A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia

Left running head: BUSSEL et al

Right running head: Phase II trial of avatrombopag in chronic ITP

Scientific section designation: CLINICAL TRIALS AND OBSERVATIONS

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Key points

1. Once-daily oral avatrombopag dose-dependently raised platelet counts over 28 days, with stable counts maintained over a 24-week extension.

2. Low rates of severe adverse events (AEs) and study drug discontinuations due to AEs occurred despite dose increases in maintenance.
Abstract

Stimulation of platelet production by thrombopoietin-receptor agonists (TPO-RAs) is an effective second-line treatment strategy in immune thrombocytopenia (ITP). Avatrombopag (E5501) is an investigational non-peptide, TPO-RA active in humans. This 28-day Phase II study assigned subjects with ITP of ≥3 months to once-daily oral avatrombopag (2.5, 5, 10, 20 mg) or placebo; subjects completing randomized treatment could enroll in a 24-week extension study. Of 64 randomized subjects, 13% (avatrombopag 2.5 mg), 53% (5 mg), 50% (10 mg), and 80% (20 mg), versus 0% for placebo, achieved a platelet count (PC) response of ≥50×10⁹/L with ≥20×10⁹/L increase above baseline at Day 28. Fifty-three (83%) subjects entered the extension study and received long-term avatrombopag treatment: 52% had a durable response (PC response at ≥75% of their platelet assessments over the last 14 weeks) and 76% achieved an overall PC response (stable response or response at any ≥2 consecutive visits). All subjects experienced ≥1 adverse event (AE) (most commonly fatigue, headache, epistaxis) with 19% (n=12) reporting ≥1 serious AE. Across studies, 10 (16%) subjects withdrew due to an AE; five of these were due to increased PC. Avatrombopag was active and generally well-tolerated with PC response rates and AE incidence comparable with other TPO-RAs. Studies were registered at http://clinicaltrials.gov/, identifiers: NCT00441090 and NCT00625443.
Introduction

Immune thrombocytopenia (ITP) is characterized by autoantibody-mediated destruction of platelets and impairment of platelet production. These dual effects often result in severe thrombocytopenia and a concomitant predisposition to bleeding, with associated morbidity and mortality.\(^1\) Primary ITP is defined as isolated immune-mediated thrombocytopenia (peripheral blood platelet count [PC] <100×10\(^9\)/L) in the absence of other causes of thrombocytopenia.\(^4\) ITP may be asymptomatic in many affected individuals, but an increased risk of bleeding and potentially fatal hemorrhage occurs in those with a PC <30×10\(^9\)/L, especially if aged >60 years or with other contributing factors.\(^5\)

First-line therapeutic approaches for subjects with ITP include corticosteroids and/or intravenous immunoglobulins – that is, IVIg (and intravenous anti-D where available) – which help to reduce the rate of immune-mediated platelet destruction. Unfortunately, most subjects experience recurrence of their thrombocytopenia once these agents are tapered or withdrawn. Subsequent treatment is guided by individualized application of clinical practice guidelines,\(^4,6,7\) and options include splenectomy, anti-CD20 agents such as rituximab, immunosuppressive agents, and thrombopoietic agents. Each of these treatments has unique benefits, limitations, tolerability considerations, and risks, with key issues including efficacy, effects on bleeding per se, morbidity, and cost.\(^8-10\)

In contrast to well-established therapies that focus on mitigating platelet destruction, stimulation of thrombopoiesis is a newer approach.\(^10\) Two thrombopoietin-receptor agonists (TPO-RAs), eltrombopag and romiplostim, have been approved for the second-line treatment of chronic ITP. Both are effective in treating chronic ITP but have practical limitations: currently in the United
States romiplostim must be given subcutaneously by a health care professional and eltrombopag has important dietary restrictions as to when it can be taken relative to food intake.\textsuperscript{11,12} Hence, interest remains high in developing TPO-RAs for the treatment of ITP.

Avatrombopag (E5501; formerly YM477 and AKR 501) is a new, investigational, orally administered, non-peptide TPO-RA. It is believed to mimic the biological effects of TPO in vitro and in vivo, and was shown to increase PC in both animal models and healthy human volunteers.\textsuperscript{13-15} Like eltrombopag, avatrombopag is thought to bind to the transmembrane domain of the TPO receptor, which is different from the binding site of native TPO and romiplostim. Avatrombopag species-specificity (only humans and chimpanzees) is attributed to the presence of histidine rather than lysine at position 499 of the TPO receptor. Avatrombopag is taken once daily and lacks significant food interactions.

Here we report the results of sequential Phase II studies of avatrombopag: a 28-day, double-blind, randomized study and a follow-on 24-week open-label extension study. These are the first studies to examine the efficacy and safety of once-daily avatrombopag for the treatment of ITP.

**Methods**

**Study design**

Study 003 (clinicaltrials.gov identifier NCT00441090) involved 19 centers in the United States and was a Phase II, double-blind, randomized, dose-ranging, placebo-controlled, parallel-group trial of avatrombopag administered orally for four weeks. Subjects completing their assigned treatment in the randomized study were eligible to enroll in the extension study 004, a 24-week, Phase II study across 17 centers (NCT00625443). Both studies were conducted following
approval by the independent ethics committees of participating centers and in accordance with
the Declaration of Helsinki; all subjects provided written informed consent.

Subjects

For the randomized study, eligible subjects:

1) were aged ≥18 years;

2) had a confirmed diagnosis of ITP, according to American Society of Hematology guidelines,16
   for ≥3 months (persistent and chronic ITP) prior to randomization;

3) had a PC within 96 hours of randomization either <30×10^9/L if they were not receiving steroid
   therapy, or <50×10^9/L if receiving a stable dose of steroids for ≥2 weeks prior to screening; and

4) had failed to respond or relapsed after responding to one prior ITP therapy. Splenectomized
   subjects were eligible if their splenectomy had been performed more than four weeks prior to
   randomization.

Other key eligibility criteria included: adequate renal (creatinine ≤1.5 times the upper limit of
normal [×ULN]) and hepatic (total bilirubin, aspartate aminotransferase [AST] and alanine
aminotransferase [ALT] all ≤3×ULN) function, no history of cardiovascular disease,
thromboembolic disease, deep vein thrombosis (DVT), or any medical condition where systemic
anticoagulation was required for more than six months. Subjects with a history of lupus
anticoagulant or antiphospholipid syndrome were not eligible. In addition, all female subjects
who were pregnant and/or lactating were excluded.
**Treatment interventions and efficacy assessments**

In the randomized study, subjects were assigned to once-daily oral avatrombopag (2.5, 5, 10, or 20 mg) or placebo in a ratio of 3:3:3:3:1, respectively, for 28 days or until withdrawal from the study. Dosing was done under fasting conditions, as food effect studies had not been performed at the time of the study execution; subsequent healthy volunteer studies have demonstrated that avatrombopag systemic exposures are not substantially altered when administered with food. Key study withdrawal criteria included administration of rescue medication for ITP, a PC increase to \( \geq 500 \times 10^9/L \), and presence of a severe (Grade 3 or 4) and/or serious adverse event (AE) related to the study drug.

In the four-week randomized study, the primary efficacy endpoint was PC response rate, defined as the proportion of subjects who achieved PC \( \geq 50 \times 10^9/L \) and minimum PC increase of \( 20 \times 10^9/L \) above baseline at Day 28. Other efficacy endpoints included changes in median and mean PC, proportion of subjects who achieved PC \( \geq 50 \times 10^9/L \) and \( \geq 100 \times 10^9/L \) on Day 28, and proportion of subjects who doubled their PC from baseline to Day 28.

In the extension study, responders at Day 28 continued on a fixed blinded regimen, taking their same daily dose of avatrombopag (or placebo) in the extension study. Non-responders at Day 28 in the randomized study were given open-label avatrombopag 10 mg once daily when they entered the extension study; increases up to 40 mg once daily were permitted as needed to maintain a PC \( > 50 \times 10^9/L \). Reductions in concomitant ITP medications were not permitted in the randomized study, but were permitted in the extension study. Dose reductions of up to 50% in concomitant ITP medications were permitted if platelet counts were \( > 200 \times 10^9/L \); further reductions were permitted at 2-week intervals if increased PCs were sustained.
The primary objectives of the extension study were to assess the safety and tolerability of avatrombopag for an additional 24 weeks. Secondary objectives assessed markers of effectiveness such as change in PC, maintenance of PC, and decrease in concomitant ITP medications. After 18 subjects had enrolled in the extension study, the protocol was amended to allow more flexible, open-label dose-escalation in 10 mg increments every 14 days to a maximum of 40 mg, depending on the subject’s PC. Responders were held to a maximum of the blinded dose of study drug plus 20 mg/day of avatrombopag, whereas non-responders could escalate their dose up to a maximum of 40 mg/day, providing individualized dosing based on response to treatment. If an excessive PC ($\geq 500 \times 10^9$/L) occurred, the dosing was stopped and the PC monitored weekly until it decreased to $\leq 200 \times 10^9$/L. Dosing was then restarted at one dose level lower.

The extension study assessed the proportion of study participants who achieved a durable response. This was defined as subjects who had PC responses at $\geq 75\%$ of their PC assessments over the last 14 weeks of the study and had a minimum of three PC measurements; if a subject had only three visits with PC measurements, all three measurements were required to be classified as a PC response for the response to be counted as durable. Per protocol, PC values were measured biweekly through Week 24. Subjects who did not meet the minimum PC measurements and those using rescue medication or needing splenectomy by definition could not have a durable response. In addition, the proportion of subjects achieving an overall response was also assessed. An overall response was defined as a durable response or a transient PC response (which was PC responses at $\geq 2$ consecutive study visits at any time during the extension study). Subgroup analyses of durable response included baseline PC category ($\leq 15 \times 10^9$/L vs. $> 15 \times 10^9$/L) and history of splenectomy.
At the end of the extension, the study drug was discontinued, followed by a 4-week follow-up period during which the PC was determined twice weekly (Weeks 1 and 2) and then once weekly (Weeks 3 and 4).

**Safety assessments**

Continuous monitoring of AEs was performed. The severity of an AE was graded by the investigator using the Common Terminology Criteria for Adverse Events (CTCAE), v3.0. Laboratory evaluations (PC, hematology, coagulation, serum chemistry, urinalysis, and electrocardiograms [ECGs]) and clinical assessments, including medical history, vital signs, and concomitant medications, were recorded at intervals during the study period. Splenic ultrasound was performed periodically during the extension study. Bleeding was reported using CTCAE v3.0, under the category of Hemorrhage/Bleeding, and the time to the first bleeding event was performed as an exploratory analysis.

**Statistical analyses**

Since this was a proof-of-concept study, it was not powered to detect statistically significant changes in efficacy outcomes. No formal inferential testing was planned, and no adjustment for multiplicity was performed; all p-values that have been reported are nominal. All analyses presented were prespecified.

Primary efficacy analyses were conducted in the intent-to-treat group that included all randomized subjects who had at least one post-baseline PC. Primary and secondary efficacy variables were examined by response rate based on the number and percentage of subjects, and summarized by treatment group using last observation carried forward. An exploratory pair-wise analysis of the primary efficacy variable was performed using Fisher’s exact test (for each pair of
treatment groups; 10 comparisons in total). Analyses of safety included all subjects who received at least one dose of study drug and had at least one post-baseline safety assessment.

Results

Subject population

Subject demographic and baseline characteristics were generally comparable across the study groups (Table 1). Sixty-four subjects received treatment in the randomized study, and 53 subjects (83%) continued into the extension study. Subject flow throughout the randomized and extension studies is shown in Figure 1. Results from each of the randomized and extension studies are described below; a summary of the key efficacy endpoints throughout both studies is included in Figure 1 for reference.

Efficacy

Randomized study

A higher proportion of subjects achieved a PC response in all avatrombopag dose groups than in the placebo group. At Day 28, the response rates were 13%, 53%, 50%, and 80%, respectively, in the avatrombopag 2.5, 5, 10, and 20 mg groups, compared with 0% in the placebo group. Most responses to avatrombopag occurred by Day 7 (Figure 2A). A clear dose response with regard to median PC over time was observed (Figure 2B); however, there was a notable decreased median PC over time from Day 14 to Day 28 in the 20 mg group.

Treatment with avatrombopag 20 mg/day resulted in a significantly greater proportion of responses (80%) compared with placebo (0%; p=0.0036). A dose-dependent relationship was evident for median PC in the secondary endpoint analyses, with the largest PC increases
occurring in the avatrombopag 20 mg dose group (Figure 2B). Avatrombopag 20 mg also resulted in a significantly higher proportion of subjects doubling their PC compared with placebo: 87% vs. 20% (p=0.0139). Eighteen subjects (30.5%) treated with avatrombopag achieved a PC ≥100×10^9/L on Day 28: eight of these (53.3% of the group, p=0.0547 vs. placebo) were in the 20 mg group. No subjects in the placebo group achieved a PC ≥100×10^9/L. The proportion of subjects with a PC ≥100×10^9/L on Day 28 in the 20 mg group (8/15 or 53%) was significantly higher than that in the 2.5 mg group (1/15 or 6.7%; p=0.0142).

**Extension study**

Of the 53 subjects enrolled in the extension study (Figure 1), 25 were responders and 28 non-responders in the randomized study. In the extension study, 40/53 (76%) and 28/53 (53%) subjects achieved an overall response and durable response, respectively.

Over the extension study period, median PC across all subjects increased from 22×10^9/L at baseline to 56×10^9/L at Week 4 (n=51) and to 112.5×10^9/L at Week 24 (n=38) (Figure 3). Most responders in the 4-week randomized study (18/25 or 72%) achieved a durable response in the extension study. In contrast, among non-responders in the randomized study, only 10/28 (36%) achieved a durable response in the extension study.

Exploratory subgroup analyses found higher rates of durable response among those with baseline PC >15×10^9/L (vs. ≤15×10^9/L) or with no history of splenectomy (Figure 4).

Twenty-four subjects were using steroids at extension study entry, of which 13 had a ≥50% reduction in steroid dose and eight permanently discontinued concomitant steroid medication (no steroid use during the last eight weeks of the extension study).
A Kaplan-Meier plot of the time to the first bleeding event for the randomized and extension studies performed as an exploratory analysis demonstrated a decrease in the proportion of subjects with bleeds by Week 14 (Supplementary Figure 1).

**Dose and dose adjustment in the extension study**

Overall, the mean and median final doses of avatrombopag at the end of the extension study were 15 mg and 10 mg, respectively. Only five of 25 responders (20%) from the randomized study required upward dose titration in the extension study, compared with 21 (75%) of the 28 non-responders.

**Safety**

**Adverse events**

The most common AEs occurring in >10% of subjects across both studies – fatigue, headache, epistaxis, and contusion – are shown in Table 2. No deaths were reported during the studies. An overall safety profile of avatrombopag during the combined studies is presented in Table 3.

In the randomized study, the most frequently reported AEs (in ≥10% of subjects who received avatrombopag) were fatigue, headache, and epistaxis; these occurred at a similar rate to placebo. The only dose-related AE observed in the randomized study was increased PC, reported in four subjects receiving 20 mg (Supplementary Table 1). Two of these subjects had PC >500×10^9/L and had to be permanently discontinued from the study. Seven subjects had reported AEs of increased PC across the combined studies. Five of these seven subjects had treatment permanently discontinued.

Six percent of subjects (n=4/63) reported five thromboembolic events. The reported thromboembolic events (and associated PCs around the time of the events) were iliac DVT.
(19×10^9/L), stroke (119×10^9/L), superficial thrombophlebitis (571×10^9/L), myocardial infarction (MI) (47×10^9/L), and retinal artery occlusion (27×10^9/L). The retinal artery occlusion was reported in the same subject who reported the MI, 14 days after that subject discontinued study drug. Two of the thromboembolic AEs (iliac DVT and MI) resulted in permanent discontinuation of the subject from the study. The subject with the report of stroke underwent a temporary withdrawal of study drug. Three of four subjects with reported thromboembolic events had other risk factors for thrombosis; for example, the subject who reported the MI and retinal artery occlusion had a significant cardiovascular history of transient ischemic attacks, MIs, coronary artery bypass graft, and angioplasty (his/her inclusion was a protocol violation).

In this study, recurrence of severe thrombocytopenia was defined as PC that dropped below 10×10^9/L upon discontinuation of avatrombopag. This occurred in 14% (n=9/64) of subjects in the follow-up period; all had received avatrombopag doses ≥10 mg. These recurrences occurred in 11% (n=1/9) at one week, 56% (n=5/9) at two weeks, 22% (n=2/9) at three weeks, and 11% (n=1/9) at four weeks after discontinuation of avatrombopag dosing. Six of these nine subjects had PC below 10×10^9/L and 10×10^9/L less than baseline upon discontinuation of avatrombopag, which is the definition of recurrence of severe thrombocytopenia used in other TPO-RA studies.17

Bleeding AEs were reported in 67% (n=43/64) of subjects, of which the majority (90%) were Grade 1 or 2 (i.e. mild to moderate). Only 6.3% (n=4/64) of subjects reported Grade 3 or 4 bleeds. The reported Grade 3 or 4 bleeding events (reported as Preferred Terms, MedDRA v10.1) were Grade 4 GI (gastric) bleed (PC 2×10^9/L), Grade 3 intracranial bleed (2×10^9/L), Grade 3 hemorrhagic diathesis (reported as increased bleeding by the investigator) (4×10^9/L), and Grade 3 epistaxis (PC was 98×10^9/L 12 days after bleed).
Avatrombopag did not have an adverse effect on renal function, nor was it associated with clinically relevant changes in coagulation. Fifteen of the 21 Grade 3-4 laboratory abnormalities that occurred across the combined randomized and extension studies were related to PC: thrombocytopenia <10×10⁹/L in eight subjects, and increased PC in seven subjects. Splenic ultrasound in the extension study identified only two investigator-assessed clinically relevant findings (splenomegaly and hyperechoic lesion). There were two events of Grade 2-3 in increased liver function tests (one ALT and one AST) in subjects receiving avatrombopag. There were no reports of ALT or AST >3×ULN, or significant risk factors for drug-induced liver injury (as demonstrated by Hy’s law cases, i.e. >3×ULN elevated aminotransferases with elevated total bilirubin and without initial findings of cholestasis [serum alkaline phosphatase activity >2×ULN]). Transient changes were observed for liver function tests and other laboratory parameters, but no dose-related trends were observed except for the aforementioned PC on treatment and decreased PC after discontinuing treatment. No clinically relevant changes in vital signs, physical examination findings, or ECG parameters occurred in the combined analyses.

The incidence of severe (Grade 3 or 4) AEs is presented in Supplementary Table 2.

_Treatment discontinuation_

Interruption of study drug treatment (temporary treatment discontinuation) as a result of an AE occurred in eight (13%) subjects across both studies (Table 3). Five of these subjects had a dose interruption due to increased PC. The three remaining subjects had a dose interruption due to Grade 2 elevated ALT (n=1), Grade 2 leukocytosis (n=1), and Grade 3 cerebrovascular accident (n=1).
Permanent treatment discontinuation as a result of an AE occurred in a combined total of 16% (n=10/63) of subjects (four in the randomized study and six in the extension study; Table 3). Across studies, increased PC was the only AE that led to permanent treatment discontinuation in more than one subject, occurring in two in the randomized study and three in the extension study. One subject, receiving avatrombopag 10 mg in both the randomized and extension studies, permanently discontinued treatment due to Grade 2 leukocytosis that occurred during the extension study. Further evaluation resulted in diagnosis of myelodysplastic syndrome (MDS, RAEB type), and the subject was discontinued from the study. Approximately one month later, Grade 4 acute myelogenous leukemia (AML, French-American-British [FAB] classification M2) developed. There was one discontinuation due to Grade 2 musculoskeletal chest pain.

**Discussion**

The Phase II randomized and open-label extension studies support further study of once-daily oral avatrombopag in subjects with ITP. Over the 28-day randomized study period, dose-dependent response rates were observed with avatrombopag (see Figures 2 and 3). Significantly more subjects responded to avatrombopag 20 mg compared with placebo. Fifty-three patients entered the extension study, and the response rate was higher than in the randomized study because of the ability to increase the doses.

Of note in the randomized study, there was an observed decrease in median PC over time from Day 14 to Day 28 in the 20 mg group (randomized study; see Figure 2B). A sensitivity analysis removing those subjects who underwent discontinuations due to increased PC at Day 14 (n=2) demonstrated that there was still a discernible decrease in median PC from Day 14 to Day 28 in
this group. Despite this apparent drop in median PC, the overall response rates at Day 14 and Day 28 in the 20 mg group (93% and 80%) were broadly comparable.

Over the course of the 24-week extension study, 53% of subjects achieved a durable response; the durable platelet response endpoint used in this study was slightly different from durable endpoints utilized in other TPO-RA trials.\textsuperscript{17,18} In the extension study, PC measurements were taken every second week, as opposed to weekly, over a 14-week period. The durable endpoint suggests the ability of avatrombopag to achieve and maintain clinically relevant PC increases. Subgroup analyses demonstrated that there were more durable responses in those subjects who had not undergone a splenectomy or who had baseline PC $>15\times10^9$/L. The lower response in splenectomized subjects might simply reflect that this is a more refractory group of subjects. Caution should be used when interpreting these subgroup analyses as the sample sizes were very small.

Ten of 28 (36%) non-responders in the randomized study had a durable response in the extension study. Subjects had an opportunity either to receive avatrombopag dosing (previous placebo subjects) or to undergo dose adjustment and receive higher-dose avatrombopag.

Treatment with avatrombopag was generally well-tolerated: low rates of severe AEs, serious AEs, and study drug discontinuations due to AEs were observed. Overall, the AE profile was comparable with those reported in previous trials of TPO-RAs; for example, in rates of thromboembolic events or recurrence of thrombocytopenia.

As expected, due to the mechanism of action of TPO-RAs, recurrence of severe thrombocytopenia developed upon discontinuation of avatrombopag in 14% of subjects. The recurrence of severe thrombocytopenia on discontinuation of avatrombopag appeared to be dose-dependent, as all nine subjects were in the higher (10 mg and 20 mg) dose groups. Tapering of
the dose has been suggested as a possible method to reduce the occurrence of severe thrombocytopenia but was not explored in this study.10

The bleeding AEs were primarily of mild to moderate severity. The bleeding resolved in all four subjects who reported a Grade 3 or 4 bleed. The frequency of bleeding events diminished over the course of treatment with the majority of events occurring by Week 14. At this time point, subjects would have had the opportunity to dose adjust to optimize their PC response.

The frequency of thromboembolic events in the long-term studies of romiplostim and eltrombopag (6% for each)19,20 is similar to the thromboembolic event rates seen in these studies (6.3%). As in the published data, the majority of subjects (i.e. 75%, n=3/4) had risk factors for thromboembolic events. No trend was noted between elevated PCs and thromboembolic events in any of these studies.

One subject developed Grade 3 leukocytosis, progressing to MDS and then AML. It is likely that this subject did not have ITP at study entry, but rather an underlying MDS. Potentially avatrombopag dosing may have stimulated an increase in blast cells in this subject. This subject’s experience suggests that bone marrow analysis early on might be prudent in cases where any suspicion of MDS exists.

Two subjects in the extension study had splenic ultrasound findings. One subject had a small change in splenic length from 10.5 cm to 12.0 cm. This subject’s AE profile and laboratory assessments revealed no other hematological disease during the study. The second subject had a 1.5 cm hyperechoic splenic lesion thought likely to represent a splenic hemangioma that remained unchanged throughout the extension study.
The primary limitation was that the current studies were not powered to derive unequivocal conclusions with a sample size of only 64 subjects, of which only five were in the placebo group. However, this was deemed an adequate sample size to determine a treatment effect while minimizing the number of subjects exposed to placebo. The small sample size limits the conclusions that can be drawn.

Further limitations pertain to the large inter-subject variability for PC (for example, as seen in Figure 3), compounded by the comparatively few dose discontinuations and interruptions.

Additional experience with avatrombopag in a wider subject population will also provide further information on any food effects that may occur such as those seen in subjects taking eltrombopag. In addition, although mild derangement of hepatic enzymes was observed in this study, no severe hepatic toxicity associated with avatrombopag was observed. Larger clinical studies are required to fully characterize avatrombopag’s hepatic safety profile.

In summary, avatrombopag achieved increases in platelet counts, was relatively well-tolerated, and had an acceptable safety profile in these two Phase II studies of subjects with ITP. Significant platelet count responses were achieved versus placebo during the 28-day randomized study, and stable platelet count responses were observed over six months in the subsequent extension study. Based on these Phase II data, avatrombopag is a candidate for further study and development in the treatment of ITP.
Acknowledgments

The authors would like to thank the study investigators, coordinators, nurses, and subjects and their families for their invaluable contributions to this study. The authors also thank David Squillacote, MD, for critical review of the manuscript. This study was sponsored by Eisai Inc. Editorial support was provided by Michael G. Pellegrino, PhD, and Gary Dever, PhD, of Complete Medical Communications, and was funded by Eisai Inc.

Authorship

Contributions:

All authors analyzed and interpreted the data, contributed towards critical revision of the manuscript, and approved the final draft.

J.B.B. and J.M. led the development and writing of the initial draft of the manuscript and provided ongoing comments on the writing.

D.J.K. provided substantial input and critical direction to the initial draft of the manuscript.

J.M. provided additional clinical information.

S.T. performed statistical analyses.

J.B.B. had final responsibility for the decision to submit for publication.

Conflict-of-interest disclosure:

J.B.B.: research support from Amgen, Cangene, GlaxoSmithKline, Genzyme, IgG of America, Immunomedics, Ligand, Eisai, Shionogi, and Sysmex. J.B.B.’s family owns stock in Amgen and
GlaxoSmithKline. J.B.B. has participated in Advisory Boards for Amgen, GlaxoSmithKline, Ligand, Shionogi, Symphogen, and Eisai.

D.J.K.: research support from Eisai, ONO, Pfizer; consultancy for Amgen, GlaxoSmithKline.

L.M.A.: research support from Eisai; Amgen speakers’ bureau.

C.M.K.: research support from Eisai and Grifols; consultancy for Amgen.

A.C.: research support from Eisai and Stago; consultancy for Baxter, Bayer, Daiichi-Sankyo, Genzyme.

K.B.P.: research support from Eisai.

S.T.: employee of Eisai, Inc.

References


Table 1. Baseline demographics and subject characteristics by treatment group and study

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<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td>1 (20)</td>
<td></td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (73)</td>
<td>11 (73)</td>
<td>12 (86)</td>
<td>10 (67)</td>
</tr>
<tr>
<td></td>
<td>4 (80)</td>
<td></td>
<td>40 (76)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline steroid use, yes, n (%)</td>
<td>4 (27)</td>
<td>8 (53)</td>
<td>6 (43)</td>
<td>10 (67)</td>
</tr>
<tr>
<td></td>
<td>3 (60)</td>
<td></td>
<td></td>
<td>25 (47)</td>
</tr>
<tr>
<td>Baseline PC ≤15×10^9/L, n (%)</td>
<td>5 (33)</td>
<td>2 (13)</td>
<td>5 (36)</td>
<td>4 (27)</td>
</tr>
<tr>
<td></td>
<td>2 (40)</td>
<td></td>
<td>15 (28)</td>
<td></td>
</tr>
<tr>
<td>History of splenectomy: yes, n (%)</td>
<td>5 (33)</td>
<td>4 (27)</td>
<td>3 (21)</td>
<td>6 (40)</td>
</tr>
<tr>
<td></td>
<td>2 (40)</td>
<td></td>
<td>17 (32)</td>
<td></td>
</tr>
</tbody>
</table>

Baseline was defined as the last observation (within four days) before the start of study drug in the randomized study.

PC indicates peripheral blood platelet count; SD, standard deviation.
Table 2. Summary of safety and most common AEs (occurring in ≥10% of subjects in the combined avatrombopag treatment groups) during the randomized and extension studies.

<table>
<thead>
<tr>
<th>No. (%) subjects with:</th>
<th>Total number of subjects receiving avatrombopag (N=64)</th>
<th>Any AE*</th>
<th>Severe AE†</th>
<th>Serious AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE</td>
<td>64 (100)</td>
<td>26 (41)</td>
<td>12 (19)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (38)</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 (33)</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>16 (25)</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>13 (20)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (14)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (14)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Severe thrombocytopenia (platelets &lt;10×10^9/L)</td>
<td>9 (14)</td>
<td>8 (13)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>8 (13)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (11)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7 (11)</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Petechiae</td>
<td>7 (11)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PC increased</td>
<td>7 (11)</td>
<td>7 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (11)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

AE indicates adverse event; PC indicates peripheral blood platelet count.

*Any grade or relationship; †Grade 3 or 4.
Table 3. Overall safety profile of avatrombopag during the randomized and extension studies

<table>
<thead>
<tr>
<th>AE category*, n (%)</th>
<th>Total number of subjects receiving avatrombopag (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE during treatment</td>
<td>64 (100)</td>
</tr>
<tr>
<td>Severe (Grade 3-4) AEs</td>
<td>26 (41)</td>
</tr>
<tr>
<td>Suspected drug-related AEs†</td>
<td>42 (66)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Serious treatment-related AEs</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Withdrawal of study drug due to AE</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Dose interruption due to AE</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
</tbody>
</table>

AE indicates adverse event.

*Subjects may fall into more than one category.

†Related AEs include those whose relationship was categorized as possible or probable by the investigator.
Figure legends

Figure 1. Flow diagram of subject disposition and response rates for the avatrombopag double-blind and extension studies.

Footnote:

*Continued Grade 3-4 thrombocytopenia (lack of efficacy); Responders indicates those subjects with a PC response of $\geq 50 \times 10^9/L$ with $\geq 20 \times 10^9/L$ increase above baseline at Day 28; Durable response indicates PC response at $\geq 75\%$ of their platelet assessments over the last 14 weeks; Overall response indicates stable response or response at any $\geq 2$ consecutive visits. In total, there were 28 (53%) and 40 (76%) subjects with durable and overall responses, respectively. AE, adverse event; PC, platelet count; SAE, serious AE.

Figure 2. Response rate (proportion of subjects who achieved PC $\geq 50 \times 10^9/L$ and minimum PC increase of $20 \times 10^9/L$ above baseline) at each time point for avatrombopag and placebo cohorts (A) and median [Q1, Q3] platelet count over time by treatment group (B) in the randomized study (LOCF).

Footnote:

For each median (second quartile) PC presented in Panel B, error bars denote the first (lower value of bar) and third (upper value of bar) quartiles.

LOCF, last observation carried forward.

Figure 3. Median [Q1, Q3] platelet count over time across all subjects in the extension study and during the four-week follow-up period (observed data).
Footnote:

For each median (second quartile) PC, error bars denote the first (lower value of bar) and third (upper value of bar) quartiles.

FL, follow-up period after avatrombopag treatment period.

Figure 4. Proportion of subjects with a durable response (PC response at $\geq 75\%$ of a minimum of three PC assessment visits occurring in the last 14 weeks of the extension study), stratified by baseline platelet count and splenectomy status in the extension study (observed data).

Footnote:

*Avatrombopag responders in the extension study.

Shown are the proportions of all avatrombopag-treated subjects with response-level PC (full analysis population). PC, peripheral blood platelet count.
Figure 1.
Figure 2.

A

Responders (%)

Day 7  Day 14  Day 21  Day 28

Placebo  Avatrombopag 2.5 mg  Avatrombopag 5 mg  Avatrombopag 10 mg  Avatrombopag 20 mg

B

Median platelet count (x 10^9/L)

Baseline  Day 7  Day 14  Day 21  Day 28

Placebo  Avatrombopag 2.5 mg  Avatrombopag 5 mg  Avatrombopag 10 mg  Avatrombopag 20 mg
Figure 3.
Figure 4.

- Baseline PC $\leq 15 \times 10^9/L$: 4 patients (n=27)
- Baseline PC $>15 \times 10^9/L$: 24 patients (n=63)
- Splenectomy: 5 patients (n=29)
- No splenectomy: 23 patients (n=64)
A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia

James B. Bussel, David J. Kuter, Louis M. Aledort, Craig M. Kessler, Adam Cuker, Kelly B. Pendergrass, Shande Tang and Joe McIntosh