blinded to treatment assignment.

Dosage was adjusted to a maximum of 75 mg daily to maintain platelet counts between 50 × 10⁹/l and 250 × 10⁹/l. Thus, the treatment dose could be increased from 25 mg to 50 mg once daily, or from 50 mg to 75 mg once daily, if the platelet counts were <50 × 10⁹/l after two consecutive weeks of treatment; otherwise, the current dose was maintained. Dosage was decreased when the platelet count was >150 × 10⁹/l. Treatment was discontinued in patients whose platelet count reached >250 × 10⁹/l until it fell back to ≤100 × 10⁹/l, whereupon eltrombopag could be resumed at the lower dosage level.

In Stage II, patients who had received eltrombopag in Stage I continued with the dose they had been administered at the end of Stage I, unless their platelet count warranted an adjustment. Patients who had received placebo in Stage I started active treatment with an initial dose of eltrombopag 25 mg daily.

Efficacy assessment measures included platelet counts, which were included in the complete blood counts at weekly scheduled study visits, along with information about use of first-aid or rescue treatment, and the incidence and severity of ITP-associated symptoms.

The primary efficacy endpoint was the proportion of patients who had a platelet count ≥50 × 10⁹/l after day 42 (week 6) during Stage I without use of rescue treatment.

Secondary efficacy endpoints during Stage I included the proportion of patients whose platelet count met both criteria of ≥30 × 10⁹/l and at least twice the baseline platelet count on at least 1 occasion between Weeks 1 and 6; the proportion of patients who achieved platelet counts ≥50 × 10⁹/l at least once during the first 6 weeks; the incidence and severity of bleeding symptoms according to the World Health Organization.
bleeding scale (Fogarty et al., 2012); time to response, defined as the time from starting treatment to the first time of achieving platelet counts ≥50 × 10⁹/l; the proportion of patients who required protocol-defined rescue treatment during Stage I (defined as either a new ITP medication, an increase in dose of concomitant ITP medication from baseline, platelet transfusion or splenectomy); the proportion of patients whose platelet count was ≥50 × 10⁹/l for at least 75% of their platelet count assessments; total duration of time a patient had a platelet count ≥50 × 10⁹/l; and maximum period of time with a platelet count continuously ≥50 × 10⁹/l.

The safety and tolerability of treatment were determined from adverse events (AE) summarized descriptively by incidence and severity, and from clinical laboratory evaluations, physical examinations, electrocardiograms and ophthalmological examinations carried out during scheduled study visits at the study centres during Stage I.

The PK and PK/PD of eltrombopag were determined using PK and platelet count assessment samples. During week 2 of Stage II (or at a later visit), patients recruited at sites that had appropriate certification for the PK study (n = 30) underwent a serial sampling schedule relative to dosing: pre-dose (0 h) then 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 24 h after dosing. The remaining patients (n = 120) gave blood samples pre-dose (0 h) then 2 to 4 h and 5 to 8 h after dosing.

**Statistical analyses**

The planned sample size of 150 patients provided at least 99% statistical power to detect a treatment difference in the primary endpoint.

The safety population comprised all randomised patients who had received at least 1 dose of the study treatment (Fig 1). The intent-to-treat (ITT) population comprised all randomised patients who received at least 1 dose of study medication and had at least 1 on-therapy platelet count. The per-protocol (PP) population was defined as per the ITT population, but excluded major protocol violators.

The analysis of the primary efficacy endpoint was performed for both the ITT and PP populations. The study was designed to assess the null hypothesis H₀: γ = 1 (no difference), or reject it in favour of the alternative hypothesis H₁: γ ≠ 1 (two-sided at 5% level), where γ is the odds ratio (OR).

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**Fig 1. Study profile and populations analysed.**

*One patient had two major protocol deviations. ITT, intent-to-treat; PP, per protocol.*
of responding to treatment with eltrombopag relative to placebo. The proportion of patients achieving platelet counts \( \geq 50 \times 10^9/l \) between Weeks 1 and 6 was compared between treatments using a logistic regression model, allowing for the use of ITP medication at baseline (Yes/No), splenectomy (Yes/No), baseline platelet count \( \leq 15 \times 10^9/l \) (Yes/No), and treatment arm. The OR and 95% confidence intervals (CI) are provided. These statistical analyses were performed for both the primary analysis dataset (treated as the primary analysis), and the secondary analysis dataset (which served as the sensitivity analysis for the robustness of the primary results).

For the primary analysis dataset, evaluations for a patient who withdrew from the study were classified as a negative response from the time of withdrawal, and for all subsequent visits during Stage I of the study. In the event of a patient’s death, information for all subsequent assessments was considered missing. All intermittent missing data (apart from deaths) were classified as missing in the primary analysis dataset.

The secondary efficacy endpoint analyses were based on the secondary analysis dataset for the ITT population in which all missing data (whether they were intermittent or due to patient withdrawal) were classified as missing. Endpoints involving proportions of patients with specified platelet counts and those who required rescue treatment were analysed based on a logistic regression model with the use of ITP medication at baseline, splenectomy, baseline platelet count \( \leq 15 \times 10^9/l \) and treatment arm as covariates.

The odds of bleeding and clinically significant bleeding in the eltrombopag-treated group relative to placebo, based on information at each Stage I assessment, were compared using a generalized linear mixed model with a Logit canonical link function for repeated binary data, which allowed for baseline dichotomized WHO bleeding grade, use of ITP medication at baseline, splenectomy, baseline platelet count and treatment arm as fixed effects. In addition, the patient was treated as a random effect and assumed to follow a normal distribution \( \sim \text{N}(0, \sigma^2) \). Time to response during Stage I was summarized using Kaplan Meier curves, and compared between treatment groups using a stratified log-rank test, stratifying for use of ITP medication at baseline, splenectomy status and baseline platelet count. The Pike estimator of the treatment hazard ratio based on the stratified log-rank test was provided, together with 95% CI. For patients who did not achieve a response, time to response was censored at the time of last scheduled visit for platelet count evaluation. The total duration and the maximum period of time a patient had a platelet count \( \geq 50 \times 10^9/l \) during Stage I were analysed by the van Elteren stratified rank test, with stratification factors as stated previously.

PK and PK/PD analyses were conducted using a population approach with non-linear mixed effects modelling methods (Farrell et al., 2014). The following covariates were explored in PK analysis: body weight, gender, estimated creatinine clearance (based on the Cockcroft Gault equation), age, body mass index, albumin, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, alkaline phosphatase and concomitant use of corticosteroids. Post-hoc estimates of steady-state eltrombopag serum concentration area under the curve from time zero to the end of the 24-h dosing interval (\( \text{AUC}_{0-24} \)) and maximum serum concentration (\( C_{\text{max}} \)) after 50 mg once daily dosing were determined based on the final PK model for each patient. The following covariates were explored in PK/PD analyses: age, gender and concomitant use of corticosteroids.

### Results

#### Patients

A total of 155 Chinese patients from 16 centres in China were enrolled into this local registration study between February 2013 and June 2014 (ClinicalTrials.gov NCT01762761).

After stratification for baseline ITP medication, splenectomy and baseline platelet count, 104 patients were randomised to receive eltrombopag and 51 to receive placebo; 149 patients completed Stage I (Fig 1). Overall, 148 patients provided samples for the PK analysis and 147 for the PK/PD analysis (PK samples were not collected from one patient who experienced a severe bleeding event due to safety concerns, and another patient had interrupted eltrombopag treatment due to a platelet count \( > 250 \times 10^9/l \) and thus did not meet the criteria for PK sample collection). The demographic and baseline clinical characteristics of the enrolled patients were similar between treatment groups (Table I).

#### Treatment efficacy

The primary endpoint (platelet count \( \geq 50 \times 10^9/l \) after Day 42) was achieved by significantly more patients in the eltrombopag group (57.7%) than the placebo group (6.0%; Table II). Odds of achieving a platelet count \( \geq 50 \times 10^9/l \) were 26.08 times greater with eltrombopag than placebo (P < 0.001). Results of sensitivity analyses of the primary endpoint for the ITT and PP populations were consistent with those of the primary analysis findings (Table II). Median platelet counts were higher in the eltrombopag group than in the placebo group at every assessment visit during Weeks 1 and 6 of treatment in the ITT population (Fig 2A). In the eltrombopag group, the median platelet counts reached \( \geq 50 \times 10^9/l \) by Week 4, and remained at this level for the remainder of Stage I. No evidence of tachyphylaxis over time was observed.

The secondary efficacy outcomes are summarized in Table III and Fig 2B. Throughout Stage I, treatment with eltrombopag was statistically significantly better than with placebo for all secondary outcome measures relating to platelet counts, including all platelet count elevation endpoints, response rates, time to response (Fig 2B) and duration of response. Eltrombopag treatment also reduced the likelihood
of requiring rescue treatment by 87% compared to placebo, and reduced the odds of any bleeding by 72% compared to placebo \((P \leq 0.001)\) (Table III).

The number of patients with any bleeding symptoms decreased from baseline to Week 6 in both treatment groups \((\text{eltrombopag} 65\% \text{ to } 16\% ; \text{placebo} 72\% \text{ to } 34\% , P = 0.001; \text{Table III and Table SI})\). At every on-treatment weekly assessment, the proportion of patients who reported any bleeding symptoms was substantially lower in those treated with eltrombopag than placebo.

Although the difference in the OR of patients with clinically significant bleeding \((\text{WHO grades} 2 \text{ to } 4)\) did not reach statistical significance \((P = 0.306; \text{Table III})\), the proportion of patients was numerically lower or similar in the eltrombopag group compared with the placebo group at every weekly assessment \(\text{Table SII})\).

### Treatment exposure

In the safety population, the median average daily dose in the eltrombopag and placebo groups was 42.1 and 53.3 mg, and the median cumulative doses were 2025.0 and 2625.0 mg, respectively.

### Safety

The data regarding AEs are summarized in Table IV. The incidence of treatment-related AEs was higher in the
eltrombopag group than in the placebo group, but the incidence of serious adverse events (SAE) was lower with eltrombopag. Most AEs (reported by 29/34 patients in the placebo group and 58/66 in the eltrombopag group) were mild or moderate in intensity (i.e., grade $\leq 2$).

One patient in the placebo group died on day three of the study. The cause of death was undetermined and the investigator concluded that the death was unrelated to the study. The AEs that led to the withdrawal of three patients (2.9%) from eltrombopag treatment were increased blood urea nitrogen and acute renal failure, increased ALT, and a cerebral infarction, respectively. Another patient reported deep vein thrombosis that was considered to be related to eltrombopag treatment, so the dosage was reduced.

On-treatment hypokalaemia was observed in 15.7% of patients receiving placebo and 10.6% of those on eltrombopag, but the investigators concluded that this was probably due to the patients’ long-term use of steroids, and treatment-related hypokalaemia rates were much lower.

Fig 2. (A) Median (interquartile range) platelet count during first 6 weeks of treatment (ITT population). (B) Time to response for a patient first achieving platelet count $\geq 50 \times 10^9/l$ (secondary analysis dataset of ITT population). CI, confidence interval; HR, hazard ratio.
Table III. Secondary efficacy outcomes in the ITT population.

<table>
<thead>
<tr>
<th>Outcome measure between weeks 1 and 6 of treatment (Stage I)</th>
<th>Eltrombopag (n = 104)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients whose platelet counts reached $\geq 50 \times 10^9/l$ at least once at least once during the first 6 weeks, n (%)</td>
<td>80 (76-9)</td>
<td>9 (18-0)</td>
</tr>
<tr>
<td>OR (95% CI) (eltrombopag/placebo)*</td>
<td>23-80 (8-54, 66-33)</td>
<td>&lt;0-001</td>
</tr>
<tr>
<td>Proportion of patients whose platelet counts were $\geq 30 \times 10^9/l$, and whose platelet counts were at least twice the baseline platelet count at least once, n (%)</td>
<td>84 (81-6)†</td>
<td>18 (36-0)</td>
</tr>
<tr>
<td>OR (95% CI) (eltrombopag/placebo)*</td>
<td>8-52 (3-84, 18-94)</td>
<td>&lt;0-001</td>
</tr>
<tr>
<td>Proportion of patients with platelet counts $\geq 50 \times 10^9/l$ in $\geq 75%$ of their platelet count assessments between weeks 1 and 6, n (%)</td>
<td>23 (22-1)</td>
<td>1 (2-0)</td>
</tr>
<tr>
<td>OR (95% CI) (eltrombopag/placebo)*</td>
<td>16-54 (2-09, 131-12)</td>
<td>&lt;0-008</td>
</tr>
<tr>
<td>Total duration of time patient achieved a platelet count $\geq 50 \times 10^9/l$, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1-85 (1-76)</td>
<td>0-23 (0-84)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1-79 (0-0 5-1)</td>
<td>0-00 (0-0 5-1)</td>
</tr>
<tr>
<td>$P$ value‡</td>
<td>&lt;0-001</td>
<td></td>
</tr>
<tr>
<td>Maximum period of time with platelet count continuously $\geq 50 \times 10^9/l$, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1-77 (1-75)</td>
<td>0-21 (0-81)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1-57 (0-5-1)</td>
<td>0-00 (0-5-1)</td>
</tr>
<tr>
<td>$P$ value‡</td>
<td>&lt;0-001</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients who required rescue treatment between weeks 1 and 6, n, (%)</td>
<td>9 (8-7)</td>
<td>17 (34-0)</td>
</tr>
<tr>
<td>OR (95% CI) (eltrombopag/placebo)*</td>
<td>0-13 (0-05, 0-37)</td>
<td>&lt;0-001</td>
</tr>
<tr>
<td>Odds (95% CI) of any bleeding</td>
<td>0-28 (0-13, 0-59)</td>
<td>0-001</td>
</tr>
<tr>
<td>(WHO bleeding scale grade 1 4)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds (95% CI) of clinically significant bleeding</td>
<td>0-59 (0-21, 1-64)</td>
<td>0-306</td>
</tr>
<tr>
<td>(WHO bleeding scale grade 2 4)§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl, confidence interval; ITT, intention-to-treat; OR, odds ratio; SD, standard deviation; WHO, World Health Organization.

*Logistic regression analysis adjusted for use of immune thrombocytopenia (ITP) medication at baseline, splenectomy, baseline platelet count $\leq 15 \times 10^9/l$, and treatment.

†No platelet count was collected on day 1 or within 48 h before the first dose in one patient; thus, this patient was not evaluable for this end-point and n = 103.

¶Van Elteren stratified rank test with stratification factors, including the use of ITP medication at baseline, splenectomy, and baseline platelet count $\leq 15 \times 10^9/l$.

§Generalized linear mixed model with a Logit canonical link function for repeated binary data, allowing for baseline dichotomized WHO bleeding grade, use of ITP medication at baseline, splenectomy, baseline platelet count $\leq 15 \times 10^9/l$, and treatment as fixed effects and patient treated as a random effect.

The most common treatment-related AEs reported by patients in the eltrombopag group were increased ALT, increased AST and increased unconjugated blood bilirubin (Table IV).

Overall, 153 patients (98-7%) underwent pre-treatment bone marrow examinations for reticulum. Of the 102 patients in the eltrombopag group, 83 biopsies were graded myelofibrosis (MF)-0 and 19 were graded MF-1 based on the European Consensus Scale (Thiele et al, 2005). In the placebo group, 38 of the 51 patients were graded MF-0 and 13 were graded MF-1.

Of the patients with hepatobiliary laboratory abnormalities, none had an ALT and/or AST level that was more than three times the upper limit of normal (ULN) accompanied by bilirubin elevation more than 2 $\times$ ULN, or more than 1-5 $\times$ ULN post-baseline. One patient in each treatment group had ALT levels that were more than 5 $\times$ ULN during the study (grade 3). These elevations were generally transient and returned to normal levels within a week. At baseline, direct bilirubin was $>35\%$ of total bilirubin in 34 patients in the eltrombopag group (32-7%) and 6 patients in the placebo group (11-8%). Post-baseline, the number of patients with increased bilirubin increased in both study groups [eltrombopag 56 (53-8%) versus placebo 22 (43-1%)]. One patient on eltrombopag had a total bilirubin $\geq 1-5 \times$ ULN on day 43, but direct bilirubin values were within the normal range.
transaminase; SAE, serious adverse event.

AE, adverse event; ALT, alanine transaminase; AST, aspartate

Discussion

This is the first randomised study to evaluate the efficacy of eltrombopag at an initial dose of 25 mg once daily in Chinese patients with relapsed chronic ITP. A statistically significant improvement was found with eltrombopag versus placebo for all primary and secondary efficacy endpoints, except clinically significant bleeding, which was numerically superior with eltrombopag compared to placebo. The primary endpoint [i.e., the odds of achieving a platelet count \( \geq 50 \times 10^9/l \) at the Day 42 (Week 6) visit] was 26.08 times greater in the eltrombopag group than the placebo group (\( P < 0.001 \)). The proportion of patients who achieved platelet counts \( \geq 50 \times 10^9/l \) with eltrombopag (57.7\%) was similar to those reported in previous studies: 59\% in an international phase III study of 50 mg eltrombopag (Bussel et al, 2009) and 60\% in a Japanese study (Tomiyama et al, 2012).

In contrast to placebo, eltrombopag treatment raised platelet counts rapidly (within 1–2 weeks, with the full treatment effect seen by Week 4), and maintained platelet counts of \( \geq 50 \times 10^9/l \) at \( \geq 75\% \) of assessment in 22.1\% of patients versus 2\% of placebo patients from weeks 1 to 6. Median platelet counts with eltrombopag were higher than those observed with placebo at assessments during weeks 1 to 6 of Stage I.

Given the potential clinical benefit of platelet count increases, even to values \(< 50 \times 10^9/l\), and in line with current practice in China, the investigators also determined the proportion of patients with platelet counts \( \geq 30 \times 10^9/l \) and at least twice the baseline platelet count on at least 1 occasion between Weeks 1 and 6, which was found to be substantially higher with eltrombopag treatment (81.6\% vs. 36.0\% with placebo; \( P < 0.001 \)).

The clinical benefit of ITP treatment is measurable not only by platelet count, but also by assessing bleeding symptoms. There was a lower incidence of any bleeding with eltrombopag than placebo at each of the 6 weekly assessments during Stage I, although clinically significant bleeding of grade 2–4 based on WHO bleeding scale was not significantly different between treatment groups.

In this study, only 16\% of patients had undergone splenectomy because Chinese patients are reluctant to undergo this procedure (Wang et al, 2005). The Chinese Haematology Society’s treatment guidelines (Thrombosis and Haemostasis Group, Haematology Society, Chinese Medical Association 2011) are generally aligned with those of the American Society of Hematology described in the introduction (Neunert et al, 2011), except that second-line treatment representing the different stages of differentiation/maturation of platelet cell development originating from bone marrow progenitor cells. The drug concentration was related to the increase in the production of platelet precursors through a scalar constant. None of the tested covariates was found to be significant for the PK/PD relationship of eltrombopag.
includes recombinant human thrombopoietin (Wang et al., 2012), which is approved in China.

Eltrombopag was generally well tolerated; analysis of the safety data did not indicate any new or clinically relevant safety issues in Chinese patients. For example, safety results from the current study and the phase 3 RAISE study in mostly Caucasian patients (Cheng et al., 2011) showed that eltrombopag treatment may be associated with a transient increase in blood bilirubin.

Thromboembolic events in patients treated with eltrombopag occurred at low rates in the current study (1%) and in RAISE (2%), and also in both romiplostim-treated patients (2.4%) and placebo-treated patients (2.4%) in another report of mostly Caucasian patients with ITP (Gernsheimer et al., 2010), although the time-periods of observation were longer in the other studies (approximately 25 weeks). A study limitation is that efficacy and safety data are only presented for 6 weeks’ treatment. Although longer-term data will be needed to confirm its long-term efficacy and safety in Chinese patients, eltrombopag has already been shown to be well tolerated and effective for 3 years in other studies that included Japanese and other East Asian patients (Katsutani et al., 2013; Saleh et al., 2013).

The PK and PK/PD of eltrombopag in Chinese patients were well characterized, and were in agreement with findings from previous PK studies in Asian populations (Gibiansky et al., 2011; Hayes et al., 2011; Tomiyama et al., 2012). The estimated AUC0–7 in steady state after eltrombopag 50 mg once daily in Chinese patients from the current study (135 μg.h/ml) was similar to the previously estimated AUC0–7 in East Asian patients (163 μg.h/ml), and was 55% higher than the estimated AUC0–7 in the other populations (87 μg.h/ml) (Gibiansky et al., 2011). This finding supports the use of the lower 25-mg starting dose in Chinese patients rather than the 50-mg starting dose used in non-East Asian patients. None of the covariates (age, gender and concomitant use of corticosteroids) examined in the Chinese patients in this study were shown to influence eltrombopag exposure and response, which suggests that individual starting-dose modifications are not warranted for Chinese patients with chronic ITP.

As mentioned previously, eltrombopag exposure is higher in East Asian patients (Gibiansky et al., 2011), and we have observed that they are more likely to achieve platelet counts >200 × 109/l when treatment is initiated at a dose of 50 mg. The dosing guidelines used in this study enabled most eltrombopag-treated patients to achieve and maintain platelet counts between 50 × 109/l and 150 × 109/l. According to the study protocol, study medication had to be reduced if platelet counts exceeded 150 × 109/l in order to reduce the risk of subsequent thrombocytosis, but only 26 eltrombopag-treated patients (16.8%) reached this platelet count level, eight (5.2%) of whom had platelet counts >250 × 109/l, indicating that this schedule was effective in maintaining safe platelet levels. The median daily eltrombopag dose was approximately 42.1 mg during the double-blind treatment period. Higher doses were reached by mostly Caucasian patients in the phase 3 RAISE study (Cheng et al., 2011). During the first 10 weeks of RAISE, the starting dose of 50 mg daily was increased to 75 mg daily in approximately 40% of patients and reduced to 25 mg daily in only approximately 20% of patients – a dosing pattern that continued through the 26-week study.

In conclusion, these results confirm that eltrombopag elevates platelet levels predictably and consistently to a safe range, and reduces bleeding symptoms in Chinese ITP patients who have relapsed after, or are refractory to, standard first-line therapy. These findings suggest a favourable risk benefit profile for eltrombopag in this population. An initial dose of 25 mg once daily is appropriate for Chinese patients with ITP.

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Conflict of interest

The authors have no competing interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Incidence of any bleeding (based on WHO bleeding scale grade 0–4) during the first 6 weeks of treatment (ITT population).

Table SII. Incidence of clinically significant bleeding (based on WHO bleeding scale grade 2–4) during the first 6 weeks of treatment (ITT population).

References


