Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial

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Summary

Background Eltrombopag is an oral, non-peptide, thrombopoietin-receptor agonist that stimulates thrombopoiesis, leading to increased platelet production. This study assessed the efficacy, safety, and tolerability of once daily eltrombopag 50 mg, and explored the efficacy of a dose increase to 75 mg.

Methods In this phase III, randomised, double-blind, placebo-controlled study, adults from 63 sites in 23 countries with chronic idiopathic thrombocytopenic purpura (ITP), platelet counts less than 30 000 per μL of blood, and one or more previous ITP treatment received standard care plus once-daily eltrombopag 50 mg (n=76) or placebo (n=38) for up to 6 weeks. Patients were randomly assigned in a 2:1 ratio of eltrombopag:placebo by a validated randomisation system. After 3 weeks, patients with platelet counts less than 50 000 per μL could increase study drug to 75 mg. The primary endpoint was the proportion of patients achieving platelet counts 50 000 per μL or more at day 43. All participants who received at least one dose of their allocated treatment were included in the analysis. This study is registered with ClinicalTrials.gov, number NCT00102739.

Findings 73 patients in the eltrombopag group and 37 in the placebo group were included in the efficacy population and were evaluable for day-43 analyses. 43 (59%) eltrombopag patients and six (16%) placebo patients responded (ie, achieved platelet counts ≥50 000 per μL; odds ratio [OR] 9·61 [95% CI 3·31–27·86]; p<0·0001). Response to eltrombopag compared with placebo was not affected by predefined study stratification variables (baseline platelet counts, concomitant ITP drugs, and splenectomy status) or by the number of previous ITP treatments. Of the 34 patients in the efficacy analysis who increased their dose of eltrombopag, ten (29%) responded. Platelet counts generally returned to baseline values within 2 weeks after the end of treatment. Patients receiving eltrombopag had less bleeding at any time during the study than did those receiving placebo (OR 0·49 [95% CI 0·26–0·89]; p=0·021). The frequency of grade 3–4 adverse events during treatment (eltrombopag, two [3%]; placebo, one [3%]) and adverse events leading to study discontinuation (eltrombopag, three [4%]; placebo, two [5%]), were similar in both groups.

Interpretation Eltrombopag is an effective treatment for managment of thrombocytopenia in chronic ITP.

Funding GlaxoSmithKline.

Lancet 2009; 373: 641–48

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Introduction

Thrombocytopenia in patients with idiopathic thrombocytopenic purpura (ITP) is due to accelerated platelet destruction and suboptimum platelet production.[1–3] The ensuing low platelet counts result in bleeding symptoms[1] that range from mild, common events, such as petechiae and bruising, to rare, serious events, such as intracranial haemorrhage.[4] Thrombopoietin is the primary cytokine stimulating thrombopoiesis. An important component of the pathophysiology of ITP is the absence of a substantial compensatory increase in thrombopoietin levels despite severe thrombocytopenia.

The primary goal of therapy for patients with chronic ITP is to keep the risk of bleeding to a minimum by increasing platelets to a safe level of at least 30 000–50 000 per μL with few treatment-associated toxic effects. Present treatment strategies have focused primarily on inhibition of platelet destruction (eg, glucocorticosteroids, intravenous immunoglobulins, intravenous anti-D, immunosuppressive drugs, splenectomy, and monoclonal antibodies directed at B cells). Although these treatments are often useful, not all patients respond to them, and they can be associated with undesirable side-effects.[5–7]

Stimulation of thrombopoiesis was explored with first-generation recombinant thrombopoietins that were tested in clinical trials primarily in healthy people and patients with chemotherapy-induced thrombocytopenia;[8,9] however, development of antibodies cross-reactive to endogenous thrombopoietin prevented their further use.[8,9] Second-generation agents were subsequently developed.

Eltrombopag is an oral, small molecule, non-peptide thrombopoietin-receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor. It stimulates the proliferation and differentiation of megakaryocytes in bone marrow, resulting in a dose-dependent increase in normally functioning platelets in

preclinical studies[10–13] and in healthy volunteers.[10,13–15] Both eltrombopag[16] and romiplostim,[17–19] a thrombopoiesis-stimulating peptibody given by subcutaneous injection once per week, have shown efficacy in increasing platelet counts in patients with chronic ITP without undue toxic effects. Additionally, in a phase II study, eltrombopag has increased platelet counts in patients with thrombocytopenia secondary to hepatitis C virus.[20]

A phase II study in patients with chronic ITP showed that eltrombopag at doses of 50 mg and 75 mg induced a substantial platelet increase with a favourable safety profile.[16] The objective of this phase III randomised study was to assess the efficacy, safety, and tolerability of once daily eltrombopag 50 mg in more than 100 adults with previously treated chronic ITP who were naive to thrombopoietic agents, and to explore the efficacy of a dose increase to 75 mg (if needed).

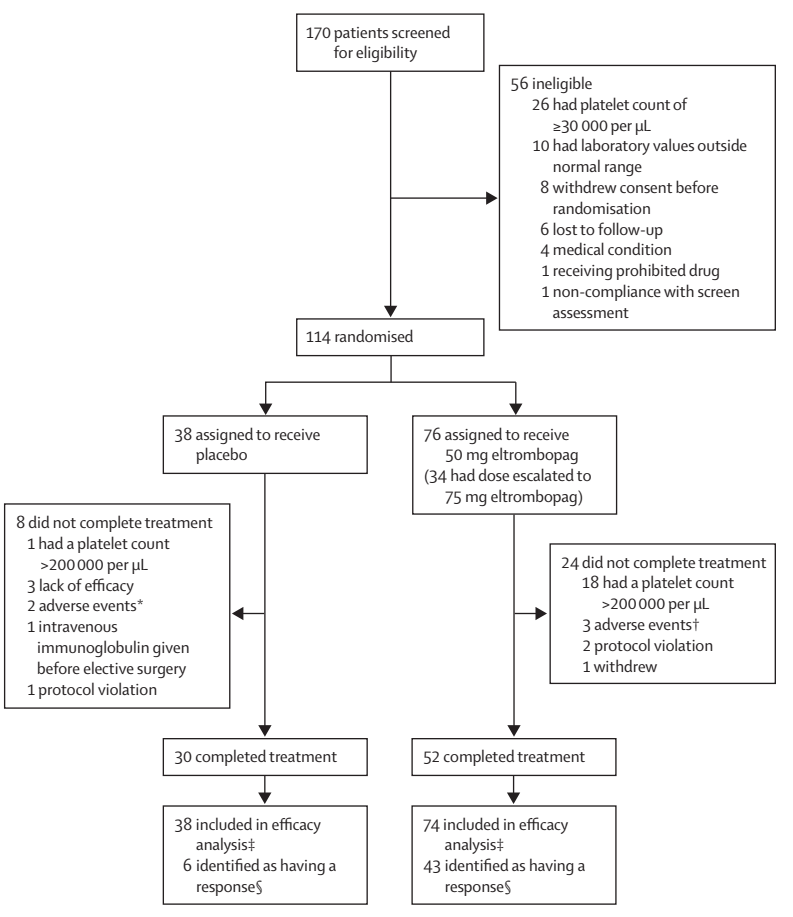

Figure 1: **Trial profile**
*One patient had cerebral haemorrhage, gastrointestinal haemorrhage, and haematuria. One patient had a facial injury. †One patient had abnormal hepatic function, one had a gastrointestinal haemorrhage, and one had a cerebral haemorrhage. ‡Efficacy population was defined as all patients randomised and treated with at least one dose of the study treatment, with baseline platelet count less than 30 000 per μL. §Achieved platelet counts 50 000 per μL or more at day 43 or responded with platelet count greater than 200 000 per μL and withdrew prematurely. 73 patients were evaluable for responder analyses in the eltrombopag group and 37 in the placebo group (one patient was non-evaluable in each group).

Methods

Patients

Patients were enrolled between Feb 6, and April 17, 2006, at 63 sites in 23 countries. Patients were required to be aged 18 years or older, have at least a 6-month history of ITP, have received at least one previous treatment for ITP, and have a pretreatment platelet count less than 30 000 per μL of blood. Patients could receive other ITP drugs as maintenance therapy (eg, glucocorticosteroids, azathioprine, danazol, ciclosporine A, and mycophenolate mofetil), and were eligible if the doses had been stable for 1 month or more and were intended to remain stable throughout the treatment period; new ITP drugs were only allowed in emergency situations. Previous therapy with immunoglobulins, immunomodulators, rituximab, and cyclophosphamide must have been completed 2 weeks or more before enrolment. Patients were excluded if they showed evidence of HIV, or hepatitis C or B infections; congestive heart failure, arrhythmia, or thrombosis within the previous year; and myocardial infarction within the previous 3 months. Women who were nursing or pregnant were not eligible, nor were patients who required use of drugs containing calcium or magnesium during the treatment period. All patients

	Placebo (n=38)	Eltrombopag 50 mg (n=76)	Total (N=114)
Age (years)			
Median (range)	51(21–79)	47 (19–84)	48 (19–84)
Mean (SD)	48 (16)	51 (17)	50 (17)
Sex			
Women	27 (71%)	43 (57%)	70 (61%)
Men	11 (29%)	33 (43%)	44 (39%)
Race			
Black	0	1 (1%)	1 (<1%)
White	26 (68%)	58 (76%)	84 (74%)
Other	12 (32%)	17 (22%)	29 (25%)
Stratification variables			
Splenectomy	14 (37%)	31 (41%)	45 (39%)
Concomitant ITP therapy*	17 (45%)	32 (42%)	49 (43%)
Baseline platelet counts ≤15 000 per μL	17 (45%)	38 (50%)	55 (48%)
Previous ITP therapies†			
≥1	38 (100%)	76 (100%)	114 (100%)
≥2	26 (68%)	56 (74%)	82 (72%)
≥3	16 (42%)	42 (55%)	58 (51%)
≥4	9 (24%)	30 (39%)	39 (34%)
≥5	7 (18%)	16 (21%)	23 (20%)

Data are number (%) unless otherwise indicated. ITP=idiopathic thrombocytopenic purpura. *Two patients reduced dose of concomitant medication (prednisone and mycophenolate, respectively) while receiving eltrombopag. †Most common previous therapies included corticosteroids (29 [76%] placebo group; 57 [75%] eltrombopag group), intravenous immunoglobulins (13 [34%] placebo group; 36 [47%] eltrombopag group), and rituximab (8 [21%] placebo group; 17 [22%] eltrombopag group).

Table 1: **Demographics and patient characteristics**

were required to have normal creatinine and liver enzyme concentrations. The study protocol was approved by the ethics committee at every institution, and all patients provided written informed consent before enrolment.

Study design and procedures

In this double-blind, placebo-controlled study, patients were randomly assigned 2:1 to receive standard of care and either eltrombopag (GlaxoSmithKline, Ware, UK) 50 mg or placebo (GlaxoSmithKline) once daily for up to 6 weeks. Randomisation was stratified by splenectomy status, use of baseline concomitant ITP therapy, and baseline platelet counts 15 000 per μL or less or greater than 15 000 per μL. Patients were randomly assigned by an in-house validated randomisation system (RANDALL). The eltrombopag dose could be increased from 50 mg to 75 mg after 3 weeks in patients whose platelet counts were less than 50 000 per μL. Treatment was discontinued in patients who attained a platelet count greater than 200 000 per μL.

The primary study endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to 50 000 per μL or more at day 43 (ie, 6 weeks after the start of treatment); patients who withdrew prematurely because of a platelet count greater than 200 000 per μL were considered responders. Patients who discontinued treatment for any other reason (eg, patient decision, lack of efficacy, adverse event) were considered non-responders irrespective of their platelet count. Secondary endpoints included platelet counts, the odds of responding during weeks 2–6, proportion of patients with platelet counts 50 000 per μL or more and at least twice the baseline amount, incidence of bleeding symptoms, safety, and tolerability. The incidence and severity of bleeding symptoms were assessed at every study visit with the WHO bleeding scale (grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; and grade 4, debilitating blood loss). All patients were assessed for safety, tolerability, and efficacy every week during treatment, and at 1, 2, 4, and 6 weeks after discontinuation of study drug. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Health-related quality of life was analysed with the acute recall version of the short form-36, version 2 (SF-36v2) questionnaire,[21] which was completed by every patient at screening and on completion of the study. Changes of more than 10 points or 0·5 standard deviations were considered clinically meaningful.[21,22]

Statistical analysis

The primary analysis compared the odds of response between eltrombopag and placebo on day 43. On the basis of results from the phase II study,[16] it was estimated that 25% and 60% of patients would respond to placebo and eltrombopag, respectively. Thus, 87 evaluable patients (58 receiving eltrombopag and 29 receiving placebo) were needed to provide 90% power at the 5% level of significance (two sided). However, to provide supplementary safety data, additional patients were recruited for a total of 76 patients randomly assigned to the eltrombopag group and 38 to the placebo group. All participants who were randomly assigned and received at least one dose of their allocated treatment were included in the intention-to-treat and safety populations. A subset of these patients, those with baseline platelet count less than 30 000 per μL, were also included in the efficacy population.

The odds of a response (platelets ≥50 000 per μL) were compared between the eltrombopag and placebo treatment groups with a logistic regression model with adjustment for the use of concomitant ITP drugs, splenectomy, and baseline platelet count (≤15 000 per μL).

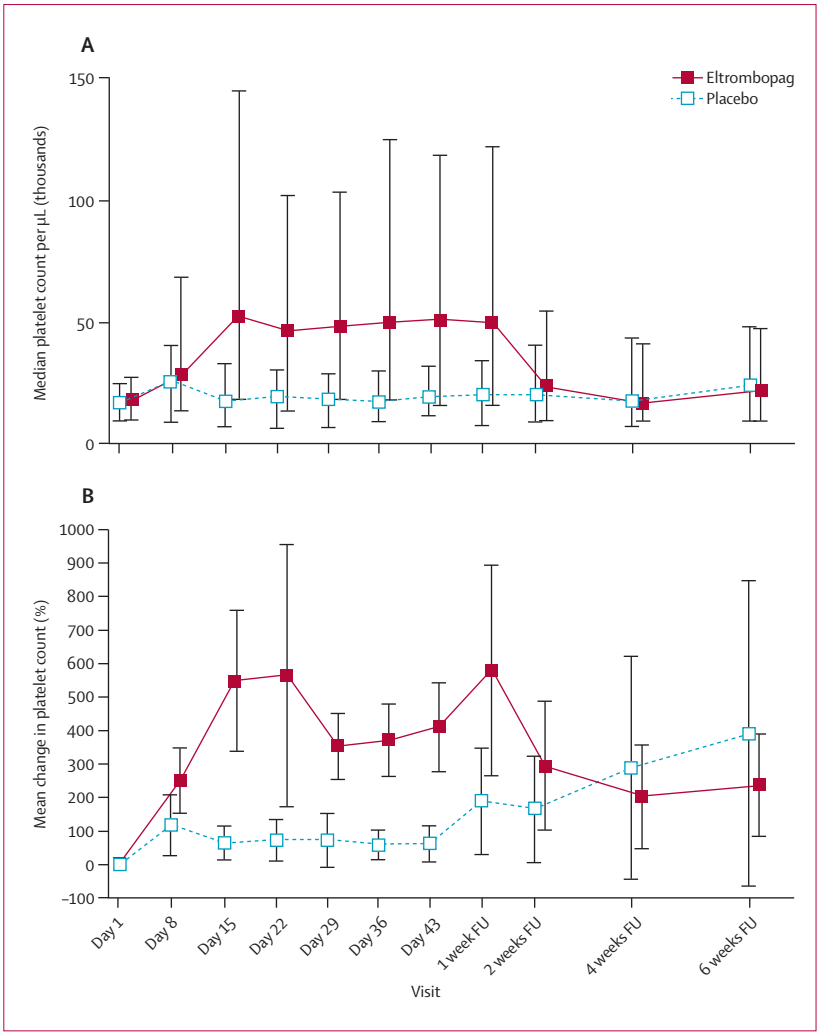

Figure 2: **Median platelet counts (A) and mean changes in platelet counts (B) at every visit***
Median platelet counts at every visit are shown with IQR, and mean changes in platelet counts from baseline at every visit are shown with 95% CIs. FU=follow-up. *Four patients who received eltrombopag and two who received placebo were still receiving study medication on or within 3 days before the day-50 assessment and were included in this analysis.

	Placebo	Eltrombopag
Day 8	118·54% (28·94 to 208·14)	250·59% (154·74 to 346·45)
Day 15	65·75% (16·63 to 114·87)	548·49% (337·65 to 759·34)
Day 22	74·13% (14·04 to 134·21)	565·60% (176·48 to 954·72)
Day 29	74·86% (–7·32 to 157·05)	355·32% (258·51 to 452·14)
Day 36	60·61% (16·14 to 105·08)	372·22% (263·94 to 480·51)
Day 43	63·60% (9·37 to 117·84)	410·02% (277·88 to 542·15)
Day 50	190·88% (32·62 to 349·15)	579·99% (265·23 to 894·76)
Day 57	166·06% (9·48 to 322·63)	295·98% (103·25 to 488·71)
Day 71	288·34% (–43·83 to 620·50)	202·49% (48·16 to 356·83)
Day 85	392·71% (–63·68 to 849·10)	238·42% (88·20 to 388·63)

Table 2: **Mean percentage change (95% CI) from baseline count**

Additionally, the relation of response to the number of previous ITP treatments, sex, and age was also assessed in post-hoc analyses. The overall type I error was 5% (two sided).

The odds of responding during weeks 2–6 of the treatment period were compared between treatment groups with a repeated measures model for binary data adjusted for the use of concomitant ITP drugs, splenectomy, and baseline platelet count (≤15 000 per μL). The generalised estimating equations method[23] was used for the observed dataset to estimate the regression model parameters, and 95% CI of the overall odds ratio was determined.

Bleeding symptoms (WHO bleeding scale, grades 1–4) were compared between the eltrombopag and placebo treatment groups at day 43 with a logistic regression model adjusted for ITP drug use at baseline, splenectomy status, and baseline platelet count (≤15 000 per μL). A comparison was also made over the 6-week treatment period with a repeated measures model for binary data, with adjustment for the same covariates and with use of generalised estimating equations method[23] to estimate the regression model parameters. Descriptive statistics were used to summarise demographic and baseline clinical characteristics, and safety data.

In a post-hoc analysis, data from patients with baseline platelet counts 15 000 per μL or less who did not respond to eltrombopag (ie, did not achieve a count ≥50 000 per μL) were examined to explore whether eltrombopag induced a clinically meaningful platelet increase to between 15 000 per μL or more and less than 50 000 per μL by day 43.

Additionally, a detailed analysis of platelet counts after treatment was done to examine whether a transient decrease of platelet counts occurred after therapy ended. Patients with a platelet count both less than 10 000 per μL and at least 10 000 per μL less than their baseline platelet count within 4 weeks after withdrawal of study drug were identified.[17]

This study is registered with ClinicalTrials.gov, number NCT00102739.

Role of the funding source

GlaxoSmithKline and the academic principal investigator (JBB) were jointly responsible for the study design and development of the study protocol. Decisions related to the content of the report were made by the principal investigator in consultation with all authors. All authors had access to the primary data, assume responsibility for the completeness of the data reported, and contributed to the writing of this report. JBB had final responsibility for the decision to submit the report for publication.

Results

Of 170 patients screened for this study, 114 were randomly assigned to treatment, none of whom had previously received a thrombopoietic agonist (figure 1). The reasons for ineligibility are shown in figure 1; the most common were a platelet count 30 000 per μL or more, laboratory values (eg, transaminases) out of normal range, and withdrawal of consent before randomisation.

Randomised patients had a median age of 48 years (range 19–84), nearly two-thirds were women, and three-quarters were white (table 1). 45 (39%) had undergone splenectomy, 49 (43%) were receiving concomitant ITP medication (most commonly prednisone), and 55 (48%) had a baseline platelet count 15 000 per μL or less. Just over half of all patients had received three or more ITP therapies (table 1) and 47 (41%) had had ITP for at least 5 years. Corticosteroids were the most commonly reported previous ITP therapy, used by 29 (76%) patients in the placebo group and 57 (75%) in the eltrombopag treatment group. Other common previous therapies included intravenous immunoglobulins (13 [34%] placebo group and 36 [47%] eltrombopag group) and rituximab (eight [21%] placebo group and 17 [22%] eltrombopag group). Only one patient in each treatment group received rituximab within 3 months of study entry (22 days previously in the placebo group and 27 days previously in the eltrombopag group). The patient in the placebo group had platelet counts less than 40 000 per μL throughout the study. Platelet counts for the patient in the eltrombopag group increased from 28 000 per μL at baseline to 50 000 per μL or greater from days 15–50, then returned to baseline values by day 71, indicating that the transient platelet response was due to eltrombopag and not rituximab therapy.

82 (72%) patients completed 6 weeks of treatment (eltrombopag, n=52; placebo, n=30; figure 1). The most common reason for not completing 6 weeks of treatment in the eltrombopag group was a platelet count greater than 200 000 per μL (18 of 24 patients).

The primary endpoint—platelet counts 50 000 per μL or more on day 43—was achieved by more patients in the eltrombopag group than in the placebo group (43 [59%] of 73 *vs* six [16%] of 37; odds ratio [OR] 9·61

[95% CI 3·31–27·86]; p<0·0001). Patients in the eltrombopag group also had significantly greater odds of responding at any point during the 6-week treatment period than did those in the placebo group (OR 8·79 [95% CI 3·54–21·86]; p<0·0001). Furthermore, more patients given eltrombopag than placebo achieved platelet counts 30 000 per μL or more (48 [66%] *vs* nine [24%]), greater than 200 000 per μL (18 [25%] *vs* one [3%]), and both 50 000 per μL or more and at least twice the baseline value (42 [58%] *vs* five [14%]). The median platelet count increased to 53 000 per μL by day 15 for patients in the eltrombopag group, and this increase was sustained for the 6-week treatment period (figure 2A). On day 43, the median platelet count in eltrombopag responders (n=43) was 144 000 per μL (IQR 92·50–268·00). The mean percentage change from baseline in platelet counts for patients given eltrombopag was double that of those given placebo at day 8 and several-fold higher throughout the remainder of the treatment period (figure 2B, table 2).

Of the 74 patients who received eltrombopag and were included in the efficacy analysis, 40 received 50 mg. 33 patients responded with platelet counts 50 000 per μL or more, 18 of whom responded with platelet counts greater than 200 000 per μL. Six did not respond at 50 mg but did not increase the dose to 75 mg, and one patient was non-evaluable. Of the 34 patients who had dose increases to 75 mg, ten responded (none above platelet counts 200 000 per μL). Of the 38 patients in the efficacy analysis who received placebo, six responded with platelet counts above 50 000 per μL (one with platelet count >200 000 per μL) and one patient was non-evaluable.

In a post-hoc analysis of the 38 patients in the eltrombopag group with baseline platelet counts 15 000 per μL or less, 16 responded: nine to eltrombopag 50 mg daily and seven to 75 mg daily. Eight of the remaining 22 patients had clinically meaningful platelet increases: five to platelet counts between 15 000 per μL and less than 30 000 per μL, and three to platelet counts 30 000 per μL or greater but less than 50 000 per μL. Of the 17 patients in the placebo group with baseline platelet counts 15 000 per μL or less, two responded to placebo with platelet counts 50 000 per μL or greater and two achieved platelet counts between 15 000 per μL and less than 30 000 per μL.

One week after discontinuation of treatment, platelet counts remained 50 000 per μL or greater in 34 (51%) of 67 evaluable patients given eltrombopag (figure 2). Platelet counts generally returned to baseline values within 2 weeks after end of treatment.

Patients responded to eltrombopag irrespective of the use of concomitant ITP drugs (p=0·77), splenectomy status (p=0·75), or baseline platelet count 15 000 per μL or less (p=0·45; figure 3A). In post-hoc analyses, response rates were higher for patients given eltrombopag than for those given placebo, irrespective of number of previous ITP therapies (p=0·31; figure 3B) and sex (data not shown). Elderly patients responded as well as younger patients did to eltrombopag (20 [50%] patients aged 18–49 years, nine [64%] aged 50–64 years, 14 [74%] aged ≥65 years responded).

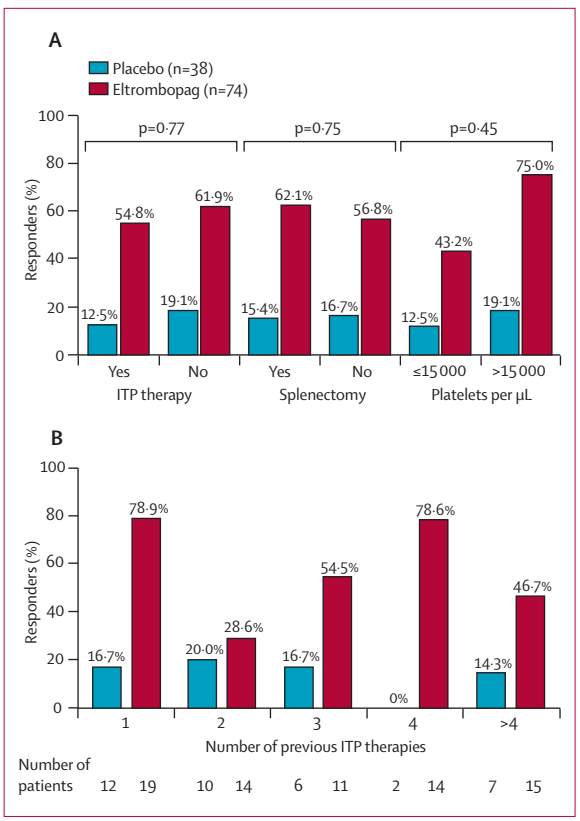

Figure 3: **Percentages of responders according to baseline stratification variables (A) and number of previous idiopathic thrombocytopenic purpura (ITP) therapies (B)***

No significant statistical interactions were recorded between treatment response and baseline stratification variables or the number of previous ITP therapies (p=0·31). *The percentages of responders according to the number of previous ITP therapies were investigated as a post-hoc analysis.

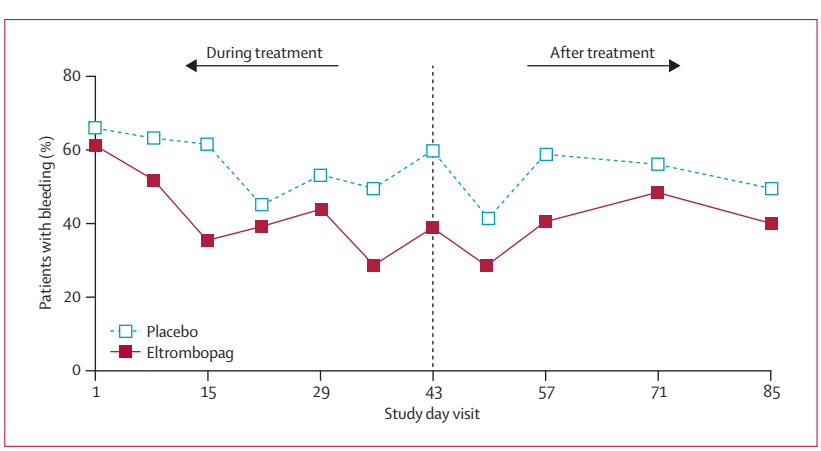

Figure 4: **Percentages of patients with any bleeding (WHO bleeding grades 1–4) during therapy (days 1–43) and after therapy (days 50–85) with eltrombopag**

	Placebo (n=38)	Eltrombopag (n=76)
Bleeding*	5 (13%)	7 (9%)
Headache	4 (11%)	6 (8%)
Nasopharyngitis	3 (8%)	5 (7%)
Nausea	0	6 (8%)
Diarrhoea	1 (3%)	4 (5%)
Protein total increased	1 (3%)	3 (4%)
Vomiting	0	4 (5%)
Arthralgia	1 (3%)	2 (3%)
Fatigue	0	3 (4%)
Myalgia	0	3 (4%)
Abdominal distension	1 (3%)	1 (1%)
Abdominal pain upper	1 (3%)	1 (1%)
Alanine aminotransferase increased	0	2 (3%)
Anaemia	0	2 (3%)
Aspartate aminotransferase increased	0	2 (3%)
Constipation	0	2 (3%)
Paraesthesia	1 (3%)	1 (1%)
Pharyngitis	1 (3%)	1 (1%)
Pharyngolaryngeal pain	1 (3%)	1 (1%)
Sinusitis	1 (3%)	1 (1%)
Upper respiratory tract infection	0	2 (3%)
Urinary tract infection	0	2 (3%)
Vertigo	0	2 (3%)
Anxiety	1 (3%)	0
Asthenia	1 (3%)	0
Cough	1 (3%)	0
Dizziness	1 (3%)	0
Face injury	1 (3%)	0
Head discomfort	1 (3%)	0
Head injury	1 (3%)	0
Hyperglycaemia	1 (3%)	0
Lethargy	1 (3%)	0
Nasal congestion	1 (3%)	0
Odynophagia	1 (3%)	0
Pain in extremity	1 (3%)	0
Papilloma	1 (3%)	0
Pruritus	1 (3%)	0
Rhinorrhoea	1 (3%)	0
Tinnitus	1 (3%)	0
Upper respiratory tract congestion	1 (3%)	0

*All reports of bleeding are included: gastrointestinal haemorrhage, cerebral haemorrhage, haematuria, gingival bleeding, contusion, and epistaxis (placebo group); and gastrointestinal haemorrhage, cerebral haemorrhage, oral mucosal bleeding, menorrhagia, haematochezia, epistaxis, and ecchymosis (eltrombopag group). In patients given eltrombopag, all patients were regarded as non-responders at the time of the event and the platelet counts most proximal to the event were all 20 000 per μL or less.

Table 3: **Adverse events reported in 3% or more of patients**

Significantly fewer patients in the eltrombopag group than in the placebo group had bleeding symptoms, as measured by the WHO bleeding scale, at day 43 (20 [39%] *vs* 18 [60%]; OR 0·27 [95% CI 0·09–0·88]; p=0·029) as well as at any point in time during the course of treatment (46 [61%] *vs* 30 [79%]; OR 0·49 [95% CI 0·26–0·89]; p=0·021; figure 4). No patients reported clinically significant bleeding (WHO grade 2–4) while platelet counts were 50 000 per μL or more during treatment. After discontinuation of eltrombopag, platelet counts returned to baseline values (figure 2), and the percentage of patients with any bleeding (WHO grades 1–4) increased compared with that recorded during treatment (figure 4).

Mean scores for health-related quality of life at baseline and at the end of the study were similar when measured by individual domains and mental and physical component scores of the SF-36v2 questionnaire for patients in both groups (data not shown). Additionally, health-related quality of life was comparable between responders and non-responders, and no significant differences were recorded between the two treatment groups (data not shown).

The proportions of patients who had one or more adverse event during the treatment phase were 45 (59%) for the eltrombopag group and 14 (37%) for the placebo group (table 3). Nausea and vomiting were the only two adverse events recorded in 5% or more of patients in the eltrombopag group and not in the placebo group. The frequency of grade 3–4 adverse events during treatment (eltrombopag, two [3%]; placebo, one [3%]) and adverse events leading to study discontinuation (eltrombopag, three [4%]; placebo, two [5%]) was similar for both groups. No deaths occurred during the study. Six patients in the eltrombopag group and one in the placebo group had increases in transaminase concentrations to twice the upper limit of normal; abnormal hepatic function caused one patient given eltrombopag on long-term concomitant danazol therapy to withdraw with a platelet count of 174 000 per μL. Gastrointestinal haemorrhage and cerebral heamorrhage caused two additional patients given eltrombopag to withdraw; both were non-responders. In the placebo group, one patient withdrew because of cerebral haemorrhage, gastrointestinal haemorrhage, and haematuria; another patient withdrew because of a facial injury. Three patients in the eltrombopag group and one in the placebo group had reports of cataract; two patients in the eltrombopag group and one in the placebo group had progression of existing cataracts. All patients with cataracts had been previously treated with corticosteroids. Eight (11%) patients receiving eltrombopag had platelet counts less than 10 000 per μL and at least 10 000 per μL less than their baseline value within 4 weeks after withdrawal of study drug, compared with five (13%) patients given placebo. Two of the eight patients with a transient decrease in platelet count given eltrombopag had bleeding symptoms (menorrhagia and gum bleeding). Both patients had had similar bleeding symptoms either before entry into the study or during therapy before the rise in platelet counts. No thromboembolic events were noted in the study.

Discussion

In this large, multicentre, randomised, placebo-controlled trial of eltrombopag treatment in chronic ITP, substantially more patients in the eltrombopag group achieved platelet counts of 50 000 per μL or greater than did those in the placebo group. Increases of platelet counts to 50 000 per μL or greater were seen within 2 weeks in more than half of patients given eltrombopag. In conjunction with the rise in platelet count, a prospective assessment showed a significant reduction in bleeding events both during and at the end of the study. Platelet counts remained at 50 000 per μL or more in roughly half of patients given eltrombopag 1 week after discontinuation of treatment, and they generally returned to baseline values within 2 weeks after the end of therapy. These findings accord with the results of a previous study[16] in patients with chronic ITP, which showed that daily eltrombopag 50 mg for up to 6 weeks increased platelet counts to 50 000 per μL or more in 70% of patients.

The primary endpoint in this study was defined as achieving a platelet count of 50 000 per μL or more after up to 6 weeks of treatment. This threshold was selected to show unequivocal improvement in platelet values even though treatment of patients with chronic ITP is typically not started at counts greater than 30 000 per μL. In view of the potential clinical benefit of platelet increases to values less than 50 000 per μL, a post-hoc analysis of patients with very low baseline platelet counts showed that several patients labelled as non-responders nonetheless had clinically important platelet increases in the eltrombopag group (ie, from <15 000 per μL to between 15 000–30 000 per μL and 30 000–50 000 per μL).

Neither the baseline stratification variables (splenectomy status, platelet count ≤15 000 per μL, and concomitant ITP drugs) nor the number of previous ITP therapies had a significant effect on the response rate to eltrombopag compared with placebo. Although the subgroups were small, the data suggested that elderly patients responded as well to eltrombopag as younger patients did.

Dose escalation was used in this study to achieve the best possible response. In the previous phase II study,[17] 50 mg had a similar effectiveness to 75 mg (70% and 81%, respectively) and almost all responses to either eltrombopag dose occurred within 21 days.[16] Furthermore, a response to a dose increase to 75 mg was thought to take effect rapidly[16]—a hypothesis that was confirmed by the 29% response rate within 1–3 weeks of dose escalation in this study. Whether non-responders would respond to a dose higher than 75 mg or to a longer duration of eltrombopag treatment is not yet known.

The primary treatment goal in chronic ITP is the prevention of bleeding complications. A significant reduction in bleeding symptoms during and at the end of the treatment period was recorded in the eltrombopag group compared with the placebo group, suggesting that the platelets produced in response to eltrombopag treatment function normally.[14]

Although no direct comparison studies have been done, the results described here for eltrombopag are similar to those reported for romiplostim—a thrombopoiesis-stimulating peptibody—in a small double-blind, placebo-controlled, phase II study of treatment over 6 weeks in patients with ITP.[17] In that study, 12 of 16 patients receiving 1 or 3 μg romiplostim per kg by subcutaneous injection every week achieved platelet counts of 50 000 per μL or greater and twice the baseline value. Romiplostim has also shown efficacy and safety in open-label, short-term, dose-finding studies[17,18] and in two double-blind studies of 24 weeks' duration.[19]

Although chronic ITP is often considered a benign disease, health-related quality of life is poor.[24] In this study, as in the phase II study,[16] scores for health-related quality of life remained fairly stable over the 6 weeks of treatment, possibly because of the short duration of treatment and the small sample size for this secondary endpoint. Most ITP treatments, such as corticosteroids, adversely affect quality of life.

In both this and the previous study,[16] eltrombopag was well tolerated, with an adverse event profile that was similar to placebo. Apart from nausea and vomiting, no quantitative differences were recorded in the side-effect profile between eltrombopag and placebo; the previous study did not record this difference. No thromboembolic events were noted in patients given either placebo or eltrombopag. Slight increases of liver enzymes were noted in six patients in the eltrombopag group, and monitoring of liver values is recommended during treatment with eltrombopag. Cataracts are being monitored because of reports in preclinical rodent studies; no excess risk has been identified in patients receiving eltrombopag to date. After the end of therapy, two patients had recurrence of bleeding symptoms associated with a decrease in platelet counts to less than 10 000 per μL and at least 10 000 per μL less than baseline value. As with any other treatment for chronic ITP, platelet counts should be monitored after discontinuation of eltrombopag to look for a transient decrease in platelet counts and to establish whether further treatment is clinically indicated.[17]

An important limitation of eltrombopag treatment in patients with ITP is that, thus far, platelet counts have not been measured systematically before day 8. The absence of evidence of a platelet increase within the first week of treatment and the presumed kinetics of stimulating platelet production do not lend support to the use of eltrombopag when an urgent platelet increase is required. Furthermore, the two large completed studies (including this trial) are of only 6 weeks' duration and do not provide information about the efficacy and safety during longer use. One of the longer-term studies intended to provide this information has recently been completed, and another is the ongoing long-term extension study in which patients have been

treated thus far up to 2 years. Although this study showed similar efficacy of eltrombopag in both splenectomised and non-splenectomised patients, how this drug will be used in the treatment paradigm for patients with chronic ITP remains to be seen.[25,26]

Contributors

JBB, DP, JMJ, DR, NS, and BM assisted with the design of the study. JBB entered patients. GC participated in screening and recruiting patients into the study, did clinical assessments during follow-up, and was responsible for data collection. TS, LK, and AS participated in the study as principal investigators. JBB, DP, BP, NS, BM, and MA contributed to the analysis of the data. JBB, BP, JMJ, DR, NS, BM, and MA helped to write the report. All authors have seen and approved the final version of the manuscript.

Conflict of interest statement

JBB has received clinical research support from Amgen, Biogen-Idec, Celgene, Genentech, GlaxoSmithKline, Genzyme, Immunomedics, MGI Pharma, and Sysmex. DP has received research funds from Amgen, Baxter, and GlaxoSmithKline. BP has received research support and funding to attend scientific meetings from Sysmex. JBB participates in the speaker's bureau programme for Baxter, and DP is on the speakers' bureau for Amgen and Baxter. BP has served on an advisory board for GlaxoSmithKline and as a consultant for Crofessionals. JMJ, DR, BM, NS, and MA are employees of GlaxoSmithKline. BB owns stock in Amgen and GlaxoSmithKline. DP, JMJ, DR, BM, NS, and MA own stock in GlaxoSmithKline. TS, GC, LK, and AS declare that they have no conflict of interest.

Acknowledgments

This study was supported by GlaxoSmithKline, Collegeville, PA, USA. The authors would like to thank the following GlaxoSmithKline employees who assisted with the analysis and/or interpretation of these data: Ruth Poulin, Kimberly Marino, Habib Hassani, and Manuel Aivado. Editorial support was provided by Brett D Mahon of MedErgy. Portions of this study were presented at the 12th Congress of the European Hematology Association, Vienna, Austria, June 7–10, 2007.

References

1 Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002; **346:** 995–1008.

2 Chang M, Nakagawa PA, Williams SA, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. *Blood* 2003; **102:** 887–95.

3 Houwerzijl EJ, Blom NR, van der Want JJ, et al. Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood* 2004; **103:** 500–06.

4 Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med* 2000; **160:** 1630–38.

5 Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. *Mayo Clin Proc* 2004; **79:** 504–22.

6 Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001; **97:** 2549–54.

7 Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med* 2007; **146:** 25–33.

8 Andemariam B, Psaila B, Bussel JB. Novel thrombopoietic agents. *Hematology Am Soc Hematol Educ Program* 2007; **2007:** 106–13.

9 Kuter DJ. New thrombopoietic growth factors. *Blood* 2007; **109:** 4607–16.

10 Kalota A, Brennan K, Erickson-Miller CL, Danet G, Carroll M, Gewirtz AM. Effects of SB559457, a novel small molecule thrombopoietin receptor (TpoR) agonist, on human hematopoietic cell growth and differentiation. *Blood* 2004; **104**: 796a (abstr number 2913).

11 Erhardt J, Erickson-Miller CL, Tapley P. SB 497115-GR, a low molecular weight TPOR agonist, does not induce platelet activation or enhance agonist-induced platelet aggregation in vitro. *Blood* 2004; **104**: 59b (abstr 3888).

12 Sellers T, Hart T, Semanik M, Murthy K. Pharmacology and safety of SB-497115-GR, an orally active small molecular weight TPO receptor agonist, in chimpanzees, rats and dogs. *Blood* 2004; **104**: 568a (abstr number 2063).

13 Erickson-Miller CL, Luengo JI, Nicholl R, et al. In vitro and in vivo biology of a small molecular weight TPO receptor agonist, SB-497115. Poster presented at the 96th American Association for Cancer Research Annual Meeting, April 16–20, 2005, Anaheim, CA, USA (abstr number 2565).

14 Jenkins JM, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. *Blood* 2007; **109:** 4739–41.

15 Provan D, Saleh M, Goodison S, et al. The safety profile of eltrombopag, a novel, oral platelet growth factor, in thrombocytopenic patients and healthy subjects. *J Clin Oncol* 2006; **24:** abstr number 18596.

16 Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007; **357:** 2237–47.

17 Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006; **355:** 1672–81.

18 Newland A, Caulier MT, Kappers-Klunne M, et al. An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura. *Br J Haematol* 2006; **135:** 547–53.

19 Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; **371:** 395–403.

20 McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; **357:** 2227–36.

21 Ware JE, Kosinski M, Dewey JE. How to score version two of the SF-36 health survey. Lincoln: QualityMetric Incorporated, 2000.

22 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; **41:** 582–92.

23 Liang K-Y, Zeger SL. Longitudinal data analysis using generalised linear models. *Biometrika* 1986; **73:** 13–22.

24 McMillan R, Bussel JB, George JN, Lalla D, Nichol JL. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. *Am J Hematol* 2008; **83:** 150–04.

25 Bussel JB, Cheng G, Saleh MN, et al. Safety and efficacy of long-term treatment with oral eltrombopag for chronic idiopathic thrombocytopenic purpura. *Blood* 2008; **112:** 1177 (abstr 3432).

26 Cheng G, Saleh MN, Bussel JB, et al. Oral eltrombopag for the long-term treatment of patients with chronic idiopathic thrombocytopenic purpura: results of a phase III, double-blind, placebo-controlled study (RAISE). *Blood* 2008; **112:** 153 (abstr 400).