

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-291

MEDICAL REVIEW(S)

Decisional Review Memorandum

Date: November 4, 2008

From: Dwaine Rieves, M.D.
Director, Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products, OND, CDER

Through: Richard Pazdur, MD
Director, Office of Oncology Drug Products

To: NDA 22-291 for PROMACTA (eltrombopag)

Subject: Risk Evaluation and Mitigation Strategy

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for PROMACTA to ensure that the benefits of the drug outweigh the following risks: 1) risk of hepatotoxicity; 2) risk for marrow fibrosis; 3) risk for hemorrhage following discontinuation of eltrombopag due to worsened thrombocytopenia than was present at baseline; 4) risk for thrombotic/thromboembolic complications due to excessive platelet counts; 5) risk for hematologic malignancy. In reaching this determination, we considered the following:

- A. The prevalence rate of chronic (adult) immune thrombocytopenic purpura (ITP) was estimated at 24 cases per 100,000 persons or 52,700 adult cases in the United States based on the 2005 census estimates. This prevalence (published in International Society on Thrombosis and Haemostasis by Feudjo-Tepie et al in 2008) was based upon analyses of the Integrated

Healthcare Information System (IHCIS) database, one of the largest US health care managed databases. McMillan (Ann Intern Med: 1997) estimates that 30% of chronic ITP cases are "refractory" and this subset is the group of patients who are most likely to receive eltrombopag. Hence, approximately 16,000 patients in the US (based on 2005 census) are general candidates for PROMACTA therapy, as indicated.

- B. PROMACTA is indicated to treat a very serious stage of chronic ITP that is generally regarded as so serious that patients are at imminent risk of death due to hemorrhage.
- C. PROMACTA has been shown to be effective in 60 to 70% of treated chronic ITP patients. This treatment effect is a remarkable response since these patients had failed most (if not all) prior therapies. The specific treatment benefit is an increase in blood platelet counts to a level that lessens the risk for serious hemorrhage.
- D. PROMACTA therapy is anticipated as life-long (many years) therapy for many patients since the indicated patient population is one that generally has no other long term therapeutic options and chronic ITP rarely spontaneously resolves.
- E. The serious adverse events signaled in the clinical development of PROMACTA are risks for hepatotoxicity and risk for hemorrhage following discontinuation of PROMACTA due to worsened thrombocytopenia than was present at baseline. Hepatotoxicity is not an event with an established background incidence in patients with chronic ITP. Hence, hepatotoxicity in the PROMACTA development program provides strong evidence of a drug-related effect.

A review describing the clinical manifestations of chronic ITP notes that almost all manifestations of chronic ITP relate to thrombocytopenia, hemorrhage and bone marrow alterations. (New England Journal of Medicine 2002;346: 995-1007). The worsened thrombocytopenia has been hypothesized as due to suppression of intrinsic thrombopoietin (TPO) levels by PROMACTA therapy.

PROMACTA also has potentially serious risks due to the risks associated with other members of the class of thrombopoietin products. These risks include the following: a risk for hematologic malignancy due to stimulation of the thrombopoietin receptor (a risk supported by *in vitro* studies); a risk for thrombotic/thromboembolic risks associated with excessive platelet counts (as may occur either due to medication errors or as patient-specific responses to the drug) as well as a risk for bone marrow fibrosis (as documented by animal studies of thrombopoietin receptor products).

The background incidence of hematologic malignancy, bone marrow fibrosis or thrombosis in chronic ITP is not known, since most patients either respond to initial therapy with prednisone or require more aggressive immunosuppressive medications or splenectomy and these therapies may alter the risks. In a long term (median of 92 months), follow-up study of 402 patients who underwent splenectomy (the patient population potentially at greatest risk for malignancy or marrow fibrosis), only 2% of patients experienced thromboses, malignancy occurred in 3%, and marrow fibrosis was not reported (Haematologica 2005: 90 (1); Vianelli et al). Together these data suggest that the risk for marrow fibrosis, malignancy and thrombosis are relatively low within the subset of patients who undergo splenectomy for chronic ITP.

F. PROMACTA is a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Under 21 CFR 208, the sponsor is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed PROMACTA. Pursuant to 21 CFR Part 208, FDA has determined that PROMACTA poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of PROMACTA. FDA has determined that PROMACTA is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, PROMACTA.

The elements of the REMS will be a Medication Guide, communication plan, elements to assure safe use (including that healthcare prescribers are specially certified, that practioners and hospitals/institutions that dispense the drug are specially certified, and safe-use conditions), an implementation system, a timetable for submission of assessments, and assessments of the REMS.

b(4)

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/s/

Rafel Rieves
11/14/2008 02:46:38 PM
MEDICAL OFFICER
REMS memo for Promacta/requires office sign off

Richard Pazdur
11/18/2008 10:04:33 AM
MEDICAL OFFICER

Summary Review for Regulatory Action

Date	October 29, 2008
From	Dwayne Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	22-291
Applicant Name	GlaxoSmithKline
Date of Submission	December 19, 2007
PDUFA Goal Date	September 19, 2008
Proprietary Name / Established (USAN) Name	Promacta™ Eltrombopag tablets
Dosage Forms / Strength	25 and 50 mg tablets
Proposed Indication(s)	"Promacta is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy."
Action/Recommended Action for NME:	Approval under accelerated approval regulations (21 CFR 314.510) "Subpart H"

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Andrew Dmytrijuk, MD & Kathy Robie Suh, MD PhD (TL)
Statistical Review	Qing Xu, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Yash Chopra, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Sue-Ching Lin, PhD & Ying Wang, PhD
Microbiology Review	not applicable (oral tablet)
Clinical Pharmacology Review	Joseph Grillo, PharmD & Young Moon Choi, PhD (TL)
DDMAC	Carrie Newcomer, PharmD (med guide review) Sean Bradley (other labeling)
DSI	John Lee, MD & Tejashri Purohit-Sheth, MD
CDTL Review	none (submission predated need for CDTL)
OSE/DMETS	Walter Fava, RPh & Linda Kim-Jung, PharmD
OSE/DDRE	Suzanne Berkman, PharmD, Mary Dempsey, Claudia Karwoski, PharmD
Pediatric and Maternal Health	Richardae Araogo, PharmD, Karen Feibus, MD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

TL = Team Leader

1. Introduction:

This New Drug Application (NDA) was submitted for eltrombopag tablets, a new molecular entity within the class of products generally referred to as "thrombopoietin (TPO) receptor agonists." TPO receptor agonists are products that stimulate the TPO receptor on bone marrow megakaryocytes and through a series of biological consequences (cell multiplication, maturation) result in blood platelet production. To date, FDA has approved one member of the TPO receptor agonist class of products—romiplostim, a biological product approved earlier in 2008.

This review will focus upon the regulatory basis for the approval recommendation, particularly considering the relatively "short term" nature of the phase 3 clinical studies and the recommendation for approval under Subpart H.

2. Background:

Clinical investigation of TPO receptor products began in the early 1990's following recombinant-technology-based synthesis of TPO and TPO-mimetic proteins. The initial clinical studies of TPO-mimetic products showed that some patients developed neutralizing antibodies to TPO, including antibodies that neutralized native, intrinsic TPO such that certain healthy volunteers developed thrombocytopenia. Consequently, subsequent product development focused upon the use of TPO receptor agonists that were molecularly designed to minimize the potential for immunogenicity.

In 2008, FDA approved romiplostim, a recombinant TPO receptor agonist that was molecularly engineered to specifically minimize the potential for immunogenicity. The approval of romiplostim was based upon two clinical studies conducted over a six month period of time. Eltrombopag is recommended for approval under the accelerated approval mechanism. This recommendation is based predominantly upon the use of clinical data from two controlled studies in which eltrombopag was administered over six weeks or less; in this situation the relatively "short term" platelet response is viewed as a surrogate endpoint reasonably likely to predict long term benefit. Additionally, the approval is recommended based upon the sponsor's requirement to verify the long term benefit in a controlled clinical study of six months or longer duration.

Eltrombopag is a chemically synthesized molecule that is proposed to bind to a transmembrane portion of the TPO receptor and initiate downstream processes within bone marrow megakaryocytes that ultimately result in platelet production. Eltrombopag is administered as a tablet and the dose is titrated to achieve and maintain the desired platelet count response.

During the clinical development of eltrombopag, the company performed an exploratory clinical study that demonstrated eltrombopag prompted platelet count increases in healthy subjects. These drug-stimulated platelets had *in vitro* platelet function characteristics generally typical of platelets. Hence, this study supported the generally accepted use of

platelet counts as an "accepted" measure of clinical benefit for clinical studies of TPO receptor agonists among patients with chronic ITP.

The clinical development of eltrombopag for chronic ITP proceeded along a pathway focused upon two indications, one related to a "short term" indication (for example, use of the product around the time of a surgical procedure) and another related to a "long term" indication. Specifically, two phase 3 clinical studies of six weeks duration were submitted with this current application in order to support a "short term" indication. The company has recently completed a phase 3 study (referred to as the RAISE study) in which patients received study drugs over a six month period of time. The results of the RAISE study are proposed to address the Subpart H considerations, specifically the need for a randomized, controlled study that verifies the ability of eltrombopag to maintain platelet counts over a prolonged (at least six months) period of time.

As described below, the "short term" clinical studies demonstrated that eltrombopag stimulated platelet counts among a population of patients with relatively refractory chronic ITP. However, discontinuation of eltrombopag at the end of the study resulted in an unacceptable amount of serious hemorrhage. Hence, one of the major findings in this NDA review was that the "short term" indication proposal was not a reasonable clinical goal among patients with chronic ITP who had few, if any alternative drug therapies.

The review team worked with the company to develop an indication for eltrombopag to be used as a chronic ITP therapy among relatively refractory patients. This indication is based upon the two phase 3 clinical studies of six weeks duration plus the supportive information from the single arm extension study. To reiterate, the recommendation for Subpart H approval is based upon:

- a) use of the "short term" platelet count response as a surrogate marker for longer platelet count responses (platelet counts are recognized as acceptable measures of clinical benefit for patients with chronic ITP)
- b) chronic ITP is a serious medical condition
- c) eltrombopag approval would provide a meaningful therapeutic benefit to patients over existing treatments because of its minimal risk for immunogenicity (based upon the small molecule characteristics). The labeling for romiplostim, the only currently marketed TPO receptor agonist, includes information regarding the risks for immunogenicity. These risks are not applicable to eltrombopag.

During this review cycle, a major amendment was assessed (related to clinical data from the extension study) that resulted in a longer review time line. Nevertheless, the pdufa goal was exceeded, in large part due to the challenges associated with development of the Risk Evaluation and Mitigation Strategy (REMS) document.

3. Chemistry, Manufacturing and Controls:

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. Importantly, most of the nonclinical studies were conducted among animal species that did not respond to eltrombopag with an increase in platelet count. Hence, the animal data were interpreted with the knowledge of this important limitation and the inability of these data to fully model the anticipated human response.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology team's findings were similar to those of the company in that eltrombopag appears to importantly undergo metabolism in the liver and the drug is vulnerable to drug interactions. Additionally, eltrombopag may function as a chelator with certain compounds in the diet (such as calcium—chelation within the intestine may impair absorption of the complex), such that dietary intake can importantly change eltrombopag absorption. These limitations are described in considerable length within the eltrombopag labeling.

Additionally, limited clinical data suggested that a 25 mg dose of eltrombopag was appropriate initial therapy for patients of Asian ethnicity as well as patients with moderate or severe liver impairment. The recommended initial eltrombopag dose is 50 mg for other patients.

6. Clinical Microbiology:

Eltrombopag is a tablet for oral administration. Hence, microbiology concerns are negligible and a microbiology review was not performed.

7. Clinical/Statistical-Efficacy:

As previously noted, this NDA was originally submitted with a request for a "short term" usage of eltrombopag (as may be necessitated by the need for elective surgery among patients who are thrombocytopenic). In support of this "short term" indication, two phase 3 clinical studies were submitted. These studies are referred to as Studies 773A and 773B, as described below.

a) Design of phase 3 studies:

Study 773 A and Study 773B were randomized, double-blind, placebo controlled studies conducted among adult patients with chronic ITP who had baseline platelet counts < 30,000/mcL despite completion of at least one prior ITP therapy. Eligible patients included those who had, as well as those who had not, undergone splenectomy. Patients were to receive the study drugs daily for no more than six weeks with termination of all dosing if a platelet count exceeded 200,000/mcL. Patients were observed for six weeks following discontinuation of the study drug.

The primary endpoint in each study was the same: a "response" defined as a platelet count $\geq 50,000/\text{mcL}$ by day 43 or drug discontinuation due to a platelet count > 200,000/mcL. Multiple secondary endpoints explored various other measures of platelet count responses, as well as changes in the World Health Organization (WHO) bleeding scores.

In Study 773 A, patients were randomized among four groups: placebo or eltrombopag at one of three dose regimens (30 mg, 50 mg or 75 mg) with the study drugs administered daily.

In Study 773B, patients were randomized between placebo and eltrombopag administered as 50 mg daily. The study drug could be increased to 75 mg daily, if patients failed to experience a predefined increase in platelet counts.

b) Results of the phase 3 studies:

Both phase 3 studies generally enrolled patients who had undergone multiple prior ITP therapies and who appeared to need an option for chronic ITP therapy. Notably, the patients were not selected based upon any specific need for "short term" therapy with a new ITP treatment. Overall, the median age was 50 years in the two studies and 60% were female. The median baseline platelet count was 18,000/mcL among all groups in the two studies.

In general, Study 773A showed a general pattern of increasing "response" within the dose cohorts, as shown below in Table 1.

Table 1. Study 773A Primary Endpoint: "Response"

Primary Endpoint	Placebo n = 27	Eltrombopag		
		30 mg n = 29	50 mg n = 27	75 mg n = 26
Platelet count $\geq 50,000/\text{mcL}$	3 (11%)	8 (28%)	19 (70%)	21 (81%)

Table 2 summarizes the results for the 50 mg dose cohort from Study 773A along with the results from Study 773B. In general, approximately 60% (58% and 70%) of patients met the primary endpoint response within the two studies, while placebo response rates were relatively minor (16% and 11%). The comparison of proportions showed a

statistically significant difference between the placebo and 50 mg eltrombopag groups ($p < 0.01$).

Table 2. Summary of Study 773A 50 mg Dose Cohort and Study 773B Primary Endpoint Results, n (%)

Study	Placebo	Eltrombopag 50 mg
773A "Responders"	3/27 (11%)	19/27 (70*)
773B "Responders"	6/38 (16%)	43/74 (58%*)

As shown in Table 3, response rates were generally similar between patients who had undergone splenectomy and patients who had not undergone splenectomy.

Table 3. Primary Endpoint in Splenectomy Subsets: Pooled Study 773A 50 mg Eltrombopag Cohorts/Placebo and Study 773B

Subset	Placebo	Eltrombopag
Splenectomy	4/27 (15%)	26/44 (59%)
No splenectomy	5/37 (14%)	36/56 (64%)

During the phase 3 studies, only seven patients underwent "hemostatic challenge" (such as a surgical procedure), consisting of three placebo group patients and four eltrombopag group patients. Additional ITP medications were required in all placebo group patients but none of the eltrombopag group patients. Only one patient needed a blood transfusion (a placebo group patient).

One of the secondary endpoints that received considerable attention during the review was the data obtained from baseline and follow-up WHO bleeding scale scores. This scale is a scale that assigns numeric grades (0 through 4), based upon subjective assessments of the extent of bleeding at any time point. The scale has not been verified for clinical meaningfulness, especially with respect to incremental changes (for example, a change from a grade 2 to a grade 1). The limitations of the scale were exemplified by the study findings, in that all changes were within the lowest grades (0 through 2) and largely by a transition from "petechiae" (grade 1) to the absence of petechiae (grade 0). Given the unclear clinical meaningfulness of the scale and the relatively trivial changes detected during the study, the review team regarded the WHO bleeding scale as solely exploratory data.

In addition to these phase 3 clinical studies, an open label, single arm study of 109 patients who had participated in an earlier eltrombopag clinical study showed that eltrombopag could achieve and maintain platelet counts above 50,000/mcL in a sizable proportion of patients. The most common eltrombopag dosage was 50 mg daily in this study, a finding that supports the recommended dosage in the eltrombopag label.

I concur with the major findings from the statistical and clinical review team.

8. Safety:

Overall, 313 patients with chronic ITP were exposed to eltrombopag, including 81 patients exposed for at least six months and 39 patients exposed for at least one year.

The major safety findings related to a risk for hepatotoxicity and hemorrhage following eltrombopag discontinuation. Additional concerns related to a risk for cataract formation/worsening as well as the general anticipated risks for all members of the TPO receptor agonist product class.

a) Hepatotoxicity:

The risk for hepatotoxicity prompted the development of a boxed warning for eltrombopag. In the two phase 3 clinical studies, one patient experienced grade 4 (CTC scale) elevations in serum liver tests during eltrombopag therapy. The patient had extensive underlying disease (chronic obstructive lung disease and heart disease) but liver test progressively increased during eltrombopag therapy, including marked increases immediately prior to hospitalization and his subsequent death. The autopsy findings did not show explicit findings of drug damage to the liver but the overall clinical pattern of the events suggested that eltrombopag hepatotoxicity could have importantly contributed to the patient's worsened condition and death. No grade 4 liver test elevations occurred in the placebo groups.

Overall, serum liver test abnormalities (predominantly grade 2 or less in severity) were reported in 10% and 8% of the eltrombopag and placebo groups, respectively.

The clinical studies showed that, with close monitoring of patients who had eltrombopag discontinued because of liver test abnormalities, eltrombopag could be safely introduced for a second attempt at therapy. The liver test findings from the clinical studies prompted the label citation to a need for regular liver test monitoring during eltrombopag therapy (every two weeks during the dose adjustment phase and then monthly).

b) Serious hemorrhage following eltrombopag discontinuation:

In the phase 3 studies, patients were followed for six weeks after eltrombopag discontinuation. This post-therapy observation period revealed the problem with use of eltrombopag solely as a "short term" therapy among patients with chronic ITP. Specifically, seven eltrombopag group patients experienced a serious hemorrhagic event and five of these patients experienced the event while "off therapy." Only one placebo group patient experienced a serious hemorrhage event (an event that occurred while "on therapy"). Hence, the studies importantly signaled that "short term" therapy was inappropriate among patients who had few, if any, alternative drug therapies for chronic ITP.

c) Cataracts:

In animal studies, eltrombopag was associated with the development of cataracts during repetitive drug administration. In the controlled clinical studies, cataracts developed or worsened in 5% of patients who received eltrombopag 50 mg daily and 3% of placebo group patients. The eltrombopag label describes the risk for cataract and recommends a baseline examination for cataract along with regular monitoring of cataract signs and symptoms.

d) Other risks common to TPO receptor products:

Eltrombopag shares risks common to other TPO receptor products, consisting of a risk for:

- thrombosis due to excessive platelet count increases (platelet counts must be monitored regularly during therapy);
- a risk for hematologic malignancy, especially among patients with myelodysplasia syndrome (based upon *in vitro* observations that the TPO receptor may function in a form of tumor promotion/facilitation; additionally limited clinical data signals a malignancy risk);
- bone marrow reticulin formation and risk for marrow fibrosis; in the extension study, seven patients had reticulin fiber deposition reported in bone marrow biopsies, including two patients who also had collagen fiber deposition.

The extent of safety concerns have necessitated development of:

- labeling to include a boxed warning for hepatotoxicity
- a Risk Evaluation and Mitigation Strategy (REMS) that provides for physician and patient education, collection of major safety outcome data in a registry-type format and restriction of prescription/dispensation to prescribers and facilities enrolled in a special program called "*Promacta Cares*."

Major Features of the REMS:

At the present time, the major features are undergoing finalization, but the major components are outlined below.

- a. A medication guide—to be dispensed concomitant with the drug.
- b. FDA-approved communication plan to include specific text for healthcare provider materials and institutional materials. The education process (as well as prescriber certification/patient registry) is referred to as the "*Promacta Cares*" program.

c. Elements to assure safe use: drug distribution is limited to prescribers and patients who enroll in the *Promacta Cares* program.

- all prescribers must be "certified" by the company; certification involves signing a specific document (prescriber enrollment form) that attests to familiarity with the labeling and agreement to comply with the expectations of the program/patient registry.

- To comply with the registry/program, prescribers must:

- sign and submit the "healthcare provider enrollment form"
- at enrollment of a patient, complete a "patient enrollment form" and "patient baseline data form."
- obtain signature of each patient to confirm participation in the program/disclosure of information to the program
- complete a form every six months to verify that continued treatment is appropriate and to actively solicit (yes/no, check list) major safety outcomes using a _____
- complete a "patient discontinuation" form if eltrombopag is discontinued; a post-discontinuation form must also be completed _____ months later (____ months after drug discontinuation).

b(4)

The REMS does not prohibit prescription of eltrombopag for non-ITP uses; however, all clinical use of the drug is tracked through the program. Similarly, the REMS _____

_____. The REMS assessments are to be performed frequently for the first two years following product launch and regularly thereafter.

Post-marketing Requirements (PMR):

The PMR are outlined below and specifically include submission of the report for the RAISE study (a study that provides longer term exposure data in a controlled setting and that should be sufficient to address the accelerated approval expectation for a confirmatory study) and the modification of the on-going extension study to obtain baseline and follow-up bone marrow results.

1. To submit the complete study report for Study TRA102537 entitled "A randomized, double blind, placebo-controlled phase 3 study, to evaluate the efficacy, safety, and tolerability of eltrombopag, a thrombopoietin receptor agonist, administered for 6 months as oral tablets once daily in adult subjects with previously treated chronic idiopathic thrombocytopenic purpura (ITP)" (the "RAISE" study).
2. To submit a complete study report for Study TRA108057 entitled "An open-label repeat dosing study of eltrombopag olamine in adult subjects, with chronic idiopathic thrombocytopenic purpura (ITP)."

3. To conduct Study TRA105325 entitled "EXTEND (Eltrombopag extended dosing study): an extension study of eltrombopag olamine in adults, with idiopathic thrombocytopenic purpura (ITP), previously enrolled in an eltrombopag study". The study protocol will be modified to include performance of bone marrow examinations prior to the initiation of eltrombopag, following 12 months of eltrombopag therapy as well as following the completion of 24 months of eltrombopag therapy; study enrollment will continue until these data are obtained from at least 150 patients. An interim report will contain, in addition to any other items, results of bone marrow evaluations for patients who have completed bone marrow evaluations at baseline and following 12 months of eltrombopag therapy.
4. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to eltrombopag during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, bone marrow reticulin formation, thrombotic events, and any serious pregnancy outcomes. These events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until _____ b(4)
5. To conduct a milk-only lactation study in the subset of women enrolled in the pregnancy registry that choose to breastfeed their infants. This study will be designed to detect the presence and concentration of eltrombopag in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Annual interim reports will be submitted until _____ b(4)

9. Advisory Committee Meeting:

The May 30, 2008 Oncologic Drugs Advisory Committee voted unanimously to recommend assessment of a favorable risk to benefit profile for eltrombopag. Multiple comments pertained to the potential need for "long term" use of the drug among patients with few or no alternatives.

10. Pediatrics:

Eltrombopag has received an Orphan Drug indication. Hence, the company is not required to propose or conduct clinical studies in the pediatric patient population. _____ b(4)

11. Other Relevant Regulatory Issues:

The FDA inspection of clinical sites disclosed acceptable evidence of data integrity. Financial disclosure expectations have been met.

To facilitate completion of the NDA review package/portfolio, this review document is finalized at a time when the REMS document is undergoing a final stage of review and development. The substance/content of the REMS document has been documented and we anticipate finalization of text within the next many days.

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/s/

Rafel Rieves
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-291
Submission Code 000

Letter Date December 19, 2007
Stamp Date December 19, 2007
PDUFA Goal Date September 19, 2008 (revised)

Reviewer Name Andrew Dmytrijuk, M.D.
Review Completion Date September 12, 2008

Established Name Eltrombopag
(Proposed) Trade Name Promacta
Therapeutic Class Thrombopoietin Agonist
Applicant Glaxo SmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Priority Designation P

Formulation Oral
Dosing Regimen 50 mg Once Daily
Indication Short-Term Treatment of Chronic
Idiopathic Thrombocytopenic
Purpura (ITP) to Increase Platelet
Counts and Reduce or Prevent
Bleeding
Intended Population Patients with ITP

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Eltrombopag is approvable for the following indication provided the risk management and post marketing recommendations are undertaken:

- Eltrombopag is indicated for the treatment of patients with chronic idiopathic thrombocytopenic purpura (ITP). The dose proposed is as follows:
 - The starting dose is 50 mg orally once daily. If the platelet count is less than 50,000/mcl the dose is increased to 75 mg only once daily. Treatment is to be continued for six weeks. Eltrombopag should be discontinued if the platelet count is greater than 200,000/mcl.
 - For patients of the East Asian ancestry 25 mg orally once daily —
The dose of eltrombopag in this patient population may be increased to 50 mg orally once daily if the platelet count is less than 50,000/mcl after 2 weeks.

The rationale for this recommendation is based on the following information:

- The efficacy of the proposed therapy in terms of increasing platelet counts in patients with ITP is supported by the pivotal studies TRA100773A and TRA 10773B. The studies were randomized, double-blind, placebo-controlled, multicenter, multinational trials.
- However, the pivotal trials failed to show efficacy in terms of a reduction or prevention of bleeding in patients with ITP. Statistical efficacy analysis with regard to multiple bleeding events at the six-week timepoint showed no statistical difference between patients treated with eltrombopag and patients treated with placebo ($p = 0.067$) in study TRA 10773B.
- In addition, the sponsor failed to show that a sizable number of patients were able to undergo a hemostatic challenge due to the lack of patience that underwent hemostatic challenge.
- In the pivotal studies patients were given a single cycle of eltrombopag for a six-week period. Because ITP is a chronic disease and it is conceivable that patients will have the need for multiple treatments with eltrombopag as their platelet count waxes and wanes and/or because patients may face various types and cycles of hemostatic challenges. The safety and efficacy of long term and/or cycled treatment of chronic ITP with eltrombopag was not studied in the pivotal trials provided in the current application. The sponsor has ongoing trials which will evaluate the safety and efficacy of this drug in these circumstances. The sponsor should submit the results and an acceptable safety and

- Cataracts
- Withdrawal and rebound-transient worsening of thrombocytopenia.
- Off label use

In order to address these risks the sponsor should undertake the usual postmarketing monitoring and reporting. In addition, the sponsor proposes a REMS which involves a registry of all ITP patients that are exposed to eltrombopag. The sponsor also proposes

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Required Phase 4 Commitments

The following should be required postmarketing:

1. The sponsor should complete the supportive studies (including RAISE, EXTEND and REPEAT) and submit them for review and analysis.
2. The sponsor should propose and implement a registry program for all patients treated with eltrombopag who have ITP.
3. _____
4. The sponsor should continue to report the safety and efficacy of eltrombopag in the ITP population as is required by 21 CFR § 314.50.

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Other Phase 4 Requests

None requested.

1.3 Summary of Clinical Findings

Brief Overview of Clinical Program

- Eltrombopag is an orally bioavailable small molecule thrombopoietin receptor (TPO-R) agonist that interacts with the transmembrane domain of TPO-R and initiates a signaling cascade similar, but not identical, to that of endogenous thrombopoietin.
- Eltrombopag is indicated for the short-term treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.
- The safety and efficacy of eltrombopag was evaluated in two randomized, double-blind pivotal studies: TRA 100773A and TRA 100773B.
- Study TRA 100773A enrolled 118 patients. In this study 30 patients were enrolled in the placebo group as well as the 30 mg and 50 mg eltrombopag treated groups. There were 28 patients enrolled in the 75 mg eltrombopag group.
- Study TRA 100773B enrolled 38 patients into the placebo group and 76 patients into the 50 mg eltrombopag treated patient group.
- At the time of the NDA submission 269 patients had been exposed to eltrombopag during the clinical development program. At the time of the 120 day safety update an additional 61 patients had been exposed to eltrombopag. At the time of the 120 day safety update is estimated that 150 patients had been exposed to eltrombopag for $\geq$ six months.

Efficacy

The study was a double-blind, randomized, multi-institutional, placebo controlled, parallel group, repeat-dose study conducted in 2 parts (part A and part B) and at essentially the same study sites. Part A was a phase 2 study while part B was a Phase 3 study. Screening was to take place up to 28 days before dosing. The “on-dose” phase of the study (both part A and B) was to involve once daily dosing of eltrombopag for 6 weeks. The primary efficacy endpoint was increased in platelet count to $\geq 50,000/\text{mcl}$ on day 43 after starting study treatment. On completion of the dosing period, subjects were to undergo follow-up assessments for 6 weeks following the final dose. The six week follow up period was proposed by the sponsor to assess the durability of the platelet response.

The study was to be conducted in adult subjects with refractory chronic ITP, defined as patients who have failed at least one previous treat for ITP, including corticosteroids, immunoglobulins, immunomodulators and/or splenectomy. Patients receiving maintenance corticosteroid therapy could participate providing their corticosteroid dose had been stable for at least 1 month prior to screening. A sufficient number of subjects were to be enrolled so that a total of 422 subjects complete this 2 part study, i.e. 272 subjects in part A and 150 subjects in part B. The sponsor was able to enroll 30 patients each into the placebo, 30 and 50 mg dose cohorts and 28 patients in the 75mg dose cohort for part A of the study (total 118 patients). In part B of the study the sponsor was able to enroll 38 patients into the placebo arm and 76 patients into the 50mg dose arm (total 114 patients).

In study TRA 100773A analysis of the primary endpoint showed that eltrombopag gave a dose dependent increase in the proportion of patients with chronic ITP who achieved a platelet count of $\geq 50,000/\text{mcl}$ on day 43 starting from a baseline platelet count $< 30,000/\text{mcl}$: 11% (3/27) of

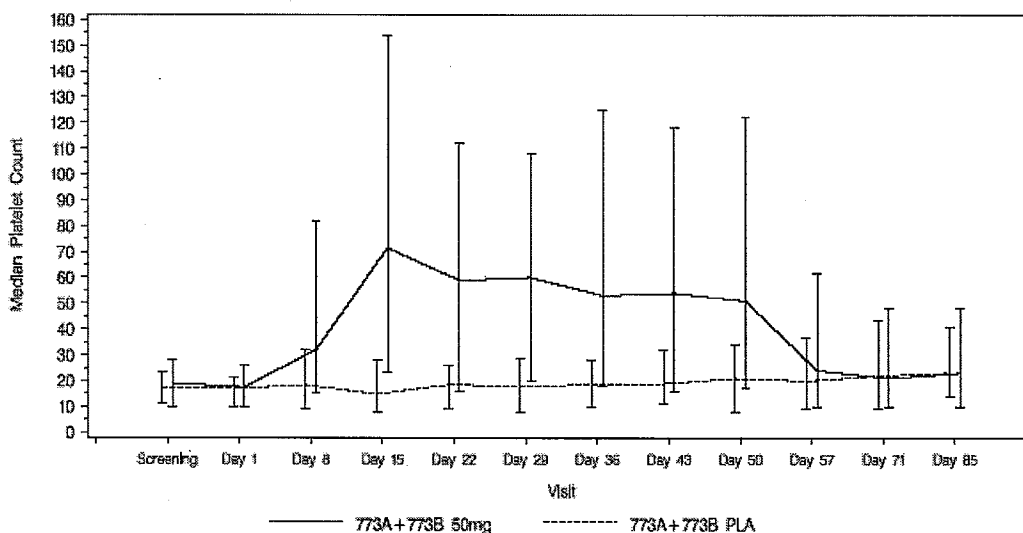
patients on placebo, 28% (8/29) of patients on 30 mg of eltrombopag, 70% (9/27) of patients on 50 mg of eltrombopag and 81% (21/26) of patients on 75 mg of eltrombopag. Patients treated with eltrombopag 50 mg or 75 mg had statistically significant greater odds of responding at day 43 compared to patients treated with placebo ($p < 0.001$). Median platelet counts for patients treated with eltrombopag 50 mg or 75 mg were higher than for patients treated with placebo at each on therapy visit. Median platelet counts in all eltrombopag treatment groups returned to baseline within two weeks of discontinuation of therapy. The sponsor reported that there was a statistically significant decrease in the percentage of eltrombopag 50 mg and 75 mg treated patients (16/27 and 12/26 patients, respectively) with any bleeding observed during the on therapy phase of the trial compared to placebo (22/27 patients). The percentage of patients with any bleeding returned to baseline levels during the off therapy phase (26/27 in the 50 mg treatment group and 26/26 in the 75 mg treatment group compared to 25/27 in the placebo treatment group). WHO grade 2-4 bleeding occurred in 5/26 (19%) of placebo treated patients and 9/39 (23%) of eltrombopag treated patients who were nonresponders compared to 3/48 (6%) of eltrombopag treated patients who were considered responders. Statistically significant interactions were observed between study medication and the use or non-use of concomitant ITP medication at the time of randomization. Logistic regression analysis showed an interaction at the 10% level of significance between the response to treatment and the use of ITP medication at randomization ($p = 0.093$). In the subgroup of patients who did not report the use of concomitant ITP medication, a dose-dependent increase in the proportion of responders was observed. A similar dose response was observed in the subgroup of patients who did report concomitant use of the ITP medications; however, the proportion of responders in the 75 mg treatment group (6/26) did not increase to the same degree as in the 50 mg treatment group (8/27). A statistically significant interaction was also observed between the study medication and baseline platelet count at randomization. Logistic regression analysis showed an interaction at the 10% level of significance between the response to treatment and baseline platelet count at randomization ($p = 0.042$). In both subgroups ($\leq 15,000/\text{mcl}$ and $> 15,000/\text{mcl}$) the proportion of responders increased in a dose-dependent manner. However the proportion of responders was higher for the 50 mg and 75 mg treatment groups with baseline platelet counts $> 15,000/\text{mcl}$ (13/16 and 12/12 patients respectively) compared to the subgroup with platelet counts $\leq 15,000/\text{mcl}$ (6/11 of patients and 9/14 patients respectively). The interaction between treatment and splenectomy status was not statistically significant. There was no statistically significant difference in the response to treatment when assessed for subgroups age, sex and race. However, data interpretation is limited due to the small number of patients in the race subgroup.

In study TRA 100773B analysis of the primary endpoint showed that eltrombopag increases platelet counts in patients with relapsed or refractory chronic ITP. In this study 16.2% (6/37) of patients on the placebo treatment arm compared to 58.9% (43/73) of patients on the eltrombopag treatment arm achieved a platelet count $\geq 50,000/\text{mcl}$ on day 43 from a baseline platelet count $< 30,000/\text{mcl}$. Patients treated with eltrombopag had statistically significant greater odds of responding at day 43 compared to patients treated with placebo ($p < 0.001$). Median platelet counts for patients treated with eltrombopag were higher than for patients treated with placebo at each on therapy visit. Median platelet counts in eltrombopag treated patients remained elevated one week after discontinuation of eltrombopag and returned to baseline within two weeks after discontinuation of eltrombopag. More patients (69%) in the placebo treatment group required a

dose increase at the day 22 visit compared to the eltrombopag treatment group (39%). More patients in the eltrombopag treatment group (11/35, 31%) responded after having their dose increased compared to the placebo treatment group (3/28, 11%). A statistically significant lower percentage of patients treated with eltrombopag experienced WHO bleeding grade 1-4 at day 43 ($p=0.029$). The interactions between treatment and each of the randomization strata were not statistically significant, which suggests that patients respond to eltrombopag similarly irrespective of their randomization strata. In addition there were no significant differences and the response to treatment when assessed for age and sex. The response to treatment based on race could not be estimated. Analyses of responders defined as patients with platelet counts $\geq 50,000/\text{mcl}$ and at least two times baseline were similar to the analyses of the primary endpoint.

The results of the primary endpoint pooled efficacy analysis for study TRA 100773A and TRA 100773B is shown graphically below for the 50 mg dose group compared to placebo. The median platelet counts and the 25th- 75th percentiles over the course of the study are shown in the figure below. As in the two individual pivotal trials, platelet count increases within two weeks of starting eltrombopag and returns to baseline approximately 2 weeks after discontinuation of eltrombopag therapy. Patients treated with placebo had minimal increase in median platelet counts.

Pooled Efficacy Analysis for Study TRA 100773A and TRA 100773B: Median Platelet Counts for Patients Treated with 50 mg Eltrombopag Compared to Placebo



- These results demonstrate that eltrombopag is effective in increasing platelet counts in patients with chronic ITP with a reasonable durability and platelet counts after discontinuation of therapy.
- In terms of bleeding, a statistically significant reduction in the proportion of patients with any bleeding at day 43 in the eltrombopag treatment group compared to patients in the placebo treatment group ($OR=0.34$, $p=0.018$) was observed in the pooled pivotal studies by logistic regression analysis adjusted for use of ITP medication at baseline,

splenectomy status, baseline platelet count and WHO bleeding grade at baseline. At the baseline visit 62% of patients treated with eltrombopag 50 mg and 59% of patients treated with placebo reported any bleeding. At the day 43 visit, 37% of patients treated with eltrombopag reported any bleeding compared to 55% of patients treated with placebo. In the pooled pivotal study analysis 35/39 patients in the eltrombopag group compared to 20/26 patients in the placebo group had a baseline WHO bleeding score of zero and a WHO bleeding score of zero at the end of therapy. In the pooled analysis of patients treated with 50 mg of eltrombopag or placebo, 26/44 patients treated with eltrombopag compared to 9/26 patients treated with placebo had a bleeding score of one at baseline and zero at the end of therapy. In the pooled pivotal analysis 4/17 patients treated with eltrombopag and 3/9 patients treated with placebo had baseline WHO bleeding scores of two at baseline and zero at the end of therapy. In the pooled analysis 2/2 patients treated with eltrombopag and 1/3 patients treated with placebo had a baseline bleeding score of three and a WHO bleeding score of zero at the end of therapy. There was no grade four bleeding in the pivotal trials. The clinical meaningfulness of the WHO bleeding score in terms of incremental changes (e.g., going from WHO bleeding score one to zero) is unclear. In addition, the investigators subjectively assigned bleeding scores and were aware of patient platelet counts at the time of bleeding assessments. These factors confound the analysis of eltrombopag's effect on bleeding.

- In the pivotal trials only seven patients faced a hemostatic challenge during the observation period. In these trials, four patients received eltrombopag (three patients received eltrombopag 50 mg with baseline platelet counts of 10,000-25,000/mcl and one patient received eltrombopag 75 mg with a baseline platelet count of 10,000/mcl). The three placebo treated patients had platelet counts ranging from 12,000-36,000/mcl. The four patients treated with eltrombopag underwent hemostatic challenges consisting of cholecystectomy (two patients), dental extraction and motor vehicle accident. The patients treated with placebo had a hemostatic challenges consisting of eye surgery, hip replacement and papilloma surgery of the throat. After treatment with eltrombopag but before the procedure the platelet counts ranged from 82,000-557,000/mcl. After placebo treatment but before the procedure the platelet counts ranged from 26,000-86,000/mcl. None of the patients treated with eltrombopag required rescue treatment. However all three placebo treated patients required rescue treatment with IVIg or tranexamic acid. No bleeding complications were reported in any of these patients. The limited number of patients who underwent hemostatic challenge does not allow for a conclusion to be drawn with regard to eltrombopag's effectiveness in preventing bleeding in patients who have undergone hemostatic challenge.

Safety

Headache was the most common adverse event and was discussed in section 7.1.5 Common adverse events.

The sponsor proposes that patients of East Asian ancestry be treated with a starting dose of eltrombopag of 25 mg orally once daily. This is based on clinical pharmacology findings that were discussed in section 5.1 of this review. The exact ancestry of a patient may be difficult to

ascertain. The potential for overdose of patients who are of East Asian ancestry may put these patients at increased risk for adverse events.

Adverse events including hepatobiliary adverse events, myelofibrosis and phototoxicity are discussed in section 7.1.6 in this review. Transient thrombocytopenia was discussed in sections 7.1.3.3.

In the two pivotal trials, TRA 100773A and TRA 100773B, all patients who were randomized and received at least one dose of study medication were included in the evaluation of safety and comprised the safety population. For study TRA 100773A the safety population included 29 patients treated with placebo, 30 patients each in the 30 mg and 50 mg eltrombopag treatment cohorts and 28 patients in the 75 mg eltrombopag treatment cohort. For study TRA 100773B there were 38 patients in the safety population treated with placebo and 76 patients in the safety population treated with eltrombopag. In addition to the safety populations evaluated in the two pivotal trials, the analysis of the safety of eltrombopag in this review incorporates three other important supportive studies: REPEAT, RAISE and EXTEND. In addition to the data presented in the original NDA submission, data from the 120 day safety update that supports the safety evaluation for this NDA was reviewed. The sponsor states in this 120 day safety update that 330 ITP patients were exposed to eltrombopag. Therefore 61 more patients were included in the safety population compared to the 269 patients in the safety population presented in the original NDA submission. The sponsor estimates that approximately 150 patients had been exposed to eltrombopag for $\geq$ six months as of the cut off date for the 120 day safety update.

At the time of the NDA submission there were four deaths reported in the ITP program and as of the safety update six deaths were reported. Serious adverse events in the pooled pivotal trials were observed in 6/67 (9.0%) of patients treated with placebo compared to 11/164 (6.7%) of patients treated with eltrombopag. Any adverse events were observed in 32/67 (47.8%) of patients treated with placebo compared to 101/164 (61.6%) of patients treated with eltrombopag. In study TRA 100773A there were 13 adverse events reported on therapy for 12 patients. On therapy bleeding adverse events were more frequent in the placebo and 30 mg treatment groups (for adverse events and six adverse events respectively) compared to the 50 mg and 75 mg treatment groups (two adverse events and one adverse event respectively).

In study TRA 100773A and in study TRA 100773B there appeared to be a trend for transient thrombocytopenia observed within four weeks of discontinuation of eltrombopag therapy. In study TRA 100773A six patients, one in the placebo arm, none in the 30 mg eltrombopag group, three in the 50 mg eltrombopag group and two in the 75 mg eltrombopag group had platelet counts $< 10,000/\text{mcl}$ and a decrease in platelet count on at least $10,000/\text{mcl}$ compared to baseline within four weeks after discontinuation of study medication. In study TRA 100773B a total of eight patients treated with eltrombopag in three patients treated with placebo had platelet counts $< 10,000/\text{mcl}$ and at least $10,000/\text{mcl}$ less than baseline platelet count within four weeks after discontinuation of study medication.

An analysis of potential drug-induced liver injury based on the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation¹ demonstrated that 16/164 patients

(9.7%) who received any dose of eltrombopag met the FDA criteria for assessment of hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. Of the 16 eltrombopag treated patients three received 30 mg, 11 received 50 mg (three increased to 75 mg in TRA 100773B) and two received 75 mg as a starting dose.

In preclinical studies phototoxicity was a recognized adverse event. In the pivotal trial TRA 100773A there were 17 adverse events listed for skin disorder. In the pivotal trial TRA 100773B there were six patients (five eltrombopag treated patients and one placebo treated patient) who developed skin related adverse events. There was one report of photosensitivity in an eltrombopag treated patient, which was characterized as a grade 2 adverse event. In this study 49/117 patients had ocular assessments in the safety population. In these 49 patients there were 14 reports of cataracts. Three patients had a cataract observed at baseline but none of these patients had cataract progression over the course of the study. There were 10 patients who had cataract observed at the time of the first ocular examination and one patient was observed to have a cataract formation after the first ocular examination. In study TRA 100773A 112/114 patients in the safety population had ocular assessments for cataracts. Cataracts were observed at baseline in nine patients of which three patients had progression of their cataracts. There were 101 patients who had no evidence other cataract observed at baseline. Of these 101 patients four patients subsequently developed cataracts.

Overall, the most common adverse events (AEs) in eltrombopag-treated subjects in the clinical pharmacology studies were headache, dizziness, somnolence, fatigue, nasopharyngitis, abdominal pain, and nausea. There was no apparent relationship between eltrombopag exposure and the incidence of AEs in the single- and repeat-dose clinical pharmacology studies in healthy subjects exposed to eltrombopag. This also appears to be the trend in the two pivotal trials based on dose alone.

- The statistical reviewer, Dr. Qing Xu in her review stated that there were several issues discovered in the review of the pivotal studies. One of the conclusions the sponsor made was that eltrombopag in the treatment of ITP patients decreases the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP. The sponsor conducted logistic regression analysis of the bleeding events, adjusting for the covariates of use of concomitant medication at randomization, splenectomy status, and baseline platelet count. However, it is obvious that the bleeding event is time dependent with multiple observations per subject. It is more appropriate to use survival analysis models based on time-to-event in multiple event setting. In her review Dr. Xu used the Andersen-Gill (AG) formulation of proportional hazards model as a counting process is performed for assessment of bleeding, using the Schoefeld residuals to test the basic assumptions of a Cox model. The proportional hazard and the functional form of the covariates are also included in her review. The results of Dr. Xu's analyses are show in the tables below.

Statistical Reviewer's summary of multiple bleeding event analysis during 6 weeks visit (Study TRA 100773A)

	Exp(coef)	Robust se	P-value
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Clinical Review
Andrew Dmytrijuk, M.D.
NDA 22-291 Submission 000
Eltrombopag (Promacta)

TRTCD	1.928	0.314	0.121
Baseline Platelet	0.821	0.306	0.3800
ITP medication use	0.350	0.276	0.2800
Splenectomy	0.305	0.219	0.0040

From the table above a P-value of 0.121 suggests that there is no statistically significant between 2 groups.

The table below shows the result using AG model without covariate for study TRA100773B.

**APPEARS THIS WAY
ON ORIGINAL**

Statistical Reviewer's summary of, multiple bleeding event analysis during 6 weeks visit (Study B)

	Exp (coef)	Robust se	P-value
TRTCD	0.781	0.135	0.067

The P-value is 0.067 suggest that there is no statistically significant between 2 groups.

Dosing Regimen and Administration

The sponsor proposes that patients with ITP be treated with 50 mg of eltrombopag orally once daily. If the platelet count is less than 50,000/mcl the dose should be increased to 75 mg orally once daily. Treatment should be continued for six weeks. Treatment with eltrombopag should be discontinued if the platelet count is above 200,000/mcl. The sponsor proposes that 25 mg orally once daily; _____ for patients of the East Asian ancestry. The dose may be increased in this patient population to 50 mg orally once daily if the platelet count is below 50,000/mcl after 2 - weeks. The support for the dosing regimen is established in the pharmacology program and pivotal trials of eltrombopag. However, whether patients of East Asian ancestry should be started on a lower dose of eltrombopag is based on population pharmacokinetic studies done in Japan. Similar studies performed in other Asian countries did not show a clear increase in exposure after dosing of eltrombopag in volunteers in these Asian countries. The pivotal trials had enrolled 31/231 patients of East Asian ancestry. This group of patients did not demonstrate any adverse events, bleeding or platelet responses outside of the range of other patients enrolled in the studies. Therefore, it is unclear if patients at East Asian ancestry require a lower starting dose of eltrombopag compared to patients of other ancestries. The dosing of special populations specifically patients at East Asian ancestry is discussed in section 1.3.6 of this review.

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Drug-Drug Interactions

Drug -Drug interaction studies were performed during the development program for eltrombopag. These studies showed that eltrombopag should be administered to patients in a fasted state or with foods low in calcium to avoid significant reductions in plasma eltrombopag exposure. Eltrombopag chelates with polyvalent cations such as aluminum, calcium, iron, magnesium and zinc. Administration of a single dose of 75 mg of eltrombopag they polyvalent cation containing antacid decreased plasma eltrombopag AUC and Cmax by 70%. Therefore, in order to avoid clinically significant reductions in plasma eltrombopag exposure, eltrombopag should not be given concurrently with other products containing polyvalent cations such as mineral supplements, antacids or dairy products. The doses should be separated by at least — hours.

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Administration of eltrombopag 75 mg once daily for five days with a single dose of rosuvastatin 10 mg increased plasma rosuvastatin Cmax by 2.03 fold and AUC by 55%. Therefore when coadministered with eltrombopag a reduced dose of rosuvastatin should be considered and careful monitoring for rosuvastatin adverse effects should be undertaken. Eltrombopag is an

inhibitor of the anion transporting polypeptide OATP1B1. Therefore concomitant administration of eltrombopag and other OATP1B1 substrates should be used with caution.

Special Populations

During the clinical development program for eltrombopag the sponsor evaluated drug exposure in patients of the East Asian ancestry. In the pharmacokinetic studies the sponsor noted that a higher exposure was observed in this patient population. Therefore, the sponsor proposes that the patients of the East Asian ancestry ——— treatment with 25 mg of eltrombopag orally once daily. The dose may be increased in this patient population to 50 mg orally once daily if the platelet count is below 50,000/mcl after 2- —weeks.

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The Clinical Pharmacology Reviewer (Dr. Joe Grillo) noted the following in his review, that plasma eltrombopag AUC(0- τ) was approximately 35% lower in healthy subjects as compared to patients with ITP. Plasma eltrombopag exposure was reported to be approximately 70% higher in some East Asian/Japanese subjects with ITP based on estimates from a population-based pharmacokinetic model. The true magnitude of this difference the healthy East Asian/Japanese population is difficult to confirm given the high variability and possible systematic errors found in some of the trails conducted in Japan. Further, an analysis of the limited number of healthy East Asian/Japanese subjects from studies conducted in the West failed to substantiate the findings from the studies conducted in Japan. FDA also noted a trend suggesting approximately 40-50% higher eltrombopag exposure in some healthy African-American subjects in several clinical pharmacology studies. This issue was not fully explored by the sponsor. These race effects are likely the result of a, yet undetermined, genetic variation in pathways (e.g., CYP1A2, UGT1A1, etc.) that have been identified as metabolizing eltrombopag and, to a lesser extent, the difference in body weight between subjects in the western and Japan studies.

Dr. Grillo's review also states that the PD response to eltrombopag was qualitatively similar in healthy East Asian/Japanese and Western subjects, with both the shape of the platelet count profile and the duration of response being comparable. However, at the same dose of eltrombopag, the absolute PD response was greater in healthy East Asian/Japanese subjects than healthy Western subjects. The magnitude of this difference was lower than that report for pharmacokinetic drug exposure.

INTRODUCTION AND BACKGROUND

1.4 Product Information

Eltrombopag is an orally bioavailable small molecule thrombopoietin receptor (TPO-R) agonist that interacts with the transmembrane domain of TPO-R and initiates a signaling cascade similar, but not identical to, that of endogenous thrombopoietin. Thrombopoietin (TPO), also known as MGDF and the ligand for the cellular myeloproliferative leukemia proto-oncogene (c-Mpl), is the principal cytokine involved in the regulation of megakaryopoiesis and platelet production.

Native TPO is a 60-70 k Dalton heavily glycosylated polypeptide of 332 amino acids produced by the liver, bone marrow and sinusoidal epithelial kidney cells.

The diagnosis of ITP remains one of exclusion. The routine diagnostic tools are complete blood count, peripheral blood film, patient history, physical examination and prompt response to high-dose steroids. In the diagnosis of ITP, the most important clinical finding is thrombocytopenia. The peripheral blood film is used to help confirm the thrombocytopenia and help rule out other potential causes of the thrombocytopenia. The patient's history may include the complaint of easy bruising or bleeding. Physical examination can show evidence of bleeding or bruising and may rule out hypersplenism as the cause of the thrombocytopenia. Some patients may undergo a bone marrow biopsy to evaluate for platelet production problems as the cause of the thrombocytopenia. A typical bone marrow finding in ITP is increased megakaryocyte count. In a European study the overall incidence of ITP among adults ranges from 1.6-3.0 per 100,000 person years of observation.² Prevalence estimates ranges from 2.1 to approximately 36.4 per 100,000 persons.³ There is no reason to expect that ITP in the United States is different compared to any other part of the world. Therefore it is possible to extrapolate the findings from the study above to the United States.

ITP is an autoimmune disorder characterized by autoantibody introduced platelet destruction and reduced platelet production leading to a low peripheral blood platelet count. ITP may be acute (< six-month duration) or chronic (> six-month duration). Acute ITP is predominantly a childhood illness and is generally self-limited. In adults chronic ITP is predominant with an onset that is often insidious and spontaneous recovery is uncommon. The clinical hallmark of the disease is an increased tendency to bleed. Peripheral blood platelets in this disease are considered to be functional however as platelet count decreases to levels $\leq 10,000/\text{mcl}$ the risk of spontaneous bleeding increases. Patients with platelet count between 30,000/mcl and $> 10,000/\text{mcl}$ are generally considered treatment candidates due to a slightly increased risk of spontaneous bleeding or increased risk of bleeding due to potential trauma. Patients with platelet counts between 30,000-50,000/mcl are generally not treated unless there is evidence of bleeding, increased risk of bleeding due to hemostatic challenge such as surgery or other daily activity of living. Patients with platelet counts $\geq 50,000/\text{mcl}$ generally do not require treatment unless the patient is to undergo a hemostatic challenge which may require a higher platelet count in order for this hemostatic challenge to be undertaken. Normal platelet counts are generally between 150,000-450,000/mcl.⁴ The frequency of death from hemorrhage in patients with platelet counts below 30,000/mcl is estimated to be between 1.6 and 3.9% per patient year although the frequency is influenced by age as well as the degree and duration of thrombocytopenia.⁵

1.5 Currently Available Treatment for Indications

A number of alternative treatments are available for patients with ITP. These include:

- Corticosteroids
- Intravenous Immunoglobulin (IVIG)
- Anti-D Immunoglobulin (WinRho)
- Splenectomy

- Vinca Alkaloids
- Danazol
- Azathioprine
- Cyclophosphamide
- Cyclosporine A
- Dapsone
- Rituximab

Currently the only drug products labeled for ITP treatment include IVIG and WinRho. Corticosteroids as well as splenectomy have long been described in the literature as potential treatments for ITP.⁶

1.6 Availability of Proposed Active Ingredient in the United States

Eltrombopag is a new molecular entity (NME) and is not currently marketed anywhere in the world.

1.7 Important Issues with Pharmacologically Related Products

Currently there are no pharmacologically related products approved or under development. Recently the immunoglobulin Romiplostim has been reviewed by the Food and Drug Administration Division of Medical Imaging and Hematology Drug Products (DMIHP). This drug is being developed for the treatment of ITP.

1.8 Presubmission Regulatory Activity

- Initial pre-IND meeting: June 11, 2004
- IND submission: September 28, 2004
- Special Protocol Assessment given by FDA for carcinogenicity studies: November 4, 2004
- End of phase 2 meeting: January 24, 2006
- Special Protocol Assessment given by FDA for clinical studies: May 19, 2006
- Pre-NDA meeting: August 2, 2007
- Priority review granted for NDA: February 28, 2008
- Orphan drug status granted: March 4, 2008

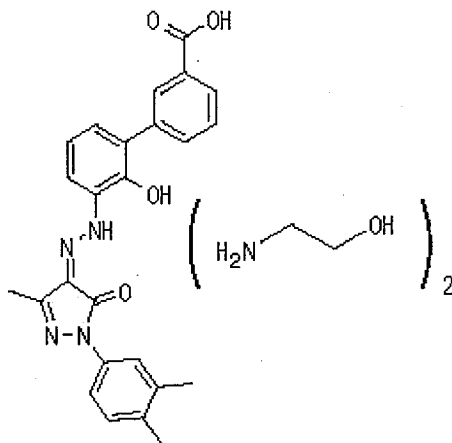
1.9 Other Relevant Background Information

Not Applicable.

2 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

2.1 CMC (and Product Microbiology, if Applicable)

As stated in the sponsor's submission, eltrombopag is the bis-monoethanolamine salt form of SB-497115. It is an orally bioavailable, small molecule. The chemical name for eltrombopag is 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2). It has the molecular formula $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$ and a molecular weight 564.65. Eltrombopag olamine has the following structural formula:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water. Eltrombopag is supplied as 25 mg and 50 mg tablets. The inactive ingredients of eltrombopag tablets are magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. The coating contains hypromellose, polyethylene glycol 400, titanium dioxide, and FD&C Yellow No. 6 aluminum lake (25 mg tablet) or FD&C Blue No. 2 aluminum lake (50 mg tablet).

2.2 Animal Pharmacology/Toxicology

The sponsor states that eltrombopag causes morbidity and mortality in repeat dose oral toxicology studies in mice at 150 mg/kg/day following nine weeks of dosing and in rats at 60 mg/kg/day following two weeks of dosing. Systemic exposure at the above doses in the mouse and rat was 664 $\mu\text{g}\cdot\text{h}/\text{ml}$ and 1044 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively. Mortality was observed in rabbits at 200 mg/kg/day after nine days at an AUC of 124 $\mu\text{g}\cdot\text{h}/\text{ml}$. The mortality observed in rabbits at 5-10 fold lower exposure than the rats is considered by the sponsor to be related to the increased sensitivity of rabbits to gastrointestinal toxicity compared to other preclinical species. Body weight loss or decreased body weight gain (≥ 40 mg/kg/day) was observed in rats and mice at doses of 300 mg/kg/day. Signs of gastrointestinal disturbance were observed in dogs given doses ≥ 100 mg/kg/day.

At non-tolerated doses ≥ 60 mg/kg/day in rats and dogs and mice at 300 mg/kg/day, these animals had eye degeneration and/or necrosis accompanied by markedly increased serum liver enzymes. In dogs only increased serum liver enzymes was observed. A microscopic change in the rat liver (midzonal hepatocellular vacuolation) was evident after 14 days at doses ≥ 20 mg/kg/day (AUC 341 $\mu\text{g}\cdot\text{h}/\text{ml}$). In the 52-week oral toxicity study in dogs there were no adverse treatment related findings at no adverse event level doses up to 30 mg/kg/day. Treatment related cataracts were observed in mice given 75 or 150 mg/kg/day and rats given 40 mg/kg/day. In these rodents the ocular changes were observed after seven weeks of treatment. Given the sensitivity of the mouse to treatment related ocular effects at exposure levels approximately twofold of the clinical exposure, the sponsor recommends that ophthalmologic examinations be performed as part of the routine safety monitoring.

Data from genotoxicity assessments suggest that eltrombopag does not present a genotoxic hazard to humans. An *in vitro* phototoxicity study was conducted and eltrombopag was observed to be toxic in the presence of ultraviolet illumination. These results suggest a potential risk for phototoxicity in humans.

b(4)

Eltrombopag did not affect female fertility at doses up to 20 mg/kg/day in rats and was not teratogenic in rats or rabbits. However, at a maternally toxic dose of 60 mg/kg/day in rats, eltrombopag treatment was associated with embryo lethality in female fertility studies. Eltrombopag did not appear to affect male rat fertility at doses up to 40 mg/kg/day.

A single dose safety and pharmacology study was conducted in female chimpanzees with eltrombopag given orally at doses up to 0.3, 1, 3 and 10 mg/kg. The sponsor reports that all doses were well tolerated and that there were no remarkable hematologic or clinical chemistry findings up to 15 days after dosing. A repeat dose safety and pharmacology study was conducted in female chimpanzees in which doses up to 10 mg/kg/day were administered for five days orally. All doses appear to be well tolerated. The platelet counts increased up to twofold above baseline.

Reviewer comment for section 2: Eltrombopag is the bis-monoethanolamine salt form of SB-497115. It is an orally bioavailable, small molecule. Treatment related cataracts were observed in mice given 75 or 150 mg/kg/day and rats given 40 mg/kg/day. In these rodents the ocular changes were observed after seven weeks of treatment. The mouse studies demonstrate that there is a potential for ocular adverse effects at exposure levels approximately twofold of the clinical exposure. It is prudent to recommend that ophthalmologic examinations be performed as part of the routine safety monitoring.

b(4)

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

The sponsor submitted information from two pivotal trials (TRA 100773A and TRA 100773B). Supportive information for the NDA is provided in studies entitled EXTEND, RAISE and REPEAT. Safety data is available from a number of clinical studies (see table under 4.2 below).

3.2 Tables of Clinical Studies

The following tables list the studies that support this NDA.

Table 1 Tabular Listing of All Clinical Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
Biopharmaceutical Studies						
TRA 102863 Relative Bioavailability	Relative bioavailability of eltrombopag oral film-coated tablet formulations manufactured at the R&D and commercial sites	OL, R, 3 group, 2 period, incomplete CO	Healthy volunteers	Treatment A eltrombopag/50mg/f tablet/(50mg)/R&D/oral/single dose/fasting Treatment B eltrombopag/50mg/f tablet/(50mg)/commercial/oral/single dose/fasting Treatment C eltrombopag/75mg/f tablet/(25mg & 50mg)/R&D/oral/single dose/fasting Treatment D eltrombopag/75mg/f tablet/(75mg)/commercial/oral/single dose/fasting Treatment E eltrombopag/100mg/f tablet/(50mg)/R&D/oral/single dose/fasting Treatment F eltrombopag/100mg/f tablet/(100mg)/commercial/oral/single dose/fasting	66	Completed with final CSR

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
487115/005 Relative Bioavailability and Food Effect	Relative bioavailability of eltrombopag oral 25mg capsule and oral 25mg film-coated tablet formulations Effect of food on bioavailability of the eltrombopag 25mg oral film-coated tablet formulation	OL, R, 3 period, CO	Healthy volunteers	Treatment A eltrombopag/50mg/Capsule/(25mg)/R&D/oral/single dose/fasting Treatment B eltrombopag/50mg/f tablet/(25mg)/R&D/oral/single dose/fasting Treatment C eltrombopag/50mg/f tablet/(25mg)/R&D/oral/single dose/effed	18	Completed with final CSR

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Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cutoff date)
TRA104631 Food Effect and Antacid Drug Interaction	Effects of high- and low-fat meals with low calcium content on the bioavailability of the eltrombopag 75mg oral film-coated tablet formulation Effect of timing of meal consumption in relation to study drug administration on eltrombopag bioavailability Effect of calcium-containing antacid on eltrombopag PK	OL, R, 5 period, CO	Healthy volunteers	Treatment A eltrombopag/75mg/film-coated tablet (75mg)/commercial/oral/single dose/fasting Treatment B eltrombopag/75mg/film-coated tablet (75mg)/commercial/oral/single dose/low-fat, low-calcium meal Treatment C eltrombopag/75mg/film-coated tablet (75mg)/commercial/oral/single dose/fasting + 30mL Gaviscon = aluminum hydroxide (1524mg) and magnesium carbonate (1425mg)/suspension/oral/single dose/fasting Treatment D eltrombopag/75mg/film-coated tablet (75mg)/commercial/oral/single dose/high-fat, low-calcium meal Treatment E eltrombopag/75mg/film-coated tablet (75mg)/commercial/oral/single dose/one hour prior to high-fat, low-calcium meal	26	Completed with final CSR

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cutoff date)
TRA105122 Bioequivalence	Bioequivalence of eltrombopag oral film-coated tablet formulations manufactured at the R&D and commercial sites	OL, R, PG, 2 period, incomplete CO	Healthy volunteers	Treatment A eltrombopag/25mg/film-coated tablet (25mg)/R&D/oral/single dose/fasting Treatment B eltrombopag/25mg/film-coated tablet (25mg)/commercial/oral/single dose/fasting Treatment C eltrombopag/50mg/film-coated tablet (50mg)/R&D/oral/single dose/fasting Treatment D eltrombopag/50mg/film-coated tablet (50mg)/commercial/oral/single dose/fasting	100	Completed with final CSR
Human Pharmacokinetic Studies						
497115/001 Single dose escalation	Safety, tolerability, PK, and platelet response following escalating single doses of eltrombopag	SB, PC, R, PG	Healthy volunteers	Treatment A eltrombopag/3mg/granules filled into capsules (26, 160, 660 mg/gm)/R&D/oral/single dose Treatment F eltrombopag/6mg/granules filled into capsules (26, 160, 660 mg/gm)/R&D/oral/single dose Treatment G eltrombopag/9mg/granules filled into capsules (26, 160, 660 mg/gm)/R&D/oral/single dose Treatment P Matched placebo	24	Completed with final CSR

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA102861 Mass Balance	Determine total recovery and relative excretion of radiocarbon in urine and feces. Compare total radiocarbon (drug-related material) in blood and plasma relative to parent plasma concentration. Identify eltrombopag metabolites.	OL	Healthy volunteers	[14C]-eltrombopag/75mg containing approximately 100µCi (0.70 mSv) of radiocarbon/solution R&D/oral/single dose	6	Completed with final CSR
TRA103452 Hepatic impairment	PK and tolerability of eltrombopag in subjects with various degrees of hepatic impairment	OL, PG	Subjects with mild, moderate, and severe hepatic impairment and healthy volunteers with normal hepatic function	eltrombopag/50mg/T tablet (50mg)/commercial/oral/single dose/fasting	33	Completed with final CSR

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA104412 Renal impairment	PK and tolerability of eltrombopag in subjects with various degrees of renal impairment	OL, PG	Subjects with mild, moderate, and severe renal impairment and healthy volunteers with normal renal function	eltrombopag/50mg/T tablet (50mg)/commercial/oral/single dose/fasting	25	Ongoing with interim data summary
TRA104603 Japanese single dose escalation	PK, safety, and platelet response following single escalating doses in healthy Japanese subjects	DB, P, C, R, CO, 4 period	Healthy Japanese volunteers	Treatment A eltrombopag/30mg/T tablet/(5mg and 25mg)/R&D/oral/single dose Treatment B eltrombopag/50mg/T tablet/(25mg)/R&D/oral/single dose Treatment C eltrombopag/75mg/T tablet/(25mg)/R&D/oral/single dose Treatment D eltrombopag/100mg/T tablet/(25mg)/R&D/oral/single dose Treatment E placebo	16	Completed with final CSR

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Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA105580 Japanese SD and RD escalation	PK, safety, and platelet response following single and repeat doses of eltrombopag in healthy Japanese subjects	SB, PC, R, PG, single and repeat dose escalation	Healthy Japanese volunteers	Treatment A eltrombopag/25mg/T tablet/(25mg)/commercial/oral/single and 10 day repeat dose Treatment B eltrombopag/50mg/T tablet/(25mg)/commercial/oral/single and 10 day repeat dose Treatment C eltrombopag/75mg/T tablet/(25mg)/commercial/oral/single and 10 day repeat dose Treatment D placebo	42	Completed with final CSR

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
Population PK and PK/PD Report incorporating data from TRA1007734, TRA1007738, 407115/002, TRA105580, TRA102860	Characterize plasma eltrombopag PK in patients with ITP Identify variables that impact plasma eltrombopag PK such as demographics, clinical laboratory parameters, and concurrent medications Explore relationships between plasma eltrombopag PK and platelet response	Population PK analysis of data across studies	Healthy volunteers and ITP subjects	Subject data from other studies	Not applicable	Completed with final report

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Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA105120 Rosuvastatin Drug Interaction	Effect of eltrombopag on plasma rosuvastatin PK	OL, 3 period, single sequence	Healthy volunteers	Treatment A rosuvastatin/10mg/ Tablet (10mg)/commercial/oral/single dose Treatment B eltrombopag/75mg/g/ Tablet (25mg and 30mg)/commercial/oral/ 4 day repeat dose Treatment C rosuvastatin/10mg/ Tablet (10mg)/commercial/oral/single dose + eltrombopag/75mg/g/ Tablet (25mg and 30mg)/commercial/oral/single dose (immediately preceded by Treatment B, i.e. total of 5 days repeat dose eltrombopag)	42	Completed with final CSR
RM2007.00695/00	Pharmacogenetic Investigation of associations with PK and PD outcomes	Not applicable	Not applicable	Subject data from other protocols	Not applicable	Completed report
XM2007/00049/00	Influence of East Asian Ethnicity on Eltrombopag PK and PD	Not applicable	Not applicable	Subject data from other protocols	Not applicable	Completed report

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
Human Pharmacodynamic Studies						
TRA 102860 Q1c	PART 1 Safety, PK, and platelet response of repeat doses of etrombopag 100mg to 200mg QD	PART 1 DB, P, C, R, PG, single and repeat dose escalation	Healthy volunteers	PART 1 Treatment A etrombopag/100mg/g/ Tablet (50mg)/commercial/oral/single and 5 day repeat dose/fasting + 2 placebo Treatment B etrombopag/150mg/g/ Tablet (50mg)/commercial/oral/single and 5 day repeat dose/fasting + 1 placebo Treatment C etrombopag/200mg/g/ Tablet (50mg)/commercial/oral/single and 5 day repeat dose/fasting	Part 1 33	Completed with final CSR

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ON ORIGINAL

Clinical Review
 Andrew Dmytrijuk, M.D.
 NDA 22-291 Submission 000
 Eltrombopag (Promacta)

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
497115/002 Single dose & repeat dose escalation CYP Probe Drug Interaction	Safety, tolerability, PK, and platelet response following escalating single and repeat doses of eltrombopag Potential for eltrombopag to inhibit or induce CYP 1A2, CYP 2C9, CYP 2C19, and CYP 3A4	Single & Repeat Dose Escalation SB, PC, R PG CYP Probe OL, single sequence, two period incomplete CO	Healthy volunteers	Treatment A eltrombopag/50 mg Capsule (50 mg) R&D/oral/singl and 10 day repeat dose Treatment B eltrombopag/100 mg Capsule (50 mg) R&D/oral/singl and 10 day repeat dose Treatment C eltrombopag/200 mg Capsule (100 mg) R&D/oral/singl and 10 day repeat dose Treatment D eltrombopag/300 mg Capsule (300 mg) R&D/oral/singl and 10 day repeat dose Treatment E eltrombopag/500 mg Capsule (250 mg) R&D/oral/singl and 10 day repeat dose Treatment F eltrombopag/750 mg Capsule (250 mg) R&D/oral/singl and 10 day repeat dose Treatment G eltrombopag/750 mg Capsule (250 mg) R&D/oral/7 day repeat dose (Days 3-9)/midazolam 5mg, caffeine 100mg, omeprazole 20mg, flurbiprofen 50mg (Day 1-2, Day 8-9) Treatment P: Placebo	97 73 for single and repeat dose escalation; 24 for CYP probe	Completed with final CSR
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
TRA100773A	Efficacy, Safety, PK, HR-QoL	R, DB, PG, PC	Previously treated adult subjects with chronic ITP	Eltrombopag 30mg, 50mg, 75mg or matching PBO; Daily oral dosing for 6 weeks	118 (117 in safety population)	Completed with final CSR

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA100773B	Efficacy, Safety, PK, HR-QoL	R, DB, PG, PC	Previously treated adult subjects with chronic ITP	Eltrombopag 50mg or matching PBO; Daily oral dosing for 6 weeks; Dose escalation to 75mg allowed for non-responders	114	Completed with final CSR
TRA102537 RAISE	Efficacy, Safety, PD, HR-QoL	R, DB, PG, PC	Previously treated adult subjects with chronic ITP	Eltrombopag 50mg or matching PBO; Daily oral dosing for 6 months; Dose modification (to 25mg or 75mg) allowed based on individual platelet counts	156	Ongoing with safety summary report through 02 Jul 2007 data
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
TRA108057 REPEAT	Efficacy, Safety, PD	NR, OL	Previously treated adult subjects with chronic ITP	Eltrombopag 50mg Daily oral dosing for up to 6 weeks, off-therapy for up to 4 weeks for 3 cycles; Dose escalation to 75mg after Day 21 allowed for non-responders	66	Ongoing with CSR through data cut off of 14 Sep 2007
TRA105325 EXTEND	Safety, Efficacy, PD, HR-QoL	NR, OL	Previously treated adult subjects with chronic ITP who enrolled in a prior eltrombopag study	Starting oral daily dose of eltrombopag 50mg, with modification to 25mg or 75mg; Dose modification allowed based on individual platelet counts	117 (109 in Safety Population)	Ongoing with CSR through data cut off of 31 Aug 2007

Clinical Review
 Andrew Dmytrijuk, M.D.
 NDA 22-291 Submission 000
 Eltrombopag (Promacta)

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cutoff date)
TRA108132 LENS	Safety	No treatment observation follow-up study	Subjects previously enrolled in an eltrombopag trial who had > 10 days dosing	None	26	Ongoing with summary report of data through 29 Jun 2007
Efficacy and Safety Studies: Other Study Reports						
TPL102357	Efficacy, Safety, PK, HR-QoL	R, DB, P G, PC	Thrombocytopenic subjects with HCV infection	Part 1: Eltrombopag 30mg, 50mg, 75mg or matching PBO; daily oral dosing for 4 weeks Part 2: Eltrombopag 30mg, 50mg, 75mg or matching PBO; Daily oral dosing in conjunction with IFN+ribavirin anti-viral therapy for 48 weeks	74	Completed with final CSR
SB497115J003	Efficacy, Safety, PD, PK	R, DB, P G, PC	Subjects with advanced solid tumors receiving carboplatin/paclitaxel	Eltrombopag 50mg, 75mg, 100mg or matching PBO; Daily oral dosing Days 2 to 11 in each 21-day cycle of chemotherapy for up to 8 cycles	183 (180 in safety population)	Completed with final CSR
TPL103922	Efficacy, Safety, PD, PK, HR-QoL	Part 1: NR, OL, RD Part 2: R, DB, P G, PC	Thrombocytopenic subjects with HCV infection	Part 1: Eltrombopag 25mg, 50mg, 75mg and 100mg Daily oral dosing until platelets $\geq 100 \text{ G/L}$, with dose escalation every 2 weeks up to a maximum 9 weeks of treatment Part 2: Eltrombopag dose from Part 1 or matching PBO; Daily oral dosing in conjunction with pegIFN+ribavirin anti-viral therapy for up to 48 weeks	Enrollment not started as of 14 Sep 2007	Ongoing

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cutoff date)
TPL108390	Efficacy, Safety, PD, PK, HR-QoL	Part 1: NR, OL, RD Part 2: R, DB, P G, PC	Thrombocytopenic subjects with HCV infection	Part 1: Eltrombopag 25mg, 50mg, 75mg and 100mg Daily oral dosing until platelets $\geq 100 \text{ G/L}$, with dose escalation every 2 weeks up to a maximum 9 weeks of treatment Part 2: Eltrombopag dose from Part 1 or matching PBO; Daily oral dosing in conjunction with pegIFN+ribavirin anti-viral therapy for up to 48 weeks	Enrollment not started as of 14 Sep 2007	Ongoing
TRC105499	Safety, PK, PD, Efficacy	NR, OL, P G, RD	Subjects with locally advanced sarcoma, at high risk for relapse or metastasis	Eltrombopag 75mg, 100mg, 150mg and 200mg starting on Cycle 2. Each group received AI chemotherapy on Days 1 – 4 of each cycle Group A: eltrombopag on Days 1 to 14 Group B: eltrombopag on Days -5 to 14 Group C: no eltrombopag in Cycle 2	8	Ongoing
TRA108109	Efficacy, Safety, PK, PD	R, DB, P G, PC	Japanese ITP subjects	Eltrombopag 12.5mg or matching PBO; Daily oral treatment for 7 weeks, with dose adjustment at 3 weeks; DB phase followed by 19-week OL phase	0	Ongoing
TRA108039	Psychometric evaluation and validation of ITP Bleeding Score in adult ITP patients	Cross sectional study	ITP adult subjects	No treatment administered; Clinician administered questionnaire	6 - no treatment	Ongoing

b(4)

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects	Study Reporting Status (Clinical Cut-off date)
TRA 109678 Collaborative Research Trial	Evaluate platelet function in vitro study	OL, PG, AC, PD	ITP, Healthy	Planned sample size is 50 adult subjects: 20 study group subjects receiving eltrombopag in ongoing studies; 10 - 20 healthy normal volunteers receiving no treatment; 10 subjects with ITP who are post-splenectomy and receiving no treatment.	38 - treated in ongoing studies or no treatment	Ongoing with summary report
OL = Open label DB = Double-blind R = Randomized PD = Rising Dose AC = Active-controlled PG = Parallel Group PC = Placebo-controlled NR = Non-randomized PD = Pharmacodynamics CO = Cross-over CSR = Clinical Study Report PBO = placebo PK = Pharmacokinetics IFN = interferon HR-QoL = Health-related quality of life						

3.3 Review Strategy

The medical review of the studies TRA 100773A and TRA 100773B is included in this document. Also included in this document is a review of the sponsor's extension study (TRA 105325). These studies were the primary studies used to understand the safety and efficacy of eltrombopag for the treatment of patients with ITP. Other studies submitted by the sponsor to support eltrombopag's efficacy and safety in the treatment of patients with ITP were reviewed.

An additional analysis of the safety of eltrombopag in ITP patients was undertaken using the combined safety database consisting of all the ITP patients exposed to eltrombopag thus far in the clinical development program.

_____ Data from these patients is not included in this review.

b(4)

3.4 Data Quality and Integrity

On February 14, 2008 the Division of Scientific Investigations (DSI) was consulted to evaluate three study sites that were used in support of this NDA. The study sites included:

- _____ (principal investigator _____) - protocol TRA 104603 and TRA 105580 who provided 16 and 42 patients into each of these studies respectively.
- Study site # _____ - protocol TRA 100773A and TRA 100773B who provided 12 and six patients into these studies, respectively.
- Study site # _____ protocol TRA 100 773A and TRA 100773B who provided 10 and one patients into these studies, respectively.

3.5 Compliance with Good Clinical Practices

All studies in the ITP setting were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocols and any amendments were approved by an Institutional Review Board prior to initiation and implementation of the studies and changes. Written informed consent provided by the patient was required and the written informed consent forms for studies TRA 100773A and in the TRA 100773B were reviewed. The informed consent, protocol violations and site-specific issues were reviewed and found to be within accepted standards.

Reviewer comment: The studies were conducted in accordance with good clinical practices and appear to be appropriate.

3.6 Financial Disclosures

Based on information available to the sponsor the _____ investigators had disclosable interests of the type described in 21 CFR 54.2 (a), (b), (c). The sponsor states that there were no investigators in the pivotal studies that exceeded the \$50,000 threshold for equity interest.

b(6)

Reviewer comment section 3: The medical review of the studies TRA 100773A and TRA 100773B is included in this document. These studies were the primary studies used to understand the safety and efficacy of eltrombopag for the treatment of patients with ITP along with the safety data from the EXTEND study. The DSI investigation did not report any major study violations. All studies in the ITP setting were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. No investigators in the pivotal studies exceeded the \$50,000 threshold for equity interest.

4 CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics

The pharmacokinetic steady state of eltrombopag after administration to patients with ITP are shown in the table below based on the sponsor's report.

Table 3 Plasma Eltrombopag AUC(0- τ) and C_{max} Estimates for Subjects with ITP in Studies TRA100773A and TRA100773B

Eltrombopag Dose, QD	N	AUC(0- τ), $\mu\text{g}\cdot\text{h/mL}$	C _{max} ^a , $\mu\text{g/mL}$
30mg	28	39.2 (31.3,49.1)	3.17 (2.45,4.10)
50mg	34	91.9 (73.6,115)	7.95 (6.46,9.79)
75mg	26	146 (122,176)	11.4 (9.39,13.9)

a. Data presented as geometric mean (95% CI). AUC(0- τ) based on population PK post-hoc estimates. C_{max} estimated using all observed concentration data collected between 2h and 6h after dosing (approximate t_{max}).

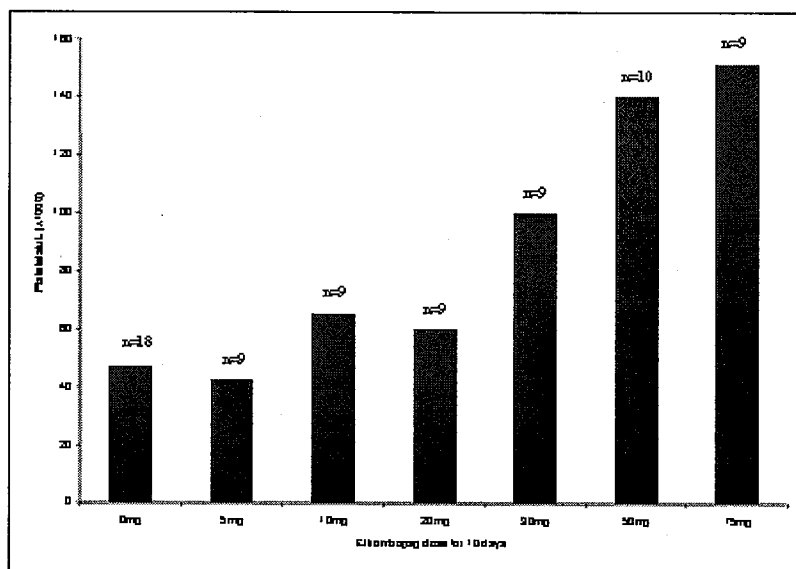
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Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Polyvalent cation-containing antacids reduced plasma eltrombopag $AUC_{0-\infty}$ by 70% and a meal with dairy- and calcium-containing products decreased plasma eltrombopag $AUC_{0-\infty}$ by 59%. The absolute oral bioavailability of eltrombopag after administration of PROMACTA in humans has not been established. Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single 75 mg solution dose was estimated to be at least 52%. Eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is not a substrate for p-glycoprotein or OATP1B1. Absorbed eltrombopag is extensively metabolized, predominately through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites, each accounting for <10% of the plasma radioactivity, due to glucuronidation and oxidation were also detected. The predominant route of eltrombopag excretion was via feces (59%), and 31% of the dose was found in the urine. Unchanged eltrombopag in feces accounted for approximately 20% of the dose; unchanged eltrombopag was not detectable in urine. The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours. Plasma eltrombopag exposure was approximately 70% higher in East Asian (i.e., Japanese, Chinese, Taiwanese, and Korean) subjects as compared to non-East Asian subjects who were predominantly Caucasian. Based on a human study with radiolabeled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag inhibited several UGT enzymes in vitro. Clinically significant drug interactions involving glucuronidation are not anticipated due to the limited contribution of individual UGT enzymes to the glucuronidation of eltrombopag and potential co-medications.

4.2 Pharmacodynamics

In study SB497115/002, the study medication was first administered orally as a single dose and, after a washout period of one week, once daily dosing for 10 days at doses of 5, 10, 20, 30, 50 or 75 mg per day. The normal intrasubject variability of platelet counts was 0.8-1.2. From baseline during the four-week time period a dose-dependent increase in platelet counts of at least 1.3 fold above baseline was observed in those cohorts that received the 20, 30, 50 and 75 mg doses. One out of nine subjects receiving active SB-497115-GR in the 20 mg cohort demonstrated a > 1.3 fold increase in the platelet count. A similar or greater increase was observed in 6/9 subjects in the 30 mg cohort and all the subjects (n = 17) in the 50 and 75 mg cohorts. The figure below shows the mean change in platelet count from baseline following 10 days of dosing with SB-497115-GR.

Figure 1 Mean (SD) Change in Platelet Count from Baseline Following 10 Days Dosing with SB-497115-GR (0 – 75 mg) in Study SB-497115/002)



The Clinical Pharmacology reviewer (Dr. Joe Grillo, review date August 26, 2008) stated in his review that plasma eltrombopag AUC(0- τ) was approximately 35% lower in healthy subjects as compared to patients with ITP. Plasma eltrombopag exposure was reported to be approximately 70% higher in some East Asian/Japanese subjects with ITP based on estimates from a population-based pharmacokinetic model. Further, an analysis of the limited number of healthy East Asian/Japanese subjects from studies conducted in the West failed to substantiate the findings from the studies conducted in Japan. FDA also noted a trend suggesting approximately 40-50% higher eltrombopag exposure in some healthy African-American subjects in several clinical pharmacology studies. This issue was not fully explored by the sponsor. These race effects are likely the result of a, yet undetermined, genetic variation in pathways (e.g., CYP1A2, UGT1A1, etc.) that have been identified as metabolizing eltrombopag and, to a lesser extent, the difference in body weight between subjects in the western and Japan studies.

Dr. Grillo's review also states that plasma eltrombopag AUC(0- ∞) was 41% higher in subjects with mild hepatic impairment, and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy subjects. It is difficult to quantify the magnitude of this effect given the high variability in the data and the failure to report unbound eltrombopag (active) concentrations in this highly protein bound (liver disease can affect the protein binding of drugs). There was a trend toward reduced plasma eltrombopag exposure in the interim analysis of data from subjects with renal impairment, but these data were inconclusive due to substantial variability as well as significant overlap in exposure between subjects with renal impairment and healthy subjects. In addition, the sponsor failed to report unbound eltrombopag

(active) concentrations in this highly protein bound (renal disease can affect the protein binding of drugs).

Dr. Grillo's review states that the PD response to eltrombopag was qualitatively similar in healthy East Asian/Japanese and Western subjects, with both the shape of the platelet count profile and the duration of response being comparable. However, at the same dose of eltrombopag, the absolute PD response was greater in healthy East Asian/Japanese subjects than healthy Western subjects. The magnitude of this difference was lower than that reported for pharmacokinetic drug exposure.

4.3 Exposure-Response Relationships

The planned doses for TRA 100773A were 30, 50 and 75 mg orally given once daily for six weeks. These dose levels were selected based upon a dose-dependent increase in platelet counts of at least 1.3 fold above baseline in healthy male subjects who received 20, 30, 50 and 75 mg once daily for 10 days as described in section 5.2 Pharmacodynamics of this review. Acceptable safety and tolerability were observed in these subjects. The dose used in study TRA 100773B was 50 mg administered orally once daily for six weeks. This dose was selected based upon a dose-dependent increase in platelet counts observed in study TRA 100773A compared to those patients who received placebo. In study TRA 100773A 16/24 (66.7%) of patients receiving 50 mg of eltrombopag met the primary endpoint (an increase in platelet count from $\leq 30,000/\text{mcl}$ at baseline to $\geq 50,000/\text{mcl}$ after 42 days of dosing or withdrawal). In this study 9/24 (37.5%) of patients receiving 50 mg doses were withdrawn early from treatment with eltrombopag due to platelet counts $> 200,000/\text{mcl}$. In addition, 18/21 (86%) of patients receiving 75 mg of eltrombopag met the primary endpoint and 11/21 (52%) were withdrawn early from eltrombopag treatment due to a rise in platelet count $> 200,000/\text{mcl}$. Similar safety and tolerability were observed in the placebo, 30, 50 and 75 mg eltrombopag treated patients ($n=104$).

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

Eltrombopag is indicated for the short-term treatment of previously treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

Methods

The clinical data upon which this application is submitted is based on the two pivotal trials TRA 100773A and TRA 100773B.

General Discussion of Endpoints

The original IND for eltrombopag (IND 63, 293 letter date September 20 8004) was reviewed by Dr. Andrew Dmytrijuk (review completed October 29, 2004) and contained the protocols for both studies TRA 100773A (part A) and TRA 100773B (part B). The primary objective of this study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once daily for 6 weeks to adult patients with refractory chronic ITP.

The secondary objectives were:

- To assess the safety and tolerability of eltrombopag when administered once daily for 6 weeks to adult patients with refractory chronic ITP
- To characterize the population pharmacokinetic profile of oral eltrombopag using a combined sparse (i.e., that these samples will be collected at any time during the defined sampling intervals) and serial pharmacokinetic sampling strategy when administered once daily for 6 weeks to adult patients with refractory chronic ITP.
- To determine the pharmacodynamic effect of eltrombopag on markers of thrombopoiesis when administered once daily for 6 weeks to adult patients with refractory chronic ITP.
- To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia when administered once daily for 6 weeks to adult patients with refractory chronic ITP.
- To assess the impact of eltrombopag on the quality of life when administered once daily for 6 weeks to adult patients with refractory chronic ITP.

The study was a double-blind, randomized, multi-institutional, placebo controlled, parallel group, repeat-dose study conducted in 2 parts (part A and part B). Part A was a phase 2 study while part B was a Phase 3 study. Screening was to take place up to 28 days before dosing. The “on-dose” phase of the study (both part A and B) was to involve once daily dosing of eltrombopag for 6 weeks. On completion of the dosing period, subjects were to undergo follow-up assessments for 6 weeks following the final dose. The six week follow up period was proposed by the sponsor to assess the durability of the platelet response.

The study was to be conducted in adult subjects with refractory chronic ITP, defined as patients who have failed at least one previous treat for ITP, including corticosteroids, immunoglobulins, immunomodulators and/or splenectomy. Patients receiving maintenance corticosteroid therapy could participate providing their corticosteroid dose had been stable for at least 1 month prior to screening. The planned enrollment was a total of 214 subjects for this 2 part study, i.e. 115 subjects in part A and 99 subjects in part B. Thirty patients were enrolled into the placebo, 30, 50 mg dose cohorts and 28 patients in the 75mg dose cohort for part A of the study (total 118 patients). In part B of the study the sponsor enrolled 38 patients into the placebo arm and 76 patients into the 50mg dose arm (total 114 patients).

The inclusion criteria were proposed to be as follows:

- Diagnosis with chronic ITP for at least 6 months prior to screening for this study with a current platelet count of $<30,000/\mu\text{l}$.
- Refractory patients who have failed at least one previous treatment for chronic ITP including corticosteroids, immunoglobulins, azathioprin, danazol, immunomodulators and/or splenectomy.
- Subjects treated with maintenance corticosteroid therapy must be receiving a steroid dose that has been stable for at least 1 month.
- No past history of myocardial infarction or clinically significant EKG findings at screening.
- Normal prothrombin time and activated partial thromboplastin time
- No history of a clotting disorder (other than ITP).
- Male or female subjects who agree to use acceptable methods of contraception (including intrauterine device) and 2 forms of barrier contraception if engaging in sexual intercourse for at least 7 days prior to the first dose of the study medication and continuing until 30 days after the final dose of the study medication.
- Age over 18 years.
- A signed and dated written consent form.

The exclusion criteria that were proposed are as follows;

- Any clinically relevant abnormality, other than ITP, identified on the screening examination or any other medical condition or circumstance, which in the opinion of the investigator makes the subject unsuitable for participation in the study.
- History of thrombosis within the last year.
- For female subjects, a positive serum or urine human chorionic gonadotropin pregnancy test at screening or predose on day 1.
- For female subjects, no current hormone replacement therapy or current oral contraceptive use.
- History of alcohol/drug abuse or dependence within 12 months of the entry into the study.
- Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.
- Use of aspirin, aspirin-containing compounds, salicylates, milk of magnesia, or non-steroidal anti-inflammatory drugs within 3 weeks of the study start and until the end of the study.
- Use of substrates of the cytochrome P450 2C9 isoenzyme.
- Consumption of any herbal or dietary supplements, excluding vitamin or mineral supplements, within 1 week of the start of the study.
- A complete blood count and/or reticulocyte count outside the standard reference range, except for platelet count.
- History of platelet aggregation that prevents reliable measurement of platelet counts.
- History of HIV, hepatitis B or hepatitis C viral infections.

Eltrombopag was supplied by the sponsor as _____ round film coated tablets containing eltrombopag equivalent to 5mg, 25mg and 50mg of SB-497115-GR free acid. Matching placebo tablets also were supplied. Patients were instructed to take the medication on an empty stomach, at least 4 hours after any food intake. The dose levels selected for this study namely, 30, 50, 75 and possibly 100mg were based on the following consideration according to the sponsor:

- A dose dependent increase in platelet counts, of at least 1.3 fold above baseline, was observed in healthy human subjects who received 20, 30, 50 and 75 mg once daily for 10 days.
- Acceptable safety and tolerability of repeat oral doses of up to 75 mg of study drug for 10 days in healthy male subjects.
- Reversibility of hepatocellular vacuolation in the rat (NOAEL mean AUC = 164µg.h/ml)
- Although the 100mg dose has not been assessed in healthy subjects and would be administered for the first time in this study, previous pharmacokinetic studies at the 100mg dose predicted a mean AUC of 90µg.h/ml. The ratio to NOAEL AUC is therefore estimated to be 2:1 according to the sponsor.

In part A, 272 adult subjects with chronic ITP were randomized equally to one of 4 treatment arms of a dose ranging study to determine an optimal dose level based on safety and efficacy data. The sponsor proposed the following treatment groups and dosing schedule for part A of the study; treatment group A1 to receive 30mg SB-495711-GR once daily for 6 weeks, treatment group A2 to receive 50mg SB-495711-GR once daily for 6 weeks, treatment group A3 to receive 75mg eltrombopag once daily for 6 weeks, treatment group A4 to receive placebo once daily for 6 weeks. There was no proposed dose adjustment in the trial.

The sponsor proposed 2 interim analyses to be conducted during part A of this study. These were to be performed when the platelet counts collected following 42 days of dosing become available for 1/3 and 2/3 of the planned maximum number of patients. At each of the interim analyses, dosing could be stopped for efficacy, lack of efficacy or safety concerns. An additional dose of 100mg was also to be tested in this part of the study as noted above, based on satisfactory safety data and inferior efficacy data from interim analyses. The sponsor proposed to randomize 102 new subjects to the 100mg or placebo treatment groups (ratio of 2:1) and to maintain the blind.

In part B of this study, the sponsor proposed that the dose that emerges from part A as the optimal dose level, based on safety and efficacy parameters using a proposed step-down and futility procedure, was to be tested further. The dose modifications for part B are shown in the table below.

Dose Modification TRA 100773B

Starting Dose	If at day 22 or any subsequent visit, platelets < 50,000/mcl	If at any time platelets $\geq$ 200,000/mcl to < 800,000/mcl	If at any time platelets $\geq$ 800,000/mcl
50 mg or placebo.	Increase the study medication to 75 mg.	Subject must be withdrawn, discontinue study medication.	Subject will be withdrawn from study and may be given low-dose aspirin or apheresed as per local procedures. Contact sponsor medical monitor.

Part B was not to be initiated before the optimal dose had been determined. The interim period between the 2 parts of the study was to be approximately 3 months. In Part B, 150 newly recruited subjects were to be randomized to one of 2 dosing arms in a 2:1 ratio of active agent:placebo. Each arm in part B was to receive once daily doses of study drug or placebo for 6 weeks. No interim analysis was planned for part B.

A randomized subject who complied with all doses of investigational product and underwent visits through day 43, for whom all safety, efficacy and pharmacokinetic samples have been collected, was to be considered as having completed the study.

A subject was also allowed to voluntarily withdraw from the study at any time. The investigator was also allowed to, at his/her discretion, discontinue the subject from participating in this study at any time. If patients were prematurely discontinued from participation for the reasons indicated below, the investigator was to perform all evaluations specified for the final visit.

Premature discontinuation was required when:

- A subject did not continue to meet inclusion and exclusion criteria.
- A subject was significantly non-compliant with the requirements of the protocol.
- A subject had an adverse event that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
- A subject required other/rescue treatment for ITP.
- A subject had a 2-fold increase in spleen size.
- A subject achieved a platelet count of $\geq$ 200,000/ μ l on therapy.

The platelet count data collected as part of the CBC, on study day 43 was used to determine the primary endpoint of the proportion of subjects with a platelet count of $\geq$ 50,000/ μ l after 42 days of dosing, in each of the treatment groups. In addition, patients who achieved a platelet count $\geq$ 200,000 at any point during the dosing of eltrombopag were considered responders. Patients who meet these criteria were referred to as treatment responders.

The proposed secondary endpoints were:

- Safety and tolerability parameters that included physical examination, blood pressure, heart rate, 12 lead EKG, splenic examination with ultrasonography, clinical laboratory tests, platelet activation and aggregation, clinical monitoring and observation and adverse events reporting.
- Population pharmacokinetic parameters of SB-495711-GR including clearance (CL/F), absorption rate constant (k_a), and volume of distribution (V/F) with assessment of potential significant covariates influencing SB-495711-GR pharmacokinetics. The relationship between the pharmacokinetics of SB-495711-GR and relevant safety and efficacy endpoints was explored.
- Pharmacodynamic parameters included platelet count and endogenous serum TPO levels during and after 6 weeks of therapy.
- Incidence and severity of symptoms associated with chronic ITP, including bleeding, bruising, petechia based on the WHO and ITP bleeding scale.
- Physical and mental health status using the SF-36v2 quality of life tool.

The schedule of the study procedures and evaluations for both parts of the study is shown in the table below.

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Study Schedule for TRA 100773A and B

Study Day	Screening Up to Day -28	Study Day										
		1	8	15	22	29	36	43 or Early Withdrawal	50 FU	57 FU	71 FU	85 FU
Informed consent	X											
Registration - RAMOS	X											
Randomization - RAMOS ¹		X ¹										
Medical history	X											
Brief physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medication review	X	X	X	X	X	X	X	X	X	X	X	X
ECG ²	X	X			X			X			X	
Pregnancy test (urine or serum)	X ³	X ³										
Pharmacogenomic sample ⁴		X										
Splenic examination by ultrasonography ⁵	X ⁶	X ⁶			X			X				X
CBC (incl. platelet count) ⁷	X	X ⁷	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry ⁸	X	X	X	X	X	X	X	X	X	X	X	X
Urine dipstick	X ⁶	X ⁶			X							
Ophthalmic Examinations ⁹	X ⁶	X ⁶						X				X
Coagulation assays (PT/INR and aPTT)	X ⁶											X
Platelet activation/aggregation ¹⁰												
Serum TPO level ¹⁰		X			X			X				X
AE questioning		X	X	X	X	X	X	X	X	X	X	X
QoL assessments ¹¹		X						X				
Bruising and bleeding assessments	X	X	X	X	X	X	X	X	X	X	X	X
Serial PK sampling ¹² OR		X	X									
Sparse PK sampling ¹³		As per Section 6.4.1.2										

1. Randomization is to occur after a pre-dose Day 1 platelet count of < 30,000/ μ L has been established (platelet count MUST be within 24 hours prior to dosing on Day 1).
2. Resting 12-lead ECG will be obtained pre-dose (Screening or Day 1), on Day 1 at tmax (3 hours); if it cannot be performed at 3 hours, record actual time ECG was performed within a 2-6h window post-dose, and on Days 22, 43 and 71. A copy of all ECGs tracings will be shipped to GSK.
3. For female subjects of child-bearing potential, a negative pregnancy test MUST be obtained within 24 hours prior to the first dose (either Screening Day -1 or Day 1, pre-dose).
4. The PGx sample can be collected at any time during the study, on or after Day 1; however it is preferred that it be collected at the earliest time point possible. See Section 14.4, Appendix 4: Pharmacogenetics.
5. Subjects who have not had a splenectomy; to be performed either at Screening or Day 1, and on Day 22, Day 43, and Day 85.
6. To be performed at Screening, or pre-dose on Day 1.
7. CBC to include platelet count, hemoglobin, hematocrit, RBC count, WBC count, WBC differential.
8. Clinical chemistries to include BUN/urea, creatinine, glucose, sodium, potassium, chloride, bicarbonate, AST, ALT, total bilirubin, CPK, alkaline phosphatase, albumin, total protein.
9. Ophthalmic examinations to be performed as described in Appendix 10: Ophthalmologic Examinations.
10. To be performed where feasible by local laboratory, according to standard procedures at local laboratory; in Part A only.
11. QoL assessments to be performed prior to any visit assessments or interactions with the investigator.
12. To be performed where feasible by local laboratory, according to standard procedures at local laboratory in Part A and B; also a single PK sample is to be performed upon subjects withdrawal due to SAE or platelet count $\geq 200,000/\mu$ L in Part B.
13. Sparse sampling (Part A only) must be performed on visits 2 weeks apart (e.g. Day 1 and 15, or Day 22 and 36) as described in Section 6.4.1.2.

Table from protocol TRA100773A and B page 1574 and 1575.

The laboratory tests that were collected are shown in the table below.

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Laboratory Tests Study TRA 100773A and B

Hematology (CBC):
Hemoglobin
Hematocrit
WBC count
WBC differential
Red blood cell count
Platelet count
Chemistry:
BUN/Urea
Creatinine
Glucose (fasting for > 8 hours, if possible)
Sodium
Potassium
Chloride
Bicarbonate
AST (aspartate aminotransferase, SGOT)
ALT (alanine aminotransferase, SGPT)
Total Bilirubin
Alkaline phosphatase
Albumin
Total Protein
Other tests:
Platelet aggregation (where feasible, Part A only)
Platelet activation (where feasible, Part A only)
Serum endogenous TPO level (central lab, Part A only)
PT/INR
aPTT

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Table from protocol for TRA 100773A and TRA 100773B page 1577.

The study medication was administered under the supervision of study personnel on day 1 only. The dose, date and time of the study medication administration was recorded in the case report forms. On all other days the subjects were required to self-administer the study medication. The sponsor proposed to encourage subject compliance with the dosage regimen as per protocol. The study medication was dispensed in bottles containing 35 tablets that were given to each subject during the clinic visits. All subjects were instructed to return their medication packs at each visit, with any unused drug, to the investigator. Subject compliance was assessed by pill counting. A record of the supplies dispensed and returned was made in the case report forms at each visit. The sponsor noted that if there are any significant irregularities in compliance, in the opinion of the investigator, the subject were to be withdrawn from the study. Minor gaps in study medication were not automatic grounds for patient withdrawal from the study.

Part A of the study was powered at 90% to detect a difference of 30% in the proportion of responders (defined as the proportion of subjects with a platelet count of $\geq 50,000/\mu\text{l}$ from a baseline count of $<30,000/\mu\text{l}$ after 42 days of dosing) for each oral dose of the study medication compared with placebo (60% response for eltrombopag vs. 30% for placebo). The study was designed to assess the null hypothesis $H_0: \delta \leq 0$ or reject it in favor of the alternative hypothesis $H_A: \delta > 0$ (one sided at 2.5% level overall) where δ is the difference in the proportion of responders for the 3 treatment groups and placebo.

Part B of the study was powered at 90% to detect a difference of 30% in the proportion of responders (defined as the proportion of subjects with a platelet count $\geq 50,000/\mu\text{l}$ from a baseline count of $<30,000/\mu\text{l}$ after 42 days of dosing) for the optimal dose of SB-497115-GR (as determined from part A) compared with placebo (60% response for SB-497115-GR vs. 30% for placebo). Part B was designed to assess the null hypothesis $H_0: \delta=0$ (no difference) or reject it in favor of the alternative hypothesis $H_A: \delta > 0$ (two sided at 5% level) where δ is the difference in the proportions of responders for SB-497115-GR groups and placebo.

The sponsor further proposed that data from all participating centers was to be pooled prior to analysis. Descriptive statistics by center were provided. A summary and listing of protocol violations was provided. Study site protocol violations appear to have been minor and inconsequential to the outcome of the studies. Demographic and baseline characteristics were summarized. Furthermore, descriptive statistics classified by treatment group were provided for reticulated platelet counts, number of platelet transfusions, number of bleeding events, safety and other pharmacodynamics parameters, pharmacokinetics and quality of life assessments.

Safety and tolerability of the study medications will be assessed from the following;

- Hematology and serum chemistry on study days 1, 8, 15, 22, 29, 36, 43, 57, 71 and 85.
- Adverse event and concomitant medication assessments throughout the study until day 57.
- Spleen size by ultrasound examination on study days 1, 22, 42, and 85.
- Other scheduled assessments as listed in the appendix will also be evaluated.
- All adverse and serious adverse events will be followed until resolution.

Dr. Dmytrijuk concluded that the studies appeared to be reasonably safe to proceed. Dr. Dmytrijuk had the following comments for the sponsor which were communicated to the sponsor in a letter dated January 21, 2005.

- 1) The proposed study may provide proof of concept. A larger trial would likely be necessary to establish the efficacy and safety of SB-497115-GR.
- 2) The sponsor should define how the baseline and on treatment platelet counts (either single values or averages) will be determined.
- 3) Two failed therapies including previous Anti-D antibody therapy should be required to define refractory ITP.
- 4) A dose of 100mg should not be given until all patients given lower doses have completed the study, including all follow-up, without exhibiting significant adverse events.
- 5) SB-497115-GR should be discontinued if the platelet count reaches $\geq 150,000/\mu\text{l}$ to prevent excess thrombocytosis.
- 6) Success should be defined as platelets $\geq 50,000/\mu\text{l}$ and at least 2 times baseline.
- 7) The clinical significance of the study would be enhanced if the response rate was more than 30% greater than that seen with placebo.
- 8) The sponsor should perform EKG at the 3 week and 6 week intervals while on dose and at the day 71 follow-up time point.

- 9) The sponsor should consider performing anti-TPO antibody testing in patients exposed to SB-497115-GR.

The sponsor responded to these recommendations in submission IND 63,293 N 009 IM dated February 24, 2005. The sponsor responded to recommendations 1, 3, 4, 5 and 6 listed above, otherwise the sponsor agreed to the recommendations. The sponsor agreed that the study part A is intended as a proof of concept. However part B would be used to establish efficacy and safety of eltrombopag in the short-term treatment of ITP. The sponsor further proposed that refractory ITP be defined as not having a response to or relapsed within three months after at least one prior ITP treatment. In addition, refractory patients with platelet counts $< 30,000/\text{mcl}$ who were receiving maintenance immunosuppressive therapy at a dose which has been stable for at least 30 days would be allowed entry into the study. The sponsor stated that the safety monitor will be reviewing all unblinded laboratory data and adverse events in real time for all subjects in this study and that a proposed 100 mg dose was projected to be below the no observed adverse effect level in animal studies. The sponsor stated that they agreed with the definition of success as a platelet count $\geq 50,000/\text{mcl}$, but not on the added definition that requires an increase of at least twice the baseline platelet count. Dr. Dmytrijuk reviewed this submission and responses were communicated to the sponsor during a teleconference held on June 20, 2005 and in a letter dated July 28, 2005. These recommendations were as follows:

- In order for the drug to be considered adequate for approval it must be supported by adequate and well-controlled studies.
- The use of the drug should be limited to patients who are refractory to therapy. The use of an unproven drug in a population that generally has no negative sequelae at platelet counts $> 10,000/\text{mcl}$ should be limited only to those patients for whom experimental therapy may prove useful (i.e., those who have failed at least one type of treatment regimen and splenectomy).
- The dosing of patients with 100 mg of eltrombopag should not proceed until all patients given lower doses have completed the study, including all follow-up, without exhibiting significant adverse events.
- In normal healthy volunteers dosing of eltrombopag was stopped at 75 mg in order to prevent platelet counts above $400,000/\text{mcl}$. It is possible that platelet counts could go beyond $200,000/\text{mcl}$ doses of 50 or 75 mg. Therefore it was recommended that the dosing of the study drug be discontinued when the platelet count was $\geq 150,000/\text{mcl}$.
- In order to fully demonstrate a robust efficacy for the drug the sponsor should have as a primary endpoint the proportion of subjects with platelet counts of $\geq 50,000/\text{mcl}$. The sponsor should perform a secondary analysis for those subjects who achieve a platelet count $\geq 50,000/\text{mcl}$ and at least two times baseline for all subjects enrolled in the study.

The sponsor did not respond to these final recommendations.

Study Design

The design of the studies TRA 100773A and TRA 100773B was discussed in section 6.1.2 General Discussion of Endpoints in this review. The studies were determined to be reasonably safe to proceed by Dr. Andrew Dmytrijuk (review completed October 29, 2004). The important design features, inclusion criteria, exclusion criteria and endpoints are summarized below. The studies were randomized, double-blind, placebo-controlled, multicenter studies.

The major common design features/inclusion criteria for study TRA 100773A and TRA 100773B are as follows:

- ITP diagnosed ≥ 6 months and platelets $\leq 30,000/\text{mcl}$ at Day 1.
- Previous ITP treatments ≥ 1 or relapsed within 3 months of prior treatment.
- Concomitant medication allowed during study with concomitant medication dose stable for 1 month prior to entry.
 - Immunoglobulin therapy and Cyclophosphamide completed 2 weeks prior to randomization.
- Age ≥ 18 yrs.
- Chemistries, coagulation studies and liver function tests within reference ranges.
- Hemoglobin ≥ 10 ; absolute neutrophil count $\geq 1500/\text{mcl}$.
- Patients were stratified according to:
 - ITP Rx (yes/no splenectomy (yes/no), baseline platelet count $\leq 15,000/\text{mcl}$ (yes/no)
- Eltrombopag treatment $\times 6$ weeks, follow-up $\times 6$ wks.
- Platelet count and bleeding check once weekly.
 - WHO and ITP bleeding scale used to characterize severity of bleeding.
- Quality-of-life using the SF-36v2 tool was evaluated at entry and day 43.
- Responders defined as:
 - Platelets $\geq 50,000/\text{mcl}$ at day 43 or platelets $> 200,000/\text{mcl}$ prior to day 43.

The major common exclusion criteria for study TRA 100 773A and TRA 100773B are as follows:

- History of thrombosis within 1 year of entry.
- Pregnant or nursing.
- Nonsteroidal anti-inflammatory drug use for > 3 consecutive days within 2 weeks of entry.
- Antacid use
- Statin use
- HIV, Hepatitis B or C, cancer history.

The endpoints for the studies TRA 100773A and TRA 100773B are as follows:

- Primary: Proportion of patients with platelet count $\geq 50,000/\text{mcl}$ at day 43.
- Secondary:
 - Odds of achieving a platelet count $\geq 50,000/\text{mcl}$ during week 2-6 (secondary endpoint for part B).
 - Proportion of patients with platelets $\geq 50,000/\text{mcl}$ and 2 x higher than baseline at day 43 (secondary endpoint for part B).
 - Analysis of pharmacokinetics.
 - Analysis of pharmacodynamics.
- Safety:
 - Incidence of bleeding over the course of the studies.
 - Adverse events.
 - Serious adverse events.

Reviewer comment: There were no significant differences from the protocols reviewed under the IND compared to those discussed above.

Efficacy Findings

Study TRA 100773A

In this study the maximum sample size per protocol was 272 patients. The study was closed to enrollment after a total of 118 patients had been randomized based on the results of the first interim analysis in which the 50 mg and 75 mg eltrombopag treatment groups showed superiority compared to placebo in terms of the proportion of patients who were defined as responders. Responders were defined as patients whose platelet count reached $\geq 50,000/\text{mcl}$ at the day 43 visit from a baseline platelet count of $< 30,000/\text{mcl}$ (p, one-sided < 0.0113). The safety population and the intention to treat population were comprised of 117 patients in each. The demographics of the patient population for study TRA 100773A is shown in the table below.

Patient Demographics Study TRA 100773A

	PBO n = 29 (%)	Eltrombopag n = 88 (%)
Median age-yrs	42	51
Female	16 (55)	57 (65)
East Asian or South East Asian	2 (7)	19 (22)
Arabic/ North African	5 (17)	9 (10)
Caucasian	20 (69)	59 (67)

The patient disposition for study TRA 100773A is show in the table below.

Patient Disposition Study TRA 100773A

Disposition Category	Number patients (%)				
	PBO	30mg	50mg	75mg	Total
ITT pop	29	30	30	29	118
Safety Pop	29	30	30	28 – One patient did not receive drug	117
Completed Study	22 (76)	23 (77)	17 (57)	12 (43)	74 (63)
Completed or d/c $\geq$ 200 K.	23 (79)	27 (90)	28 (93)	24 (86)	102 (87)
Withdrawal prematurely from study medication	7 (24)	7 (23)	13 (43)	16 (57)	43 (37)

The reasons and number of patients withdrawn prematurely from study medication in study TRA 100773A are shown in the table below.

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Reasons for Patient Withdrawal Study TRA 100773A

	PBO n (%)	30mg n (%)	50mg n (%)	75mg n (%)	Total n (%)
Withdraw for any reason	7 (24)	7 (23)	13 (43)	16 (57)	43 (37)
Plt > 200	1	4	11	12	28
AE	3	0	2	1	6
Lack of efficacy	0	2	0	1	3
Other	1	1	0	1	3
Subject decision	2	0	0	0	2
Protocol Violation	0	0	0	1	1

In this study 19 patients had one or more major protocol violations and were excluded from the per-protocol population. The most common protocol violations were clinical or laboratory evidence that the patient's underlying condition might not be ITP (six patients) and the patient's platelet count was > 30,000/mcl on day one or 24 hours prior to day one (four patients). The table below shows the reasons and number of patients that had protocol violations in study TRA 100773A.

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Protocol Violations Study TRA 100773A

Protocol Violation	PBO n	30 n	50 n	75 n
Not ITP	1	3	1	1
Plt > 30K at entry	0	1	2	1
HIV/Hep	1	1	0	1
Use of prohibited anticoagulant or diet supplement	0	0	2	1
PT/PTT or clotting disorder	0	2	0	1
Not on stable ITP con med	0	1	0	0
ITP rx with Ig	1	0	0	0

Most patients in this study had >1 prior ITP treatments. The table below shows the number of prior treatments that patients had in this study.

Prior Treatments Study TRA 100773A

No of therapies	PBO n = 29	Eltrombopag n = 88
No Rx	1	3
≥ 1	28	85
≥ 2	21	66

The table below shows the disease characteristics for patients in study TRA 100773A.

Disease Characteristics Study TRA 100773A

Characteristics	PBO n = 29	Eltrombopag n = 88
ITP concomitant medication at randomization.	6	33
Splenectomy	14	41
Platelets $\leq$ 15 K	14	42
Platelets $>$ 15 K	15	45 (data not available for 1 patient)

In addition, approximately 80% of patients in all treatment groups received at least one non-ITP concomitant medication while on treatment with eltrombopag. Concurrent use of ITP medications was allowed during the treatment period provided the dose and schedule had been stable for at least one month prior to starting study medication. Also, the majority of patients in the study complied with their study treatment regimen. In the placebo treatment group the compliance rate with the treatment regimen was 99% (standard deviation 2.07). In the 30 mg treatment group the mean compliance rate with the treatment regimen was 98.5% (standard deviation 2.97). In the 50 mg treatment group the compliance rate with the treatment regimen was 98.7% (standard deviation 7.89). In the 75 mg treatment group the compliance rate with the treatment regimen was 98.8% (standard deviation 3.04).

The primary efficacy endpoint was a shift from a baseline platelet count of $< 30,000/\text{mcl}$ to $\geq 50,000/\text{mcl}$ after up to 42 days of dosing with eltrombopag. Analysis of the primary endpoint demonstrated that eltrombopag increased the number of patients achieving the primary endpoint in a dose-dependent manner after up to six weeks of dosing. The table below shows the results of the primary efficacy endpoint analysis for study TRA 100773A.

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Primary Efficacy Endpoint Study TRA 100773A

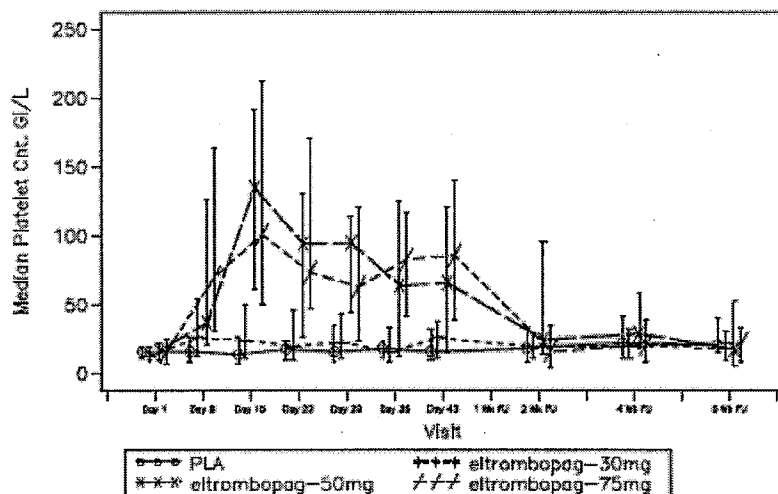
	PBO n = 27	30mg n =29	50mg n = 27	75mg n = 26
Responders at day 43	3	8	19	21
Odds ratio	NA	3.09	21.96	38.82
95% CI	NA	0.69, 13.75	4.72, 102.23	7.62, 197.73
p-value (one-sided)	NA	0.070	< 0.001	< 0.001

Both the 50 mg and 75 mg eltrombopag treatment groups achieved a statistically significant treatment effect compared to placebo as shown above and met the prespecified p - value ($p < 0.011$) for stopping the study at the first interim analysis.

Median platelet counts in the eltrombopag 50 and 75 mg treatment groups showed an elevation of platelets as early as day eight and continued to rise to day 15. A slight decrease in the median platelet count was observed after day 15 in the eltrombopag 50 and 75 mg treatment groups. This decrease is explained by the number of patients withdrawn after day 15 from the 50 and 75 mg treatment groups due to platelet counts above 200,000/mcl. In the placebo group 1/27 patients had platelet count above 200,000/mcl and 1/27 patients achieved a platelet count above 400,000/mcl by the day 43 visit. In the 30 mg treatment group 4/29 patients achieved platelet counts above 200,000/mcl and 1/29 patients achieved a platelet count above 400,000/mcl by the day 43 visit. In the 50 mg treatment group 10/27 patients achieved platelet counts above 200,000/mcl and 6/27 patients achieved a platelet counts above 400,000/mcl by the day 43 visit. In the 75 mg treatment group in 13/26 patients achieved a platelet count above 200,000/mcl and 4/26 patients achieved a platelet count above 400,000/mcl by the day 43 visit. The figure below shows the median platelet counts over the course of the study for those patients who continued on treatment at each time point.

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Median Platelet Counts TRA 100773A (ITT Population)



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The WHO bleeding scale characterizes bleeding as follows: grade 0 - no bleeding; grade 1- petechiae; grade 2- mild blood loss; grade 3- gross blood loss; grade 4 -debilitating blood loss. WHO bleeding scale grades 2-4 are considered clinically significant. WHO bleeding grade 2-4 was evaluated posthoc. No patients had grade four bleeding at any time during the study. At day 43 the percentage of patients with any bleeding (score grade 1-3) decreased from baseline in the eltrombopag 50 and 75 mg treatment groups during treatment but returned to near baseline proportions by two weeks after therapy (day 57). The percentage of patients with any bleeding in the placebo treatment group remained unchanged between the baseline, day 43 and day 57 visits. The bleeding assessments by visit during the study, based on the WHO bleeding scale, are shown on the table below.

Bleeding Assessment Study TRA 100773A

Assessment Visit	Treatment Group, n (%)			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
Baseline	27	29	27	26
Grade 0	12 (44.4)	10 (34.5)	10 (37.0)	7 (28.0)
Grade 1 – Grade 3	15 (55.6)	19 (65.5)	17 (63.0)	18 (72.0)
Grade 4	0	0	0	0
Day 43 Visit	22	24	16	12
Grade 0	11 (50.0)	14 (58.3)	12 (75.0)	9 (75.0)
Grade 1 – Grade 3	11 (50.0)	10 (41.7)	4 (25.0)	3 (25.0)
Grade 4	0	0	0	0
Day 57 Visit	25	26	26	26
Grade 0	11 (44.0)	12 (46.2)	14 (53.8)	10 (38.5)
Grade 1 – Grade 3	14 (56.0)	14 (53.8)	12 (46.2)	16 (61.5)
Grade 4	0	0	0	0

Data Source: Table 7.22

WHO grade 2-4 bleeding occurred in 5/26 (19%) of placebo treated patients and 9/39 (23%) of eltrombopag treated patients who were nonresponders compared to 3/48 (6%) of eltrombopag treated patients who were considered responders.

A decrease in the number of patients after day 15 of eltrombopag treatment in the 50 mg and 75 mg eltrombopag treatment groups which may be explained by the observation that the majority of patients withdrawn after day 15 in these treatment groups were withdrawn due to platelet counts > 200,000/mcl as is shown in the table below. Of note, patients who discontinued study medication continued to participate in the follow-up visits and their data was included in the follow-up visits (2, 4 and 6 weeks after discontinuation of the study medication i.e. nominal days 57, 71 and 85).

Withdrawal due to Platelet Count > 200,000/mcl

	PBO n (%)	30mg n (%)	50mg n (%)	75mg n (%)	Total n (%)
Withdrew for any reason	7 (24)	7 (23)	13 (43)	16 (57)	43 (37)
Plt > 200	1	4	11	12	28

Subgroup analyses were performed on patients based on randomization stratification variables and posthoc subgroup analyses were based on age, sex, and race. These analyses were performed on the efficacy population. An analysis of responders at day 43 demonstrated that eltrombopag increased platelet counts in a dose-dependent manner after up to six weeks of dosing for patients who did or did not use a concomitant ITP medication at the time of randomization. These results are shown on the table below. Logistic regression analysis showed an interaction at the 10% level of significance between the response to treatment and the use of ITP medication at randomization (p= 0.093).

Proportion of Responders Who Did and Did Not Use Concomitant ITP Medication (Efficacy Population)

Day 43 Visit	Treatment Group and Use of ITP Medication at Randomization, n (%)							
	PBO N=27		30mg N=29		50mg N=27		75mg N=26	
	Yes	No	Yes	No	Yes	No	Yes	No
n	6	21	9	20	11	16	10	16
Responders	1 (16.7)	2 (9.5)	4 (44.4)	4 (20.0)	3 (27.7)	11 (68.8)	6 (60)	15 (93.8)

Data Source: Table 7.12

Analysis of responders at day 43 demonstrated that eltrombopag increased platelet counts in a dose-dependent manner after up to six weeks of dosing for patients regardless of splenectomy status. A higher percentage of patients in the 50 and 75 mg treatment groups who were not splenectomized achieved a platelet count $\geq$ 50,000/mcl compared to patients who were refractory

following splenectomy. No significant interaction between response and splenectomy status was observed which indicates that the proportion of patients responding increases with increasing dose in both subgroups.

Proportion of Responders Who Had or Had Not Undergone Splenectomy (Efficacy Population)

Day 43 Visit	Treatment Group and Splenectomy Status, n (%)							
	PBO N=27		30mg N=29		50mg N=27		75mg N=26	
	Yes	No	Yes	No	Yes	No	Yes	No
n	14	13	14	15	15	12	10	16
Responders	2 (14.3)	1 (7.7)	3 (21.4)	5 (33.3)	8 (53.3)	11 (91.7)	7 (70.0)	14 (87.5)

Data Source: Table 7.15

Eltrombopag increased platelet counts in a dose-dependent manner at day 43 for patients who had a baseline platelet count $\leq 15,000/\text{mcl}$ and for those who had platelet counts $> 15,000/\text{mcl}$. Logistic regression analysis showed an interaction at the 10% level of significance between the response to treatment and baseline platelet count at randomization ($p=0.042$). Patients with higher platelet counts at baseline tended to be more likely to respond to eltrombopag therapy.

Proportion of Responders Who Had Baseline Platelet Counts $> 15,000/\text{mcl}$ or $\leq 15,000/\text{mcl}$ (Efficacy Population)

Day 43 Visit	Treatment Group and Baseline Platelet Count (GiL), n (%)							
	PBO N=27		30mg N=29		50mg N=27		75mg N=26	
	≤ 15	> 15	≤ 15	> 15	≤ 15	> 15	≤ 15	> 15
n	14	13	15	14	11	16	14	12
Responders	1 (7.1)	2 (15.4)	5 (33.3)	3 (21.4)	6 (54.6)	13 (81.2)	9 (64.3)	12 (100)

Data Source: Table 7.18

Patients were characterized by age into the following groups: 18-49 years, 50-64 years and ≥ 65 years for the analysis of responders day 43. For all three age groups the percentages of responders in the eltrombopag treatment group were greater than in the placebo treatment group. The percentage of responders was higher in the 50 mg and 75 mg treatment groups than in the 30 mg treatment group. The statistical effect of treatment by age interaction could not be estimated by the sponsor since there were no responders in the ≥ 65 year category for the placebo treatment group. The responders by age at the day 43 visit are shown in the table below.

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Responders by Age at Day 43 (Efficacy Population)

Age Category	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
18 to ≤49 years of age				
n	20	11	15	9
Responders, n (%)	2 (10.0)	2 (18.2)	10 (66.7)	7 (77.8)
Responders with platelets >200 Gi/L, n (%)	1 (5.0)	0	7 (46.7)	5 (55.6)
50 to ≤64 years of age				
n	6	10	9	11
Responders, n (%)	1 (16.7)	5 (50.0)	6 (66.7)	9 (81.8)
Responders with platelets >200 Gi/L, n (%)	0	3 (30.0)	2 (22.2)	5 (45.5)
≥65 years of age				
n	1	8	3	6
Responders, n (%)	0	1 (12.5)	3 (100)	5 (83.3)
Responders with platelets >200 Gi/L, n (%)	0	1 (12.5)	1 (33.3)	3 (50.0)

Data Source: Table 7.30, Table 7.38

When patients were analyzed by sex subgroups for the analysis of responders at the day 43 visit there was no clear difference in the pattern of response to treatment as is shown in the table below.

Responders by Sex at Day 43 (Efficacy Population)

Sex	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
Female				
n	16	15	19	19
Responders, n (%)	2 (12.5)	5 (33.3)	14 (73.7)	15 (79.0)
Responders with platelets >200 Gi/L, n (%)	1 (6.25)	2 (13.3)	9 (47.4)	11 (57.9)
Male				
n	11	14	8	7
Responders, n (%)	1 (9.1)	3 (21.4)	5 (62.5)	6 (85.7)
Responders with platelets >200 Gi/L, n (%)	0	2 (14.3)	1 (12.5)	2 (28.6)

Data Source: Table 7.29, Table 7.37

In the analysis of response by race, most categories of race had insufficient representative numbers of patients for comparison of responders at the day 43 visit as is shown in the table below. However, as is shown in the table below, Asian responders achieved a platelet count > 200,000/mcl compared to other race categories.

Responders by Race at Day 43 (Efficacy Population)

Race Category	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
African American/African				
n	1	1	0	0
Responders, n (%)	0	0	0	0
Responders with platelets >200 Gi/L, n (%)	0	0	0	0
East Asian				
n	2	1	7	2
Responders, n (%)	0	1 (100)	3 (42.9)	2 (100)
Responders with platelets >200 Gi/L, n (%)	0	0	2 (28.6)	2 (100)
South-East Asian				
n	0	3	4	1
Responders, n (%)	0	2 (66.7)	3 (75)	1 (100)
Responders with platelets >200 Gi/L, n (%)	0	0	2 (50.0)	1 (100)
Arabic/North African				
n	4	1	3	5
Responders, n (%)	1 (25.0)	0	3 (100)	4 (80.0)
Responders with platelets >200 Gi/L, n (%)	0	0	2 (66.7)	2 (40.0)
White/Caucasian/European				
n	19	23	13	18
Responders, n (%)	2 (10.5)	5 (21.7)	10 (76.9)	14 (77.8)
Responders with platelets >200 Gi/L, n (%)	1 (5.3)	4 (17.4)	4 (30.8)	8 (44.4)
Other/Mixed				
n	1	0	0	0
Responders, n (%)	0	0	0	0
Responders with platelets >200 Gi/L, n (%)	0	0	0	0

Data Source: Table 7.31, Table 7.39

Patients were analyzed for the maximum number of weeks of continuous platelet response as a posthoc analysis. The 50 mg and 75 mg treatment groups showed a substantial proportion of patients with ≥ 5 continuous weeks of response up to day 43. Patients in the placebo group had a response of ≥ 4 weeks. The table below shows the durability of platelet response to study medication.

Post Hoc Analysis: Durability of Platelet Response (Efficacy Population)

Continuous Response	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
≥ 5 weeks	0	3 (10)	7 (23)	5 (18)
≥ 4 weeks	0	3 (10)	8 (27)	5 (18)
≥ 3 weeks	1 (3)	3 (10)	10 (33)	10 (36)

Source Data: Table 7.123

Anecdotal data regarding hemostatic challenges were collected during the study. There were four patients enrolled in study TRA 100773A who had a hemostatic challenge during the 12 week study (patient numbers 175, 395, 410 and 1065). The narratives for the hemostatic challenges are as follows:

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- Patient 175: this patient was a 53 year-old white female with ITP. Previously the patient had been treated with prednisone and WinRho for a period of approximately 10 years. During the study the patient did not receive concomitant ITP medication. The patient was on 50 mg of eltrombopag once daily. The patient's platelet counts were at baseline 17,000/mcl, 192,000/mcl at day 8 and 428,000/mcl at day 15 at which time the study medication was discontinued. One week later on day 22 the patient had an exacerbation of cholelithiasis. On day 24 the patient underwent a cholecystectomy. Post-therapy platelet counts at 2, 4 and 6 weeks posttherapy were 114,000/mcl, 100,000/mcl and 50 3000/mcl respectively. The patient did not receive rescue ITP treatment or blood product support. There was no unexpected bleeding. The patient's hemoglobin decreased 5 days postoperatively but increased to baseline within two weeks postoperatively. On day 15 prior to her operation her hemoglobin was 150g/L. Her day five, week four and six postoperative hemoglobin levels were 129 g/L, 144 g/L and 142 g/L respectively.
- Patient 395: this patient was a 52 year-old East Asian female with ITP. The patient's prior ITP treatments included corticosteroids, WinRho, danazol, vincristine and splenectomy. The patient was on danazol and prednisone with stable doses for approximately 1 year prior to study entry. The patient was treated with 50 mg of eltrombopag once daily. The patient's baseline platelet count was 10,000/mcl and by day 22 the patient's platelet count increased to 369,000/mcl and she was discontinued from study medication. Seven days after therapy the patient underwent a laparoscopic cholecystectomy. The patient had no other treatment for her ITP and experienced no bleeding complications during or after her surgery. The patient's platelet counts after therapy decreased from 319,000/mcl 14 days post eltrombopag therapy to 5000/mcl 42 days after discontinuation of eltrombopag therapy.
- Patient 10: this patient is a 36-year-old East Asian female with ITP. Her prior ITP therapies included intravenous immunoglobulin, corticosteroids, danazol, azathioprine, cyclosporine, mycophenolate mofetil and splenectomy. The patient was on steroid therapy at study entry which had been stable according to the study entry criteria. The patient was treated with placebo. The patient's baseline platelet count was 12,000/mcl. The patient had a grade 1 bleed on day eight of therapy. On day 15 the platelet counts remained unchanged and she was removed from study medication in order to receive intravenous immunoglobulin prior to glaucoma surgery. The patient received intravenous immunoglobulin on day 15 and 16. On day 19 (five days after discontinuation of eltrombopag therapy) the patient underwent glaucoma surgery with no bleeding complications. The patient's platelet count 25 days after discontinuation of the eltrombopag therapy was 26,000/mcl. The patient's platelet count 53 days after therapy was 16,000/mcl.
- Patient 1065: this patient is a 57 year-old Caucasian female with ITP. The patient's prior ITP therapy included steroids, Platelet Transfusions, WinRho and splenectomy. The patient's ITP therapy at the time of study entry was stable according to the entry criteria. The patient was treated with 75 mg of eltrombopag once daily. The patient's baseline platelet count was 10,000/mcl and it was recorded that the patient had grade 1 bleeding. On day eight of her eltrombopag therapy her platelet count was 491,000/mcl and she was discontinued from study medication. One day after she was discontinued from

eltrombopag therapy the patient had a car accident. The severity of the car accident was not reported. The patient reported no consequences from her car accident including no bruising or bleeding. Fourteen days after discontinuation of eltrombopag therapy the patient's platelet count was 4000/mcl at which time she initiated cyclophosphamide therapy with a return in her platelet count to 704,000/mcl 30 days after discontinuation of eltrombopag while on cyclophosphamide therapy.

Reviewer comment: In study TRA 100773A the primary endpoint was achieved by 11% of subjects on placebo compared to 28%, 70% and 81% of patients on eltrombopag 30 mg, 50 mg and 75 mg respectively. The odds of treatment response was statistically significant in the 50 mg and 75 mg treatment groups ($p < 0.001$) compared to the placebo.

Study TRA 100773B

A total of 114 patients were enrolled in this study (76 randomized to the eltrombopag arm and 38 randomized to placebo). The safety population and the intention to treat population each contain 114 patients. A total of 52 patients (68%) in the eltrombopag treatment arm and 30 patients (79%) in the placebo treatment arm completed the study, i.e., received all six weeks of study medication. The demographics of the patient population for study TRA 100773B is shown in the table below.

Patient Demographics for Study TRA 100773B

	PBO n = 38 (%)	Eltrombopag n = 76 (%)
Median age-yrs	51	47
Female	27 (71)	43 (57)
East Asian or South East Asian	7 (18)	12 (16)
Arabic/ North African	3 (8)	5 (7)
Caucasian	23 (61)	53 (70)
Other	2 (5)	4 (5)

The table below shows the disposition of the patients in study TRA 100773B.

Patient Disposition Study TRA 100773B

Disposition category	Number patients (n,%)		
	PBO n (%)	Eltrombopag n (%)	Total n (%)
ITT pop	38	76	114
Safety pop	38	76	114
Completed	30 (79)	52 (68)	82 (72)

study			
Completed or d/c $\geq$ 200K	31 (82)	70 (92)	101 (87)
Withdrawal	8 (21)	24 (32)	32 (28)

The reasons and number of patients withdrawn prematurely from study medication in study TRA 100773B are shown in the table below.

Reasons for Withdrawal from Study TRA 100773B

	PBO n (%)	Eltrombopag n (%)	Total n (%)
Withdraw for any reason	8 (21)	24 (32)	32 (28)
Plt > 200 K	1 (3)	18 (24)	19 (17)
AE	2 (5)	3 (4)	5 (4)
Lack of efficacy	2 (5)	0	2(2)
Other	2 (5)	0	2 (2)
Subject decision	0	1(1)	1(<1)
Protocol Violation	1 (3)	2 (3)	3(3)

In this study six patients (one patient in the placebo arm and five patients in the eltrombopag arm) had one or more major protocol violations and were excluded from the per protocol population. Two patients in the eltrombopag treatment arm were excluded due to evidence that the patient's underlying condition was not ITP and platelet count was $\geq 30,000/\text{mcl}$ at day one or within 24 hours prior to dosing on day one. Two patients both in the placebo treatment arm were identified as protocol violators after database freeze and unblinding of the treatment arms. The sponsor included these patients in the efficacy analyses including the per protocol analysis. Both of these patients had received intravenous immunoglobulin (patient 1444 received intravenous immunoglobulin on day one and patient 1399 received intravenous immunoglobulin on day seven). The types of protocol violations and the number of patients that had these protocol violations are shown in the table below for the intention to treat population.

Protocol Violations Study TRA 100773B

Protocol Violation	PBO n	Eltrombopag n
Not ITP	0	2
Plt > 30K at entry	0	2
HIV/Hep	1	0
Use of prohibited anticoagulant or diet supplement	0	0
PT/PTT or clotting disorder	0	0
Not on stable ITP con med	0	0
ITP rx with Ig	0	1

In this study all patients had ≥ 1 prior ITP treatment. The table below shows the number of prior treatments that patients had in this study.

Prior Treatments Study TRA 100773B

No of therapies	PBO n = 38 (%)	Eltrombopag n = 76 (%)
No Rx	0	0
≥ 1	38 (100)	76 (100)
≥ 2	26 (68)	56 (74)

The table below shows the disease characteristics for patients in study TRA 100773B.

Disease Characteristics Study TRA 100773B

Characteristics	PBO n = 38 (%)	Eltrombopag n = 76 (%)
ITP con meds at rnd	17 (45)	32 (42)
Splenectomy	14 (37)	31 (41)
Platelets ≤ 15 K	17 (45)	38 (50)
Platelets > 15 K	21 (55)	38 (50)

In addition, 61% of patients in both treatment groups received at least one non-ITP concomitant medication during the study. Concurrent use of prespecified ITP medications was allowed during the treatment phase of the study provided the dose and schedule had been stable for at least one month prior to entry into the study and was to remain as such during the study. In the placebo treatment group the compliance rate with the treatment regimen was 98.7% (standard deviation 3.136). In the eltrombopag treatment group the compliance rate with the treatment regimen was 98.9% (standard deviation 2.773).

The primary efficacy endpoint was defined as the proportion of patients with the platelet count $\geq 50,000/\text{mcl}$ after up to 42 days of dosing compared to the baseline platelet count of $<30,000/\text{mcl}$. Analysis of the primary endpoint demonstrated that the percentage of patients achieving the primary endpoint after six weeks of dosing was significantly greater in the eltrombopag treated group compared to the placebo treated group. The table below shows the results of the primary efficacy endpoint analysis for study TRA 100773B.

Primary Efficacy Endpoint Study TRA 100773B

	PBO n = 38	Eltrombopag n = 76
Responders at day 43	6	43
Odds ratio for Active/PBO treatments	NA	9.61
95% CI	NA	3.31, 27.86
p-value (two-sided)	NA	< 0.001

Patients with platelet counts $< 50,000/\text{mcl}$ on or after day 22 were permitted to have their dose of eltrombopag increased to 75 mg (or matching placebo). More patients (69%) in the placebo

treatment group required a dose increase at the day 22 visit compared to the eltrombopag treatment group (39%). More patients in the eltrombopag treatment group (11/35, 31%) responded after having their dose increased compared to the placebo treatment group (3/28, 11%). At the day 29 and 36 visits a similar percentage of patients had dose increases in both treatment groups. The table below shows the number of patients with a dose increase by visit in the intent to treat population.

Proportion of Patients with Dose Increase by Visit (Efficacy Population)

	Treatment Group, n (%)	
	PBO N=38	Eltrombopag N=76
Total subjects with dose increased	28 (74)	35 (46)
Day 22 Visit		
n	32	56
Dose increase	22 (69)	22 (39)
Day 29 Visit		
n	32	53
Dose increase	4 (13)	10 (19)
Day 36 Visit		
n	30	52
Dose increase	2 (7)	3 (6)

Data Source: Table 7.30

Note: n = total number of subjects still on treatment at the Study Day Visit.

The sponsor performed a logistic regression analysis of the percentage of patients with a day 43 platelet count $\geq 50,000/\text{mcl}$ and at least two times baseline using the primary data set for the efficacy population which confirmed the results of the primary endpoint and is shown on the table below.

Secondary Endpoint Platelets $\geq 50,000/\text{mcl}$ and 2x Baseline Study
TRA 100773B (Efficacy Population)

Day 43 visit	Treatment group	
	PBO n = 38 n (%)	Eltrombopag n = 74 n (%)
Responders n (%)	5 (13.5)	42 (57.5)
Odds ratio for Active/PBO treatments	NA	11.18
95% CI	NA	3.63, 34.36
p - value (two-sided)	NA	< 0.001

The baseline median platelet counts were similar in the two treatment groups. From day one to day 43 visits the median platelet counts for the eltrombopag treatment group were higher than in the placebo treatment group and the increase in the median platelet count was maintained throughout the on therapy phase of the study. For the placebo treatment group the median platelet count on each on therapy visit remained $< 26,000/\text{mcl}$. The median platelet count for the eltrombopag treatment group was $> 55,000/\text{mcl}$ beginning on day 15 and remained at this level

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or higher for the rest of the on therapy visits. The table below shows the platelet counts for all patients by visit.

Platelet Counts by Visit TRA 100773B (ITT Population)

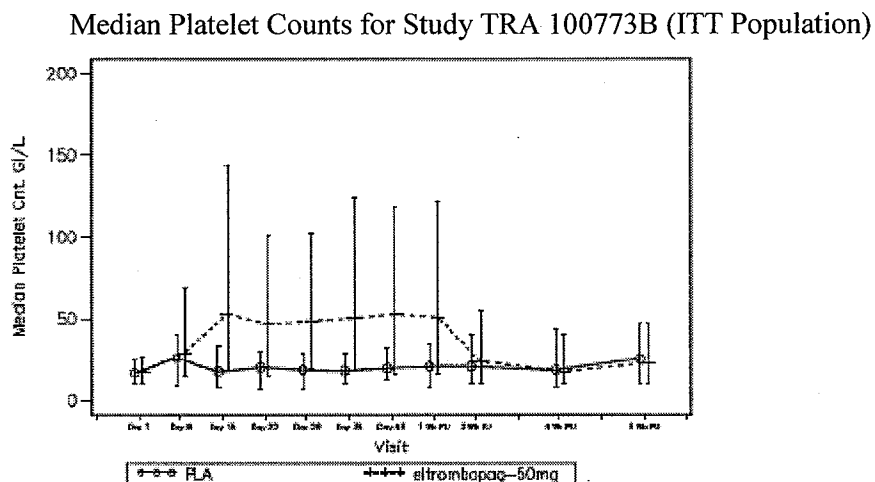
Assessment Visit	Treatment Group	
	PBO N=38	Eltrombopag N=74
Day 1 Visit		
N	29	65
Median	17.0	18.0
Min - Max	3 - 29	0 - 30 ^a
Day 8 Visit		
N	38	74
Median	25.5	29.5
Min - Max	2 - 250	0 - 216
Day 15 Visit		
N	37	72
Median	19.0	55.5
Min - Max	2 - 250	0 - 532
Day 22 Visit		
N	38	74
Median	20.5	62.0
Min - Max	0 - 250	1 - 532
Day 29 Visit		
N	38	74
Median	18.5	67.5
Min - Max	0 - 250	1 - 532
Day 36 Visit		
N	38	74
Median	18.0	67.2
Min - Max	3 - 250	1 - 532
Day 43 Visit		
N	37	73
Median	18.0	69.0
Min - Max	2 - 250	1 - 532

Data Source: Table 7.10

a. Subject 1567 had a baseline platelet count of 29.8611, which was rounded to 30 for this table.

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The median platelet counts with the 25th and 75th percentiles throughout the course of this trial are presented graphically in the figure below where plotted values represent only those who continued on treatment at that timepoint. Median platelet counts in the eltrombopag treatment group showed an elevation as early as day 15 and remained elevated through day 50. A slight decrease in the median platelet count was observed after day 15 in the eltrombopag treatment group. Platelet levels remained elevated $\geq 47,000/\text{mcl}$ throughout daily administration of eltrombopag between days 15 and 43. One week following discontinuation of eltrombopag median platelet counts remained elevated. Two weeks following discontinuation of eltrombopag median platelet counts returned to baseline levels. Median platelet counts in the placebo treatment group remained consistently lower than those in the eltrombopag treatment group through the first post-therapy visit.



Data Source: Figure 3.2
 Day 1 = Baseline, Day 8-43=On-treatment Visits, FU=Off-treatment follow up Visits

A greater percentage of patients in the eltrombopag treatment group achieved a platelet count > 200,000/mcl compared to placebo. The table below shows the number of patients with platelet counts > 200,000/mcl at day 43.

Proportion of Patients with Platelet Counts > 200,000 /mcl (Efficacy Population)

	Treatment Group	
	PBO N=38	Eltrombopag N=74
Baseline, n	37	73
Mean (SD)	16.5 (8.74)	17.1 (9.19)
Day 43 Visit		
Mean (SD)	31.1 (44.64)	115.0 (117.95)
Change from Baseline Mean (SD)	14.6 (43.19)	97.9 (115.54)
Model-adjusted Change from Baseline Mean (SE)	15.0 (15.77)	99.6 (11.27)
Mean Difference from PBO		84.6
95% CI		(46.80, 122.40)
p-value		<0.001

Data Source: Table 7.12
 SE=standard error

Patients with platelet counts < 50,000/mcl on or after day 22 were permitted to have their dose increased to eltrombopag 75 mg (or matching placebo). More patients (69%) in the placebo treatment group required a dose increase at day 22 compared to the eltrombopag treatment group (39%). More patients in the eltrombopag treatment group (11/35, 31%) responded after having their dose increased compared to the placebo treatment group (3/28, of 11%). At the day 29 and 36 visits a similar percentage of patients had dose increases in both treatment groups. The table below shows the number of patients with dose increases by visit.

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Proportion of Patients with Dose Increase TRA 100773B (Efficacy Population)

	Treatment Group, n (%)	
	PBO N=38	Eltrombopag N=76
Total subjects with dose increased	28 (74)	35 (46)
Day 22 Visit		
n	32	56
Dose increase	22 (69)	22 (39)
Day 29 Visit		
n	32	53
Dose increase	4 (13)	10 (19)
Day 36 Visit		
n	30	52
Dose increase	2 (7)	3 (6)

Data Source: Table 7.30

Note: n = total number of subjects still on treatment at the Study Day Visit

Patients with WHO bleeding scale grades 1-4 demonstrated a decreased incidence of bleeding on eltrombopag treatment relative to baseline compared to those who received placebo treatment. Of note, no patients developed grade 4 bleeding. The table below shows the WHO bleeding scale on assessment of patients at baseline, day 43, day 50 and day 57.

Number of Patients by WHO Bleeding Grade TRA 100773B (Efficacy Population)

Assessment Visit	Treatment Group, n (%)	
	PBO N=38	Eltrombopag N=74
Baseline, n	35	70
Grade 0	12 (34.3)	27 (38.6)
Grade 1 – Grade 4	23 (65.7)	43 (61.4)
Day 43 Visit, n	30	51
Grade 0	12 (40.0)	31 (60.8)
Grade 1 – Grade 4	18 (60.0)	20 (39.2)
Day 50 Visit, n	29	65
Grade 0	17 (58.6)	46 (70.8)
Grade 1 – Grade 4	12 (41.4)	19 (29.2)
Day 57 Visit, n	34	72
Grade 0	14 (41.2)	43 (59.7)
Grade 1 – Grade 4	20 (58.8)	29 (40.3)

Data Source: Table 7.24

Subgroup analyses were performed on patients based on randomization stratification variables including ITP medication at randomization, splenectomy status and platelet counts. In addition subgroup analyses were performed based upon age, sex and race. These analyses were performed on the efficacy population.

Logistic regression analysis showed no significant interaction between the response to treatment and the use of ITP medication at randomization ($p=0.766$). The table below shows the number of responders by use of ITP medication at randomization.

Proportion of Responders by Concomitant ITP Medication Use (Efficacy Population)

	Treatment Group and Use of ITP Medication at Randomization, n (%)			
	PBO N=33		Eltrombopag N=74	
	Yes	No	Yes	No
Day 43 Visit				
n	16	21	31	42
Responders	2 (12.5)	4 (19.1)	17 (54.8)	26 (61.9)

Data Source: Table 7.15

There was no significant interaction between response and splenectomy status ($p=0.747$). The table below shows the number of responders by splenectomy status at the day 43 visit.

Proportion of Responders by Splenectomy Status (Efficacy Population)

	Treatment Group and Splenectomy Status, n (%)			
	PBO N=33		Eltrombopag N=74	
	Yes	No	Yes	No
Day 43 Visit				
n	13	24	29	44
Responders	2 (15.4)	4 (16.7)	18 (62.1)	25 (56.8)

Data Source: Table 7.18

Patients were characterized by age into the following groups: 18-49 years, 50-64 years and ≥ 65 years for the analysis of responders at the day 43 visit. For all three age groups the percentages of responders in the eltrombopag treatment group were greater than the placebo treatment group with the highest percentage of responders in the ≥ 65 year age group. The table below shows the responders by age at the day 43 visit. There was no significant treatment by age interaction since the pattern of response was similar in all categories.

Proportion of Responders by Age (Efficacy Population)

Age Category	Treatment Group	
	PBO N=33	Eltrombopag N=74
18 to 49 years of age		
n	18	40
Responders, n (%)	4 (22.2)	20 (50.0)
Responders with platelets $>200 \text{ GiL}$, n (%)	0	6 (15.0)
50 to 64 years of age		
n	13	14
Responders, n (%)	1 (7.7)	9 (64.3)
Responders with platelets $>200 \text{ GiL}$, n (%)	0	5 (35.7)
≥ 65 years of age		
n	6	19
Responders, n (%)	1 (16.7)	14 (73.7)
Responders with platelets $>200 \text{ GiL}$, n (%)	1 (16.7)	7 (36.8)

Data Source: Table 7.35, Table 7.48

There was a greater percentage of responders at the day 43 visit in the eltrombopag treatment group compared to the placebo treatment group for both males and females. However a higher percentage of responses were seen in females compared to males. There were no male responders in the placebo treatment group and therefore a valid treatment by gender interaction

could not be estimated by the sponsor. The table below shows the responders by sex at the day 43 visit.

Proportion of Responders by Sex (Efficacy Population)

Sex	Treatment Group	
	PBO N=36	Eltrombopag N=74
Female		
n	26	40
Responders, n (%)	6 (23.1)	27 (67.5)
Responders with platelets >200 GiL, n (%)	1 (3.9)	14 (35.0)
Male		
n	11	33
Responders, n (%)	0	16 (48.5)
Responders with platelets >200 GiL, n (%)	0	4 (12.1)

Data Source: Table 7.34, Table 7.42

When patients were analyzed by race for response at the day 43 visit most categories had insufficient numbers of patients for statistical comparison the percentage of responders in the eltrombopag treatment group was greater than in the placebo treatment group. The numbers of responders by race at the day 43 visit is shown in the table below.

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