Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study

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Summary

Background **Eltrombopag is an oral thrombopoietin receptor agonist for the treatment of thrombocytopenia. We aimed to compare the response to once daily eltrombopag versus placebo in patients with chronic immune thrombocytopenia during a 6-month period.**

Methods **We undertook a phase 3, double-blind, placebo-controlled study in adults with previously treated immune thrombocytopenia of more than 6 months' duration who had baseline platelet counts lower than 30 000 per μL. Patients were randomly allocated (in a 2:1 ratio) treatment with local standard of care plus 50 mg eltrombopag or matching placebo once daily for 6 months. Randomisation was done centrally with a computer-generated randomisation schedule and was stratified by baseline platelet count (≤15 000 per μL), use of treatment for immune thrombocytopenia, and splenectomy status. Patients, investigators, and those assessing data were masked to allocation. Dose modifications were made on the basis of platelet response. Patients were assessed for response to treatment (defined as a platelet count of 50 000–400 000 per μL) weekly during the first 6 weeks and at least once every 4 weeks thereafter; the primary endpoint was the odds of response to eltrombopag versus placebo. Analysis was by intention to treat. This study is registered at ClinicalTrials.gov, number NCT00370331.**

Findings **Between Nov 22, 2006, and July 31, 2007, 197 patients were randomly allocated to treatment groups and were included in the intention-to-treat analysis (135 eltrombopag, 62 placebo). 106 (79%) patients in the eltrombopag group responded to treatment at least once during the study, compared with 17 (28%) patients in the placebo group. The odds of responding were greater in patients in the eltrombopag group compared with those in the placebo group throughout the 6-month treatment period (odds ratio 8·2, 99% CI 3·59–18·73; p<0·0001). 37 (59%) patients receiving eltrombopag reduced concomitant treatment versus ten (32%) patients receiving placebo (p=0·016). 24 (18%) patients receiving eltrombopag needed rescue treatment compared with 25 (40%) patients receiving placebo (p=0·001). Three (2%) patients receiving eltrombopag had thromboembolic events compared with none in patients on placebo. Nine (7%) eltrombopag-treated patients and two (3%) in the placebo group had mild increases in alanine aminotransferase concentration, and five (4%) eltrombopag-treated patients (*vs* none allocated to placebo) had increases in total bilirubin. Four (7%) patients taking placebo had serious bleeding events, compared with one (<1%) patient treated with eltrombopag.**

Interpretation **Eltrombopag is effective for management of chronic immune thrombocytopenia, and could be particularly beneficial for patients who have not responded to splenectomy or previous treatment. These benefits should be balanced with the potential risks associated with eltrombopag treatment.**

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Introduction

In chronic immune thrombocytopenia, previously known as idiopathic thrombocytopenic purpura,[1] antiplatelet antibodies accelerate platelet destruction and simultaneously prevent the release of platelets from megakaryocytes, resulting in mild to serious bleeding.[1–4] The primary goal of treatment for this disorder is to prevent bleeding by increasing the platelet count to a stable, safe range with the fewest possible treatment-associated adverse effects.[2,3,5] Most treatments (eg, corticosteroids, immunoglobulins, and splenectomy) mainly reduce destruction of antibody-coated platelets; however, treatment is not always effective and can be restricted by adverse effects.[2] By contrast, the novel thrombopoietic receptor agonists, eltrombopag[6,7] and romiplostim,[8–11] stimulate platelet production.[12] Romiplostim has shown efficacy in chronic immune thrombocytopenia.[8–11] Eltrombopag is an oral, small-molecule, non-peptide thrombopoietin receptor agonist that has shown efficacy and safety in patients with chronic immune thrombocytopenia in two 6-week placebo-controlled studies[6,7] and two open-label studies.[13,14] Eltrombopag also increases platelet counts in patients with other thrombocytopenic disorders, including thrombocytopenia related to hepatitis C virus infection and its treatment[15] and chemotherapy-induced thrombocytopenia.[16] We aimed to compare the platelet response to once daily eltrombopag versus placebo in patients with chronic immune thrombocytopenia during a 6-month period.

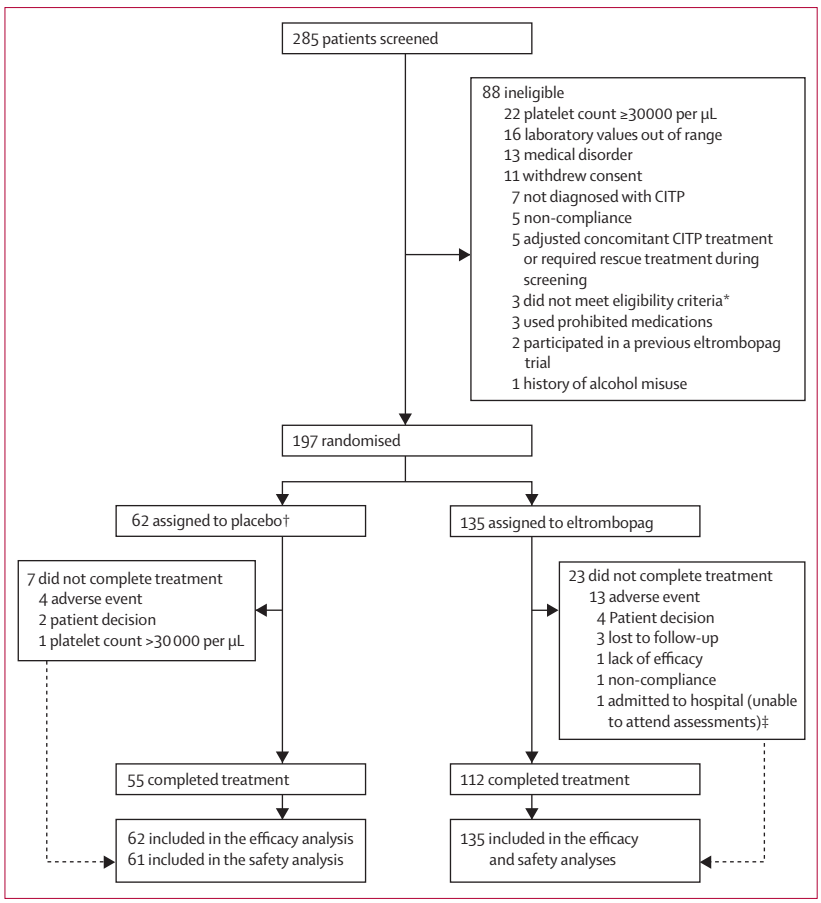

Figure 1: **Trial profile**
CITP=chronic immune thrombocytopenia. *Not otherwise specified by the site. †One patient did not receive placebo, and was included in the efficacy analysis, but not the safety analysis. ‡Spinal compression fracture at day 118 prevented the patient from undergoing further assessments; however, the patient could be assessed for safety and efficacy until that time.

Methods

Patients

Patients were enrolled in this double-blind, placebo-controlled, phase 3 study between Nov 22, 2006, and July 31, 2007, from 75 sites in 23 countries. The ethics committee at each institution approved the protocol and amendments, and all patients provided written informed consent before enrolment. This study was undertaken in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations. Eligible patients were aged 18 years and older and had primary immune thrombocytopenia of more than 6 months' duration,[17,18] had baseline platelet counts lower than 30000 per µL, and had responded to one or more previous treatments for their disorder. Concomitant treatments for immune thrombocytopenia were allowed, provided that the dose was stable for 4 weeks or longer before randomisation (≥3 months for ciclosporin, mycophenolate mofetil, or danazol) and remained unchanged during the first 6 weeks of the study. Patients had to have completed treatment with immunoglobulins at least 1 week before enrolment and have decreasing platelet counts. Splenectomy, rituximab, and cyclophosphamide had to have been completed at least 4 weeks before enrolment and romiplostim more than 30 days before enrolment.

The main exclusion criteria were participation in a previous eltrombopag study, evidence of HIV infection, hepatitis B or C infection, cardiovascular disease, or arrhythmia, and a history of malignant disease, chemotherapy or radiotherapy, or arterial or venous thrombosis plus two or more thrombosis risk factors (eg, smoking, diabetes, hypercholesterolaemia, or hereditary thrombophilic disorders).

Randomisation and masking

Patients were randomly allocated in a two-to-one ratio to receive treatment with local standard of care plus either 50 mg eltrombopag (GlaxoSmithKline, Ware, UK) or matching placebo once daily for 6 months. Randomisation was done centrally and stratified by baseline platelet count (≤15000 per µL), use of treatments for their disorder, and splenectomy status; a block size of six within each stratum was used. The randomisation schedule was computer generated with an in-house validated randomisation system, and was generated by a member of the GlaxoSmithKline statistics and programming group, who held a statistical consultation role for the rest of the trial. All randomisations were done with RAMOS, an automated interactive voice recognition telephone randomisation and drug ordering system. Patients, investigators, and those assessing the data were masked to allocation.

Procedures

Dose modifications were made on the basis of individual platelet response. Dose increases (to a maximum of 75 mg once daily) were allowed after day 22 for patients with platelet counts lower than 50000 per µL. Dose decreases (to 25 mg once daily) were required for patients with platelet counts higher than 200000 per µL; for patients with platelet counts higher than 400000 per µL, study treatment was interrupted and resumed at the next lowest dose when platelet count fell to less than 150000 per µL. After 6 weeks, patients with platelet counts of 100000 or more per µL for at least 2 successive weeks could reduce or discontinue concomitant treatments. Use of rescue treatments was allowed. Patients who received rescue treatments were regarded as non-responders for the duration of rescue treatment and until platelet counts fell lower than 50000 per µL after ceasing rescue treatment.

Patients were assessed weekly for efficacy and safety during the first 6 weeks and at least once every 4 weeks thereafter. Weekly assessments for 4 weeks were required after any change in dose of study drug or concomitant treatment. Post-treatment assessments occurred at weeks 1, 2, and 4 and months 3 and 6. Each patient was assessed for response (defined as a platelet count of

50 000–400 000 per μL) at each assessment during the 6-month treatment period; the primary endpoint was the odds of response to eltrombopag versus placebo during this period. As described above, any assessment, irrespective of platelet count, was regarded as a non-response if it occurred during a period of rescue treatment.

Specified secondary efficacy endpoints were median platelet counts, the proportion of patients who responded at 75% or more of assessments, mean cumulative weeks of response, mean maximum weeks of continuous response, bleeding symptoms, reduction of baseline treatment for immune thrombocytopenia, and use of rescue treatment. Bleeding was assessed with the WHO bleeding scale (grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss). For the secondary endpoint of median platelet counts, all platelet counts were included in the analysis irrespective of whether the patient received rescue treatment. Rescue treatment was defined as new treatment for chronic immune thrombocytopenia, an increased dose of baseline treatment, platelet transfusion, or splenectomy. A post-hoc analysis of patients who completed 26 weeks of treatment assessed the proportion of patients with a durable response, defined as achieving a response in at least 6 of the last 8 weeks of treatment and never receiving rescue treatment.[10] Because patients with a stable platelet count and a stable dose were assessed monthly, not all patients had eight assessments.

At visits at which health-related quality of life was evaluated, this assessment was completed before all other assessments. The acute recall version of the short form-36, version 2 (SF-36v2) questionnaire was used to measure health-related quality of life at baseline and at weeks 6, 14, and 26 or on discontinuation of study drug.[19] Measurement of fatigue with the vitality domain of the SF-36v2 was supplemented by use of the fatigue subscale of the functional assessment of chronic illness therapy (FACIT)-fatigue questionnaire.[20,21] The effect of bleeding on quality of life was assessed with a six-item subset from the functional assessment of cancer therapy-thrombocytopenia (FACT-Th6) questionnaire.[22] Changes to physical and mental energy and social motivation were assessed with the short form of the motivation and energy inventory (MEI-SF) questionnaire.[23]

Adverse event reports (graded with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) and laboratory assessments were completed at each on-treatment and post-treatment visit. On the basis of preclinical findings, ocular examinations were done at baseline and regularly during the study.

Statistical analyses

On the basis of previous studies,[6,7] we estimated that 60% of patients would respond to eltrombopag and 25% to placebo; therefore, 120 evaluable patients (80 eltrombopag, 40 placebo) were needed for 90% or more power at a 1% (two-sided) significance level. To provide sufficient power for secondary analyses and to allow for missing data, 189 patients were to be randomly assigned treatment. No interim analyses were planned. Descriptive statistics were used to summarise demographic and baseline characteristics and safety data. We included all patients randomly allocated treatment in the intention-to-treat population; the safety population was defined as all patients randomly allocated treatment who received at least one dose of study drug.

We compared the odds of a response to treatment at any time during the 6-month treatment period between groups for the intention-to-treat population using a repeated-measures model for binary data adjusted for the randomisation stratification variables. This model used information provided by each patient at each assessment. We chose a binary response variable in preference to a transformation of platelet count data to reduce the effect that outliers might have had on the analysis. Generalised estimating equation methodology was used to estimate the parameters of the regression model, with an exchangeable working correlation structure that assumed the correlation between any two measures within a patient were the same.[24] The primary analysis used data from nominal visits (defined as weeks 1–6 inclusive, and weeks 10, 14, 18, 22, and 26). Because of the nature of dose

	Placebo (n=62)	Eltrombopag (n=135)
Median age (years)	52·5 (43–63)	47·0 (34–56)
Sex (female)	43 (69%)	93 (69%)
Ethnic origin		
White	44 (71%)	101 (75%)
Asian	13 (21%)	21 (16%)
Other	5 (8%)	13 (10%)
Stratification variables		
Platelet count ≤15 000 per μL*	30 (49%)	67 (50%)
Splenectomy	21 (34%)	50 (37%)
Concomitant CITP treatment	31 (50%)	63 (47%)
Median platelet count (platelets per μL)	16 000 (9000–24 000)	16 000 (8000–22 000)
Bleeding symptoms†	47 (77%)	98 (73%)
Clinically significant bleeding symptoms†	17 (28%)	30 (22%)
Number of previous CITP treatments‡		
Two or more	50 (81%)	105 (78%)
Three or more	32 (52%)	75 (56%)
Four or more	20 (32%)	51 (38%)
Five or more	11 (18%)	35 (26%)

Data are number (%) or median (IQR). Bleeding symptoms included WHO bleeding scale grades 1–4; clinically significant bleeding symptoms included grades 2–4. CITP=chronic immune thrombocytopenia. *Placebo, n=61; one patient had a missing baseline platelet count. †Placebo, n=61; one patient did not have a baseline bleeding assessment. ‡Corticosteroids were the most frequently reported previous CITP treatment (eltrombopag, n=119, 88%; placebo, n=56, 90%).

Table 1: **Baseline characteristics**

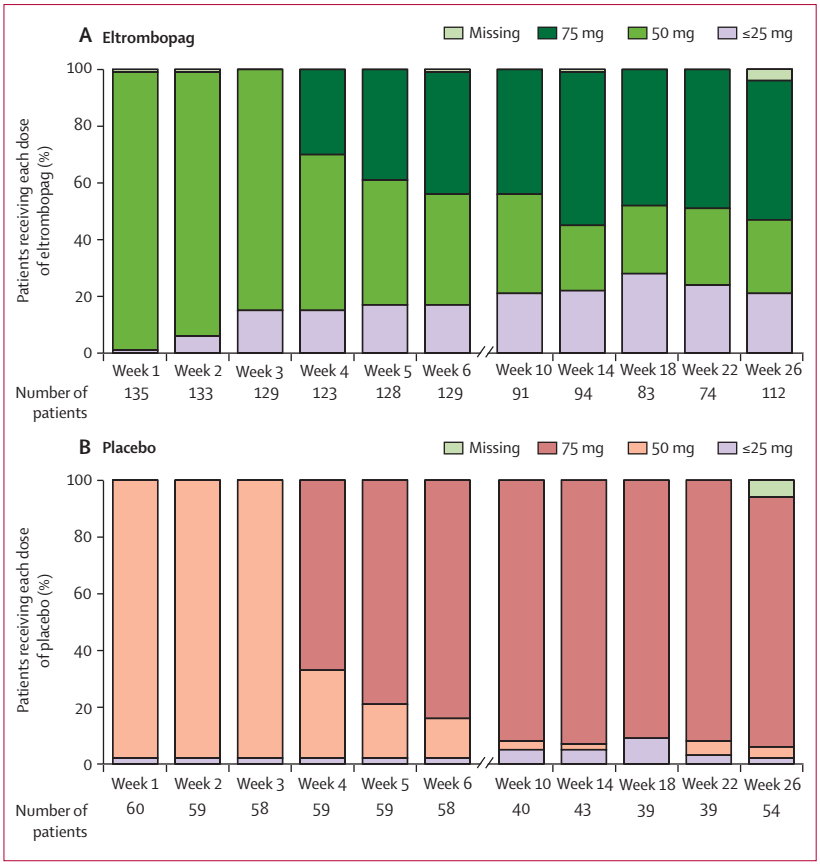

Figure 2: **Proportions of patients who took each dose of study drug during treatment**
Dose of study drug could be increased to 75 mg from week 3 (ie, day 22).

adjustments allowed in the study and the corresponding need for weekly platelet counts, for patients without an assessment at a nominal visit, the information from the immediately preceding, non-nominal visit was used, provided the patient had not withdrawn from the study. Assessments for patients who withdrew early from the study were classified as negative from the time of withdrawal and for all subsequent nominal visits. Prespecified subgroup analyses of the primary endpoint to assess interactions between response to treatment and splenectomy status, baseline platelet count, and baseline treatment for immune thrombocytopenia were evaluated at the 10% significance level.

We used a logistic regression model adjusted for the randomisation stratification variables to evaluate between-group differences in the proportions of patients who achieved a response at 75% or more of on-treatment assessments, reduced baseline concomitant treatments, and received rescue treatment. We compared the odds of any bleeding (WHO grades 1–4) and clinically significant bleeding (WHO grades 2–4) during the 6-month treatment period between treatment groups using a repeated-measures model for binary data adjusted for the randomisation stratification variables and dichotomised baseline WHO bleeding grade. Changes from baseline in health-related quality of life scores were analysed with a repeated-measures model adjusted for baseline score. The predictive strength of association between either SF-36v2 or FACT-Th6 scores and platelet counts and bleeding symptoms was estimated by use of unadjusted linear longitudinal regression models. All p values were two-sided; no adjustments were made for multiple testing.

This study is registered with ClinicalTrials.gov, number NCT00370331.

Role of the funding source

The protocol was developed by the principal investigators and employees of the sponsor. Data were collected and analysed by the sponsor. All authors had access to the primary data and vouch for the completeness and accuracy of the data and analyses. Interpretation of the data and decisions related to the content of the report were made through collaboration among all authors. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of 285 patients screened, 197 were randomly allocated treatment (62 placebo, 135 eltrombopag; figure 1). Demographic and baseline disease characteristics were similar between treatment groups (table 1). Baseline platelet counts were 15 000 per μL or lower in 97 (49%) patients, and 71 (36%) had not achieved a sustained response to splenectomy. 17 patients discontinued treatment early because of adverse events: 13 patients in the eltrombopag group (alanine aminotransferase increases [four]; thromboembolic events [two]; and cataract, duodenal-ulcer haemorrhage, urticaria, rash, tachycardia, headache, and rectosigmoid cancer [one each]); and four patients in the placebo group (cataract [two]; abnormal renal function test results, alanine aminotransferase increases, or hyperkalaemia [one], and fatal brain-stem haemorrhage [one]). In a post-hoc analysis, 19 (21%) of 91 patients were receiving 25 mg or less of eltrombopag daily by week 10, and 40 (44%) were receiving 75 mg, whereas 37 (93%) of 40 patients assigned placebo were receiving the equivalent of 75 mg daily (figure 2).

Median platelet counts increased from 16 000 per μL (IQR 8000–22 000) to 36 000 per μL (13 000–74 000) after a week of treatment with eltrombopag. From day 15 throughout treatment with eltrombopag, median platelet counts were between 53 000 per μL (22 000–97 000) and 73 500 per μL (32 000–131 000) (figure 3). By contrast, median platelet counts for the placebo group remained between 17 500 per μL (8000–29 000) and 23 000 per μL (10 000–40 000) during treatment, despite the use of rescue treatment by 25 (40%) patients. 106 (79%) patients in the eltrombopag group responded to treatment at least once during the study, compared with 17 (28%) patients in the placebo group. The odds of responding were roughly eight times greater in patients in the eltrombopag group compared

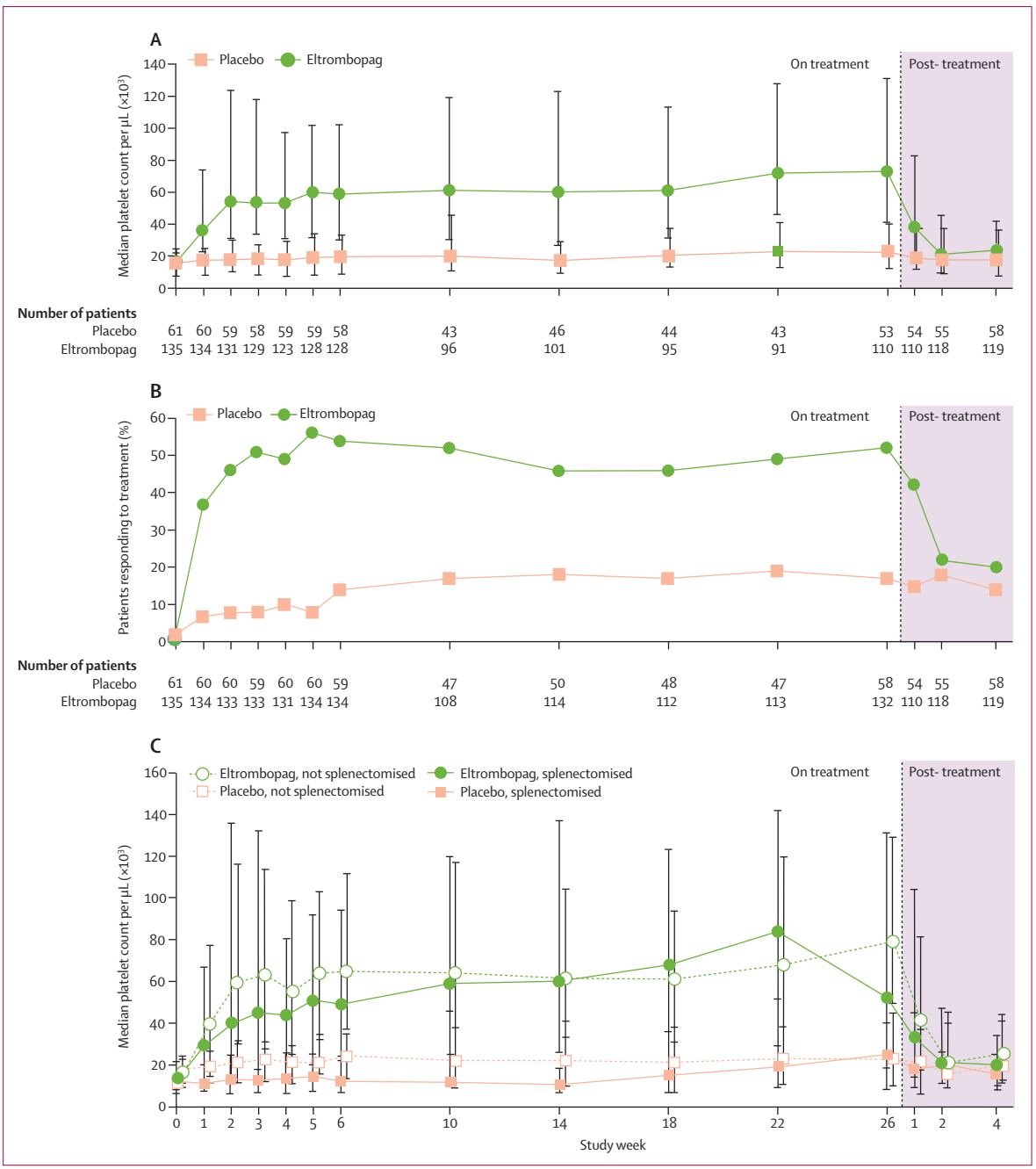

Figure 3: **Median platelet counts (A), proportions of patients who responded to treatment (B), and median platelet counts by splenectomy status (C) at each nominal study visit**

Patients responding to treatment were those who had a platelet count of 50 000–400 000 per µL at a study visit. Median platelet counts are shown with IQRs.

with those in the placebo group throughout the 6-month treatment period (odds ratio [OR] 8·2, 99% CI 3·59–18·73; p<0·0001; figure 3). There was no evidence of differences in the effect of eltrombopag compared with placebo in any of the prespecified subgroup analyses—similar responses were reported irrespective of splenectomy status (figure 3), baseline platelet count, or baseline treatment use.

A greater proportion of patients receiving eltrombopag (n=51, 38%) versus placebo (n=4, 7%) responded at 75% or more of assessments (OR 10·53, 95% CI 3·48–31·91; p<0·0001). Of the 106 patients in the eltrombopag group who responded at least once during the study, 64 (60%) responded at 75% or more of subsequent assessments. Of the 17 patients in the placebo group who responded at least once during the study, eight (47%) responded at 75%

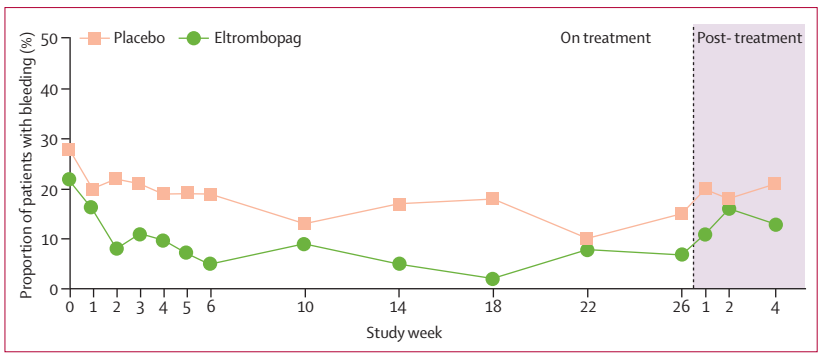

Figure 4: **Proportions of patients with clinically significant bleeding (WHO bleeding scale grades 2–4)**

or more of subsequent assessments. The maximum continuous response was a mean of 12·0 weeks (SD 8·29) and mean cumulative response was 14·3 weeks (8·39) for eltrombopag patients. In a post-hoc analysis of all available platelet counts, 57 (60%) of 95 patients receiving eltrombopag achieved a durable platelet response compared with four (10%) of 39 patients receiving placebo (p<0·0001). A durable response was seen in 19 (51%) of 37 splenectomised and 38 (66%) of 58 non-splenectomised patients in the eltrombopag group.

In the eltrombopag group, the rates of bleeding (WHO grades 1–4) and clinically significant bleeding (WHO grades 2–4; figure 4) were reduced from baseline by roughly 50% from day 15 throughout the 6-month treatment period and returned to near baseline after discontinuation of eltrombopag. 106 (79%) patients receiving eltrombopag and 56 (93%) patients receiving placebo experienced bleeding at least once between day 8 and the end of treatment; clinically significant bleeding was reported for 44 (33%) of patients receiving eltrombopag and 32 (53%) of patients receiving placebo. The odds of bleeding and clinically significant bleeding throughout the 6-month treatment period were 76% and 65% less, respectively, in patients treated with eltrombopag compared with placebo (OR 0·24, 95% CI 0·16–0·38; p<0·0001 and OR 0·35, 95% CI 0·19–0·64; p=0·0008).

37 (59%) of 63 patients in the eltrombopag group reduced or discontinued baseline treatments compared with ten (32%) of 31 patients allocated placebo (OR 3·10, 95% CI 1·24–7·75; p=0·02). Corticosteroids were the most frequently tapered or discontinued drugs (31 [84%] of 37 eltrombopag patients, nine [90%] of ten placebo patients). Rescue treatment was administered to 24 (18%) patients receiving eltrombopag versus 25 (40%) receiving placebo (OR 0·33, 95% CI 0·16–0·64; p=0·001). During treatment with eltrombopag and placebo, respectively, 18 (13%) and 23 (37%) received a new drug, six (4%) and four (6%) received an increased dose of concomitant treatment from baseline, and seven (5%) and four (6%) received a platelet transfusion; no patients underwent splenectomy during treatment. Of those who received rescue treatment, roughly 60% in each group received corticosteroids (14 of 24 patients taking eltrombopag, 15 of 25 patients allocated placebo). Of note, fewer patients in the eltrombopag group (14 patients, 10%) needed supplemental corticosteroids than in the placebo group (15 patients, 24%).

Significantly greater improvements from baseline were shown for patients receiving eltrombopag than for those receiving placebo for the physical role (difference 5·4, 95% CI 0·5–10·3; p=0·03; limits in frequency or duration of activities), vitality (3·9, 0·1–7·7; p=0·045; physical or mental fatigue), emotional role (5·4, 0·8–10·1; p=0·02; emotional limits in roles or accomplishments), and the mental component summary scores (2·1, 0·2–4·0; p=0·03) of the SF-36v2 and the FACT-Th6 score (1·5, 0·5–2·5; p=0·004). Improvement for patients treated with eltrombopag compared with placebo was not significant for the bodily pain (difference 5·1, 95% CI –0·5 to 10·6; p=0·07), social function (4·1, –0·6 to 8·9; p=0·09), and physical component summary scores (1·3, –0·2 to 2·9; p=0·09) of the SF-36v2, the MEI-SF score (3·3, –0·6 to 7·3; p=0·10), and the FACIT-Fatigue score (1·6, –0·2 to 3·5; p=0·08).

In patients receiving eltrombopag, five of the eight SF-36v2 domain scores (physical function, physical role, vitality, social function, and emotional role), both SF-36v2 summary scores, and the FACT-Th6 score at week 26 were significantly improved from baseline (all p<0·05; figure 5); no significant improvements were reported for patients receiving placebo. Improvements in health-related quality of life were significantly associated not only with eltrombopag-mediated increases in platelet counts (p=0·034 to <0·001, depending on domain), but also with decreases in WHO bleeding (p=0·002 to <0·001, depending on domain).

Similar incidences of on-treatment adverse events were reported for both groups. Adverse events were mainly grade 1–2 in severity (table 2). Nausea and vomiting were reported by at least 5% more patients receiving eltrombopag than placebo, whereas dyspepsia, peripheral oedema, insomnia, epistaxis, and ecchymosis were reported by at least 5% more patients receiving placebo (table 2). Grade 3 or higher adverse events occurred during treatment in 20 (15%) patients receiving eltrombopag versus seven (11%) receiving placebo. In the placebo group, most grade 3 or higher events were bleeding events, with four patients (7%) having 11 bleeding events, including one patient who had a fatal brain-stem haemorrhage (table 3). By contrast, grade 3 or higher adverse bleeding events were reported for only three (2%) eltrombopag-treated patients, all of whom had platelet counts lower than 50 000 per µL at the time of their event. The rate of on-treatment bleeding serious adverse events was significantly lower in patients receiving eltrombopag (one, <1%) versus placebo (four, 7%; p=0·03). Post-treatment bleeding events were reported by a lower proportion of patients receiving eltrombopag (six, 4%) compared with placebo (six, 10%).

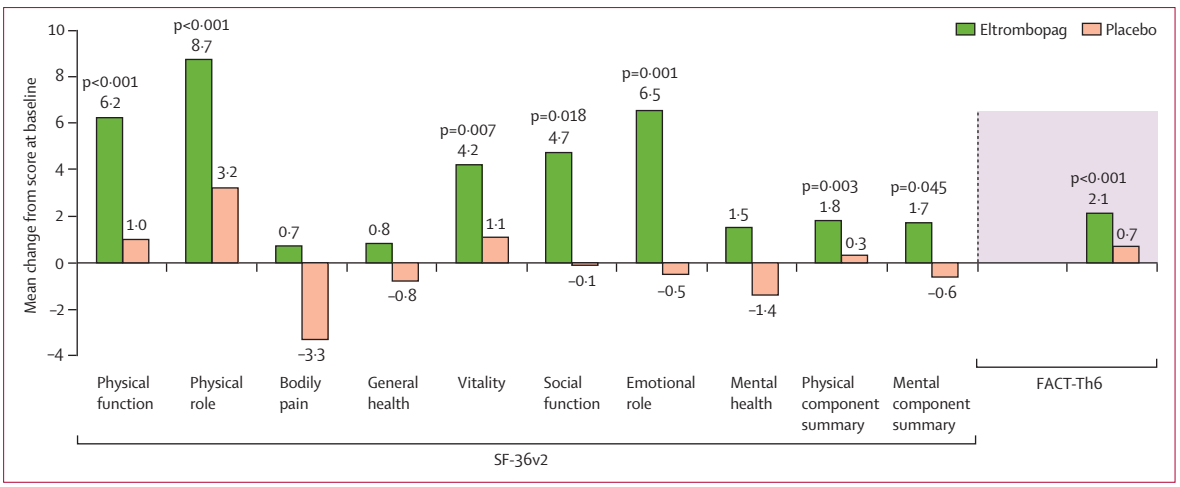

Figure 5: **Mean changes from baseline in SF-36v2 and FACT-Th6 scores***

p values are for change in score from baseline to week 26 for each treatment group. SF-36v2=Short Form-36, version 2. FACT-Th6=Functional Assessment of Cancer Therapy-Thrombocytopenia. *Physical and mental component summary scores were normalised to the 1998 US Census.

Increases of alanine aminotransferase concentration to three or more times the upper limit of normal occurred in more patients receiving eltrombopag (nine, 7%) than placebo (two, 3%; table 3). Increases of total bilirubin more than 1·5 times the upper limit of normal occurred in five (4%) patients receiving eltrombopag and in none of those allocated placebo (table 3). One patient (1%) receiving eltrombopag and one patient (2%) receiving placebo were withdrawn from the study because of increases in alanine aminotransferase concentration of grade 3 severity or more. All alanine aminotransferase abnormalities resolved—in six patients during treatment with eltrombopag and in three patients after treatment was interrupted or discontinued. Of the five patients with increased indirect bilirubin, three patients had Gilbert's syndrome, one had an isolated increase that resolved while on treatment, and one patient had pre-existing liver disease.

Two patients receiving eltrombopag had on-treatment thromboembolic events: grade 4 pulmonary embolism (platelet count 42 000 per μL 6 days before the event; risk factors were smoking and lupus anticoagulant) and grade 3 deep vein thrombosis (platelet count 49 000 per μL 5 days before the event; risk factors were smoking and oral contraceptives). A third patient with rectosigmoid cancer had a postoperative grade 4 pulmonary embolism 5 days after discontinuing eltrombopag because of the cancer diagnosis (platelets 2000 per μL 11 days before the event; risk factors were preoperative immunoglobulins, admission to hospital without prophylactic anticoagulation, intra-abdominal surgery, and cancer).

No clinically significant differences were recorded between treatment groups in the proportions of patients with progression of existing or new diagnosis of cataracts, malignant disease (table 3), or transient decreases in platelet counts[8] during the first 4 weeks after treatment discontinuation (7% in both groups; eltrombopag, nine; placebo, four).

Discussion

Our results showed that eltrombopag maintained platelet counts between 50 000 per μL and 400 000 per μL, reduced risk of bleeding, and substantially improved health-related quality of life in patients with chronic immune thrombocytopenia during 6 months of treatment. By contrast, platelet counts remained low in patients receiving placebo despite use of rescue treatment in 40% of patients. Patients responded to eltrombopag throughout the 6 months of treatment, irrespective of splenectomy status. In a post-hoc analysis,[25] the rate of durable response to eltrombopag was high in both non-splenectomised (66%) and splenectomised (51%) patients. This finding contrasts with those of a romiplostim study[10] in which less than 40% of patients achieved a durable response. Another important clinical benefit of increased platelet count is a reduction in bleeding risk. In RAISE, rates of bleeding were reduced both when measured prospectively and when reported as an adverse event; this result is similar to adverse event reports for romiplostim.[10]

In two 6-week placebo-controlled studies,[6,7] eltrombopag significantly increased platelet counts and reduced bleeding symptoms in patients with chronic immune thrombocytopenia (n=232). 74 patients with cirrhosis related to hepatitis C virus infection and platelet counts between 20 000 and 70 000 per μL were randomly allocated to receive placebo or eltrombopag. Patients taking eltrombopag had increased platelet counts and were able to complete 12 weeks of antiviral therapy with interferon.[16] Thus, on the basis of both these short-term results and 6-month treatment period in RAISE, eltrombopag increased platelet count and

	Placebo (n=61)†	Eltrombopag (n=135)
Any adverse event with ≥5% incidence	56 (92%)	118 (87%)
Headache	20 (33%)	41 (30%)
Diarrhoea	6 (10%)	17 (13%)
Nausea	4 (7%)	16 (12%)
Nasopharyngitis	8 (13%)	14 (10%)
Upper respiratory tract infection	7 (11%)	14 (10%)
Fatigue	8 (13%)	13 (10%)
Limb pain	6 (10%)	9 (7%)
Increased ALT concentration	4 (7%)	10 (7%)
Vomiting	1 (2%)	10 (7%)
Urinary tract infection	4 (7%)	9 (7%)
Arthralgia	3 (5%)	9 (7%)
Oropharyngeal pain	3 (5%)	9 (7%)
Myalgia	2 (3%)	8 (6%)
Pharyngitis	1 (2%)	8 (6%)
Increased AST concentration	2 (3%)	7 (5%)
Epistaxis	6 (10%)	7 (5%)
Back pain	3 (5%)	7 (5%)
Influenza	3 (5%)	7 (5%)
Cough	4 (7%)	6 (4%)
Upper abdominal pain	5 (8%)	6 (4%)
Constipation	5 (8%)	6 (4%)
Dizziness	6 (10%)	5 (4%)
Pruritus	5 (8%)	4 (3%)
Cataract‡	4 (7%)	4 (3%)
Hypertension	3 (5%)	4 (3%)
Peripheral oedema‡§	6 (10%)	2 (1%)
Dyspepsia‡§	4 (7%)	2 (1%)
Ecchymosis	4 (7%)	2 (1%)
Insomnia‡	4 (7%)	2 (1%)
Anxiety	3 (5%)	2 (1%)
Conjunctival haemorrhage	3 (5%)	2 (1%)
Contusion	3 (5%)	2 (1%)
Neck pain	3 (5%)	2 (1%)
Non-cardiac chest pain	3 (5%)	2 (1%)
Abdominal distension	3 (5%)	1 (<1%)
Conjunctivitis	4 (7%)	1 (<1%)
Fall	3 (5%)	1 (<1%)
Face swelling	3 (5%)	1 (<1%)
Cellulitis‡	4 (7%)	0
Eye swelling	3 (5%)	0
Any grade 3 or 4 adverse event	7 (11%)	20 (15%)
Death	1 (2%)	0

ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Severity of adverse events, including bleeding adverse events, was reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). †One patient allocated placebo was excluded from the safety population because no study drug was administered. ‡Events typically associated with corticosteroid use. §Significantly lower for eltrombopag versus placebo on the basis of a two-sided Fisher's exact test (p=0·01).

Table 2: **Adverse events during treatment***

	Placebo (n=61)†	Eltrombopag (n=135)
Bleeding adverse event*		
On-treatment bleeding event	19 (31%)	26 (19%)
On-treatment serious bleeding event‡	4 (7%)	1 (<1%)
Post-treatment bleeding event	6 (10%)	6 (4%)
Post-treatment serious bleeding event§	1 (2%)	2 (1%)
Thromboembolic event	0	3 (2%)
ALT ≥3 times the upper limit of normal	2 (3%)	9 (7%)
Total bilirubin >1·5 times the upper limit of normal	0	5 (4%)
Cataract¶**	6 (10%)	11 (8%)
Malignant disease||	1 (2%)	1 (<1%)
Hyperglycaemia ≥7·22 mmol/L**††	30 (50%)	42 (31%)
Reoccurrence of thrombocytopenia‡‡	4 (7%)	9 (7%)

ALT=alanine aminotransferase. *Severity of adverse events, including bleeding adverse events, was reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). †One patient allocated to placebo was excluded from the safety population because no study drug was administered. ‡Significantly lower for eltrombopag versus placebo on the basis of a two-sided Fisher's exact test (p=0·03). §Bleeding reported for one patient in each treatment group more than 30 days after study discontinuation; the remaining patient had a bleeding event while undergoing abdominal surgery for rectosigmoid cancer without prophylactic anticoagulant treatment. ¶Based on ocular examination; incident cataract (eltrombopag, n=7; placebo, n=3); cataract progression (eltrombopag, n=4; placebo, n=3). ||Malignant diseases were rectosigmoid cancer in one patient on day 92 of eltrombopag treatment and transformation of myelodysplastic syndrome to acute myeloid leukaemia in one patient 173 days after discontinuation of placebo. **Events typically associated with corticosteroid use. ††Significantly lower for eltrombopag than for placebo on the basis of a logistic regression analysis adjusted for baseline glucose above threshold and for baseline diabetes (OR 0·417, 95% CI 0·207–0·841; p=0·02). ‡‡Defined as patients with platelet counts lower than 10 000 per μL and at least 10 000 per μL lower than baseline during the first 4 weeks of interruption (>1 day) or discontinuation of study treatment.

Table 3: **Events of special interest**

reduced bleeding symptoms, while improving health-related quality of life.

Although eltrombopag was generally well tolerated during treatment in RAISE, transient increases of alanine aminotransferase and indirect bilirubin concentrations were reported, perhaps related to the metabolism of both eltrombopag and bilirubin by UGT1A1. All aminotransferase abnormalities resolved; however, aminotransferase and bilirubin should be monitored before initiation of and during eltrombopag treatment, and treatment stopped if necessary.[26] The rate of thromboembolic events in patients treated with eltrombopag in this study (three patients, 2%) is similar to or lower than that reported previously for this patient population (2·4–6·1%), although the duration of observation varies between reports.[27,28] Immune thrombocytopenia has been speculated to be associated with prothrombotic characteristics.[29] In our study, thromboembolic events do not seem to be associated with maximum platelet counts during eltrombopag treatment;[30] platelet counts proximal to the thromboembolic events were lower than 50 000 per μL. Although all three patients had several risk factors, no

unifying features were noted. The patients were managed in accordance with local standard of care. In another open-label study,[31] 13 (4%) of 299 patients treated with eltrombopag had 16 thromboembolic events. All patients had risk factors for thrombosis. No association was shown with proximal platelet count, age, dose, or time to onset. The recorded incidence was not higher than that in the general population of patients with immune thrombocytopenia. Eltrombopag treatment should proceed with caution in patients with known predispositions to thrombosis, and patients at risk of thrombosis should be closely monitored.

There was no evidence of worsened thrombocytopenia and serious bleeding after discontinuation of eltrombopag as compared with placebo; platelet counts generally returned to baseline levels within 2 weeks. Platelet counts should be closely monitored for at least 2 weeks after discontinuation of any treatment for immune thrombocytopenia. No bone-marrow data for the presence or absence of reticulin were derived from this study; however, a preliminary report of 86 patients with immune thrombocytopenia treated with eltrombopag for up to 18 months in a long-term extension study showed no evidence of clinical symptoms typically associated with myelofibrosis or other myeloproliferative bone-marrow abnormalities.[32]

Post-hoc analyses showed a significant reduction in the occurrence of steroid-associated side-effects, including dyspepsia, peripheral oedema, and hyperglycaemia with eltrombopag. Reductions in steroid use presumably contributed to the improved health-related quality of life in patients receiving eltrombopag. The relevance of these findings is supported by analyses of patient-perceived burden of steroid treatment for chronic immune thrombocytopenia[33,34] and by results of earlier studies showing that present treatment for chronic disease is unsatisfactory and is associated with significant morbidity and mortality.[35]

On the basis of these findings, eltrombopag seems to be beneficial for patients who have refractory immune thrombocytopenia, who have not responded to splenectomy, or who have had temporary or negligible responses to treatments such as corticosteroids, immunoglobulins, or rituximab and continue to have bleeding symptoms. Currently, these patients have few alternatives, many of which have not been well assessed in randomised studies or are less effective in splenectomised patients than in non-splenectomised patients.[36–39] Additionally, eltrombopag might be considered for some patients with chronic immune thrombocytopenia who have not undergone splenectomy either because they are not suitable candidates or because they wish to avoid the procedure. Where eltrombopag fits in the existing treatment approach before splenectomy remains to be established because the effects of chronic use are still under investigation, but monthly platelet counts and continued monitoring of potential safety issues are necessary. Further studies will help to establish how eltrombopag should best be used in the management of patients with chronic immune thrombocytopenia.

Contributors

MNS, SV, BM, MAr, NLS, and JBB assisted with the design of the study. GC, MNS, CM, and JBB participated in entering and screening patients into the study. GC was the principal investigator. SV, BM, MAi, MAr, and NLS, contributed to the analysis of the data. All authors contributed to the writing of the manuscript, and all authors have seen and approved the final version of the report.

Conflicts of interest

GC reports receiving research support and lecture fees from GlaxoSmithKline. MNS reports receiving lecture fees from Bristol-Myers Squibb and GlaxoSmithKline and consulting fees from GlaxoSmithKline. CM reports participating in an advisory board for GlaxoSmithKline. SV, BM, MAi, MAr, and NLS are full-time employees of GlaxoSmithKline and report having equity ownership in the company. JBB reports receiving research support from Amgen, Cangene, Eisai Inc, Genzyme, GlaxoSmithKline, Immunomedics, Ligand, and Sysmex; having equity ownership in Amgen and GlaxoSmithKline; participating in the speaker's bureau programme for Scienta; and participating in advisory boards for Amgen, Eisai Inc, GlaxoSmithKline, Ligand, and Shionogi.

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References

1 Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; **113:** 2386–93.

2 Arnold DM, Kelton JG. Current options for the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 2007; **44:** S12–23.

3 Stevens W, Koene H, Zwaginga JJ, Vreugdenhil G. Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights. *Neth J Med* 2006; **64:** 356–63.

4 Cooper N, Bussel J. The pathogenesis of immune thrombocytopaenic purpura. *Br J Haematol* 2006; **133:** 364–74.

5 Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood* 2005; **106:** 2244–51.

6 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.

7 Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **373:** 641–48.

8 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.

9 Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood* 2009; **113:** 2161–71.

10 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.

11 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.

12 Stasi R, Evangelista ML, Amadori S. Novel thrombopoietic agents: a review of their use in idiopathic thrombocytopenic purpura. *Drugs* 2008; **68:** 901–12.

13 Bussel JB, Psaila B, Saleh MN, et al. Efficacy and safety of repeated intermittent treatment with eltrombopag in patients with chronic idiopathic thrombocytopenic purpura. *Blood* 2008; **112:** 3431.

14 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:** 3432.

15 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.

16 Baranwal A, Fraser L, Jayawardene D, Jagiello-Gruszfeld A, Bondarenko I, Mendoza J. Efficacy and safety of eltrombopag, a novel, oral platelet growth factor on platelet counts in patients with cancer receiving carboplatin/paclitaxel chemotherapy. *Support Care Cancer* 2007; **15:** 761. Abstr P-168.

17 George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; **88:** 3–40.

18 British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 2003; **120:** 574–96.

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

20 Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol* 2005; **32:** 811–19.

21 Lai JS, Cella D, Chang CH, Bode RK, Heinemann AW. Item banking to improve, shorten and computerize self-reported fatigue: an illustration of steps to create a core item bank from the FACIT-Fatigue Scale. *Qual Life Res* 2003; **12:** 485–501.

22 Cella D, Beaumont JL, Webster KA, Lai JS, Elting L. Measuring the concerns of cancer patients with low platelet counts: the Functional Assessment of Cancer Therapy—thrombocytopenia (FACT-Th) questionnaire. *Support Care Cancer* 2006; **14:** 1220–31.

23 Fehnel SE, Bann CM, Hogue SL, Kwong WJ, Mahajan SS. The development and psychometric evaluation of the Motivation and Energy Inventory (MEI). *Qual Life Res* 2004; **13:** 1321–36.

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

25 Stasi R, Cheng G, Saleh MN, et al. Durable and overall platelet responses in patients with chronic idiopathic thrombocytopenic purpura during long-term treatment with oral eltrombopag by splenectomy status: the RAISE study. *Haematologica* 2009; **94:** 3. Abstr. 0231.

26 PROMACTA (eltrombopag) tablets, for oral use. Package insert. Research Triangle Park, NC, USA: GlaxoSmithKline, 2010.

27 Gernsheimer TB, George JN, Aledort LM, et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). *J Thromb Haemost* 2010; published online March 3. DOI:10.1111/j.1538-7836.2010.03830.x.

28 Sarpatwari A, Bennett D, Logie JW, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. *Haematologica* 2010; **95:** 1167–75.

29 Zelcer S, Bussel JB. Thrombosis in patients with immune thrombocytopenic purpura (ITP): a case series. *J Thromb Haemost* 2003; **1:** abstr P1169.

30 Bussel JB, Cheng G, Saleh MN, Vasey S, Aivado M, Brainsky A. Thromboembolic events observed in eltrombopag clinical trials in chronic immune thrombocytopenic purpura. *Blood* 2009; **114:** abstr 2423.

31 Saleh MN, Bussel JB, Cheng G, et al. Long-term treatment of chronic immune thrombocytopenic purpura with oral eltrombopag: results from the EXTEND study. *Blood* 2009; **114:** abstr 682.

32 Saleh MN, Bussel JB, Meyer O, et al. Results of bone marrow examinations in patients with chronic immune thrombocytopenic purpura treated with eltrombopag. *Blood* 2009; **114:** abstr 1326.

33 Grotzinger K, Matzdorff A, Brown TM, Horblyuk R, Brainsky A. Corticosteroids for the treatment of chronic idiopathic thrombocytopenic purpura: patient-perceived burden. *Haematologica* 2009; **94:** 96. Abstr 0242.

34 Matzdorff A, Arnold G. Treatment of chronic immune thrombocytopenic purpura: the patients' perspective. *Eur J Haematol* 2007; **78:** 381–88.

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

36 Boruchov DM, Gururangan S, Driscoll MC, Bussel JB. Multiagent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP). *Blood* 2007; **110:** 3526–31.

37 George JN. Management of patients with refractory immune thrombocytopenic purpura. *J Thromb Haemost* 2006; **4:** 1664–72.

38 Psaila B, Bussel JB. Refractory immune thrombocytopenic purpura: current strategies for investigation and management. *Br J Haematol* 2008; **143:** 16–26.

39 Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. *Blood* 1995; **85:** 351–58.