

PROMACTA (ELTROMBOPAG TABLETS)

FDA ONCOLOGIC DRUG ADVISORY COMMITTEE

BRIEFING DOCUMENT

TABLE OF CONTENTS

	PAGE
1. EXECUTIVE SUMMARY	4
1.1. Unmet Medical Need.....	4
1.2. Background.....	4
1.3. Efficacy.....	6
1.3.1. Short-term Dosing Studies (TRA100773A, TRA100773B, REPEAT)	6
1.3.2. Long-term Dosing Study (TRA105325/EXTEND)	7
1.4. Safety	8
1.4.1. Pivotal Short-term Dosing Studies (TRA100773A, TRA100773B)	9
1.4.2. Entire ITP Safety Database	9
1.5. Overall Benefit and Risk Assessment	10
1.6. Conclusions.....	11
2. INTRODUCTION AND BACKGROUND	12
2.1. Idiopathic Thrombocytopenic Purpura.....	12
2.2. Current Therapies and Management of Patients with ITP - Significant Unmet Medical Need	13
2.3. Rationale for Eltrombopag Development in ITP	16
2.4. Clinical Development Program.....	16
2.4.1. Phase I Studies.....	18
2.4.2. Phase II.....	19
2.4.3. Phase III.....	19
2.5. Regulatory Interactions	20
3. NON-CLINICAL TOXICOLOGY	21
4. OVERVIEW OF CLINICAL PHARMACOLOGY	21
4.1. Summary.....	21
4.2. Safety in Clinical Pharmacology Studies.....	22
5. OVERVIEW OF EFFICACY	23
5.1. Study Design and Methodology	23
5.1.1. Short-term Treatment Studies (TRA100773A, TRA100773B and REPEAT).....	23
5.1.2. Long-term Dosing Study (EXTEND)	26
5.2. Study Population	26
5.2.1. Short-term Treatment Studies (TRA100773A, TRA100773B and REPEAT).....	26
5.2.2. Long-term Treatment Study (EXTEND)	29
5.3. Efficacy Results.....	31
5.3.1. Short-term Placebo-controlled Pivotal Studies (TRA100773A and TRA100773B)	31
5.3.2. Intermittent Short-term Dosing Study (REPEAT).....	37
5.3.3. Long-term Dosing Study (EXTEND)	40
5.4. Efficacy Conclusions	48
6. OVERVIEW OF SAFETY.....	50

6.1.	Extent of Exposure in ITP Studies.....	51
6.1.1.	Exposure in the Short-term Treatment Studies.....	52
6.1.2.	Exposure in the Long-term Treatment Studies (EXTEND and RAISE)	53
6.2.	Analysis of Adverse Events.....	54
6.2.1.	Short-term Dosing Studies.....	55
6.2.2.	Long-term Dosing Studies (EXTEND and RAISE).....	56
6.3.	Serious Adverse Events and Deaths.....	56
6.3.1.	Serious Adverse Events (SAEs)	56
6.3.2.	Deaths.....	57
6.4.	AEs Leading to Withdrawal from the Study.....	59
6.4.1.	Short-term Dosing Studies (TRA100773A, TRA100773B and REPEAT)	59
6.5.	Adverse Events and Safety Assessments of Special Interest.....	60
6.5.1.	Hepatobiliary Laboratory Abnormalities	60
6.5.2.	Overall Assessment of Thromboembolic Events	63
6.5.3.	Transient Decrease in Platelet Counts	65
6.5.4.	Blood Smear and Bone Marrow Analyses	67
6.5.5.	Malignancies	72
6.5.6.	Potential Risks Based on Non-clinical Observations	73
6.5.6.1.	Cataract.....	73
6.5.6.2.	Renal-related events	75
6.5.6.3.	Skin and subcutaneous-related AEs	76
6.5.6.4.	Cardiac-related events	77
6.6.	Exposure and Safety in Other Indications.....	77
6.6.1.	Subjects with Hepatitis C – TPL102357.....	77
6.6.2.	Subjects with Cancer – SB497115/003	79
6.7.	Safety Conclusions	80
7.	RISK MANAGEMENT	82
7.1.	Overview	82
7.2.	Risk Minimization Action Plan	83
7.2.1.	RiskMAP Goals.....	84
7.2.2.	RiskMAP Objectives	84
7.2.3.	Targeted Education and Outreach.....	85
7.2.4.	Reminder Systems.....	86
7.2.5.	Performance-linked Access Tools	86
7.3.	RiskMAP Evaluations.....	86
7.4.	Additional Pharmacovigilance Activities and Targeted Studies.....	87
7.4.1.	Pharmacovigilance (Routine and Active Surveillance)	87
7.4.2.	Targeted Studies.....	87
7.5.	Summary of the Risk Management Plan.....	89
8.	BENEFIT RISK ASSESSMENT AND CONCLUSIONS	89
9.	REFERENCES	93

1. EXECUTIVE SUMMARY

1.1. Unmet Medical Need

Chronic idiopathic thrombocytopenic purpura (ITP) is an uncommon autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a chronically low peripheral blood count (<150 Gi/L). The clinical hallmark of the disease is an increased pathological tendency to bleed, spontaneously or after minimal trauma. It is widely recognized that platelet counts of <30 Gi/L are especially associated with an increased incidence of bleeding complications, such as skin, mucosal and intracerebral bleeding [George, 1996; BCSH, 2003; Cines, 2002].

All current ITP treatments (e.g. corticosteroids) address the destruction component of the disease. Most treatments (including splenectomy) for long-term chronic use have significant tolerability issues generally associated with immunosuppression, and are associated with significant morbidity, and for some agents, even mortality [Portielje, 2001]. Few of the agents have been tested in controlled clinical trials and none have demonstrated a significant reduction in the bleeding associated with the low platelet counts [Cines, 2005; George, 2004; BCSH, 2003]. The vast majority of drugs are prescribed off-label (e.g. azathioprine, danazol, vinca alkaloids and rituximab) and have variable and often only transient efficacy in patients with chronic ITP.

The day to day clinical management of patients with chronic ITP is therefore, a significant problem. There is a high unmet medical need for a safe, well-tolerated and consistently effective short-term or intermittent treatment for patients who have a transient decrease in platelet counts or need to have an increased platelet counts for procedures/surgeries. Further unmet medical need exists for tolerable, long-term chronic treatments for patients whose platelet counts are continually <30 Gi/L, current treatments are often ineffective or have side effects associated with significant morbidity and mortality.

1.2. Background

Eltrombopag is an orally bioavailable, small molecule thrombopoietin receptor (TPO-R) agonist being developed for the treatment of a variety of medical disorders associated with thrombocytopenia.

Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades similar, but not identical, to that of endogenous thrombopoietin (TPO), thus inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Daily administration of eltrombopag in healthy and thrombocytopenic humans results in a dose-dependent increase in platelet counts in the peripheral blood within 1 to 2 weeks. In addition to patients with ITP, eltrombopag has also been shown to raise platelet counts in thrombocytopenic patients with chronic hepatitis C [McHutchison, 2007].

GSK has designed the eltrombopag clinical development program to provide a new therapeutic option to previously treated patients with chronic ITP who require either short-term or long-term clinical management. Endpoints in both the short-term and long-term ITP clinical trials have focused on platelet count elevation and a reduction in bleeding.

GSK has completed the two largest placebo-controlled trials which have demonstrated short-term efficacy and safety of eltrombopag (TRA100773A and TRA100773B) in subjects with chronic ITP. In addition, an ongoing intermittent dosing study, TRA108057/REPEAT, designed in agreement with the FDA, provides efficacy and safety data supporting repetitive short-term treatments with eltrombopag.

Two ongoing long-term treatment studies, a long-term extension study (TRA105325/EXTEND) and a randomized, placebo-controlled long-term treatment study (TRA102537/RAISE), have been conducted to support a long-term treatment indication for patients with platelet counts consistently below 30Gi/L. Currently, long-term safety data is available from both trials and long-term efficacy data is available from EXTEND.

Throughout the development of eltrombopag, GSK has interacted with the FDA and reached agreements on the NDA package used to support marketing authorization.

Specific agreements reached with the FDA include:

- Agreement that there is a medical need for safe and effective agents that raise platelets for a short period of time even in the setting of a chronic disease such as chronic ITP;
- Agreement on the clinical endpoint used in the pivotal trials and that the results of the two randomized, placebo-controlled, short-term studies could provide the principle evidence of safety and efficacy for the short-term indication;
- Agreement that interim data from REPEAT and EXTEND studies will support the NDA;
- The proposed safety database is adequate for an NDA submission for the short-term treatment of ITP;

GSK and the FDA have had several discussions regarding the Risk Management Plan for eltrombopag including potential elements that may be incorporated into the proposed plan. Based on these discussions, the proposed RiskMAP includes several tools which are described later in this briefing document (Section 7.2); among the tools included is active surveillance. Additionally, the proposed RiskMAP has been designed to encompass potential risks of chronic administration of eltrombopag.

During the NDA review, GSK and the FDA have mutually raised the issue of whether data contained within the current NDA from EXTEND supports a more general ITP indication in addition to the short-term indication sought in the initial application.

1.3. Efficacy

1.3.1. Short-term Dosing Studies (TRA100773A, TRA100773B, REPEAT)

Randomized, placebo-controlled studies

- TRA100773A (N=117) and TRA100773B (N=114) were independently conducted, multi-center, randomized, double-blind placebo-controlled clinical trials designed to meet regulatory standards for demonstration of efficacy and safety in adequate and well-controlled clinical trials.
- In the 2 trials, approximately 40% of subjects were refractory following splenectomy and 60% of subjects received no concomitant ITP medication. The baseline median platelet count in the pooled analysis was 17 Gi/L and over 50% of subjects had received ≥ 3 prior therapies for their disease.
- Eltrombopag effectively and consistently raised platelet levels during short-term treatment in subjects with previously-treated chronic ITP. The odds of treatment response in the eltrombopag group relative to placebo was statistically significant ($p < 0.001$).

	TRA100773A		TRA100773B	
	Placebo	50mg	Placebo	50mg
Primary endpoint Responders with platelets ≥ 50 Gi/L at Day 43 ^a	11%	70%	16%	59%
Odds-ratio	21.96		9.61	
95% CI	(4.72, 102.23)		(3.31, 27.86)	
p-value ^b	<0.001		<0.001	

a. Platelets at treatment discontinuation for subjects who withdrew due to achieving platelet counts > 200 Gi/L.

b. One-sided for TRA100773A and two-sided for TRA100773B.

- Response to eltrombopag at any point over the entire treatment period (Weeks 2-6) was more likely compared to placebo (OR [95% CI]: 13.89 [6.59, 29.29], $p < 0.001$).
- Eltrombopag raised platelet counts relatively quickly: in both trials, $> 30\%$ of subjects responded with an increase of platelet counts ≥ 50 Gi/L by Day 8, 50% of subjects responded by Day 15, following treatment with eltrombopag 50 mg. Platelet levels remained elevated for approximately 1 week after discontinuing eltrombopag.
- In both studies, more than 50% of subjects responded with a clinically meaningful increase in platelet counts, regardless of baseline platelet counts, use of concomitant medication and splenectomy status.
- A statistically significant decrease in bleeding symptoms, measured by the WHO Bleeding Scale, was observed throughout the treatment period of the trial in patients treated with eltrombopag compared to placebo (OR=0.48; 95% CI [0.29, 0.80]); $p = 0.005$).

- Subjects treated with eltrombopag were able to effectively master hemostatic challenges (e.g., diagnostic or surgical procedures) without additional treatments to elevate their platelet counts, whereas placebo treated subjects required treatment to elevate their platelet counts.

Intermittent dosing study (TRA108057/REPEAT)

- REPEAT is a multi-center, open-label, phase II study designed to evaluate the efficacy, safety and tolerability of eltrombopag, 50 mg once daily, over 3 cycles in adult subjects with previously treated, chronic ITP. Prior to initiating the REPEAT protocol, FDA advice and input on the protocol was obtained and appropriate revisions were incorporated into the final protocol.
- The primary endpoint in REPEAT was consistency (durability of response) defined as the proportion of subjects who responded to eltrombopag treatment in Cycle 2 or 3 (given a response in Cycle 1). A response within a cycle was defined as a platelet count ≥ 50 Gi/L and at least 2x baseline (baseline is defined as Day 1 of each cycle) after up to 42 days of eltrombopag dosing.
- Sixty-six subjects were treated with eltrombopag: 33% were receiving ITP medication upon entry and 30% had been splenectomized prior to entry; the median baseline platelet count was 30 Gi/L.
- Consistent response (≥ 50 Gi/L and $\geq 2x$ baseline) to eltrombopag was observed based upon analysis of the primary endpoint. Eighty-eight percent of subjects who responded in Cycle 1, responded again in Cycle 2 or 3 (Exact 95% CI: 0.72, 0.97). Greater than 85% of subjects responded in all three cycles regardless of splenectomy status, use of concomitant ITP medications and baseline platelet count.
- Across all three cycles the percentage of subjects responding (≥ 50 Gi/L and $\geq 2x$ baseline) at each on-therapy visit was consistent. By Day 8 and Day 15 of each cycle, $>60\%$ and $>75\%$ of subjects had responded, respectively. Approximately 30% of subjects in each cycle achieved platelet counts >200 Gi/L in all 3 cycles by Day 15 of each cycle.
- Across all three cycles the median platelet count elevations were similar, both in terms of time course and magnitude, with elevations generally above 100 Gi/L from Day 8 in each cycle to 1 week after interruption of eltrombopag..
- A 50% decrease in bleeding was observed in each on-treatment period compared to baseline, confirming the inverse relationship between platelet counts and bleeding symptoms.
- Across all 3 cycles, subjects were able to effectively master hemostatic challenges (e.g., diagnostic and surgical procedures) without additional treatments to elevate their platelet counts.

1.3.2. Long-term Dosing Study (TRA105325/EXTEND)

- EXTEND is an ongoing single arm, open-label, dose-adjustment study that is evaluating the long-term safety and efficacy of eltrombopag as a treatment for patients with ITP that were previously enrolled in an eltrombopag trial (e.g.,

TRA100773A, TRA100773B, REPEAT or RAISE). This study allowed individualized dosing of eltrombopag and reduction or discontinuation of concomitant ITP medication.

- One hundred and nine patients had received eltrombopag in EXTEND at the clinical cut-off date for the NDA. The median baseline platelet count in EXTEND subjects was 18 Gi/L, 37% of subjects were receiving ITP medication at baseline and 44% were refractory following splenectomy.
- Median platelet counts rose to 87 Gi/L in the second week of treatment and generally remained ≥ 50 Gi/L throughout the trial.
- The majority of subjects (54%) had continuous uninterrupted platelet counts ≥ 50 Gi/L for at least 10 consecutive weeks, with 24% achieving continuous, consecutive elevation of platelet counts ≥ 50 Gi/L for more than 6 months.
- Although the study is not a randomized double-blind, placebo-controlled trial, this sustained clinically meaningful increase in platelet counts in this patient population is indicative of the effectiveness of eltrombopag, as there is a low natural variability of platelet counts in subjects treated with placebo as observed in the long-term romiplostim (AMG531) clinical trials [Kuter, 2008].
- Patients responded to eltrombopag regardless of baseline use of concomitant ITP medication or prior splenectomy.
- Ninety-two percent of subjects that responded in TRA100773A or TRA100773B also achieved platelet counts ≥ 50 Gi/L on EXTEND.
- The incidence of any bleeding (WHO Grades 1-4) and clinically significant bleeding (Grades 2-4) decreased by approximately 50% from baseline throughout the trial. Severity of bleeding was associated with platelet counts; subjects with platelet counts ≥ 50 Gi/L had a lower incidence of clinically significant bleeding events, compared to subjects with platelet counts < 50 Gi/L.
- In EXTEND, subjects were able to effectively master hemostatic challenges (e.g., diagnostic or surgical procedures) in general without additional treatments to elevate their platelet counts.

1.4. Safety

The safety database for eltrombopag, as agreed with the FDA, is comprised of two completed double-blind, placebo-controlled studies (TRA100773A and TRA100773B), two ongoing, single-arm, open-label eltrombopag studies, (TRA108057/REPEAT-intermittent short-term treatment and TRA105325/EXTEND- long-term treatment), and one blinded placebo-controlled study (TRA102537/RAISE- long-term treatment).

- A total of 495 patients with chronic ITP have been enrolled in eltrombopag clinical trials. Of these, 330 patients with ITP have received eltrombopag and 81, 39 and 12 patients have been exposed for at least 6, 12 and 15 months respectively (excluding subjects from the currently blinded RAISE study).

- Including an estimated two-thirds of blinded RAISE subjects who would have received eltrombopag, a total of 460 subjects with chronic ITP have been exposed to eltrombopag and >150 subjects have been exposed for at least 6 months.

1.4.1. Pivotal Short-term Dosing Studies (TRA100773A, TRA100773B)

- Eltrombopag had a well-defined safety profile in 231 subjects in the 2 pivotal trials. No clinically meaningful differences in incidence or severity of the most common ($\geq 5\%$) adverse events (AEs) were observed between subjects treated with eltrombopag 50 mg compared to placebo.
- Headache was the most commonly reported AE (eltrombopag 50 mg: 8%; placebo: 15%) followed by nasopharyngitis, nausea, fatigue and arthralgia. Nausea was the only AE with an incidence in the eltrombopag-treated subjects $\geq 5\%$ higher than for placebo-treated subjects.
- Similar incidences of SAEs (12% and 11%) and discontinuations due to AEs (7% and 5%) were observed in the placebo and eltrombopag 50mg treatment groups, respectively.
- No dose-dependent pattern of AEs was observed across the eltrombopag 30 mg, 50 mg, and 75 mg treatment groups in TRA100773A.
- Preclinical findings that indicated potential for phototoxicity, cataracts and renal tubular toxicity do not appear to translate to clinical consequences during short-term use.
- Increases in hepatobiliary laboratory values (ALT or AST $\geq 3x$ ULN; or bilirubin or alkaline phosphatase [AP] $>1.5x$ ULN) were observed in 10% of patients who received eltrombopag, compared to 8% of patients who received placebo.

1.4.2. Entire ITP Safety Database

- Across the entire program (excluding RAISE), the incidence of hepatobiliary laboratory abnormalities as defined in the draft FDA Guidance document is 9% (29/330). In the blinded RAISE study, the incidence is 10% (20/196).
- Thromboembolic events were reported during the clinical trials in patients with chronic ITP. However, the frequency (2.6%) was similar or less than that reported in the literature for patients with chronic ITP (3%) [[Aledort](#), 2004], in epidemiology studies (6.9 %) [Study [WEUKSTV1116](#)] or reported with other thrombopoietic agents (4.4 %) [[Romiplostim](#) briefing document].
- As expected following discontinuation of eltrombopag, platelet counts returned to near baseline levels. In the pivotal studies, a transient decrease in platelet counts <10 Gi/L and 10 Gi/L less than baseline was observed in patients treated with eltrombopag (10%) and those treated with placebo (6%). However, this numerical decrease was not associated with a clinically significant increase in bleeding.
- Similarly, in REPEAT and EXTEND, although some subjects had numerical decrease in platelet counts <10 Gi/L and 10 Gi/L less than baseline following discontinuation (10% and 3%, respectively) or interruption of eltrombopag (8% in

EXTEND), these decreases were not accompanied by clinically meaningful increases in bleeding symptoms or need for rescue medication.

- In the intermittent and long-term studies, evidence of potentially abnormal cells upon examination of WBC differentials prompted a peripheral blood smear. No subject had peripheral blood smear findings of clinical relevance upon re-testing.
- Bone marrow biopsies were collected from 19 patients in EXTEND patients treated with eltrombopag for >12 months. Reticulin or collagen fibers were detected in 7 patients (including one patient with pre-treatment biopsy showing reticulin fibers). There were no AE reports, clinical consequences, laboratory abnormalities or withdrawal from treatment as of 12 April 2008.
- Preclinical findings that indicated potential for phototoxicity, cataracts and renal tubular toxicity do not appear to translate into clinical consequences.

1.5. Overall Benefit and Risk Assessment

Adult chronic ITP is a serious disease, and a significant therapeutic challenge as stated in the recent editorial in *The New England Journal of Medicine*:

“Hematologists everywhere are thwarted by patients with ITP in whom every available treatment has failed to improve the platelet count” [Schwartz, 2007].

- Eltrombopag effectively and consistently raised platelet levels during short-term, intermittent and long-term treatment of patients with previously-treated chronic ITP. Clinically meaningful increases in platelet counts were observed, regardless of baseline platelet counts, use of concomitant medication and splenectomy status.
- Eltrombopag raises platelet counts relatively quickly: in all trials, >30% of subjects responded with an increase of platelet counts ≥ 50 Gi/L by Day 8, 50% of subjects by Day 15, following 50 mg eltrombopag. The maximal response can be expected to occur within 3 weeks of daily administration. Platelet levels remained elevated for approximately 1 week after stopping medication.
- Eltrombopag could be an excellent option from a clinical perspective to plan invasive procedures or operations with a lead time of 2 to 3 weeks.
- Consistent response to eltrombopag was observed following 3 intermittent treatment cycles: 88% of subjects who responded in Cycle 1, responded again in Cycle 2 or 3 (Exact 95% CI: 72%, 97%).
- During long-term treatment, the majority of subjects (54%) had clinically meaningful periods of continuous uninterrupted platelet counts ≥ 50 Gi/L for at least 10 consecutive weeks, with 24% achieving continuous, consecutive elevation of platelet counts ≥ 50 Gi/L for more than 6 months.
- In all studies, improvements in platelet counts were accompanied with a decrease in bleeding symptoms, as measured by the WHO Bleeding Scale, and subjects treated with eltrombopag were able to effectively master hemostatic challenges without additional treatments to elevate their platelet counts.

- The following are considered identified risks of eltrombopag: hepatobiliary laboratory abnormalities and transient decreases in platelet counts following discontinuation of treatment.
- Potential risks of eltrombopag are: thromboembolic events; cataracts; photosensitivity; and renal tubular toxicity.
- The potential for off-label use in indications where the benefit risk ratio of eltrombopag has not been adequately studied, especially given the effectiveness of eltrombopag and the oral formulation.
- Potential risks of other thrombopoietic agents include bone marrow fibrosis; and hematologic malignancies.
- GSK has proposed a comprehensive risk management plan to both assess and mitigate identified and potential risks of short- and long-term treatment with eltrombopag. The key features of the eltrombopag RiskMAP include:
 - Targeted education for patients, healthcare professionals, and pharmacies;
 - Acknowledgement by patient and physician of information in the patient information leaflet and prescribing information, respectively;
 - Limits on drug supply with each prescription;
 - Mandatory enrollment of prescribers and patients into a safety tracking database;
 - Controlled distribution by only authorized pharmacies; and
 - Active surveillance by collection and analysis of safety information.

1.6. Conclusions

Eltrombopag is a new therapeutic option for the most difficult to treat ITP population—those who have a great unmet medical need both for rapid, predictable and safe short-term platelet count elevations and for long-term chronic treatment because of platelet counts consistently $<30\text{Gi/L}$. Based on the data from the ITP clinical development program, the clear clinical benefit (as indicated by increases in platelet count, reduction in bleeding and successful mastering of homeostatic challenges) of eltrombopag has been demonstrated. A positive benefit risk relationship exists supporting the approval of eltrombopag for the treatment of subjects with chronic ITP.

GSK believes that eltrombopag can address the unmet medical need for the short-term treatment of patients with chronic ITP. TRA100773A and TRA100773B are the two largest randomized, placebo-controlled studies performed to date in adults with chronic ITP and platelet levels $<30\text{Gi/L}$. The REPEAT study has provided efficacy and safety data supporting the use of eltrombopag as an intermittent, short-term treatment of patients with chronic ITP. The results from these 3 studies have clearly demonstrated the efficacy and safety of eltrombopag as a short-term therapeutic option for previously treated chronic ITP, justifying the indication statement proposed in the NDA:

"PROMACTA 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."

In the large, open-label extension study, EXTEND, safety and efficacy data from over 200 and 100 patients, respectively, have been analyzed. The data from the EXTEND study clearly demonstrate the long-term and durable effect of eltrombopag on platelet counts and reduction in bleeding, addressing the unmet medical need for a new long-term treatment option for patients with chronic ITP. These data, and the data from REPEAT, support the chronic use of eltrombopag. Although the short-term indication was the indication sought in the initial application, the FDA stated during the review process that a general or chronic indication may be considered. As such, GSK has tailored the risk management plan to encompass chronic administration of eltrombopag. Therefore, the indication for consideration could be:

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

The efficacy of PROMACTA for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) was established in short-term (6-week) controlled trials.

The effectiveness of PROMACTA in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials."

2. INTRODUCTION AND BACKGROUND

2.1. Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a low peripheral blood platelet count (<150Gi/L). As indicated by the term 'idiopathic', the exact etiology of ITP is unknown. Thrombocytopenia is a frequent finding in several medical disorders; as such, the diagnosis of ITP remains one of exclusion [BCSH, 2003]. Routine diagnostic tools are blood count, peripheral blood film, patient history, physical examination and prompt response to high dose steroids.

Literature on the epidemiology of ITP is limited; however, it clearly demonstrates the orphan nature of the disease. The overall incidence of ITP among adults ranges from 1.6 to 6.6 per 100,000 persons/year of observation [Neylon, 2003; McMillan, 1997]; adult prevalence estimates range from 9.5 to approximately 23.6 per 100,000 persons [Segal, 2006; Feudjo-Tepie, 2008]. The variability in the estimated prevalence is likely to reflect differences in data sources and analytical methods used in studies. GlaxoSmithKline (GSK) has conducted an internal epidemiological study to estimate the year 2006 prevalence of chronic adult ITP using a large US claims database (Integrated Healthcare Information Services, IHCIS) [Deitz, 2006]. The projected number of patients with ITP in the US in 2006 was estimated to be 85,000 (prevalence of 28.37 per 100,000) to 108,000 (prevalence of 36.37 per 100,000) cases, depending on the stringency of the

inclusion criteria (i.e., whether the second occurrence of ITP diagnosis in a patient record had to be within six months of the first).

The clinical hallmark of the disease is an increased, pathological tendency to bleed, spontaneously or after minimal trauma. In principle, there is an inverse relationship between platelet count and bleeding risk - the lower the platelet count, the higher the risk of bleeding complications, although other factors, such as age, also affect the individual bleeding risk in patients with chronic ITP. It is widely recognized that platelet counts of <30Gi/L are especially associated with an increased incidence of bleeding complications [George, 1996; BCSH, 2003]. Hemorrhages in patients with such low platelet count may be mild, like petechiae and bruising, but severe hemorrhages such as hemoptysis, gastrointestinal (GI) and genitourinary tract bleeding are also well known complications of the disease [Cines, 2002]. The most serious and life-threatening complications are intracranial hemorrhages, which are associated with significant mortality [Mueller-Eckhardt, 1977; Cohen, 2000; McCrae, 2001]. The frequency of death from hemorrhage in patients with platelet counts <30Gi/L is estimated to be between 1.6 and 3.9% per patient-year, although the frequency is influenced by age, and degree and duration of thrombocytopenia [Cohen, 2000]. The morbidity and mortality observed in patients with ITP is not exclusively a consequence of low platelet counts, but is also related to side effects of current treatment modalities that have serious sequelae [Portielje, 2001].

2.2. Current Therapies and Management of Patients with ITP - Significant Unmet Medical Need

ITP can be classified either as acute (≤ 6 months) or chronic (> 6 months) in nature. In the adult (chronic) form of the disease, most patients have chronic thrombocytopenia with platelet counts <150 Gi/L. Onset is often insidious and spontaneous recovery is uncommon. Disease management in individual patients with chronic ITP may differ throughout the course of the disease and may include emergency, short-term and long-term treatment. Emergency treatment is necessary in patients presenting with severe bleeding. Short-term treatment may be implemented in patients with chronic ITP to manage a hemostatic challenge. A hemostatic challenge may be a transient decrease in platelet count (e.g. due to a viral infection or normal disease fluctuation), or a bleeding episode that does not require emergency treatment. Additional scenarios where short-term treatment may be necessary are to raise platelets above a threshold required for a medical intervention or preventative procedure where bleeding is predictable (such as colonoscopy, surgical or dental procedures), or to allow patients to participate in activities that may increase their chance of bleeding, for example vocational and physical recreation activities. The goal of short-term treatment of chronic ITP is to elevate the platelet count for the duration of the hemostatic challenge (typically 2-3 weeks). The agents used in short-term treatment should allow some degree of predictability of effect as well as have a reasonably high likelihood of elevating the platelet counts to the desired levels. Patients with chronic ITP and platelets routinely less than 30 Gi/L may require long-term treatment to increase platelet counts and thereby reduce the number of bleeding events and the need for rescue medications. Long-term treatment may also allow subjects to resume normal occupational or physical work-related activities, where a low platelet count can be a hindrance or even prohibitive due to the risk of bleeding. The goal of

long-term treatment is to provide the minimal amount of therapy required to maintain platelet levels in a safe or adequate range (e.g. 50-400 Gi/L).

The choice of disease management in patients with chronic ITP is based primarily on platelet count and severity of bleeding. All current clinical guidelines issued by hematologic societies focus on the platelet count as the key parameter to assess the bleeding risk in patients with ITP. In general, medical treatment to elevate platelet counts to a safe range is recommended if patients' platelet count is below <30Gi/L [George, 1996; BCSH, 2003; Stevens, 2006]. However, it is important to realize that these guidelines are based on only Level III or IV evidence (Table 1).

Table 1 Definition of the Level of Evidence for ITP Therapies

Level of Evidence	Study Design
I	Randomized, low false positive and negative errors
II	Randomized, high false positive and negative errors
III	Non-randomized, with concurrent control
IV	Non-randomized, with historical controls
V	Case series without control or expert opinion

The various treatments available for emergency, short-term and long-term disease management of patients with chronic ITP are listed (Table 2). First- and second-line treatments are delineated, as well as treatments for patients whose disease has either relapsed or is refractory. The need for a short-term treatment for patients with a chronic disease, such as ITP, may seem counterintuitive. However, short-term disease management is in agreement with treatment guidelines which suggest that the goal of disease management in patients with chronic ITP is to maintain platelet counts at a 'safe' level with the smallest amount of intervention possible and the least associated risks [Cines, 2005]. In fact, the only drugs currently approved for use in the US for the treatment of ITP are the intravenous immunoglobulins (anti-D and IVIg), which have short-term efficacy and were approved on the basis of Level III evidence [Bussel, 1991]. These studies demonstrated elevation of platelet counts for a short-term period in patients with chronic ITP; of note, no evidence for effect in re-treatment was demonstrated in the trials supporting the marketing applications for these agents. First-line treatments of adult ITP with corticosteroids or intravenous immunoglobulins are effective in increasing platelet counts in about 70% of adult ITP patients, approximately 50% of whom will achieve platelet counts in the normal range.

Table 2 Disease Management of Chronic ITP

Initial Diagnosis		Relapsed/Refractory Disease	
First Line Treatments	Level of Evidence	Second Line Treatments	Level of Evidence
Corticosteroids	II	Splenectomy	V
Anti-D	III	Alternate Therapies: Vinca alkaloids, Danazol, High dose corticosteroids, Azathioprine, Cyclophosphamide, Cyclosporine A, Dapsone	V
IVIg	III		

However, many patients suffer relapse when the steroid dose is lowered, or when regular administration of IVIg is discontinued; the side effects of steroids and the other drugs (medications listed in [Table 2](#)) are also often rate-limiting for further treatment.

According to published treatment guidelines, second-line therapy typically involves splenectomy, the safety and efficacy of which has not been assessed in well-controlled clinical studies in patients with chronic ITP, and is primarily based upon Level V evidence [[George](#), 1996; [BCSH](#), 2003]. Splenectomy is considered an effective therapy in many patients, leading to an increase in the platelet count in approximately 50 to 80% of patients depending upon the severity of the disease. Disadvantages and side effects include surgical complications, relapse, and impaired ability to clear infections, with a markedly higher risk of developing sepsis for the rest of their lives and the need to take prophylactic antibiotics [[Andres](#), 2003; [Park](#), 2000].

When patients are refractory to treatment with corticosteroids, IVIg and/or splenectomy, they are treated with alternative therapies, including vinca alkaloids, danazol, high dose corticosteroids, azathioprine, cyclophosphamide, cyclosporine A and dapsone. There are only very limited data to support the use of these agents (Level V evidence) and, according to US and European guidelines, these agents are only recommended for use in patients when there is an urgent need to elevate the platelet count [[George](#), 1996; [BCSH](#), 2003]. However, due to the poor tolerability and variable, unpredictable efficacy of these therapies, physicians and patients often decide for a “watch and wait” approach and institute active treatment only when an increase in bleeding becomes significant and/or the platelet count drops to dangerously low levels. The treatment of chronic ITP is therefore, often a significant clinical management problem, as all treatments to date are associated with significant morbidity, and for some agents, mortality [[Portielje](#), 2001].

Transient decreases in platelet count can occur in patients with ITP, especially during or shortly after viral infections. In such instances, short-term treatment is being used, such as treatment with IVIg, steroids or blood products like platelet transfusions. The same strategy is used to raise platelets above a threshold for medical intervention or preventative procedures where bleeding is predictable (such as colonoscopy, surgical or dental procedures), or to allow patients to participate in activities that may increase their chance of bleeding, for example, physical work, sports or some recreational activities. However, due the poor tolerability and variable, unpredictable efficacy of these therapies,

a significant unmet medical need exists for reliable, safe and proven treatments for these short term treatment periods. Similarly, new therapeutics in ITP for long-term treatment should raise platelet counts and reduce or eliminate bleeding symptoms, thus decreasing the need for currently used therapies, such as platelet transfusions, chronic corticosteroids, repeated IVIg infusions, cytotoxic ITP drugs and splenectomy and their associated morbidities.

2.3. Rationale for Eltrombopag Development in ITP

Eltrombopag olamine (SB-497115-GR), the bis-monoethanolamine salt form of eltrombopag, is an orally bioavailable, small molecule thrombopoietin receptor (TPO-R) agonist being developed for the treatment of a variety of medical disorders associated with thrombocytopenia. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades similar to but not identical to that of endogenous thrombopoietin (TPO) and thrombopoietic mimetics [i.e., no protein kinase B (AKT) activation], inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag has no effect on platelet aggregation or activation *in vitro* nor does it prime platelets for activation or aggregation. Daily administration of eltrombopag in healthy and thrombocytopenic humans results in a dose-dependent increase in platelet counts in the peripheral blood within 1 to 2 weeks. Therefore, eltrombopag is an attractive candidate for diseases like chronic ITP where decreased platelet production is a component of the disease.

The rationale for the development of eltrombopag in chronic ITP is twofold. First, published data suggest that reduced platelet production is a component of ITP [Aledort, 2004; McMillan, 2005]. Kinetic studies using 111-Indium labeled platelets revealed that platelet turnover is low in some patients with ITP, particularly in those with severe disease [Heyns, 1986]. This might reflect an impairment of megakaryocytes in ITP [Cooper, 2006], that leads to premature death of these platelet-producing cells in the bone marrow. In one study, apoptosis has been observed in about 78% of megakaryocytes in patients with ITP [Houwerzijl, 2004]. Furthermore, *in vitro* studies have found evidence for deficient platelet production in patients with ITP [Bellucci, 1991; Parker, 1998].

Second, endogenous TPO levels in patients with chronic ITP are often paradoxically normal or below normal, suggesting that megakaryopoiesis could be stimulated further by a thrombopoietic agent [Aledort, 2004]. Therefore, thrombopoietic agents might represent a new treatment option due to their ability to increase platelet production in patients with chronic ITP. Stimulating megakaryocyte growth and differentiation within the patient's own bone marrow should lead to a rise in the patient's own platelets, thereby avoiding exposure to donated platelets and immunosuppressive agents. Recent published studies have provided strong Level 1 evidence demonstrating the effectiveness of investigational agents targeting thrombopoiesis, such as eltrombopag, at elevating platelet counts in patients with chronic ITP [Bussel, 2007; Kuter, 2008].

2.4. Clinical Development Program

There are several types of disease management approaches that patients with chronic ITP may need: emergency, short-term and long-term maintenance treatment. The

administration of eltrombopag may be an effective management option for short-term treatment and long-term maintenance treatment, but is not an option for emergency treatment of chronic ITP patients, as elevation of platelets is not observed until 7-14 days after initiating treatment with eltrombopag.

GSK has designed the eltrombopag clinical development program to provide a new therapeutic option to previously treated patients with chronic ITP who require either short-term or long-term clinical management, following standard first- and second-line treatment options (Table 2), consistent with ITP patient populations with the greatest unmet medical need.

The efficacy and safety of eltrombopag for the short-term treatment of patients with chronic ITP has been clearly demonstrated, principally based on the results of two pivotal studies, TRA100773A and TRA100773B (Table 3). GSK designed these studies to allow dosing with study medication for up to 6 weeks. These studies are the two largest randomized, placebo-controlled studies performed to date in adults with previously-treated chronic ITP and platelet levels $<30\text{Gi/L}$, with 117 and 114 such subjects treated, respectively. The studies demonstrate that eltrombopag could effectively, consistently and quickly (within 1 to 2 weeks) raise platelet levels during short-term treatment in adults who had relapsed after, or were refractory to, standard ITP therapy. These improvements in platelet counts were accompanied by a decrease in bleeding symptoms as measured by the World Health Organization (WHO) Bleeding Scale.

In addition, an ongoing intermittent dosing study, TRA108057/REPEAT, designed in collaboration with the FDA, provides efficacy and safety data supporting repetitive short-term treatments with eltrombopag.

Two ongoing long-term treatment studies, a long-term extension study (TRA105325/EXTEND) and a pivotal long-term treatment study (TRA102537/RAISE), have been conducted to support the long-term treatment indication for patients who need prolonged treatment because of the increased risk of bleeding problems associated with platelet counts persistently below 30Gi/L . Currently, long-term safety and efficacy data is available from the EXTEND trial. Additional long-term safety data (blinded) are provided from the ongoing placebo-controlled study, RAISE.

Table 3 Pivotal and Supportive ITP Studies

GSK Study Number	Study Design	Dose Groups	Baseline Platelet Count	Status at NDA
Pivotal Studies				
TRA100773A	Double-blind, randomized, placebo-controlled	eltrombopag 30mg, 50mg, 75mg, and placebo	<30Gi/L	Completed
TRA100773B	Double-blind, randomized, placebo-controlled	eltrombopag 50mg, and placebo	<30Gi/L	Completed
Supportive Studies				
TRA108057/ REPEAT	Open-label, single-group, repeat-dose	eltrombopag 50mg	≥20Gi/L to ≤50Gi/L	Ongoing
TRA105325/ EXTEND	Open-label, long-term dose-adjustment extension for subjects who were enrolled in previous studies	eltrombopag 50mg starting dose	N/A	Ongoing
TRA102537/ RAISE	Double-blind, randomized, placebo-controlled long-term dosing	eltrombopag 50mg starting dose and placebo	<30Gi/L	Ongoing

N/A = not applicable

2.4.1. Phase I Studies

The goal of the clinical pharmacology evaluation of eltrombopag was to support the short-term treatment of ITP patients by describing the pharmacokinetics (PK) of eltrombopag in healthy subjects, in ITP patients, and in special populations, by providing information on drug-drug interactions, giving guidance on dosing eltrombopag with regard to food, supporting the commercial formulation through bioequivalence testing, and summarizing the pharmacodynamic response and the safety of eltrombopag in healthy adult subjects, including the results of a thorough QTc study.

These objectives were met through the conduct of 13 phase I clinical pharmacology studies, including single-dose and repeat-dose escalation studies in healthy subjects enrolled in the UK, US and Japan (Table 4).

Table 4 Clinical Pharmacology Package

Study	Description
497115/001	First administration to humans (3 to 9mg)
497115/002	Single and repeat dose escalation (placebo, eltrombopag 5 to 75mg QD) and CYP450 cocktail drug interaction
TRA102860	PK & safety of higher doses (placebo, eltrombopag 50 to 200mg QD) and Definitive QTc (placebo, moxifloxacin, eltrombopag 50 and 150mg QD)
TRA102861	Mass balance (14C radiolabel study)
TRA105122	Pivotal bioequivalence (Phase II vs Phase III tablets, 25mg and 50mg)
TRA102863	Relative bioavailability (tablets)
497115/005	Relative bioavailability (tablets vs capsules) and Food effect (standard high-fat breakfast)
TRA104631	Food effect (low-calcium meals) and Antacid drug interaction
TRA105120	Rosuvastatin drug interaction
TRA103452	Hepatic impairment
TRA104412	Renal impairment
TRA104603	Single dose escalation in Japanese subjects (placebo, eltrombopag 30-100mg)
TRA105580	Single and repeat dose escalation in Japanese subjects (placebo, eltrombopag 25-75mg)

2.4.2. Phase II

The phase II program was initiated to determine the safety and efficacy of eltrombopag treatment in several indications. Of the three exploratory phase II programs, one was in ITP (Study TRA100773A), with the others being in hepatitis C associated thrombocytopenia (Study TPL102357) and chemotherapy-induced thrombocytopenia (Study SB497115/003). TRA100773A was a global, randomized, double-blind, placebo-controlled, dose-ranging phase II trial in previously-treated adults with chronic ITP and platelets <30Gi/L. Randomization was stratified by splenectomy status, use of concomitant ITP therapy and platelet counts ≤ 15 Gi/L.

An additional phase II study, REPEAT, is a global open-label study in adults with chronic ITP. REPEAT was designed to assess the efficacy and safety of repeated, short-term (up to 6 week) dosing of eltrombopag. The REPEAT study is a supportive safety and efficacy study for the short-term indication and is currently ongoing.

2.4.3. Phase III

Currently, three phase III studies of eltrombopag in ITP have been initiated in patients with chronic ITP. Brief descriptions of the trials are given below:

- TRA100773B was a global, randomized, double-blind, placebo-controlled phase III trial in adults with chronic ITP and platelets <30Gi/L. The patient population and stratification variables were the same as in TRA100773A.

- TRA105325/EXTEND is a global, open-label extension study open to adults with ITP who have previously participated in a prior eltrombopag study. This study was designed to assess the long-term safety and tolerability of eltrombopag, as well as the durability of response over long-term treatment periods. EXTEND is a supportive long-term safety and efficacy study and is currently ongoing.
- TRA102537/RAISE is a global, randomized, double-blind, placebo-controlled phase III trial in adults with chronic ITP and platelets <30Gi/L. This study was designed to assess efficacy and safety of eltrombopag in adults with chronic ITP dosed for up to 6 months. For this application, RAISE is a supportive long-term safety study and is currently ongoing.

2.5. Regulatory Interactions

Throughout the development of eltrombopag, GSK has interacted with the FDA and reached agreements on key points such as clinical study design and the NDA package used to support marketing authorization.

Early in the clinical development program for eltrombopag, the FDA and GSK reached agreement that platelet counts are the basis for treatment decisions in ITP and therefore, clinically important increases in platelet count are an acceptable endpoint for standard approval. However clinical outcomes, such as bleeding, should be evaluated as secondary endpoints.

Additionally, there was agreement that there is a medical need for safe and effective agents that raise platelets for a short period of time even in the setting of a chronic disease such as chronic ITP.

These interactions and agreements were the basis for the placebo-controlled study designs of studies TRA100773A and TRA100773B. These two adequate and well-controlled studies are the primary basis of evidence used to support the indication sought in the NDA.

In discussions with the FDA regarding the data package needed to support marketing authorization, it was noted by the agency that data from the repetitive dosing trial, REPEAT, would be important in the assessment of efficacy. GSK and the FDA reached agreement that interim data from the REPEAT and EXTEND studies will support the NDA. It was also agreed that the proposed safety database was adequate for an NDA submission for the short-term treatment of ITP.

GSK and the FDA have had several discussions regarding the Risk Management Plan for eltrombopag including potential elements that may be incorporated into the proposed plan. Based on these discussions, GSK submitted to the FDA a revised Risk Management Plan which included a Risk Minimization Action Plan (RiskMAP). The proposed RiskMAP includes several tools which are described later in this briefing document (Section 7.2); among the tools included is active surveillance. Additionally, the proposed RiskMAP has been tailored towards the chronic administration of eltrombopag.

During the NDA review, GSK and the FDA have mutually raised the possibility of whether data contained within the current NDA from EXTEND supports a general ITP indication in addition to the short-term indication sought in the initial application.

3. NON-CLINICAL TOXICOLOGY

Eltrombopag has undergone a comprehensive non-clinical toxicological evaluation to support its clinical use. The toxicity profile of eltrombopag has been defined in single and repeat dose toxicity studies of up to 13 weeks in mice, 28 weeks in rats and 52 weeks in dogs. In addition, repeat dose toxicity was assessed in 2 year carcinogenicity studies in mice and rats. The principal non-clinical toxicology findings associated with eltrombopag treatment include cataracts (in rodents), evidence of renal toxicity (in rodents) and hepatotoxicity (in rodents and dogs). In vitro, phototoxicity has been observed, however, no in vivo phototoxicity has been observed in rodents following acute and chronic exposure to eltrombopag and light. There was no evidence of immunotoxicity associated with eltrombopag treatment. Eltrombopag was not teratogenic or carcinogenic.

4. OVERVIEW OF CLINICAL PHARMACOLOGY

4.1. Summary

- Eltrombopag was well-tolerated in 568 subjects who received eltrombopag (doses ranged from 3 mg to 200 mg for up to 10 days) in 13 Phase 1 studies, including 524 healthy adult subjects, 25 subjects with hepatic impairment, and 19 subjects with renal impairment.
- Eltrombopag demonstrated no effect on cardiac repolarization in a definitive QTc study.
- In healthy adult subjects, a dose-dependent increase in platelet count was observed after 5 to 10 day repeat dosing with eltrombopag. Maximum platelet counts were observed approximately 2 weeks after initiating dosing, and returned to within normal limits within 2 weeks after discontinuation of eltrombopag dosing.
- In healthy subjects, peak concentrations occurred between 2 and 6 hours after dosing. The plasma elimination half-life of eltrombopag was approximately 21 to 32 hours.
- Pharmacokinetics are linear, plasma eltrombopag AUC(0- τ) increased in a dose proportional manner between 50 mg and 200 mg. C_{max} increased in a dose proportional manner between 50 mg and 150 mg. In addition, eltrombopag demonstrated time-invariant pharmacokinetics (PK).
- Administration of eltrombopag with a standard high-fat meal that contained calcium or with polyvalent cation-containing antacid significantly reduced plasma eltrombopag exposure whereas, low-calcium meals (<50 mg calcium), regardless of fat content, had minimal impact on plasma eltrombopag exposure. Therefore, eltrombopag should be administered fasted or with low-calcium foods only. A 6-

hour separation between the time of administration of eltrombopag and products containing polyvalent cations (e.g., antacids, mineral supplements, and dairy products) is recommended.

- Eltrombopag inhibited OATP1B1 in vitro. In healthy adult subjects, eltrombopag increased exposures of rosuvastatin, an OATP1B1 substrate. Plasma rosuvastatin C_{max} increased 2.03 fold and AUC(0-∞) increased 55%. A reduced dose of rosuvastatin should be considered when co-administered with eltrombopag and careful monitoring for side effects should be undertaken.
- Based on data from a phase I clinical study, no clinically significant interactions are expected when eltrombopag and CYP substrates, inducers, or inhibitors are co-administered.
- Eltrombopag PK is not expected to be altered to a clinically significant extent when co-administered with UGT inhibitors. In vitro, eltrombopag was an inhibitor of several UGT enzymes, with greatest potency for UGT1A9 (IC₅₀ of 3.0 μM, 1.3 μg/mL).
- In healthy adult subjects and in patients with idiopathic thrombocytopenia purpura (ITP), plasma eltrombopag AUC(0-τ) was approximately 70-80% higher in subjects of East Asian heritage as compared to non-Asian patients who were predominantly Caucasian. A dose reduction should be considered for East Asian patients.

4.2. Safety in Clinical Pharmacology Studies

Eltrombopag was well tolerated when administered as single and repeat doses for up to 10 days in healthy adult subjects. Eltrombopag demonstrated a lack of effect on cardiac repolarization in a definitive QTc study.

The occurrence of AEs was low across all studies included in the integrated safety analysis of Phase I studies. The most frequently reported AE was headache, which was reported in all dose groupings including placebo.

No deaths were reported in any clinical pharmacology study. One serious adverse event (SAE) was reported by a healthy subject who experienced severe abdominal pain, and noted by the investigator as probably related to a viral infection. The SAE was considered by the investigator to be not related to study medication.

5. OVERVIEW OF EFFICACY

5.1. Study Design and Methodology

5.1.1. Short-term Treatment Studies (TRA100773A, TRA100773B and REPEAT)

Placebo-controlled pivotal studies (TRA100773A and TRA100773B)

Overview of study design

Protocol TRA100773 was a double-blind, randomized, placebo-controlled study that consisted of two separate and independent pivotal studies, TRA100773A and TRA100773B. TRA100773A was a global dose-ranging phase II trial that used an adaptive sequential design and TRA100773B was a global, phase III trial. Both were independently conducted, multi-center, randomized, double-blind, placebo-controlled clinical trials designed to meet regulatory standards for demonstration of efficacy and safety in adequate and well-controlled clinical trials. In both studies, randomization was stratified based upon splenectomy status, use of concomitant ITP medications and baseline platelet count ($\leq 15 \text{Gi/L}$).

The adaptive sequential design of TRA100773A allowed efficient identification of efficacious doses through two planned interim analyses, while minimizing the risk of exposing subjects to doses that were ineffective, or presented safety concerns. In TRA100773A, adult subjects with chronic ITP were randomized on a 1:1:1:1 basis to placebo, or one of three different doses of eltrombopag (30mg, 50mg or 75mg) to determine the optimal phase III starting dose, based on efficacy, safety and PK data. Based on the results of TRA100773A, subjects with near identical eligibility criteria were randomized on a 1:2 basis to placebo:eltrombopag 50mg, the starting dose in TRA100773B.

Treatment was administered for up to 6 weeks. This duration of treatment was chosen to allow 2-3 weeks for platelet response to occur and to allow subjects to have an elevated platelet count for another 3-4 weeks. This duration of elevation is consistent with that provided by currently available therapies approved for the short-term elevation of platelet counts, the intravenous immunoglobulins [Bussel, 1991].

Efficacy and safety assessments were scheduled every week during the on-therapy period, and at 1 (TRA100773B only), 2, 4 and 6 weeks during the post-therapy period to assess the durability of the platelet response.

During the treatment period, study medication was to be discontinued in subjects who attained a platelet count $>200 \text{Gi/L}$. This platelet count threshold was chosen for two reasons. First, discontinuation of study medication at this platelet count threshold was instituted to reduce the risk of subsequent thrombocytosis. Second, subjects had achieved a 'safe/adequate' platelet count, which was sufficient to allow subjects to master a hemostatic challenge over the succeeding days.

Efficacy endpoints

The primary endpoint in both TRA100773A and TRA100773B was the proportion of subjects who responded with a platelet count of ≥ 50 Gi/L after up to 42 days of dosing (compared to a baseline count of < 30 Gi/L). Subjects who withdrew from the study due to achieving a platelet count > 200 Gi/L, as required by the protocol, were also considered to be responders in the primary dataset. In agreement with the FDA, subjects who discontinued treatment prior to Day 43 for any reason other than platelet count > 200 Gi/L were classified as non-responders, irrespective of their last on-therapy platelet count. In the subsequent sections on efficacy summarizing the results from these studies, the term “Day 43” is denoting the day the subject was taken off the therapy which could include any day before Week 6 due to platelet counts > 200 Gi/L as mentioned above. Days 50, 57, 71 and 85, are days +7, +14, and so on, after the subject comes off therapy. In the safety sections, however, the terms “Day 43, 50, 57, 71 and 85” denote the actual day on study, which are Day 43, Day 50, Day 57, and so on. Supportive data analyses were performed using a dataset of all platelet counts during the treatment and follow-up periods, whether or not the subject discontinued treatment prematurely (observed dataset). Platelet count elevation was chosen as the primary endpoint of the study as patients with chronic ITP are treated routinely based on their platelet counts due to the inverse relationship between platelet counts and risk of bleeding. The threshold of ≥ 50 Gi/L was chosen as it is above the recommended platelet count for the majority of minor surgical procedures [BCSH, 2003], and is consistent with the precedent set with the approval of anti-D and IVIg for the treatment of patients with ITP.

Secondary endpoints included: platelet count of ≥ 50 Gi/L and 2x baseline count (TRA100773B only); shift from baseline platelet count of < 30 Gi/L to ≥ 50 Gi/L over Weeks 2-6 of treatment using a repeated measures model for binary data with generalized estimating equations (GEE) methodology [Liang, 1986] to estimate the regression model parameters (TRA100773B only); pharmacodynamics (median platelet counts); and bleeding signs and symptoms. Bleeding symptoms were assessed using the WHO Bleeding Scale in both studies; in Study TRA100773B, bleeding was also assessed by the ITP Bleeding Score.

Intermittent dosing study (REPEAT)

Overview of study design

REPEAT was a multi-center, open-label, single-group, repeat-dose, phase II study designed to evaluate the efficacy, safety and tolerability of eltrombopag, 50mg once daily, over 3 cycles in adult subjects with previously treated, chronic ITP. A cycle was defined as an eltrombopag on-therapy period of up to 6 weeks and an off-therapy period of up to 4 weeks.

Patients with chronic ITP were eligible provided they had received at least one prior ITP therapy (including medical treatments and/or splenectomy) and had platelet counts of ≥ 20 Gi/L and ≤ 50 Gi/L. As in the pivotal studies, potential confounding variables (such as concomitant ITP medication) were to be kept constant throughout REPEAT. As off-therapy periods were necessary to examine eltrombopag re-treatment, subjects entering

REPEAT were required to have a higher baseline platelet count than in the pivotal studies to minimize any potential bleeding risk by participation in the study. Subjects who did not respond in Cycle 1 were not eligible to continue into Cycle 2.

Platelet count data was collected weekly throughout the study and used as part of the assessment of efficacy, including intra-individual comparisons of platelet rise, peak, duration of response and trough. To confirm the clinical benefit associated with elevation in platelet counts, bleeding signs and symptoms were assessed at each visit and hemostatic challenges were captured. Additionally, use of rescue therapy was collected and summarized.

Prior to initiating the REPEAT protocol, FDA advice and input on the protocol was obtained (Agency response 06Dec2006) and appropriate revisions were incorporated into the final protocol.

In REPEAT, the dosing regimen was similar to TRA100773B, the pivotal Phase III study. Within each cycle, subjects were dosed for up to 6 weeks with an allowance for a dose increase on or after Day 22 if a subject's platelet count did not rise above 50Gi/L. Subjects were to discontinue dosing with eltrombopag if a platelet count >200Gi/L was attained. The off-therapy period of 4 weeks for each cycle was chosen as platelet counts for the majority of TRA100773A and TRA100773B patients had returned to baseline levels by Week 2 or 3 following discontinuation of eltrombopag. The off-therapy period of up to 4 weeks also allowed analysis of transient decrease in platelet counts after discontinuation of eltrombopag.

A placebo control arm was not included in this study because few subjects who received placebo would respond and proceed beyond Cycle 1 of the study, making comparisons of efficacy and safety of eltrombopag versus placebo over repeated cycles of administration impossible. As such, REPEAT was designed as a single arm, open-label study.

Efficacy endpoints

The primary endpoint in REPEAT was consistency (durability of response) defined as the proportion of subjects who responded to eltrombopag treatment in Cycle 2 or 3 (given a response in Cycle 1). A response within a cycle was defined as a platelet count $\geq 50\text{Gi/L}$ and at least 2x baseline (baseline is defined as Day 1 of each cycle) after up to 42 days of eltrombopag dosing.

Secondary efficacy endpoints included: proportion of subjects achieving a platelet count of $\geq 50\text{Gi/L}$ and at least 2x baseline in at least 80% of assessments during Weeks 2-6 of study treatment in each cycle; analysis of platelet count at baseline, peak and trough levels over 3 cycles; proportion of subjects requiring rescue treatment over the 3 cycles; and the incidence and severity of bleeding signs and symptoms. Bleeding symptoms were assessed using the WHO Bleeding Scale and the ITP Bleeding Score.

In addition, diagnostic and/or surgical procedures scheduled during the treatment periods of REPEAT were collected with regard to type and bleeding complications.

5.1.2. Long-term Dosing Study (EXTEND)

Overview of study design

EXTEND was a single arm, open-label, dose-adjustment study designed to evaluate the safety and efficacy of eltrombopag as a treatment for subjects with ITP who have previously been enrolled in an eltrombopag trial (e.g., TRA100773A, TRA100773B, RAISE or REPEAT). This study allowed dosing of eltrombopag at an individualized dose for each subject. In addition, the ability to reduce the dose of concomitant ITP medication in the presence of eltrombopag, while maintaining platelet counts $\geq 50\text{Gi/L}$ was assessed. This study also examined retreatment with eltrombopag in subjects who had received eltrombopag in their previous study.

Efficacy endpoints

The primary endpoint for the EXTEND study was safety. Secondary efficacy endpoints included: proportion of subjects maintaining a platelet count $\geq 50\text{Gi/L}$ and $\geq 30\text{Gi/L}$; proportion of subjects who received eltrombopag in a prior study and responded again in EXTEND; maximum duration of platelet response ($\geq 50\text{Gi/L}$ and $\geq 30\text{Gi/L}$); ability to reduce or taper off concomitant ITP medications; proportion of subjects needing rescue treatment; and the incidence and severity of bleeding signs and symptoms. Bleeding symptoms were assessed using the WHO Bleeding Scale and the ITP Bleeding Score. In addition, diagnostic and/or surgical procedures scheduled during EXTEND were collected with regard to type and bleeding complications.

5.2. Study Population

5.2.1. Short-term Treatment Studies (TRA100773A, TRA100773B and REPEAT)

Placebo-controlled pivotal studies (TRA100773A and TRA100773B)

A total of 231 subjects with chronic ITP were randomized and treated in the pivotal studies TRA100773A (N=117; includes 59 subjects from 30 and 75 mg groups), and TRA100773B (N=114). Data for subjects enrolled in the placebo and 50mg treatment groups from each study were pooled. The percentage of subjects who discontinued treatment prematurely from the studies was higher in the eltrombopag 50mg group compared to the placebo group, due primarily to the subjects achieving a platelet count $>200\text{Gi/L}$. Subjects who achieved platelet counts $>200\text{Gi/L}$ were discontinued from study medication as required by the protocols, for 2 reasons: 1) the treatment goal, a rapid rise in platelets has been achieved; and 2) to minimize the risk of thrombocytosis with platelet count $>400\text{Gi/L}$ (Table 5).

Table 5 Subject Disposition in the Pivotal Studies

	Pooled 773A + 773B	
	PBO N=67	50mg N=106
Completed study, n (%)	52 (78)	69 (65)
Completed study or discontinued prematurely due to platelets \geq 200 Gi/L, n (%)	54 (81)	98 (92)
Discontinued prematurely from study medication for any reason, n (%)	15 (22)	37 (35)
Platelets >200Gi/L	2 (3)	29 (27)
Adverse event	5 (7)	5 (5)
Protocol violation	1 (1)	2 (2)
Lack of efficacy	2 (3)	0
Subject decision	2 (3)	1 (<1)
Other	3 (4)	0

Baseline demographic and disease characteristics

Demographic characteristics of the patient populations in both studies were similar and typical of the chronic ITP patient population studied in the literature [Cines, 2002] (Table 6). The median age in both studies was approximately 50 years and approximately 60% of subjects were female. The majority of subjects in both studies were White (73%), followed by Asian (20%). There was a difference between the two studies in the percentage of female and percentage of Asian subjects randomized to the eltrombopag 50mg treatment group. In TRA100773A, a higher percentage of subjects randomized to the 50mg treatment group were female (70%) and Asian (40%), compared to the percentage of female (57%) and Asian (16%) subjects randomized to the 50mg treatment group in TRA100773B.

Table 6 Demographic Characteristics for the Pivotal Studies

	Pooled 773A + 773B	
	PBO N=67	50mg N=106
Age, yrs		
Median	46.0	46.5
Min – Max	18-85	19-84
Sex, n (%)		
Female	43 (64)	64 (60)
Male	24 (36)	42 (40)
Race, n (%)		
African American/African	1 (1)	1 (<1)
American Indian/Alaskan Native	2 (3)	4 (4)
Asian	10 (15)	24 (23)
White	51 (76)	76 (72)
Other/Mixed	3 (4)	1 (<1)

Key baseline disease characteristics were similar between Studies TRA100773A and TRA100773B (Table 7) and subjects enrolled in both trials were representative of the previously-treated chronic ITP population described in the literature with a great unmet medical need [George, 1996; BCSH, 2003; Cines, 2002]. The median baseline count was 17 Gi/L in the placebo treatment group versus 17.5 Gi/L in the eltrombopag 50 mg treatment group. The severity of the disease in the patient population is indicated by the fact that approximately 40% of subjects were refractory following splenectomy with baseline platelet counts <30 Gi/L. Approximately 60% of subjects in both treatment arms were not taking ITP medications at time of randomization, which indicates that the currently available treatment options were either ineffective, or the risks of the current treatment options were considered higher than the spontaneous increased bleeding risk in this patient population. These patient characteristics are a reflection of the disease severity and are indicative of a patient population with a significant unmet medical need.

Table 7 Baseline Disease Characteristics for the Pivotal Studies

	Pooled 773A + 773B	
	PBO N=67	50mg N=106
Use of ITP medication at randomization, n (%)		
Yes	23 (34)	44 (42)
No	44 (66)	62 (58)
Splenectomy status, n (%)		
Yes	28 (42)	46 (43)
No	39 (58)	60 (57)
Baseline platelet count, n (%)		
≤15Gi/L	31 (46)	50 (47)
>15Gi/L	36 (54)	55 (52)

Substantial proportions of subjects in each treatment group had ≥3 prior ITP therapies (Table 8), with proportions being higher for the 50mg subjects (57%) compared to placebo subjects (45%). Corticosteroids were the most commonly reported prior ITP medication taken by 76-83% of subjects in each treatment group in Studies TRA100773A and TRA100773B, followed by IVIg (~40%), danazol and rituximab (both ~20%).

Table 8 Number of Prior ITP Therapies Received by Subjects in the Pivotal Studies

ITP Therapies	Pooled 773A + 773B	
	PBO N=67	50mg N=106
No prior therapies, n (%)	1(1) ^a	0
≥1 prior therapy, n (%)	66(99)	106(100)
≥2 prior therapies, n (%)	47(70)	80(75)
≥3 prior therapies, n (%)	30(45)	60(57)
≥4 prior therapies, n (%)	21(31)	42(40)
≥5 prior therapies, n (%)	15(22)	26(25)

a. Subject had a history of chronic corticosteroid use recorded under ocular risk factors in the eCRF

Intermittent dosing study (REPEAT)

Sixty-six subjects were treated with eltrombopag as of the 14 September 2007 cut-off date for this efficacy analysis. At that time, 33 subjects were ongoing in the study, 19 (29%) had completed treatment and 14 subjects had discontinued from eltrombopag prematurely. The most common reason for premature discontinuation was platelet counts >200Gi/L in Cycle 3 (8 subjects, 12%) followed by subject decision (2 subjects, 3%) and 1 subject (2%) each for the following: AE, lack of efficacy, relocation and platelet counts \geq 50Gi/L for 14 weeks after completion of eltrombopag dosing in Cycle 1.

Baseline demographic and disease characteristics in REPEAT

The demographic characteristics of the 66 subjects in REPEAT were similar to those observed in the pivotal short-term studies. The median age of patients in the REPEAT study was 50.5 years of age and the majority of patients were female (68%). The majority of patients enrolled were White Caucasian (71%) and East Asian (15%).

As expected based upon protocol entry criteria requiring higher entry platelet counts (20 Gi/L to 50 Gi/L) than in the pivotal studies (<30Gi/L), key baseline disease characteristics were somewhat different between subjects in the REPEAT study and those in the pivotal studies. Compared to 42% of subjects in the pivotal studies (eltrombopag 50 mg treatment group), 33% of subjects in REPEAT were receiving ITP medication at baseline. Also, 30% of subjects in REPEAT were splenectomized, compared with 43% in the pivotal studies had a previous splenectomy. In REPEAT, 44% of subjects had platelet counts between 20 and 30Gi/L, and 47% had platelet counts from >30 to 50Gi/L.

All subjects in REPEAT reported previous treatment with ITP medications and as observed in the pivotal studies, corticosteroids were the most commonly reported prior ITP medications taken by subjects in REPEAT (77%), followed by IVIg (39%) and rituximab (21%). Approximately 40% of subjects had received \geq 3 prior ITP therapies.

5.2.2. Long-term Treatment Study (EXTEND)

Of the 117 subjects enrolled in EXTEND as of the NDA cut-off for this efficacy analysis, 109 subjects were included in the ITT population (Table 9). In EXTEND, the most common reason for withdrawal from the study was lack of efficacy (11%).

Table 9 Withdrawal of Subjects in EXTEND

	EXTEND
	N=109
Withdrawal for Any Reason, n(%)	31 (28)
Lack of efficacy	12 (11)
Subject decision	8 (7)
Adverse event	7 (7)
Protocol violation	1(<1)
Non-compliance	1(<1)
Other	2 (2)

NOTE: Subjects in EXTEND were not withdrawn from the study due to platelet counts greater than 200Gi/L, in contrast to the pivotal studies. Subjects who achieved a platelet count >200Gi/L were to decrease the dose or frequency of eltrombopag.

Baseline demographic and disease characteristics

Demographic characteristics in EXTEND were generally similar to characteristics in the pivotal studies. The median age of patients in the EXTEND study was 47 years of age and the majority of patients were female (64%). The majority of patients enrolled were White Caucasian (61%) and East Asian (17%) (Table 10).

Table 10 Demographic Characteristics in EXTEND (ITT Population)

	EXTEND
	N=109
Age, yrs	
Median	47.0
Min - Max	19-82
Sex, n (%)	
Female	70 (64)
Male	39 (36)
Race, n (%)	
African American/African	1 (<1)
American Indian or Alaskan Native	5 (5)
Asian - East Asian	19 (17)
Asian - South-East Asian	2 (2)
Asian - Central/South Asian	3 (3)
White - Arabic/North African	12 (11)
White - White/ Caucasian/European	67 (61)
Other/Mixed	0

Baseline characteristics in EXTEND were similar to those in the pivotal studies, with the exception that 31% of subjects had baseline platelet counts ≥ 30 Gi/L. EXTEND entry criteria did not contain a maximum platelet count as one of the key secondary endpoints was to reduce the use of concomitant ITP medications. In EXTEND, 44% of subjects were splenectomized upon entry into the study and 63% of subjects were not receiving concomitant ITP medications at baseline (Table 11).

Table 11 Baseline Disease Characteristics in EXTEND

	EXTEND N=109
Use of ITP medication at randomization, n (%)	
Yes	40 (37)
No	69 (63)
Splenectomy status, n (%)	
Yes	48 (44)
No	61 (56)
Baseline platelet count, n (%)	
<15Gi/L	49 (45)
≥15Gi/L	60 (55)
<30Gi/L	76 (70)
≥30-50Gi/L	18 (17)
>50Gi/L	15 (14)

All subjects enrolled into EXTEND reported previous treatment with ITP medications and as observed in the pivotal studies, corticosteroids were the most commonly reported prior ITP medications in EXTEND subjects (77%), followed by IVIg (40%), danazol (24%), rituximab (24%) and anti-D (23%). Approximately 50% of subjects had received ≥3 prior ITP therapies and 30% had received ≥5 prior therapies.

5.3. Efficacy Results

5.3.1. Short-term Placebo-controlled Pivotal Studies (TRA100773A and TRA100773B)

Primary endpoint

The primary endpoint (shift from baseline platelets <30Gi/L to platelets ≥50Gi/L) was achieved in both pivotal studies during up to 6 weeks of short-term treatment ([Table 12](#)).

In TRA100773A, the primary endpoint was achieved by 11% of subjects on placebo, compared to 28%, 70% and 81% of subjects on eltrombopag 30mg, 50mg and 75mg, respectively. The odds of treatment response was statistically significant in the 50mg and 75mg groups ($p<0.001$) compared to placebo.

In TRA100773B, the primary endpoint was achieved by 16% of subjects in the placebo, compared to 59% of subjects in the eltrombopag treatment arm. The odds-ratio of treatment response to placebo was statistically significant ($p<0.001$). The results of these two pivotal studies provide Level I (randomized, double blind, placebo-controlled) evidence demonstrating a predictable, significant elevation of platelet counts to safe platelet levels in this disease setting.

Table 12 Primary Endpoint - Pivotal Studies (Efficacy Population)

	TRA100773A		TRA100773B	
	PBO N=29	50mg N=30	PBO N=38	50mg N=76
Efficacy Population, N	27	27	38	74
Platelets \geq 50 Gi/L at Day 43 ^a , n (%)	3 (11.1)	19 (70.4)	6 (16.2)	43 (58.9)
Odds ratio ^a	21.96		9.61	
95% CI	(4.72, 102.23)		(3.31, 27.86)	
p-value ^b	<0.001		<0.001	

a. The odds ratio indicates the odds of responding to eltrombopag compared to placebo.

b. One-sided for TRA100773A and two-sided for TRA100773B.

In TRA100773B, subjects with platelet counts $<$ 50Gi/L on or after Day 22 were permitted to have their dose increased to eltrombopag 75mg (or matching placebo). More subjects (69%) in the placebo treatment group required dose increases at the Day 22 Visit or afterwards compared to the eltrombopag treatment group (39%). An additional 11 patients (31%) responded after having their dose increased to 75 mg, compared to 3 patients in the placebo treatment group (11%).

Primary endpoint by baseline disease characteristics and demographics

In both studies, subjects in all randomization strata (splenectomy status, use of concomitant ITP medication and baseline platelet count) responded to eltrombopag, indicating that eltrombopag is able to raise platelet counts across all subgroups. There was:

- No difference in the primary endpoint between splenectomized (59%) and non-splenectomized patients (64%); $p=0.661$;
- No difference in the primary endpoint between patients on concomitant ITP medications (60%) and those not on concomitant ITP medications (64%); $p=0.893$; and
- No significant difference in the primary endpoint based upon baseline platelet counts: 46% response for patients with platelets $<$ 15Gi/L and 77% response for patients with platelets \geq 15Gi/L; $p=0.443$.

When the primary endpoint was analyzed by the subgroups of age, race and sex, a similar response to treatment was observed for each subgroup, confirming that eltrombopag is able to elevate platelet levels in subjects regardless of age, sex or race.

Additional platelet count analyses

Platelet count responses were analyzed over the entire treatment period, as well as response at each single (weekly) time point. An additional analysis was performed to analyze response using a repeated measures model for binary data (GEE) incorporating all the platelet count measurements over Weeks 2 to 6 (Table 13). The results obtained in both studies confirmed that subjects treated with eltrombopag 50mg were significantly

more likely to have platelet counts ≥ 50 Gi/L at any point over the entire treatment period than subjects who received placebo ($p < 0.001$).

A small absolute increase in platelet counts (e.g., from 10 Gi/L to 20 Gi/L) can mean the difference between experiencing bleeding symptoms and being symptom free for patients with chronic ITP. Therefore, the percentage of subjects whose platelet count at Day 43 was at least 2 times baseline, but not necessarily ≥ 50 Gi/L, was analyzed. A statistically significant treatment effect was observed for the eltrombopag treatment groups in both studies compared to placebo ($p < 0.001$).

Response was also analyzed based upon achieving a platelet count ≥ 50 Gi/L and $\geq 2x$ baseline at Day 43 (Table 13). The pattern of response was similar to the primary efficacy analysis (Table 1), with a statistically significant treatment effect compared to placebo ($p < 0.001$) in both studies.

A greater number of subjects achieved a platelet count > 200 Gi/L in the eltrombopag 50mg treatment groups ($\geq 25\%$) compared to placebo ($< 4\%$) in Study TRA100773A and in Study TRA100773B in the primary datasets (Table 13). Per protocol, these subjects discontinued study medication and were considered responders for the analysis of the primary dataset.

Table 13 Summary of Response Parameters - Pivotal Studies

	TRA100773A		TRA100773B	
	Placebo	50mg	Placebo	50mg
Efficacy Population	N=27	N=27	N=38	N=74
Response Analysis				
Odds of responding in Weeks 2 – 6, GEE analysis	29.84		8.79	
95% CI	(9.57, 93.00)		(3.54, 21.86)	
p-value ^a	< 0.001		< 0.001	
Platelet count				
2x baseline at Day 43, n (%)	5 (18.52)	22 (81.48)	7 (18.92)	51 (69.86)
Odds ratio	21.62		10.43	
95% CI	(5.21, 89.70)		(3.89, 27.95)	
p-value ^a	< 0.001		< 0.001	
Platelet pharmacodynamics				
Platelets > 200 Gi/L, n (%)	1 (3.7)	10 (37.0)	1 (2.7)	18 (24.7)
Median platelet count at Day 43 (Observed data), Gi/L	16	66	20	53
Min – max	4 – 70	2 – 258	2 – 120	4 – 268

a. One-sided in TRA100773A and two-sided in TRA100773B.

Median platelet counts in subjects treated with eltrombopag 50mg were consistently ≥ 50 Gi/L from Day 15 and at each subsequent on-therapy assessment when the platelet count data for the pivotal studies were pooled (Figure 1). The full treatment effect of eltrombopag on platelet count was seen within 2 to 3 weeks of daily treatment, with the majority of responders in the eltrombopag 50 mg group having achieved a near maximal

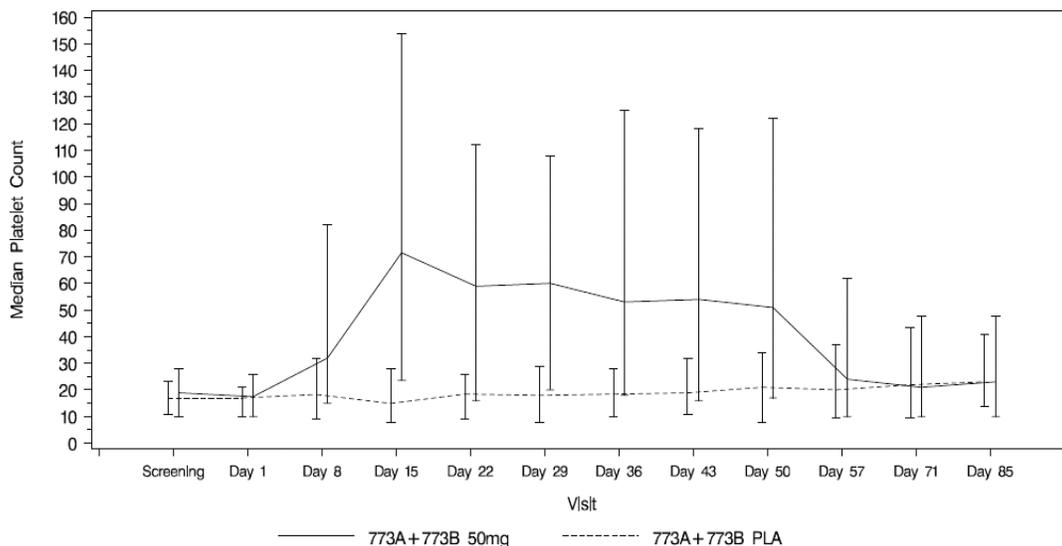
platelet count response by this time point. TRA100773A and TRA100773B had similar results following administration of eltrombopag 50 mg, with >30% of patients responding with an increase of platelet counts ≥ 50 Gi/L by Day 8, and 50% of patients responding by Day 15 in both trials.

In contrast, median platelet counts in the placebo treatment groups did not rise above 30 Gi/L at any point during the trials. Clinically, this distinction is critical as persistently low platelet counts of <30 Gi/L are associated with an increased incidence of spontaneous and induced bleeding, such as bruising, mucosal bleeding and intra-cranial hemorrhage [Cines, 2002].

The median platelet levels remain elevated (>50 Gi/L) throughout daily administration of 50mg eltrombopag (Days 15-43) in the pooled data. On Day 43 (the last day of treatment), median platelet counts were 66Gi/L and 53Gi/L in the eltrombopag 50 mg arms in TRA100773A and TRA100773B, respectively. In contrast, Day 43 median platelet counts were 16 and 20Gi/L in the placebo treatment arms in TRA100773A and TRA100773B, respectively (Table 13).

TRA100773B included a visit one week after discontinuation of study medication (Day 50). Median platelet counts in the 50mg treatment group remained elevated one week after discontinuation of eltrombopag; however, within two weeks following discontinuation of eltrombopag, median platelet values in the eltrombopag 50 mg treatment groups in both studies returned to baseline levels. There was no drop in the median platelet levels below the baseline platelet count levels at any time during the follow up period.

Figure 1 TRA100773A and TRA100773B Median Platelet Counts (Pooled Data)



Note: Bars represent the 25th to 75th percentiles for each treatment group.

Analyses of Bleeding

The most important clinical benefit of raising platelet count in patients with severe thrombocytopenia is a decrease in the risk of bleeding. In the pivotal studies, the analysis of bleeding across all eltrombopag trials was three-fold:

- Bleeding adverse events were captured as part of the standard safety evaluation of subjects in the clinical studies to evaluate safety and efficacy of eltrombopag for short-treatment of chronic ITP;
- The WHO Bleeding Scale, historically the most widely accepted tool by clinicians to assess bleeding symptoms, was used in eltrombopag trials to assess the severity and extent of bleeding at each visit on- and off-therapy during the pivotal trials; and
- Medical procedures (surgical, dental, and preventative) and associated outcomes were prospectively collected in Study TRA100773B and collected retrospectively in Study TRA100773A.

WHO Bleeding Scale

The WHO Bleeding Scale has 5 grades: Grade 0 - no bleeding; Grade 1 –petechiae; Grade 2 - mild blood loss; Grade 3 - gross blood loss; and Grade 4 - debilitating blood loss. To analyze the data, subjects' assessments were summarized into categories: no bleeding (Grade 0), any bleeding (Grade 1 to Grade 4) and clinically significant bleeding (Grade 2 to Grade 4).

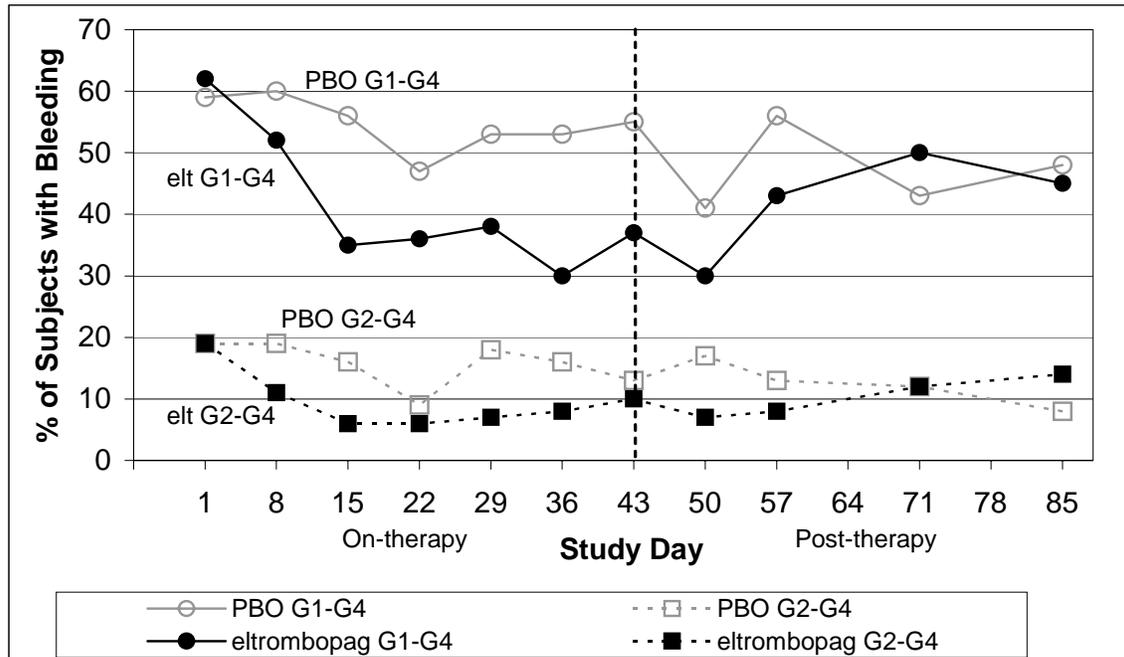
A statistically significant reduction in the proportion of subjects with any bleeding at Day 43 in the eltrombopag-treated subjects compared to subjects in the placebo treatment group (OR=0.34, p=0.018) was observed in the pooled pivotal data, by logistic regression analysis adjusted for study, use of ITP medication at baseline, splenectomy, baseline platelet count and WHO Bleeding Grade at baseline. Additionally, a lower proportion of eltrombopag subjects had any bleeding over the course of their treatment (Day 8 up to Day 43) compared to subjects in the placebo treatment group (OR=0.48, p=0.005).

In both trials, a decreased incidence of any bleeding (Grade 1 to Grade 4) was observed relative to baseline in subjects who received eltrombopag (Figure 2). At the baseline visit, 62% of subjects treated with eltrombopag 50mg and 59% of subjects treated with placebo reported any bleeding. At the Day 43 Visit, 37% of subjects treated with eltrombopag reported any bleeding, compared to 55% of subjects treated with placebo.

As expected, given that platelet counts remain elevated in approximately 50% of patients 1 week after discontinuation of eltrombopag, the proportion of subjects with any bleeding remained lower one week after discontinuation in the eltrombopag treatment group (Figure 2). Two weeks after discontinuation of study medication, the proportion of subjects in both pivotal studies with any bleeding was similar in the eltrombopag treatment groups compared to placebo.

Similarly, a reduction in the percentage of subjects with clinically significant bleeding (WHO Grade 2-4) compared to baseline in the eltrombopag treatment groups was observed on treatment and one week after discontinuation from eltrombopag.

Figure 2 Percentages of Subjects with Any Bleeding or Clinically Significant Bleeding in the Pivotal Studies - Pooled Data (Observed Data)



Subjects With Hemostatic Challenges

Data regarding hemostatic challenges were collected retrospectively in TRA100773A and prospectively in TRA100773B.

Seven subjects faced a hemostatic challenge during the observation period of the pivotal trials (Table 14). Four subjects received eltrombopag, three at 50mg (baseline platelets 10Gi/L, 17Gi/L and 25Gi/L) one at 75mg (baseline platelets 10Gi/L) and three subjects received placebo (baseline platelets 12Gi/L, 18Gi/L and 27Gi/L). Each eltrombopag subject successfully mastered the hemostatic challenge (two surgeries, teeth extraction and car accident) without needing rescue medication or having any bleeding complications. In contrast, 2 of the 3 placebo subjects required IVIg to elevate their platelet counts prior to the procedure.

Table 14 Summary of Hemostatic Challenges in TRA100773A and TRA100773B by Subject

Treatment	Hemostatic Challenge	Platelets pre/post, (Gi/L)	Rescue Treatment	Bleeding (Y/N)
Eltrombopag				
	Cholecystectomy	428/114	None	N
	Laposcopic cholestectomy	369/319	None	N
	Teeth extracted	80/82	None	N
	Car accident	491/557	None	N
PBO				
	Trabulectomy of the right eye	12/26	IVIg 3 + 4 days prior to procedure	N
	Total hip replacement	25/86	IVIg x 2 days, platelet transfusions	NA
	Extirpation of a 'papillomatic change' in her throat	36/32	Transexamic acid	N

5.3.2. Intermittent Short-term Dosing Study (REPEAT)

The REPEAT trial is ongoing; efficacy data presented are as of the 14 September 2007 clinical cut-off for the NDA submission.

Primary endpoint

The primary endpoint in REPEAT was the proportion of subjects who achieved platelets ≥ 50 Gi/L and at least 2x baseline in Cycle 2 or 3, given they achieved this response in Cycle 1. In this study, response was defined differently than in the pivotal studies, due to different baseline platelet count requirements in the studies. In REPEAT, baseline platelet counts were to be between 20 and 50 Gi/L (compared to < 30 Gi/L in the pivotal studies) and response was defined as at least 50 Gi/L and ≥ 2 x baseline.

Subjects who responded in Cycle 1 were eligible for treatment in Cycles 2 and 3. Of the 51 subjects in the ITT population who achieved platelet counts ≥ 50 Gi/L and at least 2x baseline in Cycle 1, 33 and 16 were evaluable for response in Cycles 2 and 3, respectively (Table 15). The rest of the 51 subjects were still on-therapy in Cycle 2 or Cycle 3 at the time of this analysis.

The analysis of the primary endpoint demonstrated that 88% of subjects who responded in Cycle 1 responded again in Cycle 2 or 3. There is 95% confidence that the true proportion of subjects who will respond again in Cycle 2 or 3 (given a response in Cycle 1) is between 72 and 97%. Thus, the primary endpoint was achieved even though the study was still ongoing at the time of this analysis.

Thirteen of the 16 subjects evaluable in all 3 cycles (81%) responded in all 3 cycles (Exact 95% CI: 54%, 96%).

Table 15 Primary Endpoint - REPEAT

	Eltrombopag 50mg (N= 51)
Response in Cycle 1	51
Evaluable in Cycle 2 or 3, n	33
Responders in Cycle 1 and in Cycle 2 or 3, n(%)	29 (88)
Proportion	0.88
95% CI for Proportion (Exact Methods)	(0.72, 0.97)
Evaluable in Cycle 2 and 3, n	16
Responders in Cycle 1 and in Cycle 2 and 3, n(%)	13 (81)
Proportion	0.81
95% CI for Proportion (Exact Methods)	(0.54, 0.96)

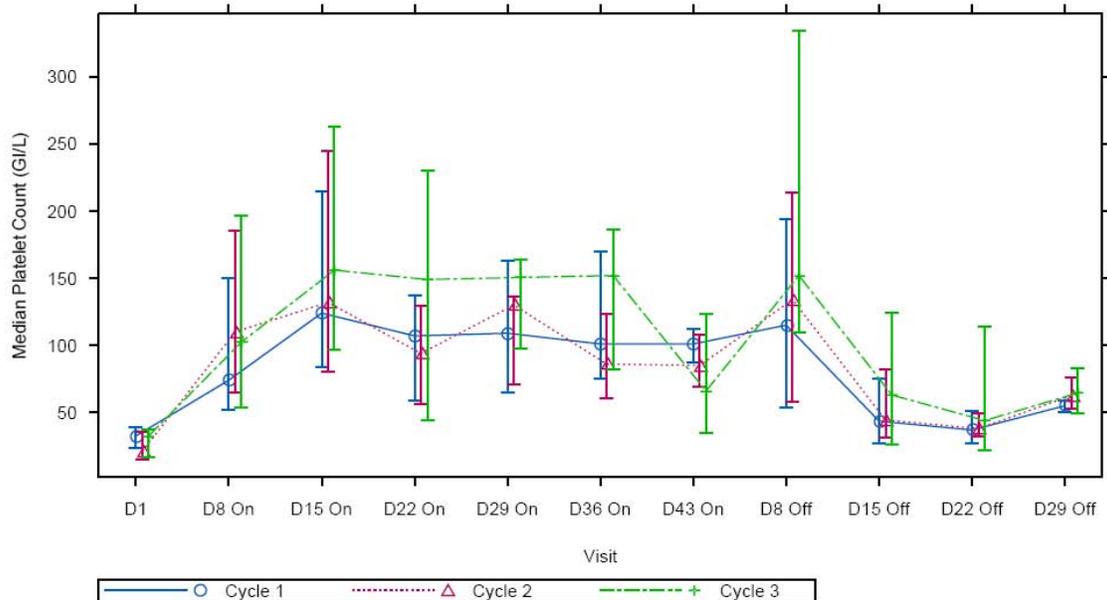
Consistency of response was observed regardless of demographic characteristics (age, sex and race) and baseline disease characteristics (splenectomy status, use of concomitant ITP medications and baseline platelet count) when the primary endpoint was analyzed by subgroups.

Additional platelet count analyses

Across all three cycles, the median platelet counts at baseline of each cycle were below 35 Gi/L (Figure 3). No consistent decrease in median platelet counts on Day 1 on-therapy was observed in Cycles 2 and 3 compared to Cycle 1. Elevation in median platelet counts was observed by Day 8 of each cycle, with the median platelet counts of 74, 110 and 102.5 Gi/L observed in Cycles 1, 2 and 3, respectively. By Day 15, median platelet counts were 124, 132 and 156 Gi/L in each cycle, respectively.

Similar to the results in the pivotal studies, median platelet counts remained >100Gi/L across all three cycles of treatment 1 week after discontinuation of eltrombopag. Two weeks after discontinuation, platelet counts in each cycle returned to near baseline levels. There was no decrease in median platelet levels below baseline at any time during any of the 3 follow-up periods in the study.

Figure 3 Median Platelet Counts by Visit Across Cycles (Observed data) REPEAT



Analyses of Bleeding

WHO Bleeding Scale

At baseline in Cycles 1, 2 and 3, the percentage of subjects who had any bleeding (Grades 1-4) reported was 49%, 59% and 32 %, respectively.

No Grade 3 or 4 bleeding was reported during the study as of the clinical cut-off. In each cycle, the number of subjects with any bleeding and clinically significant bleeding decreased during the on-therapy treatment period, starting within one week on-therapy in each cycle.

As expected during the off-therapy period of each cycle, bleeding tended to increase following discontinuation of eltrombopag in line with the decrease of platelet counts during the off-therapy periods. As the study is still ongoing, the numbers of subjects contributing to each visit, especially in Cycle 3 is relatively low at the time of this analysis.

Hemostatic Challenges

Seven subjects experienced at least one hemostatic challenge during REPEAT (Table 16). None of these subjects required additional treatment to elevate their platelet count before or after the procedure. There was no abnormal bleeding reported during or after the procedures, and no subject required rescue medication indicating that the eltrombopag stimulated platelets worked normally and provided clinical benefit to the subjects. It can be safely assumed that the subjects undergoing colon polypectomy, TUR of the prostate

or cardiac catheterization either could not have had the procedures or would have needed rescue medication to allow the procedures to be performed if they had not been treated with eltrombopag.

Table 16 Summary of Hemostatic Challenges in REPEAT by Subject

Procedure	Platelets (Gi/L), pre/post	Rescue	Bleeding
Endoscopic sinus surgery	83/359	No	Post procedural hemorrhage (Grade 1) 'bloody nasal discharge post surgery' ^a
Cardiac catheterization	178/101	No	No
Colonoscopy	101/112	No	No
Tooth extraction	150/128	No	No
Transurethral resection of the prostate	126/261	No	No
Colonoscopy ^b	107/85	No	No
Colon polypectomy	130/123	No	No
Dental cleaning	81/490	No	No

a. Investigator reported no abnormal bleeding problems encountered during the medical procedure associated with thrombocytopenia.

b. Investigator reported no abnormal bleeding problems encountered during the colonoscopy.

5.3.3. Long-term Dosing Study (EXTEND)

The EXTEND trial is ongoing; efficacy data presented are as of the 31 August 2007 clinical cut-off for the NDA submission.

The primary endpoint of EXTEND was safety. Efficacy analyses were included as secondary endpoints and focused on the ability of eltrombopag to provide long-term and durable platelet responses. Enrollment was not restricted by platelet count and subjects were allowed to enroll with platelet counts ≥ 50 Gi/L as the ability to reduce concomitant ITP medications was to be assessed in this study. The effect of eltrombopag on bleeding symptoms was also investigated.

Although the study is not a randomized double-blind, placebo-controlled trial, a sustained clinically meaningful increase in platelet counts in this patient population would be indicative of the effectiveness of the eltrombopag, especially given the low natural variability of platelet counts in subjects treated with placebo as observed in the long-term romiplostim clinical trials [Kuter, 2008].

Platelet count analyses

At baseline, 16 of 109 subjects (15%) had baseline platelet counts ≥ 50 Gi/L. A total of 86/108 evaluable subjects (80%) achieved platelet counts ≥ 50 Gi/L at least once during

the study; the majority of these subjects (65%) had baseline platelet counts less than 50 Gi/L.

Median platelet counts

Median platelet counts rose from 18 Gi/L at baseline to 87 Gi/L in the second week of treatment and generally remained ≥ 50 Gi/L throughout the trial. The proportion of subjects with platelet counts ≥ 50 Gi/L at each visit between Week 2 and 41 was $>50\%$ (with 2 exceptions) without a decline over time. Graphical representations of weekly median platelet counts and the mean weekly eltrombopag dose on study are provided (Figure 4, Figure 5, Figure 6).

Median Platelet Counts by Baseline Disease Characteristics

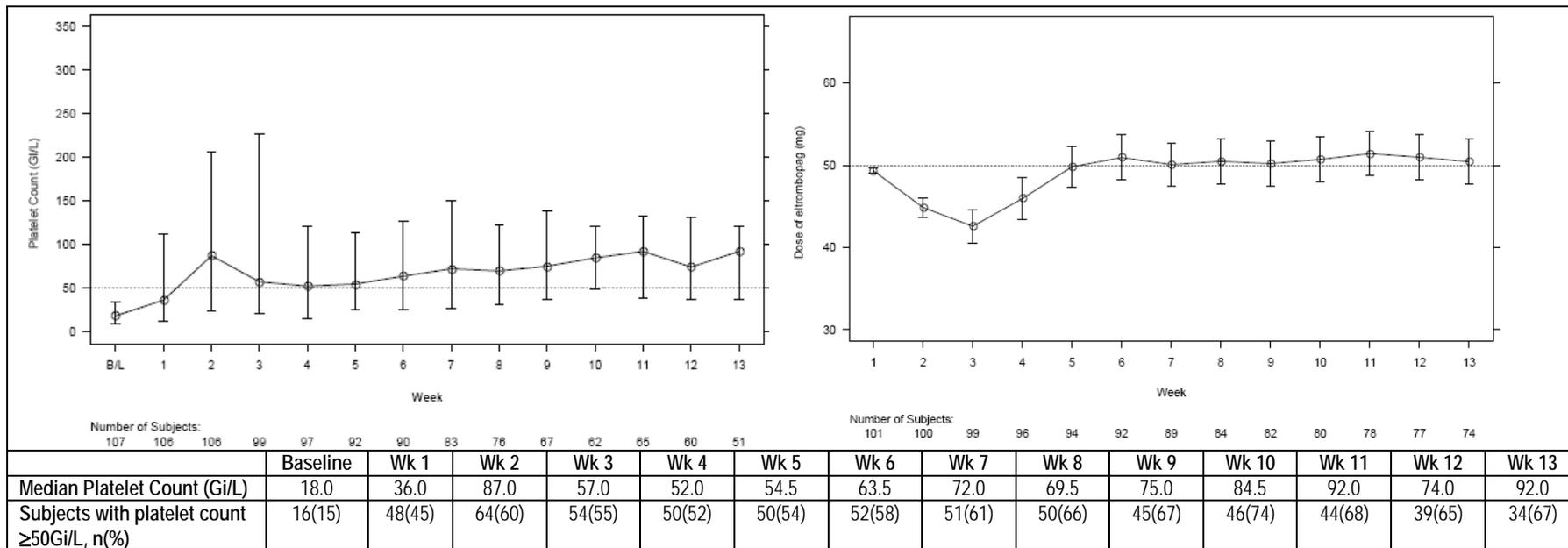
A similar response to eltrombopag was observed throughout the study regardless of whether or not subjects were taking concomitant ITP medication at baseline and regardless of splenectomy status, with median platelet counts generally ≥ 50 Gi/L at each weekly visit.

The majority of subjects regardless of baseline platelet count achieved platelet counts ≥ 50 Gi/L as evidenced by medians >50 Gi/L for most weeks; however, the time course and the magnitude of the median platelet count elevation appeared to be different depending on baseline platelet count. Subjects with baseline platelet counts of 30-50 Gi/L or >50 Gi/L had median platelet counts consistently ≥ 50 Gi/L beginning after 1 week of treatment with eltrombopag.

Subjects with baseline platelet counts <30 Gi/L achieved median platelet counts >50 Gi/L after week 7, but throughout the study, their median platelet counts were lower than that for subjects with higher baseline platelet counts.

A similar elevation in median platelet counts was observed in EXTEND patients from the pivotal trials, compared to the entire EXTEND population, with median platelet counts ≥ 50 Gi/L for the vast majority of weeks on the trial. When median platelet counts from only responders in the pivotal trials were examined, median platelet counts were generally between 50 and 100 Gi/L throughout the trial. Median platelet counts from subjects treated with placebo in the pivotal trials were similar to the entire EXTEND population with median platelet counts ≥ 50 Gi/L for the vast majority of weeks on the trial.

Figure 4 Median Platelet Counts, Mean Daily Dose and Percentage of Subjects with Platelet Counts 50Gi/L or More - Baseline to Week 13

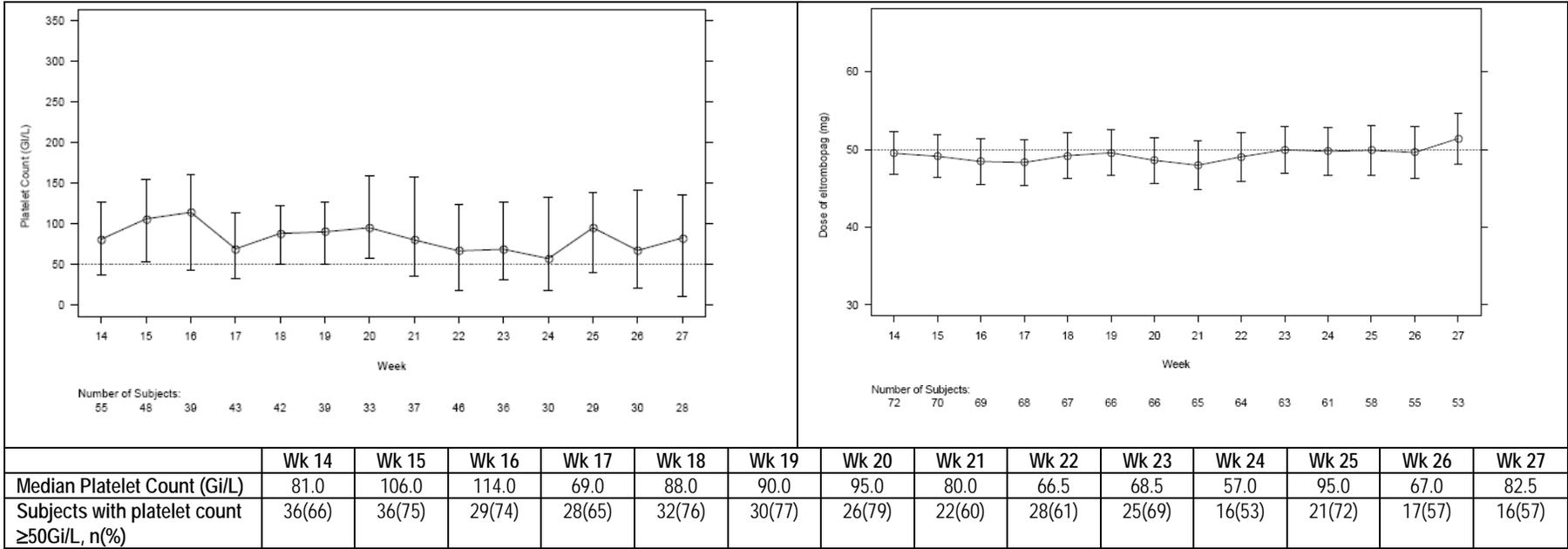


Bars represent 25th and 75th percentiles.

Observations outside the 25th and 75th percentiles are identified as possible outliers, and are labeled with their subject number.

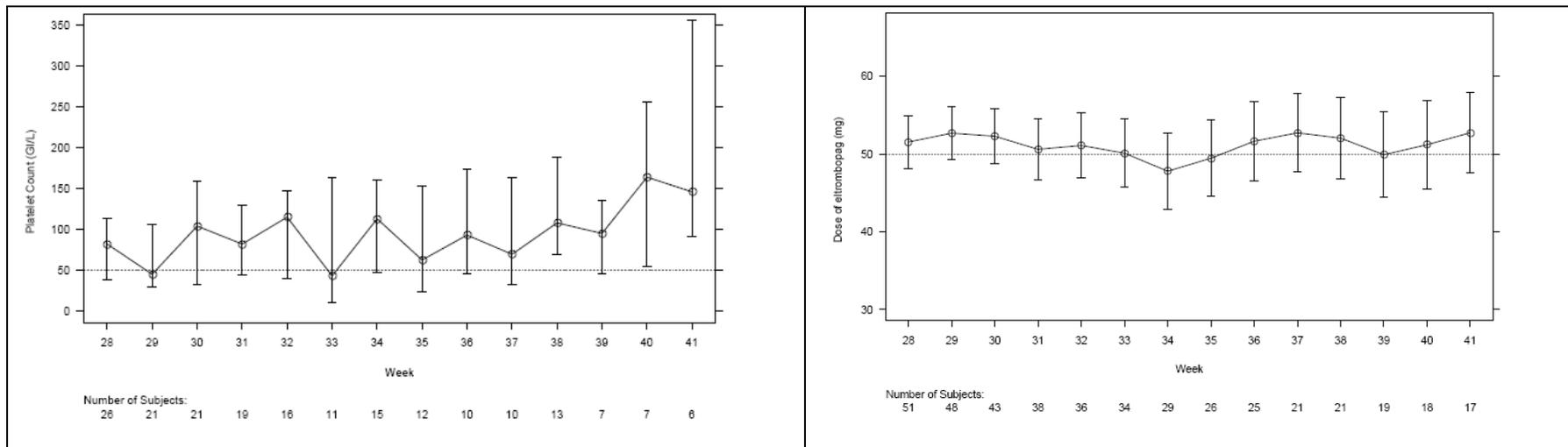
The mean is represented by a "+" symbol.

Figure 5 Median Platelet Counts, Mean Daily Dose and Percentage of Subjects with Platelet Counts 50Gi/L or More – Week 14 to Week 27



Bars represent 25th and 75th percentiles.
 Observations outside the 25th and 75th percentiles are identified as possible outliers, and are labeled with their subject number.
 The mean is represented by a "+" symbol.

Figure 6 Median Platelet Counts, Mean Daily Dose and Percentage of Subjects with Platelet Counts 50Gi/L or More – Week 28 to Week 41



	Wk 28	Wk 29	Wk 30	Wk 31	Wk 32	Wk 33	Wk 34	Wk 35	Wk 36	Wk 37	Wk 38	Wk 39	Wk 40	Wk 41
Median Platelet Count (Gi/L)	82.0	45.0	104.0	82.0	115.0	43.0	113.0	62.5	93.0	69.5	108.0	95.0	164.0	146.0
Subjects with platelet count ≥ 50 Gi/L, n(%)	17(65)	10(48)	14(67)	14(74)	11(69)	4(36)	10(67)	7(58)	7(70)	6(60)	11(85)	5(71)	6(86)	5(83)

Bars represent 25th and 75th percentiles.
 Observations outside the 25th and 75th percentiles are identified as possible outliers, and are labeled with their subject number.
 The mean is represented by a "+" symbol.

Durability of Platelet Count Elevation ≥ 50 Gi/L

The maximum continuous duration of platelet count elevation was reported based on the number of weeks that subjects had been in the study.

The majority of subjects (54%) experienced prolonged (≥ 10 weeks) continuous elevation of platelets ≥ 50 Gi/L while receiving eltrombopag (Table 17). Twenty-four percent of subjects who had been in the study for ≥ 25 weeks had a maximum continuous elevation ≥ 50 Gi/L of 25 weeks or longer.

It should be considered that the denominator at each time period includes all subjects available at each particular time point, including 21 subjects who remained in the study for up to 48 weeks without having achieved a single count above 50 Gi/L. Patients were allowed to stay in the study without having achieved platelet counts above 50 Gi/L if physician and patients saw clinical benefit (usually a clinically meaningful decrease in bleeding symptoms) in the absence of eltrombopag-associated side effects.

Sixteen subjects with a baseline platelet count ≥ 50 Gi/L were also included in this analysis.

Table 17 Maximum Continuous Weeks of Maintaining Platelet Counts 50 Gi/L or More

Number of Continuous Weeks ^a (wks)	Number of Subjects in the Study for the Designated Duration				
	≤ 12 weeks ^a	>12 to ≤ 24 weeks ^a	>24 to ≤ 48 weeks ^a	>48 to ≤ 72 weeks ^a	Total n ^b /N ^c (%)
	n	n	n	n	
Total	32	14	54	9	109
No continuous wks	18	8	6	1	33/109 (30)
≥ 1 wks response	14	6	48	8	76/107 (71)
≥ 4 wks response	2	5	41	8	56/101 (55)
≥ 7 wks response	1	5	35	8	49/89 (55)
≥ 10 wks response	0	4	31	8	43/80 (54)
>13 wks response		1	24	7	32/74 (43)
>16 wks response		1	24	6	31/70 (44)
>19 wks response		0	21	6	27/67 (40)
>22 wks response			15	6	21/66 (32)
>25 wks response			11	4	15/63 (24)
>28 wks response			10	4	14/56 (25)
>31 wks response			7	3	10/41 (24)
>34 wks response			3	3	6/31 (19)
≥ 37 wks response			0	3	3/24 (13)
≥ 43 wks response				2	2/17 (12))
≥ 52 wks response				1	1/4 (25)

a. Weeks on study in this analysis are determined based on known exposure to eltrombopag up to cut-off date

b. n= the number of subjects with continuous elevation of platelet counts of indicated duration

c. N=the total number of subjects exposed to eltrombopag for the indicated duration up to the cut-off date

Additional analyses on the EXTEND platelet count data included in the NDA submission have been performed to ascertain the effect of eltrombopag on endpoints recently presented in a publication of results of romiplostim in patients with chronic ITP [Kuter,

2008]. Two placebo-controlled romiplostim trials were conducted, one in patients without a splenectomy and one in subjects with a prior splenectomy.

A durable platelet response, excluding subjects who received rescue medication (conservatively defined as an increased dose of baseline ITP medication, a new ITP medication, platelet transfusion and/or splenectomy), was achieved in 55% of subjects (Table 18). An overall platelet response, excluding subjects who received rescue medication, was achieved in 82% of subjects. There was no difference in the percentage of splenectomized and non-splenectomized patients with a durable platelet response (56% and 53%, respectively) or an overall platelet response (84% and 80%, respectively) in EXTEND.

The median number of weeks with a platelet response for EXTEND subjects on the study for ≥ 3 months and ≥ 6 months was 19 and 22 weeks, respectively.

In comparison, the published data from the pooled romiplostim studies demonstrated a 49% durable response in the romiplostim treated patients compared to 2% in the placebo treated patients [Kuter, 2008]. The pooled overall platelet response observed was 83% with romiplostim treated patients compared to 7% in placebo treated subjects. The mean number of weeks on study with a platelet response in the pooled romiplostim trials was 13.8 weeks in romiplostim treated patients compared to 0.8 weeks in the placebo treated subjects. A differential response to romiplostim was observed in patients with a prior splenectomy compared to non-splenectomized patients, with only 38% of splenectomized romiplostim treated patients achieving a durable platelet response compared to a 61% in non-splenectomized patients.

Table 18 Durable and Overall Platelet Response and Weeks with Platelet Response (ITT Population)

	Eltrombopag
Subjects treated for ≥ 6 months	N=59
Durable platelet response ^a , n(%)	30 (55)
Overall platelet response ^b , n(%)	45 (82)
Weeks with a platelet response (≥ 50Gi/L and 2x baseline)	
Subjects on study ≥ 3 months	N=74
Mean (SD)	18.8 (13.37)
Median (min, max)	19 (0, 48)
Subjects on study ≥ 6 months	N=59
Mean (SD)	21 (13.32)
Median (min, max)	22 (0, 48)

- Durable platelet response was defined as platelets ≥ 50 Gi/L and 2x baseline for at least 6 of the last 8 weeks in the first 6 months in EXTEND.
- Overall platelet response was defined as durable response plus transient response (platelets ≥ 50 Gi/L and 2x baseline for at least 4 consecutive weeks at any point during the first 6 months in EXTEND).

Response in EXTEND Following Response in Prior Study

The majority (92%) of 49 subjects who responded in the pivotal studies and enrolled in EXTEND also achieved a platelet count ≥ 50 Gi/L in EXTEND.

To control for subjects who started EXTEND with a baseline platelet count already ≥ 50 Gi/L, platelet counts ≥ 50 Gi/L and at least 2x baseline were also assessed. Using these response criteria, 90% of subjects who had responded in the pivotal studies also achieved platelet counts ≥ 50 Gi/L and $\geq 2x$ baseline during EXTEND.

Nineteen of the 30 subjects (63%) enrolled in EXTEND who had received placebo in the previous pivotal studies (13 in TRA100773A and 17 in TRA100773B), achieved platelet counts in EXTEND ≥ 50 Gi/L for at least 75% of their assessments.

ITP Medication Dose Reduction

The effect of eltrombopag on the reduction and/or sparing of concomitant ITP therapies while maintaining a platelet count > 50 Gi/L was evaluated. At baseline 40 subjects (37%) reported use of ITP medications, of which 24 started to reduce or discontinue concomitant ITP medications.

Eighteen of the 24 subjects (75%) were able to stop or reduce the use of one or more baseline ITP medications and did not require any subsequent rescue treatment as of the clinical cut-off date. Fourteen of the 24 subjects (68%) were able to stop one or more baseline ITP medications completely; 3 of these subjects discontinued both danazol and prednisolone. Medications discontinued were: prednisone (prednisolone) in 10 subjects; danazol in 4 subjects; and dexamethasone, mycophenolic acid, and oxymethalone in 1 subject each.

An additional 4 subjects (17%) had their dose or frequency of prednisone (prednisolone) reduced on study.

Analyses of Bleeding

WHO Bleeding Scale

The incidence of any bleeding (WHO Grades 1-4) and clinically significant bleeding (Grades 2-4) decreased by approximately 50% from baseline throughout the trial (Table 19). At the majority of time points assessed through week 41, WHO Grade 1 bleeding events make up over half of the total bleeding events reported.

Table 19 Summary of Subjects with WHO Bleeding Grades in EXTEND

WHO Bleeding Scale	Baseline	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 42
	N=109	N=89	N=60	N=40	N=29	N=22	N=9	N=10
Grades 1 – 4	69 (63)	31 (35)	15 (25)	9 (23)	8 (28)	6 (27)	1 (11)	1 (10)
Grades 2 – 4	23 (21)	9 (10)	2 (3)	2 (5)	3 (10)	2 (9)	1 (11)	0

Hemostatic Challenges

Thirteen subjects had at least one procedure during the study. These hemostatic challenges ranged greatly in terms of bleeding risk, from tooth repair, colonoscopy and bone marrow biopsies to arthroscopy and uterine polypectomy. The hemostatic challenges with the greatest bleeding risk (arthroscopy, CT guided aspirate of lung and uterine polypectomy) were performed without bleeding complications and without additional treatment to elevate platelets, thus confirming an additional clinical benefit of eltrombopag in subjects with chronic ITP.

5.4. Efficacy Conclusions

Pivotal studies

- Eltrombopag effectively and consistently raised platelet levels during short-term treatment in subjects with previously-treated chronic ITP. In the pooled analysis, the primary endpoint (shift from baseline platelets <30 Gi/L to platelets ≥50 Gi/L) was achieved by 62% of subjects on eltrombopag 50 mg compared to only 14% of subjects on placebo. The odds of treatment response in the eltrombopag group relative to placebo (OR [95%CI]: 12.40 [5.18, 29.72]) was statistically significant (p<0.001).
- In both studies, more than 50% of subjects responded with a clinically meaningful increase in platelet counts, regardless of baseline platelet counts, use of concomitant medication and splenectomy status.
- Response to eltrombopag at any point over the entire treatment period (Weeks 2-6) was more likely compared to placebo (OR [95%CI]: 13.89 [6.59, 29.29], p<0.001).
- Eltrombopag raised platelet counts relatively quickly: in both trials, >30% of subjects responded with an increase of platelet counts ≥50 Gi/L by Day 8, 50% of subjects responded by Day 15, following treatment with eltrombopag 50 mg. Platelet levels remained elevated approximately 1 week after discontinuing eltrombopag.
- A statistically significant decrease in bleeding symptoms, measured by the WHO Bleeding Scale, was observed in patients treated with eltrombopag compared to placebo. In the pooled analysis, 55% of subjects in the placebo treatment group versus 37% on the eltrombopag 50 mg treatment group, had any (WHO Grades 1 to 4) bleeding (relative odds of bleeding = 0.34, 95% CI [0.14,0.83]; p=0.018). The relative odds of bleeding between Weeks 2 and 6 in the eltrombopag group was significantly less compared to placebo (OR=0.48; 95% CI [0.29, 0.80]); p=0.005).
- Subjects treated with eltrombopag were able to effectively master hemostatic challenges (e.g., diagnostic or surgical procedures) without additional treatments to elevate their platelet counts, whereas placebo treated subjects required treatment to elevate their platelet counts.

Intermittent dosing study (TRA108057/REPEAT)

- Consistent response (≥ 50 Gi/L and $\geq 2x$ baseline) to eltrombopag was observed based upon analysis of the primary endpoint. Eighty-eight percent of subjects who responded in Cycle 1, responded again in Cycle 2 or 3 (Exact 95% CI: 0.72, 0.97). Greater than 85% of subjects responded in all three cycles regardless of splenectomy status, use of concomitant ITP medications and baseline platelet count.
- Across all three cycles the percentage of subjects responding (≥ 50 Gi/L and $\geq 2x$ baseline) at each on-therapy visit was consistent. By Day 8 and Day 15 of each cycle, $>60\%$ and $>75\%$ of subjects had responded, respectively. Approximately 30% of subjects achieved platelet counts >200 Gi/L in all 3 cycles by Day 15 of each cycle.
- Across all three cycles the median platelet count elevations were similar, both in terms of time course and magnitude, with elevations generally above 100 Gi/L from Day 8 in each cycle to 1 week after interruption of eltrombopag.
- A 50% decrease in bleeding was observed in each on-treatment period compared to baseline, confirming the inverse relationship between platelet counts and bleeding symptoms.
- Across all 3 cycles, subjects were able to effectively master hemostatic challenges (e.g., diagnostic and surgical procedures) without additional treatments to elevate their platelet counts.

Long-term dosing study (TRA105325/EXTEND)

- Median platelet counts rose to 87 Gi/L in the second week of treatment and generally remained ≥ 50 Gi/L throughout the trial.
- The majority of subjects (54%) had clinically meaningful periods of continuous uninterrupted platelet counts ≥ 50 Gi/L for at least 10 consecutive weeks, with 24% achieving continuous, consecutive elevation of platelet counts ≥ 50 Gi/L for more than 6 months.
- Although the study is not a randomized double-blind, placebo-controlled trial, this sustained clinically meaningful increase in platelet counts in this patient population is indicative of the effectiveness of eltrombopag, as there is a low natural variability of platelet counts in subjects treated with placebo as observed in the long-term romiplostim (AMG531) clinical trials [[Kuter, 2008](#)].
- Patients responded to eltrombopag regardless of baseline use of concomitant ITP medication or prior splenectomy.
- Ninety-two percent of subjects that responded in TRA100773A or TRA100773B also achieved platelet counts ≥ 50 Gi/L on EXTEND.
- The incidence of any bleeding (WHO Grades 1-4) and clinically significant bleeding (Grades 2-4) decreased by approximately 50% from baseline throughout the trial. Severity of bleeding was associated with platelet counts; subjects with platelet counts

≥50 Gi/L had a lower incidence of clinically significant bleeding events, compared to subjects with platelet counts <50 Gi/L.

- In EXTEND, subjects were able to effectively master hemostatic challenges (e.g., diagnostic or surgical procedures) in general without additional treatments to elevate their platelet counts.

6. OVERVIEW OF SAFETY

The safety profile of eltrombopag has been evaluated in over 1000 subjects in 22 completed or ongoing GSK sponsored clinical studies globally. The doses of eltrombopag used in these studies ranged from 3 mg to 200 mg. The duration of treatment with eltrombopag ranged from 1 day in healthy volunteers to up to 560 days in subjects with ITP in the safety update dataset.

Data from 5 clinical studies are available to assess the safety profile of eltrombopag in patients with chronic ITP ([Table 20](#)). The safety of short-term and intermittent short-term dosing was established in 2 double-blind placebo-controlled studies of up to 6 weeks dosing (TRA100773A, N=117; and TRA100773B, N=114) and 1 open-label study with 3 cycles of repeated short-term treatment of eltrombopag (REPEAT, N=66).

The safety profile of long-term dosing with eltrombopag was established primarily based upon data from the open-label extension study (EXTEND, N=207). Additionally, blinded safety data are presented from the double-blind, placebo-controlled RAISE study (N=196), in which patients (randomized 2:1 to eltrombopag and placebo, respectively) receive study medication for 6 months.

In all 5 trials, a total of 495 patients with ITP have been enrolled. Currently, a total of 330 ITP subjects are known to have been exposed to eltrombopag in TRA100773A, TRA100773B, REPEAT and EXTEND. Additionally, approximately 2/3 of patients in the blinded RAISE study have been exposed to eltrombopag (~130 subjects); therefore, approximately 460 subjects with chronic ITP have been exposed to eltrombopag and more than 150 ITP subjects have been exposed for at least 6 months.

In addition, 568 subjects from Phase 1 studies including 524 healthy volunteers, 25 subjects with hepatic impairment and 19 subjects with renal impairment have received eltrombopag (ranged from 3 mg to 200 mg). In other indications (hepatitis C and cancer), an additional 190 patients have received eltrombopag and 64 have received placebo in completed studies.

Table 20 Tabulation of Subjects Contributing to the Safety Analysis of Eltrombopag (Safety Population)

	Total Eltrombopag exposure ^a (any dose)	Placebo	Blinded study treatment
Subject Population	N	N	N
ITP Studies			
TRA100773A	88	29	
TRA100773B	76	38	
REPEAT/TRA108057	66		
EXTEND/TRA105325	100 ^{b,c}		
RAISE/TRA102537			196
Subtotal ITP studies	330^a	67	196
Subjects in Phase 1 Studies	568 ^d	47 ^f	
Primary Safety Database	898	114	196
Other Indications			
Completed studies ^g	190	64	
Total	1088	178	196

- a. Subjects who received study medication in more than one study are counted only once.
- b. Includes 33 subjects who received eltrombopag for the first time in EXTEND (previously received placebo in TRA100773A or TRA100773B) and 67 subjects who were previously enrolled in the blinded RAISE study.
- c. In addition, there were 107 subjects in EXTEND who received eltrombopag in a previous study (TRA100773A, TRA100773B, REPEAT).
- d. Includes 524 healthy subjects, 25 subjects with hepatic impairment, 19 subjects with renal impairment.
- e. Includes 166 healthy subjects, 25 subjects with hepatic impairment, 19 subjects with renal impairment.
- f. Five healthy subjects received placebo (1 subject) or a comparator (3 received moxifloxacin, 1 received rosuvastatin) in a cross-over study but withdrew prior to receiving a dose of eltrombopag.
- g. Other indications = CIT and HCV studies with final CSR (SB497115/003 and TPL102357, respectively).

6.1. Extent of Exposure in ITP Studies

Cumulative exposure data for all 330 subjects with ITP who received eltrombopag in these completed double-blind or ongoing, open-label studies are reported. The total cumulative exposure of eltrombopag in this patient population is documented by combining the exposure of the short term studies TRA100773A, TRA100773B and REPEAT with the cumulative eltrombopag exposure in EXTEND as of the cut-off date for this analysis. As the RAISE study remains blinded to treatment allocation, no RAISE data is included in this exposure analysis.

The median average daily dose was 50.0 mg of eltrombopag, consistent with the proposed starting dose. The median number of days exposed to eltrombopag was 70 days, with a range from 2 to 560 days. The total number of subject-months on treatment with eltrombopag was 1448 (calculated as N x mean days on eltrombopag x [12 / 365.25]).

An exposure plot of all subjects exposed to eltrombopag is presented (Figure 7); this data is also tabulated (Table 21). Excluding RAISE subjects, a total of 81 subjects have been

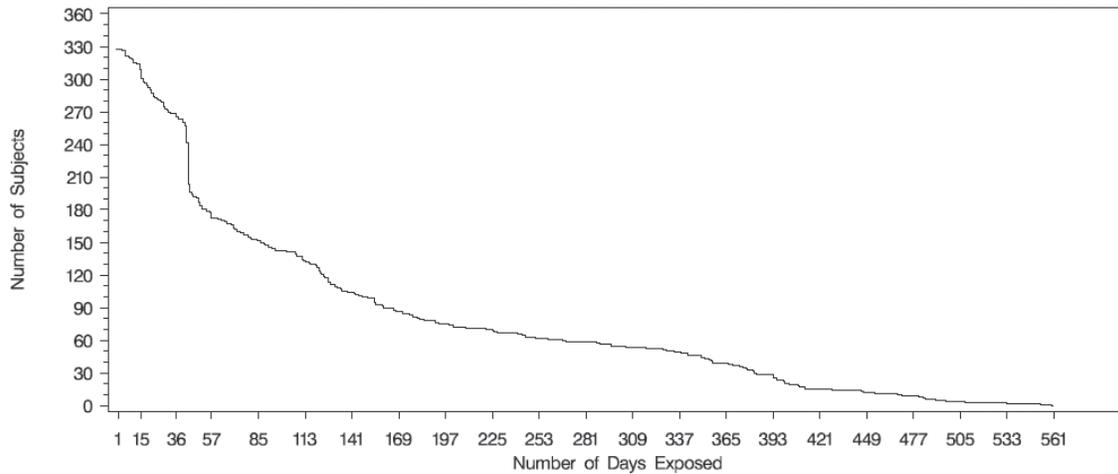
exposed to eltrombopag for at least 6 months and 39 subjects have been exposed to eltrombopag for at least 1 year.

Table 21 Number of Subjects Exposed to Eltrombopag by Treatment Duration (Safety Update)

Duration of Exposure	Eltrombopag (excluding RAISE) N=330	Eltrombopag (including RAISE estimate) N=460
≥ 1 day, n	328	458
≥ 6 months, n	81	155
≥ 12 months, n	39	39
≥ 15 months, n	12	12

If estimated RAISE data were included, the number of subjects with 6 months exposure to eltrombopag would increase to approximately 150 subjects, significantly increasing the number of subjects who have been exposed to eltrombopag up through 6 months across the program.

Figure 7 Cumulative Exposure to Eltrombopag in Days (Safety Update)



6.1.1. Exposure in the Short-term Treatment Studies

Placebo-controlled Pivotal Studies (TRA100773A and TRA100773B)

The median number of days exposed to placebo was 42 and the median number of days exposed to eltrombopag 50 mg was 43 (Table 22). The total number of patient-months on treatment was 83 and 121 for subjects who received placebo and eltrombopag 50 mg, respectively.

Table 22 Summary of Exposure in Pivotal Studies - Pooled Data

Days on Study Drug	773A + 773B	
	Placebo N=67	50mg N=106
Number of subjects, n	67	106
Mean (SD)	37.7 (11.47)	34.8 (12.61)
Median (min, max)	42.0 (5, 49)	43.0 (8, 51)
Total Subject-Months on Treatment	83	121

a. Subject-Months calculated as N x mean days on eltrombopag x (12 / 365.25).

Intermittent Short-term Dosing Study (REPEAT)

The median duration of exposure based on the number of days exposed to eltrombopag in REPEAT was double that (80.5 days) compared to the exposure in the pivotal studies due to the fact that subjects could have received more than 1 cycle of treatment in REPEAT (Table 23).

Table 23 Summary of Exposure to Eltrombopag in REPEAT

Days on Study Drug	REPEAT ^a Eltrombopag N=66
Number of subjects, n	66
Mean (SD)	82.3 (37.89)
Median (min, max)	80.5 (15, 135)
Total Subject-Months on Treatment	178 ^b

a. Cumulative data for Cycles 1, 2 and 3.

b. Subject-Months calculated as N x mean days on eltrombopag x (12 / 365.25).

6.1.2. Exposure in the Long-term Treatment Studies (EXTEND and RAISE)

The median duration of exposure in EXTEND is approximately 4.5-fold longer than in the pivotal studies, with exposures for more than 6 months (Table 24). The total number of patient-months on treatment in EXTEND was 1089.

For subjects enrolled in EXTEND, the total cumulative exposure to eltrombopag is included by combining the eltrombopag exposure in EXTEND with the eltrombopag exposure in the previous study, if applicable.

In the blinded RAISE study, the median days on study medication was 180, with 1031 total subject-months of exposure to study medication.

Table 24 Summary of Exposure to Eltrombopag in EXTEND and RAISE

	EXTEND Eltrombopag N=207	RAISE Blinded N=196
Days on study drug		
N	199 ^a	196
Mean (SD)	166.6 (146.33)	160.1 (44.64)
Median (min, max)	98.0 (2, 518)	180.0 (5, 241)
Total Subject-Months on Treatment	1089^b	1031^b

- a. Eight subjects had one exposure record with a start date and no end date, which excludes them from these calculations.
- b. Subject-Months calculated as N x mean days on eltrombopag x (12 / 365.25).
- c. NA = not applicable, as the RAISE study is blinded.

6.2. Analysis of Adverse Events

Across the ITP program, the adverse event (AE) reported with the highest incidence in subjects exposed to eltrombopag was headache (20%), followed by nasopharyngitis, diarrhea and upper respiratory tract infection (Table 25). The most common AEs ($\geq 5\%$) were generally consistent with those seen in the individual studies regardless of duration of treatment or repeated exposure.

Table 25 Adverse Events with an Incidence of 5% or More in ITP Subjects Exposed to Eltrombopag

Adverse Event, n (%)	Eltrombopag N=330 ^a
Any Event	249 (75)
Headache	66 (20)
Nasopharyngitis	34 (10)
Diarrhea	32 (10)
Upper respiratory tract infection	34 (10)
Fatigue	30 (9)
Arthralgia	25 (8)
Nausea	23 (7)
Epistaxis	24 (7)
Vomiting	18 (5)
Anemia	20 (6)
Cough	15 (5)
Back pain	18 (5)

- a. Subjects with an AE occurring more than once in a study or in both EXTEND and the previous study are counted only once.

The overall frequency of AEs based on subject-months of treatment for all eltrombopag-treated subjects, and by study, shows a relatively consistent picture (Table 26). In the pooled pivotal data, subjects receiving eltrombopag had a lower frequency of AEs than

subjects receiving placebo. Long-term exposure in EXTEND and RAISE did not result in an elevated frequency of AEs compared to short-term treatment.

Table 26 Frequency of AEs During the On-therapy Period

	Any ITP Study	773A + 773B		REPEAT	EXTEND	RAISE
	Eltrombopag	PBO	50 mg	50 mg	50 mg	Blinded
	N=330	N=67	N=106	N=66	N=207	N=196
Total AEs On-therapy	1300	116	143	257	815	1142
Total Subject-months Exposed ^a	1448	83	121	178	1089	1031
Frequency of AEs/Subject-months ^b	0.90	1.40	1.18	1.44	0.75	1.11

Data Source: SDAP Table 8.1, SDAP Table 8.21

a. Subject Months calculated as N x mean days on eltrombopag x (12 / 365.25).

b. Frequency was calculated by Total AEs / Total Subject-Months.

6.2.1. Short-term Dosing Studies

Placebo-controlled pivotal studies (TRA100773A and TRA100773B)

When individual AEs were analyzed based on pooled data from the two pivotal studies, the most common AEs ($\geq 5\%$) reported during the on-therapy (days study drug was taken +1 day) period in the eltrombopag 50 mg treatment group were headache, nasopharyngitis, nausea, fatigue and arthralgia (Table 27). The rates of these AEs were similar between the placebo and 50 mg treatment groups, with the exception of nausea. Nausea was the only AE with an incidence in eltrombopag-treated subjects $\geq 5\%$ higher than for placebo-treated subjects.

Table 27 On-Therapy Adverse Events at 5% or More Total Incidence in the Pivotal Studies – Pooled Data

Preferred Term	773A + 773B	
	Placebo N=67	50mg N=106
Any AE, n (%)	32 (48)	60 (57)
Headache	10 (15)	9 (8)
Nasopharyngitis	3 (4)	6 (6)
Nausea	0	6 (6)
Fatigue	5 (7)	4 (4)
Arthralgia	4 (6)	2 (2)

In TRA100773A, subjects were dosed with placebo, 30 mg, 50 mg or 75 mg eltrombopag. No dose-dependent patterns in the incidence of AEs, drug-related AEs, SAEs or AEs leading to withdrawal during the entire study were noted across treatment groups in TRA100773A (placebo, 30 mg, 50 mg and 75 mg eltrombopag).

The incidence of hepatobiliary AEs was low in the eltrombopag 50 mg treatment group. Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) each were reported for 2% of the subjects in the eltrombopag 50 mg group. No subjects treated with placebo had increases of ALT or AST reported as AEs. However, 1 subject treated with placebo and 1 subject treated with eltrombopag 50 mg each had an SAE of “hepatitis” or “toxic hepatitis” reported, associated with elevations of ALT and AST.

Intermittent short-term dosing study (REPEAT)

Overall, 54 subjects in REPEAT experienced at least one AE (82%). The most commonly reported AEs in the REPEAT study were headache (23%), fatigue (15%), nasopharyngitis (15%), diarrhea (12%) and back pain (11%). Increased ALT was reported as an AE in 3% of subjects in REPEAT and increased AST was reported in 2% of subjects in REPEAT. There was no apparent increase in the percentage of AEs or the severity of AEs reported in Cycles 2 or 3 compared to Cycle 1.

6.2.2. Long-term Dosing Studies (EXTEND and RAISE)

Overall, 139 subjects in EXTEND experienced at least one AE (82%). The most commonly reported AEs in the EXTEND study were headache (15%), upper respiratory tract infection (13%) and diarrhea (10%). AEs of increased ALT and AST were reported in 4% and 3% of subjects in EXTEND, respectively.

In the blinded RAISE, study, 166 subjects experienced at least one AE (85%). The most commonly reported AEs in the RAISE study were headache (33%), diarrhea (12%), nasopharyngitis (11%), fatigue (11%), upper respiratory tract infection (11%) and nausea (10%). Increased ALT was reported as an AE in 7% of subjects in the blinded RAISE study and increased AST was reported for 5% of subjects in RAISE.

6.3. Serious Adverse Events and Deaths

6.3.1. Serious Adverse Events (SAEs)

Short-term dosing studies (TRA100773A, TRA100773B and REPEAT)

Placebo-controlled pivotal studies

A similar incidence in SAEs was observed in the placebo and eltrombopag 50 mg treatment arms in an analysis of pooled data from TRA100773A and TRA100773B: placebo (7 events in 5 subjects [5%]) and eltrombopag 50 mg groups (7 events in 4 subjects [4%]). No on-therapy SAEs were reported for subjects who received 30 mg or 75 mg in TRA100773A.

Bleeding complications were the most frequently reported SAEs. Three subjects experienced bleeding SAEs on-therapy and all events occurred in subjects who either received placebo or did not respond to eltrombopag (platelets <15 Gi/L).

Two subjects experienced hepatic SAEs. One placebo subject reported “toxic hepatitis” and one eltrombopag 50 mg subject experienced “hepatitis”, which was associated with cardiopulmonary failure probably due to sepsis of pulmonary origin, according to two independent autopsy reviews (Section 6.3.2, Deaths).

Intermittent Short-term Dosing Study (REPEAT)

One on-therapy SAE of pneumonia was reported in REPEAT as of the SAE cut-off date for the Safety Update. This SAE was not considered related to study medication by the investigator.

Long-term dosing studies (EXTEND and RAISE)

EXTEND

In the EXTEND study, 38 on-therapy SAEs were reported for 17 subjects (8%). The overall incidence of on-therapy SAEs in EXTEND was similar to the incidence of SAEs reported in the eltrombopag 50 mg group for the entire duration of TRA100773A and TRA100773B (10%).

One subject experienced a pulmonary embolism on-therapy that led to withdrawal, which the investigator considered related to eltrombopag. SAEs of hyperbilirubinemia and increased ALT in one subject were considered related to study medication. All other SAEs were considered unrelated to study medication.

RAISE

In the blinded RAISE study, a total of 37 on-therapy SAEs were reported in 26 subjects (13%). A total of 15 SAEs were considered related to study medication.

Four subjects experienced bleeding SAEs, though none were considered drug-related. Three subjects experienced SAEs of headache, all of which were considered drug-related. Two subjects experienced thromboembolic SAEs; the events for both subjects were considered drug-related. Three subjects experienced SAEs of elevated transaminases, 2 of which were considered drug-related.

6.3.2. Deaths

Deaths have been reported for 6 subjects across the ITP program as of 18 Feb 2008. With the exception of one subject in TRA100773A, the cause of death in each patient was considered unrelated to study medication by the investigator. The causes of death are listed below by study.

TRA100773A eltrombopag 50 mg

- Cardiopulmonary failure (unrelated); embolism and pulmonary embolism (related, identified upon autopsy):

- This subject had a medical history of pneumonectomy for right lung carcinoma with concomitant medications including prednisone due to asthma and emphysema and experienced SAEs of renal insufficiency and hepatitis which were considered by the investigator as related to eltrombopag. An initial autopsy report showed multiple thromboembolic events (peripheral vessels of liver and kidneys). The autopsy material was subsequently reviewed by two independent pathologists. They concluded that marked centrilobular congestion in the liver with focal ischemic necrosis was consistent with a terminal low-flow state due to severe heart failure with no inflammatory changes in the liver. Their findings were consistent with multiple organ failure arising from cardiorespiratory insufficiency, which was probably initiated by pulmonary sepsis. The thromboembolic events noted in initial report were assessed as being near-terminal events resulting from a low cardiac output state, instead of causing it.

EXTEND eltrombopag

- Motor vehicle accident (passenger).
- Hypovolemic shock:
 - Secondary to gastrointestinal hemorrhage 55 days after last dose of eltrombopag. This subject was a non-responder and had a platelet count <10 Gi/L at the time of the event.
- Multi-organ failure secondary to septic shock of pulmonary origin, acute respiratory insufficiency and acute renal failure:
 - Six weeks prior to her death, the patient was hospitalized with a pulmonary infection and progressive acute respiratory insufficiency, requiring treatment with broad spectrum IV antibiotics, IVIg and vasopressors. Twelve hours after admission the patient's condition deteriorated and she required intubation and ventilatory support. Chest x-ray showed evidence of parenchymal involvement and thoracic CT scan demonstrated infected bronchiectases and no evidence of pulmonary embolism. Treatment with study medication was discontinued. No anticoagulation was given. One week after admission, a DVT of the left common femoral vein was diagnosed. Her clinical course was further complicated by renal failure, urinary tract infection and a tachyarrhythmia. One week prior to her death, the patient developed symptoms of septic shock, and a multi-resistant pseudomonas aeruginosa strain was cultured from her bronchial secretions. Multiple organ failure ensued.
- Sudden death (no post-mortem examination). The investigator's verbatim report of possible causality: "Acute bleed, acute cerebral hemorrhage vs. acute myocardial infarction vs. acute arrhythmia and cardiac arrest vs. sepsis syndrome in a patient with fever on steroids.":
 - The subject's medical history was significant for splenectomy, basal cell carcinoma, breast carcinoma, obesity (BMI 45), anxiety, depression, left bundle branch block, prolonged QT, arthritis, gastroesophageal reflux disease and bronchiolitis obliterans organizing pneumonia. Concomitant and recent

medications included two drugs known to prolong QTc interval (formoterol and venlafaxine).

RAISE blinded study medication

- Brain stem hemorrhage:
 - The subject did not respond to blinded study medication and had a platelet count <10 Gi/L at the time of the event.

6.4. AEs Leading to Withdrawal from the Study

6.4.1. Short-term Dosing Studies (TRA100773A, TRA100773B and REPEAT)

Placebo-controlled, Pivotal Studies (TRA100773A and TRA100773B)

In the pooled analysis of the pivotal studies, a low number and percentage of subjects in the treatment groups withdrew from study medication due to an AE without any organ-specific pattern of toxicity: 5 subjects in the placebo group (7%) and 5 subjects in the 50 mg treatment group (5%). AEs leading to withdrawal were considered related to study medication for 4 placebo subjects and 2 eltrombopag-treated subjects.

In the 75 mg treatment group in TRA100773A, one subject (Subject 167) withdrew due to AEs of urticaria and tonsillitis, both of which were considered related to study medication by the investigator. No subjects were withdrawn due to AEs in the 30 mg treatment group.

Intermittent Short-term Dosing Study (REPEAT)

In the REPEAT study, a total of 1 subject (2%) was discontinued from study medication due to 3 AEs. These AEs were as follows: tachycardia (Grade 1), feeling jittery (Grade 2), and headache (Grade 2). All 3 AEs were considered related to study medication by the investigator.

Long-term Dosing Studies (EXTEND and RAISE)

In EXTEND, a total of 8 subjects (4%) were withdrawn from study medication due to 13 AEs. In the blinded RAISE study, a total of 14 subjects (7%) were withdrawn due to 19 AEs. Each individual AE is presented by subject for both studies ([Table 28](#)).

Table 28 Cumulative Listing of AEs Leading to Withdrawal in EXTEND and RAISE

Study and Dose Group	N (%)	Events by Subject
EXTEND 50mg eltrombopag N=207	8 (4)	Pulmonary embolism ^a Deep vein thrombosis ^a Road traffic accident ^b Fatigue ^a , Headache ^a , Muscle spasms ^a Increased ALT, Increased AST, Increased bilirubin Increased ALT ^a , Hyperbilirubinemia ^a Pulmonary embolism Petechiae ^a
RAISE Blinded treatment N=196	14 (7)	Brain stem hemorrhage ^b Pulmonary embolism ^a , Pulmonary infarct ^a , Superficial thrombophlebitis ^a Subcapsular cataract ^a Venous thrombosis (limb) ^a Abnormal renal function, Increased ALT, Hyperkalemia Increased ALT ^a Increased AST ^a Headache Tachycardia ^a Rash ^a Rectosigmoid cancer ^c Hepatic enzyme increased ^a ALT increased ^a Cataract ^a Urticaria ^a

a. AEs considered to be related to study medication by the investigator.

b. Fatal SAE

c. Relationship unknown.

6.5. Adverse Events and Safety Assessments of Special Interest

6.5.1. Hepatobiliary Laboratory Abnormalities

Background

The potential for hepatobiliary side effects was analyzed because of evidence of liver toxicity in toxicology studies at non-tolerated doses in rats and dogs and because the predominant route of excretion for eltrombopag in humans is hepatic (approximately 60%). In addition, eltrombopag is an inhibitor of OATP1B1, which is also one of the transporters that move indirect bilirubin from the serum into the liver cells. Therefore, eltrombopag-mediated inhibition of OATP1B1 may cause elevation of indirect bilirubin in subjects treated with eltrombopag, as has been shown for other drugs [Campbell, 2004; Cui, 2001].

To assess the potential for hepatobiliary side effects, data across the ITP clinical program was analyzed according to a draft FDA guidance document on the pre-marketing clinical evaluation of drug-induced liver injury (DILI), issued in October 2007. The draft guidance document recommends evaluation of patients with elevations of aminotransferases (AT: ALT and AST), bilirubin and alkaline phosphatase (AP), beginning at $\geq 3x$ ULN (AT) and $>1.5x$ ULN (bilirubin and AP). Of particular importance are elevations of AT $>3x$ ULN in conjunction with bilirubin $>1.5x$ ULN not associated with confounding factors (Hy's Rule). GSK has followed this guidance in the analysis of hepatobiliary laboratory abnormalities across eltrombopag clinical trials and results are presented below.

Clinical Data

In the placebo- controlled trials, 16/164 subjects (10%) who received any dose of eltrombopag met at least one of the FDA criteria for assessment of hepatobiliary laboratory abnormalities, compared to 5/67 subjects (8%) in the placebo group. Further analysis of the hepatobiliary laboratory data showed that more subjects receiving eltrombopag treatment (n=11; 7%) had pre-existing elevations of hepatobiliary laboratory values as compared to subjects in the placebo treatment group (n=3; 5%). Across the entire ITP program, the incidence of FDA-defined hepatobiliary laboratory abnormalities in subjects who received eltrombopag was 9% (29/330; excluding subjects from the blinded RAISE study). In the blinded RAISE study, the incidence of subjects with hepatobiliary laboratory abnormalities was 10% (20/196).

Three patients exposed to eltrombopag across the program had elevations of AT $\geq 3x$ ULN and total bilirubin $>2x$ ULN, all associated with confounding factors. Details for each patient are provided below:

- One patient in TRA100773A had elevated aminotransferases (AT) $>3x$ ULN in conjunction with total bilirubin $>2x$ ULN. This subject died from cardiopulmonary failure, probably due to sepsis of pulmonary origin. This subject had a medical history of pneumonectomy for right lung carcinoma with concomitant medications including prednisone due to asthma and emphysema and experienced SAEs of renal insufficiency and hepatitis which were considered by the investigator as related to study medication. According to two independent pathologists reviewing the autopsy material, there was marked centrilobular congestion in the liver with focal ischemic necrosis consistent with a terminal low-flow state due to severe heart failure with no inflammatory changes in the liver. This subject is not considered a Hy's Rule case due to the confounding factors.
- One patient had pre-existing abnormal hepatobiliary laboratory values at baseline (ALT of $3.6x$ ULN, AST of $2.1x$ ULN, and a total bilirubin of $1.1x$ ULN). The subject also had a history of cholecystitis, and cholecystectomy and while in EXTEND, on study day 258, this patient had an SAE of acute cholangitis with peak levels of ALT $4.8x$ ULN, AST $5.7x$ ULN, bilirubin $5.3x$ ULN, and AP $1.5x$ ULN. At the onset of the SAE, the subject had symptoms of sudden epigastric pain, abdominal tenderness, and vomiting. These symptoms resolved a few days after initiation of intravenous antibiotic treatment. Per protocol, the treatment with

eltrombopag was stopped on Study Day 294 due to the GSK Liver Stopping Criteria. However, the clinical chemistry tests at the day of stopping eltrombopag already showed a decrease of ALT to 1.5x ULN, of AST to 1.1x ULN, and of bilirubin to 4.6x ULN, while AP had returned to the normal range. Albumin levels remained WNL during the entire study period. The subject took several concomitant ITP and non-ITP medications including azathioprin, cyclosporine A, as well as metformin, simvastatin, amoxicillin+clavulanate, lorazepam and chlorphenamine, occasionally among others. There were no clinical sequelae. This subject is not considered a Hy's Rule case due to the confounding factors.

- One patient's bilirubin elevation (maximum 4.3xULN) was documented as indirect hyperbilirubinemia (90% of the total bilirubin). Hemolysis was ruled out and the reason for indirect hyperbilirubinemia remained unclear. The increase in bilirubin preceded the start of the increase of ALT by 49 days. The initial ALT elevation began approximately 3 months following the first dose of eltrombopag in EXTEND and peaked at 6.5x ULN. Albumin remained WNL during the entire study period. There were no clinical sequelae. This subject is not considered a Hy's Rule case due to indirect hyperbilirubinemia.

Hepatobiliary laboratory abnormalities in Asians and White Caucasian subjects

The percentage of subjects in each study who received eltrombopag and met the FDA criteria for assessment of hepatobiliary laboratory abnormalities were analyzed and are presented by race (Asians and White Caucasians), along with the associated odds ratio (95% CI) of Asians/White Caucasians (Table 29).

Table 29 Hepatobiliary Laboratory Abnormalities That Met the FDA Criteria by Race

Study	Race	N	HBLA, n(%)	Odds Ratio (95% CI)
TRA100773A	Asian	19	3 (16)	1.66 (0.37, 7.38)
	White Caucasian	59	6 (10)	
TRA100773B	Asian	12	2 (17)	2.45 (0.39, 15.25)
	White Caucasian	53	4 (8)	
EXTEND	Asian	30	5 (17)	5.12 (1.38, 19.01)
	White Caucasian	133	5 (4)	
REPEAT	Asian	10	0	ND
	White Caucasian	47	2 (4)	
RAISE ^a	Asian	34	6 (18)	2.70 (0.91, 8.05)
	White Caucasian	136	10 (7)	

a. Treatment currently blinded.
 ND = not determined

In the EXTEND study, it appears that Asians had a higher incidence of hepatobiliary laboratory abnormalities than White Caucasians. However, for the whole Asian population, maximum shift from baseline figures for AST, ALT, bilirubin and AP did not reveal a general trend towards greater shifts from baseline in Asians. No clinically

meaningful differences in the hepatobiliary safety profile of eltrombopag were found with regard to age and sex.

Summary

Eltrombopag treatment can be associated with hepatobiliary laboratory abnormalities. However, there were no deaths caused by these abnormalities, there were no lasting clinical sequelae, and no subjects met Hy's Rule. The reason for the apparent increased frequency of hepatobiliary laboratory abnormalities in Asian patients compared to White Caucasians is currently unclear, and could be related to an increased exposure to eltrombopag in Asians (Section 4.1).

Details regarding management of this identified risk are discussed in Section 7.

6.5.2. Overall Assessment of Thromboembolic Events

Background

There is evidence that patients with ITP have a higher risk of thromboembolic complications compared to a non-ITP population. The incidence of thromboembolic events reported in patients with chronic ITP in the literature is 3% [Aledort, 2004]. In a retrospective epidemiology study examining a large U.S. health claims database, 6.9% of ITP patients experienced at least one thromboembolic event, compared to 4.0% in non-ITP patients. The adjusted incidence rate ratio (IRR) of occurrence of any thromboembolic events comparing the ITP population to non ITP populations was 1.80 (95% CI 1.45 – 2.23) [Study WEUKSTV1116]. In clinical trials with another agent that stimulates platelet production, the incidence of thromboembolic events in patients exposed to romiplostim (4.4%) was nearly identical to that of patients exposed to placebo (4.3%) [Romiplostim briefing document].

Clinical data

There have been thromboembolic events reported during treatment with eltrombopag in clinical trials in subjects with chronic ITP. However, the frequency (2.6%) was similar or less than that reported in the literature (3%) [Aledort, 2004], in epidemiology studies (6.9 %) [Study WEUKSTV1116] and in studies with another thrombopoietic agent (4.4 %) [Romiplostim briefing document].

A total of 11 subjects had a confirmed or suspected thromboembolic event (Table 30). Platelet counts proximal to the event (the most proximal count) ranged between 14 Gi/L and 407 Gi/L, and 6 of 11 subjects had platelet counts below 100 Gi/L at the time of the event. All patients had at least one risk factor for thromboembolic events. The most frequent risk factors were:

- Hospitalization prior to the thromboembolic event without prophylactic anticoagulation in 4 patients with venous thromboembolism (EXTEND: 1133 and 1272; RAISE: 589; and TRA100773A: 144); and

- Treatment with IVIg 5-8 days before the thromboembolic event in 3 patients (EXTEND: 71 and 1272, and RAISE: 589); the use of IVIg has been reported as a risk factor for thromboembolic events [Marie, 2006].

Table 30 Thromboembolic Events in the ITP Clinical Program

Study	Subject ID	Event(s)	Outcome
TRA100773A	144	Pulmonary embolism; emboli in peripheral vessels of kidney and liver	Fatal
EXTEND	55	Transient ischemic attack	Resolved
EXTEND	71	Pulmonary embolism	Resolved
EXTEND	81	Deep vein thrombosis	Improving
EXTEND	1133	Pulmonary embolism	Resolved
EXTEND	1163	Unsteadiness, speech impairment, dizziness (suspected ^a prolonged reversible ischemic neurologic deficit)	Resolved
EXTEND	1272	Deep vein thrombosis	Fatal
EXTEND	1273	Deep vein thrombosis	Resolved
RAISE ^b	589	Pulmonary embolism	Resolved
RAISE ^b	641	Pulmonary embolism	Resolved
RAISE ^b	896	DVT	Resolved

a. Suspected case was identified based on symptoms potentially compatible with thromboembolism reported as AEs, even when a thromboembolic event was not diagnosed or reported by the investigator.

b. All 3 RAISE subjects were unblinded to fulfil regulatory reporting requirements and were receiving eltrombopag.

Two patients with thromboembolic events died due to sepsis of pulmonary origin. All remaining patients recovered from the confirmed or suspected thromboembolic event.

Platelet function

Platelets generated in response to treatment with eltrombopag have a similar aggregation and activation pattern compared to platelets from control subjects not exposed to eltrombopag based upon a comprehensive series of non-clinical and clinical studies designed to ascertain the effect of eltrombopag on platelet function. Results are summarized below:

- platelet function in the presence of eltrombopag in vitro does not enhance activation or aggregation of platelets obtained from healthy volunteers;
- platelets from healthy volunteers and ITP subjects treated with eltrombopag function normally in in-vitro assessments of platelet activation and aggregation;
- the lifespan of platelets produced following treatment with eltrombopag appears to be normal (7-10 days) as platelet elevations are maintained one week following discontinuation of eltrombopag and return to baseline levels two weeks following discontinuation; and

- platelets produced following treatment with eltrombopag effectively reduce bleeding signs and symptoms (assessed via the WHO Bleeding Scale) and allow subjects to successfully master hemostatic challenges without additional support to elevate platelets or minimize bleeding.

Summary

Based on the data in the literature, epidemiological findings and those reported during the development of other thrombopoietic agents, the data from the eltrombopag ITP program do not seem to indicate an increased risk for thromboembolic events during or after treatment with eltrombopag. Additionally, eltrombopag produced platelets have a similar aggregation and activation pattern compared to platelets from healthy volunteers or ITP patients not exposed to eltrombopag.

Details regarding management of this potential safety risk are discussed in Section 7.

6.5.3. Transient Decrease in Platelet Counts

Background

As an agonist of the TPO-R, eltrombopag stimulates platelet production. Following removal of eltrombopag therapy in patients with chronic ITP, it is expected that platelet counts will return to baseline levels. Thorough analyses of all ITP clinical studies were performed to determine whether any systematic or patient specific decrease in platelet counts below baseline levels were observed within the 4 weeks following discontinuation of eltrombopag.

The most important potential effect of withdrawal from eltrombopag and the subsequent return of platelet counts to baseline levels is the occurrence of bleeding complications. The use of rescue medication and transient decreases in platelet counts (below 10 Gi/L and a decrease of >10 Gi/L from baseline [Bussel, 2006]) are other means to assess withdrawal effects of eltrombopag.

The intermittent, short-term dosing study (REPEAT) was designed specifically to analyze the effect of withdrawal of eltrombopag following 3 repeated cycles of short-term treatment. Participants in REPEAT had baseline platelet counts between 20 Gi/L and 50 Gi/L, in contrast to the patients in the pivotal, short-term studies who had platelet counts <30 Gi/L. Two analyses were performed in addition to those mentioned above: identification of patients with an absolute platelet count below 20 Gi/L and a decrease of >10 Gi/L from baseline and identification of patients with a shortened off-therapy period between cycles of treatment.

In the long-term dosing study (EXTEND), patients who were permanently withdrawn from eltrombopag and patients who had temporarily dose interruptions of eltrombopag were also assessed (bleeding AEs, rescue medication and transient decrease of platelet counts). As in REPEAT, the analysis included patients with an absolute platelet count below 20 Gi/L and a decrease of >10 Gi/L from baseline.

Clinical data

Short-term, placebo-controlled pivotal trials (TRA100773A and TRA100773B)

In the placebo-controlled pivotal trials, no systematic trend was observed when the median lowest platelet counts in the 4 weeks following discontinuation of study medication (placebo: 15 Gi/L; eltrombopag 50mg: 17 Gi/L) were compared to the median baseline platelet counts in each treatment group (placebo: 17 Gi/L; eltrombopag: 17.5 Gi/L).

In the placebo-controlled pivotal studies, 10% of patients treated with eltrombopag and 6% of patients treated with placebo experienced a transient decrease in platelet counts after treatment with eltrombopag had been stopped. With the exception of 1 female subject with a history of menorrhagia who experienced a Grade 3 AE of menorrhagia during the post-therapy observation period, these drops in platelet counts were not associated with clinically meaningful bleeding events.

Intermittent short-term dosing study (REPEAT)

No clinically significant bleeding AEs were reported within four weeks following discontinuation of eltrombopag in any cycle of REPEAT. Two subjects reported minor bleeding (Grade 2 AE of 'bruised ankle' after a fall; and Grade 1 petechiae) AEs during an off-therapy period.

Eleven out of 66 subjects received a rescue medication (conservatively defined as a composite of any new ITP medication, any increased dose of concomitant ITP medication from baseline, platelet transfusion and/or splenectomy) after the last dose of eltrombopag in the study. Six of 11 received a rescue medication which could have resulted in rapid elevation within days after initiation.

A total of 20 subjects (30%) had a transient decrease in off-therapy platelet counts <20 Gi/L and 10 Gi/L less than baseline compared to baseline; 7 patients (11%) had a transient decrease of platelet counts <10 Gi/L and 10 Gi/L less than baseline. No clinically relevant consequences associated with these transient decreases were observed.

A total of 25 subjects had a shortened off-therapy period in at least one cycle.

Long-term dosing study (EXTEND)

In EXTEND, nine out of 207 patients had a transient decrease in platelet counts from baseline following either a dose interruption or a permanent withdrawal of eltrombopag. Four of the 9 patients had platelet counts <20 Gi/L and a decrease of at least 10 Gi/L from baseline, and 5 of the 9 patients had platelet counts <10 Gi/L and at least 10 Gi/L less than baseline. None of these patients with a transient decrease in platelet counts following either dose interruption or permanent discontinuation of eltrombopag had bleeding AEs reported in conjunction with the transient decrease. Three of the 9 patients with a transient decrease in platelet counts received rescue medication following a dose interruption of eltrombopag.

Summary

As expected following discontinuation of eltrombopag, platelet counts returned to near baseline levels, usually within 2 weeks. In the pivotal studies, 10% of patients treated with eltrombopag and 6% of patients treated with placebo had a transient decrease in platelet counts <10 Gi/L and 10 Gi/L less than baseline. This numerical decrease in platelet counts was not associated with a clinically significant increase in bleeding.

Following repeated cycles of administration of eltrombopag in REPEAT, no increase in the incidence or severity of transient decrease of platelet counts was observed across cycles. No clinically significant bleeding was observed following discontinuation of eltrombopag in any cycle.

Little evidence of transient decreases in platelet counts following discontinuation or interruption of eltrombopag was observed in the EXTEND study.

The definition of the transient decrease of platelet counts below baseline has not been validated, and its application in clinical trials has shortcomings: 1) a detailed, systematic evaluation of transient decrease of platelet counts after treatment with other ITP drugs, like IVIG or steroids, has not been performed. This lack of comparison makes it difficult to put the fluctuation of platelet counts after treatment with eltrombopag into perspective; 2) in the pivotal studies, one baseline platelet count value is compared to several post-dosing platelet count values; 3) platelet counts vary in patients with chronic ITP, spontaneously or due to viral or bacterial infections; and 4) the measurement of platelet counts below 10 Gi/L has limited precision.

6.5.4. Blood Smear and Bone Marrow Analyses

Background

Data from other thrombopoietic agent studies suggest there is a potential risk exists that chronic stimulation of megakaryocytes with thrombopoietin receptor agonists might lead to a pathological increase of reticulin or collagen fibers in the bone marrow. The main concern is that prolonged, chronic treatment with these drugs could lead to an increase of reticulin and collagen fibers in the bone marrow, ultimately replacing the bone marrow and thereby causing a clinical situation comparable to primary osteomyelofibrosis.

Myelofibrosis has been associated with many different types of conditions including autoimmune diseases [Frisch, 1982; Aharon, 1997]. One particular study analyzed the occurrence of reticulin fibrosis in 40 subjects with ITP identified from clinical records in a retrospective survey of BM biopsy material [Mufti, 2007]. In that analysis, 13 ITP subjects (33%) had no reticulin (Grade 0), whereas 27 ITP subjects (67%) showed a reticulin formation between Grade 1 and Grade ≤ 2 . In hematologically healthy individuals, reticulin fibers have been documented in the bone marrow (Grade 1 in 27% and Grade 2 in 4% of individuals) [Beckman, 1990]. This mild to moderate increase in reticulin fibers in the bone marrow of healthy volunteers and subjects with chronic ITP complicates the analysis of a potentially drug-induced deposition of reticulin/collagen fibers in the bone marrow.

The best available methodology for the diagnosis of increased reticulin or collagen fibers in the bone marrow is a bone marrow biopsy. The sponsor originally planned to request bone marrow biopsies as a requirement for entry in the ITP studies with eltrombopag, but got strong feedback from subjects and investigators that such a request would severely limit the willingness of subjects to enter the clinical trials. Most patients with chronic ITP are reluctant to agree to this invasive, painful procedure that usually has little, if any therapeutic consequences for the treatment of their chronic ITP. Therefore, the sponsor looked for other, indirect and less invasive ways to track clinical consequences of a possible negative effect of eltrombopag on the bone marrow, as described below, primarily through repeated analyses of peripheral blood smears.

In the intermittent short-term study (REPEAT) and the long-term studies (EXTEND and RAISE), automated WBC differentials were requested each time a blood sample was taken to measure the platelet count. If the automated WBC differentials revealed evidence of abnormal cells, a peripheral blood smear checked by an experienced laboratory technician or a physician was to be performed. Should the peripheral blood smear confirm the presence of immature or dysplastic cells not consistent with the diagnosis of ITP, a bone marrow biopsy was to be performed.

All collected peripheral blood smear data were analyzed and searched at the investigator sites for the occurrence of immature cells, such as myeloblasts, nucleated red blood cells (NRBC) or any other abnormality in the blood smear that would not be typical for subjects with chronic ITP. The data documented below from the REPEAT, EXTEND and RAISE studies is up to and including the data cut-off date for the 120 day safety update.

Effective September 10, 2007, the long-term safety study TRA105325/EXTEND was amended to include a bone marrow biopsy for subjects dosed with eltrombopag for one year to monitor bone marrow morphology following long term treatment with eltrombopag. The reasoning was that subjects who had experienced clinical benefit with the drug as evidenced by their long term participation in the EXTEND study, would be more agreeable to a bone marrow examination compared to the subjects at the beginning of the study when it is unclear whether they would respond to the drug or not. An inherent weakness of this strategy is that no baseline morphology before start of eltrombopag therapy is available for these subjects.

The investigators were specifically instructed to ask the pathologists for evidence of increased reticulin or collagen fibers in the bone marrow biopsies.

Clinical data

Peripheral blood smear

As of the safety update cut-off date for REPEAT, EXTEND, and RAISE, 9,149 WBC differentials were performed and prompted a total of 97 blood smears from 51 subjects across the 3 studies.

Thirteen subjects had immature or dysplastic findings that were either nonspecific (e.g. acanthocytes), or compatible with ITP (e.g. Howell Jolly bodies in splenectomized subjects or a small number of meta-/myelocytes [$\leq 2\%$]).

Five subjects had peripheral blood smear findings of potentially clinical relevance (1% nucleated RBCs or 1% peripheral blasts); however, these findings were found on a single blood smear for each subject, they were not reproducible upon re-testing and therefore did not prompt bone marrow biopsies. No subject had peripheral blood smear findings of potential clinical relevance upon re-testing.

Bone marrow biopsies

Bone marrow biopsies were collected from 19 of 56 eligible subjects in EXTEND who were treated with eltrombopag; 17 of them had been treated for >12 months (Table 31). The obtained bone marrow reports were analyzed for a description of the following: reticulin staining, presence of reticulin fibers, collagen fibers, and bone marrow cellularity. The median age of subjects with bone marrow biopsies was 58 years (range: 35-82).

Bone marrow cellularity data is available from 17 subjects of the 19 subjects with a bone marrow biopsy. No subject had a significant decrease in cellularity documented on their bone marrow report. Cytogenetics and bone marrow blast count data were available for 5 and 8 subjects, respectively, and none of these subjects showed an abnormal karyotype or bone marrow blast count (>3%).

Reticulin information was described as none, focal, mild, moderate, or by Grade (Bauermeister Scale: 0-4, or European Consensus Guidelines 2005: 0-3). Reticulin or collagen fibers were detected in 7 subjects (including one subject with pre-treatment biopsy showing reticulin fibers). There were no AE reports, clinical consequences, laboratory abnormalities or withdrawal from treatment as of 12 April 2008.

No subject had documentation of reticulin Grade >3. Five of the 7 subjects (Subjects 53, 124, 127, 128, 1161) reported a “mild” or “focal-mild” reticulin formation, including Subject 127, mentioned above with pre-existing reticulin fibers documented. Two of the 7 subjects (Subjects 61 and 1241) had a report of collagen formation and are therefore described below.

- Subject 61, an 80 year old female had a bone marrow report that described “reticulin and trichrome stains show moderate fibrosis, moderate increase in Type 3 collagen (reticulin) and a mild increase in Type 1 collagen. These findings may be related to the subject’s underlying ITP and/or therapy.” The diagnosis in the summary statement of the report stated “1) megakaryocytic hyperplasia and atypia and 2) atypical lymphoid aggregates.” The subject’s CBC was normal with the exception of platelet count (66 Gi/L) and the subject is continuing treatment in EXTEND.
- One subject had documentation of reticulin by the pathologist in the summary statement of the bone marrow report (Subject 1241). The bone marrow report for this subject, a 54 year old male with chronic ITP in Thailand, states “hypercellular trilineage marrow with proliferation of abnormal (dysplastic) megakaryocytes”

together with “myelofibrosis grade 2/3” (using European Consensus Guideline 2005 Grading). Although this subject did not have a platelet response to eltrombopag >50 Gi/L, platelet counts increased from baseline (4 Gi/L) to >30 Gi/L and clinical benefit was documented by the investigator as a reduction in bleeding symptoms. Currently, this subject is continuing in EXTEND. The results of a bone marrow several years prior to receiving eltrombopag were received after submission of the 120-day safety update, and showed pre-existing Grade 1 reticulin.

Summary

No subject had peripheral blood smear findings of clinical relevance upon re-testing.

No clinically relevant effects of eltrombopag on the bone marrow in subjects treated for a median of 13 months with eltrombopag in the EXTEND study were detected. The analysis is hampered by the small number of available 12 month biopsies and the lack of pre-treatment biopsies for comparison in the majority of subjects.

The sponsor continues to collect more bone marrow biopsies during long term treatment in EXTEND to better characterize potential long term treatment effects of eltrombopag on the bone marrow in subjects with chronic ITP.

Table 31 12 Month Bone Marrow Biopsies (received as of 08 April 2008)

Subj. ID	Age	Months ^a	Platelets ^b Gi/L	WBC x10 ⁹ /L	Hb (g/dl)	Reticulin Grade*	Reticulin increase*	Collagen	Cellularity*	Cellularity (%)
12	77	2	29	9.1	118	n.c.	n.c.	n.c.	Mild-moderate to hyper	60-70%
53	82	17	59	8.5	14.6	2	mild	no	hyper	50%
61	80	11	66	6.6	12.6	NA	moderate	Mild increase	n.c.	80%
76	68	12	50	6.7	13.7	n.c.	n.c.	n.c.	normal-mildly hyper	40-50%
124	39	18	6	5.8	3.7	n.c.	focal, mild	n.c.	hyper	80%
125	55	17	69	6.5	12.9	0	no	n.c.	normal	40%
126	35	17	82	9.9	16.3	0	no	n.c.	normal	70%
127	58	8	29	6.7	12.2	n.c.	focal, mild	n.c.	mildly hyper	60-70%
128	62	17	3	10.5	9.5	n.c.	focal, mild	n.c.	mildly hyper	60%
141	45	13	7	9.5	12.4	n.c.	n.c.	n.c.	normal	40%
643	36	12	60	7.2	10.1	n.c.	no	n.c.	normal	n.c.
816	62	18	205	6.2	15.1	n.c.	n.c.	n.c.	n.c.	n.c.
818	52	15	99	5.9	14.1	0	focal, mild	n.c.	n.c.	60%
819	45	12	70	8.16	16.4	0	some	no	n.c.	50-55%
822	76	11	122	5.15	102	n.c.	n.c.	n.c.	n.c.	n.c.
1161	60	13	123	6.9	13.2	2+	mild	n.c.	normal-mildly hyper	n.c.
1211	43	12	20	6.02	11.2	n.c.	n.c.	n.c.	n.c.	20-40%
1212	69	12	72	10.8	12.1	n.c.	n.c.	n.c.	n.c.	20-30%
1241	54	15	11	6.0	11.4	MF-2	See Grade	yes	Normal-mildly hyper	n.c.

SB497115/TRA 105325

n.c.=no comment made in the bone marrow report.

- a. Months on study until bone marrow exam was done.
- b. Platelet count most proximal to the bone marrow biopsy.

6.5.5. Malignancies

Background

The association of ITP and hematological malignancies has been widely recognized [Soederberg, 2006; Stern, 2007].

In a GSK sponsored epidemiology study [Study WEUKSTV1116], submitted with the NDA to the FDA), the risk of blood malignancies among subjects with chronic ITP (N=3,131) compared to a non ITP population (N=9392) was examined. The analysis used eligibility and medical claims collected during 2000-2006 from a large US health insurance plan. In the statistical modelling, after adjusting for age, gender and other variables, the adjusted IRR for ITP vs non-ITP populations was 3.88 (95% CI: 1.43-10.56) for lymphoma overall , 5.03 (95% CI: 1.84-13.75) for Non-Hodgkin's lymphoma (NHL); and 32.71 (95% CI: 7.58-141.14) for leukemia. Although the confidence intervals were wide, all adjusted IRRs were elevated and statistically significant. The study found an association of an increased risk for select blood cancers for subjects with chronic ITP compared to the non ITP population.

At the ODAC meeting on 12 March 2008 for romiplostim, cases of solid and hematological malignancies were reported in the romiplostim ITP safety database. Therefore, the eltrombopag safety database was searched for newly diagnosed malignancies in the pivotal and supportive ITP studies.

Clinical data

Compiling all available data across the clinical ITP program, the occurrence of all newly diagnosed malignancies is 3/460 (0.7%), including the 130 subjects from RAISE who are estimated to have received eltrombopag. Two carcinomas were diagnosed during treatment with eltrombopag (pancreatic carcinoma and sigmoid colon adenocarcinoma) and one subject was diagnosed with diffuse large B-cell lymphoma. Brief narratives of each subject are provided below.

- Subject 711: A 71 year old white Caucasian male diagnosed with ITP in 1995. He had a history of intermittent abdominal pain for which a cholecystectomy was performed in December 2006; abdominal pain persisted after the surgery. In January 2007 diabetes was diagnosed. He received the first dose of eltrombopag in June 2007, with a good platelet response. Adverse events reported included nausea, anorexia and worsening of abdominal pain. Hyperbilirubinemia and weight loss were documented. An abdominal CT scan showed a pancreatic body mass causing obstruction of the pancreatic duct. One week after the last dose of eltrombopag in Cycle 3, an endoscopic ultrasound with fine needle aspiration of the pancreatic lesion was performed (November 2007) which confirmed the diagnosis of primary pancreatic carcinoma. The lesion was deemed non-resectable and chemotherapy was initiated. The cancer was considered not related to eltrombopag by the investigator.
- Subject 12: A 77 year old white female diagnosed with ITP in 2004 was enrolled in EXTEND in January 2008. Her medical history is significant for hypertension, a non

specified arrhythmia and fatigue. In the prior study (REPEAT), persistent fatigue was noted. On study day 49 the subject palpated nodes on her anterior chest wall and posterior neck. No fever or night sweats were reported. A breast ultrasound showed a mass which upon initial biopsy did not show malignant changes. An abdominal CT scan showed a 'large nodal mass'. An additional biopsy of chest wall nodes performed on study day 57 led to the diagnosis of diffuse large B cell lymphoma. The event was reported as a Grade 3 SAE, considered not related to eltrombopag, and the subject was withdrawn from EXTEND.

- Subject 589: A 59 year old white Caucasian female who received her first ITP treatment in 2006 was enrolled in RAISE in April 2007. Her baseline platelet count was 6Gi/L; the subject did not respond to treatment with study medication. On study day 91 she experienced minor rectal bleeding. A rectosigmoid colon tumor was diagnosed following a colonoscopy. The cancer was reported by the investigator as a Grade 4 SAE with an unknown relationship to the study medication. To fulfil regulatory reporting requirements this subject was unblinded and had received eltrombopag 50mg, subsequently dose increased to 75mg. The subject was hospitalized and surgical exploration was scheduled for two days later. Treatment with study medication was discontinued. The subject received IVIg before surgery. The surgical procedure (hemicolectomy) took place as planned with no reported intraoperative complications. Pathology analysis revealed an adenocarcinoma of the rectosigmoid colon, classified as stage I, G2, pT2, pN0, V0, R0, with no lymph node involvement or metastases. On day 1 post-surgery the subject developed a bilateral pulmonary embolism, after which anticoagulation with heparin was started. On day 2 post surgery she required transfusion of red blood cells and laparotomy for intra-abdominal bleeding. On post operative day 8, a pneumonia was diagnosed; she was transferred and treated at another hospital and was discharged after five weeks. No modification in the platelet count has been noted since the removal of the tumor. After recovering from surgery and a subsequent pulmonary infection, the subject enrolled in the EXTEND study, where her platelet counts have not significantly improved with the treatment.

Summary

These data do not suggest an excess risk for the development of malignancies in subjects on treatment with eltrombopag.

6.5.6. Potential Risks Based on Non-clinical Observations

6.5.6.1. Cataract

Background

Based on preclinical findings in rodents, GSK consulted with external clinical ophthalmology experts and added detailed ocular assessments to the clinical studies. Chronic use of corticosteroids is perhaps the most well-known risk factor for development of cataracts. Therefore, the development of cataracts in subjects with chronic ITP enrolled in eltrombopag clinical trials should be viewed in light of the high

background incidence of cataracts in this subject population due to prior/current use of chronic corticosteroids.

Subjects enrolled in the TRA100773A, TRA100773B, REPEAT, EXTEND and RAISE were assessed for cataract risk factors and other ocular health history at their first ocular exam on study. The following assessments were performed at each ocular exam: visual acuity, slit lamp evaluation of anterior ocular structures using Age-Related Eye Disease Study (AREDS) lens opacity grading protocol, slit lamp biomicroscopy of posterior pole features, and indirect ophthalmoscopy of posterior and peripheral retinal features.

An independent Clinical Events Committee (CEC) was utilized to review the data from the ophthalmic assessments across the eltrombopag clinical development program. A CEC was assembled to provide external objective medical review of the ocular data because of the broad protocol definition of report of cataract, the low threshold for detection, and the considerable variability that exists regarding the clinical definition of a cataract.

The CEC members reviewed ophthalmologic data from the completed pivotal studies (TRA100773A and TRA100773B) at the time of this report and adjudicated the presence or absence of cataracts from treatment blinded data for subjects of interest. Where possible the CEC, made attributions of possible relatedness to study medication.

The CEC has not reviewed the data from the ongoing studies (REPEAT, EXTEND and RAISE). CEC review is planned when final study data are available.

Clinical data

The majority of the study population assessed in the pivotal studies, TRA100773A and TRA100773B, had risk factors associated with cataractogenesis, including chronic corticosteroid use, age and gender. Chronic corticosteroid use was the most frequently reported cataract risk factor. Of the 231 subjects in all treatment groups (30 mg, 50 mg, 75 mg, placebo) in the pivotal studies, 8 of the 161 subjects who had one or more ocular examinations reported events that met the criteria of either an incident report of cataract or progression of pre-existing cataract. Two of these subjects received placebo and 6 received eltrombopag (50 mg: 5 subjects; 75 mg: 1 subject)

While on study or in follow-up, 5 subjects had an incident report of cataract that was not observed at baseline. Three subjects reported progression of a pre-existing cataract while on study or in follow-up. All but one of these subjects reported risk factors for cataractogenesis at the first ocular exam on study. All subjects had use of corticosteroids prior to beginning treatment on study reported as a risk factor and/or documented as a prior medication.

None of the 8 'reports of cataract' met the protocol defined criteria for an ocular event of clinical concern (i.e. a visual acuity changes of >0.3 logMAR and/or changes of 2 or more grades on the AREDS scale, and/or progression requiring surgery). There did not appear to be a definitive relationship between these reports and treatment arm, duration of exposure to eltrombopag nor time to report of cataract.

Summary

Based on review of data from the pivotal studies the independent CEC has found no convincing signal of ocular toxicity related to eltrombopag in studies TRA100773A and TRA100773B.

In summary, the clinical data observed to date do not suggest that eltrombopag poses an increased risk for cataractogenesis.

6.5.6.2. Renal-related events

Background

Based on interim results from a 2-year carcinogenicity study in mice that showed dose-related renal tubular toxicity, subjects' safety data were analyzed for any signs, symptoms or diagnoses that could be directly or indirectly associated with compromised renal function, or renal toxicity. Medical review of all potentially renal-related AEs (e.g. any event including the terms “renal” or “kidney”, bilateral peripheral edema, newly diagnosed hypertension, sodium/potassium alterations) was performed and changes in creatinine concentrations from baseline were used as a surrogate to evaluate renal function in subjects.

In the intermittent short-term dosing study (REPEAT) and the longer term dosing studies (EXTEND and RAISE), serum creatinine values were evaluated for moderate changes from baseline (defined as the average of Screening and Day 1 creatinine values) of ≥ 27 $\mu\text{mol/L}$ (~ 0.3 mg/dL) and for two or more consecutive elevations of ≥ 27 $\mu\text{mol/L}$ (~ 0.3 mg/dL).

Clinical data

In the placebo-controlled pivotal, short term trials a similar incidence of potentially on-therapy renal-related AEs was observed in subjects treated with eltrombopag (5%, 8/164) and subjects treated with placebo (6%, 4/67). The events were generally mild (Grade 1) and none led to withdrawal from study medication.

In the intermittent or long-term studies, renal-related AEs were generally mild to moderate (Grade 1 or 2) and none led to withdrawal from study medication. The vast majority ($>95\%$) of subjects had serum creatinine values within normal ranges during the study. No Grade 3 or Grade 4 creatinine toxicity was observed in any of the studies. When serum creatinine values were evaluated for moderate changes from baseline (≥ 27 $\mu\text{mol/L}$ [≥ 0.3 mg/dl] and $> \text{ULN}$), $<3\%$ of subjects in each study met these criteria (at 2 or more consecutive assessments), and $<1\%$ had this change from baseline (at 2 or more consecutive assessments and $> \text{ULN}$ of creatinine value); there was no clear relationship to study drug treatment.

Summary

Based on the analysis of renal-related AEs and laboratory analyses across the ITP clinical program, eltrombopag does not appear to cause clinically meaningful adverse effects on renal function.

6.5.6.3. Skin and subcutaneous-related AEs

Background

Based on results in pre-clinical in vitro phototoxicity studies, skin and subcutaneous-related AEs were analyzed across the eltrombopag clinical program. The following specific skin- and subcutaneous-related events were investigated for a possible relationship to sun or ultraviolet light exposure: rash, pruritus, itching, skin exfoliation, skin discoloration, ulcer, dermatitis, urticaria.

Clinical data

In the placebo-controlled pivotal studies, on-therapy AEs classified under the system organ class of 'skin and subcutaneous' were distributed across both the placebo and eltrombopag treatment groups, with an incidence of 4% (3/67 subjects) and 9% (15/164 subjects), respectively. Most of the AEs were Grade 1 and considered related to study treatment. However, there was no pattern in the type of skin or subcutaneous AE reported across treatment arms. One subject who received eltrombopag 50mg developed a Grade 2 sun "poisoning rash" after visiting a solar tanning salon (photosensitivity reaction). This event resolved and was considered by the investigator to be unrelated to study medication. Two subjects who received 75 mg in TRA100773A, experienced events associated with sun exposure: one Grade 3 rash and one Grade 2 urticaria. Both events were considered by the investigator to be related to study medication. In the pivotal studies, 1 AE of urticaria led to a permanent withdrawal from study medication.

In the intermittent (REPEAT) or long-term studies (EXTEND and RAISE), the vast majority of events were Grade 1 and Grade 2 in severity. In REPEAT, 8 skin- and subcutaneous-related AEs were reported in 7 subjects (11%). In EXTEND, 40 events were reported in 28 subjects (14%) and in the blinded RAISE study, 38 subjects (19%) experienced 64 events. Two subjects in EXTEND had eltrombopag temporarily interrupted due to a skin or subcutaneous AE (Grade 2 urticaria; Grade 3 SAE of cellulitis) and 2 subjects in the blinded RAISE study were withdrawn from treatment as a result of a skin and subcutaneous-related AE (Grade 1 rash; Grade 2 urticaria). No AEs reported in these 3 studies were found to be associated with sun exposure, and there was no clear association between the onset of these skin- and subcutaneous-related events and study medication. Two of the skin and subcutaneous-related AEs led to a permanent discontinuation from study medication (both occurred in the long-term treatment study RAISE).

Subjects receiving eltrombopag are instructed to take appropriate precautions to avoid excessive exposure to strong direct sunlight and/or ultraviolet exposure and to use protective clothing, sunglasses and sunscreen.

Summary

No pattern in the type of skin or subcutaneous AE reported has been observed and no clear association between the onset of these skin- and subcutaneous-related events and study medication was found.

6.5.6.4. Cardiac-related events

Cardiac-related AEs were analyzed because eltrombopag was found to be an inhibitor of hERG channel tail current in vitro.

There was no effect on cardiac repolarization in a definitive QTc study and no evidence of cardiotoxicity was observed across the ITP clinical program in subjects treated with eltrombopag in the pivotal short-term, intermittent short-term or long-term dosing trials.

6.6. Exposure and Safety in Other Indications

6.6.1. Subjects with Hepatitis C – TPL102357

This was a double-blind, randomized, placebo-controlled, multi-center, dose-ranging, parallel group, phase II pilot study in male and female subjects with HCV infection and platelet counts of 20 to <70 Gi/L who were otherwise eligible to begin treatment with peginterferon and ribavirin. The results of the study were recently published in the NEJM [[McHutchison, 2007](#)].

Subjects were randomized equally (1:1:1:1) into one of four treatment groups and stratified according to baseline platelet count: 20 to <50 Gi/L and ≥ 50 to <70 Gi/L, to ensure equal distribution within treatment groups.

The study was conducted in two phases, Parts 1 and 2. Subjects were treated with oral tablets of eltrombopag at 30 mg, 50 mg, 75 mg, or placebo once daily for a total duration of 12-16 weeks, starting 4 weeks prior to initiating weekly anti-viral therapy (Part 1) and for 8-12 weeks during weekly anti-viral therapy (Part 2). The study was stopped early with 74 subjects enrolled because the statistical stopping criterion was met ($p < 0.0001$ for the analysis of the primary endpoint) in the second interim analysis.

The overall incidence of AEs in the entire study is summarized ([Table 32](#)).

Table 32 Overall Incidence of Adverse Events in Study TPL102357 (Part 1 and Part 2) – Safety Population

During Entire Study	Treatment Group, n (%)			
	Placebo N=18	30mg N=14	50mg N=19	75mg N=23
Any AE	11 (61)	14 (100)	17 (89)	20 (87)
Any SAE	1 (6)	3 (21)	1 (5)	2 (9)
AEs related to study medication	3 (17)	5 (36)	8 (42)	8 (35)
AEs leading to withdrawal	0	3 (21)	1 (5)	1 (4)

The most common side effects noted during Part 1 (eltrombopag alone) were headache, dry mouth, upper abdominal pain, and nausea, which were predominantly of mild severity. No evidence of a dose-response effect was seen. In Part 2 (eltrombopag and antiviral therapy), side effects were consistent with those associated with peg-interferon-based therapy and eltrombopag did not appear to add to the toxicity that these subjects experienced.

Two hepatobiliary AEs were reported; both occurred while on-therapy. One subject had biliary tract disorder and 1 subject had hyperbilirubinemia.

- Subject 327, a 56-year-old white female, was in the 50 mg eltrombopag treatment group. During Part 2 (antiviral phase) on Day 122 while receiving eltrombopag and 1 day after completing ribavirin therapy, this subject experienced a biliary tract disorder (increase in the size of the extrahepatic bile duct). The event was a non-serious, Grade 1 event that did not resolve and was not considered to be related to study medication by the investigator.
- Subject 764, a 72-year-old white female with a history of diabetes mellitus, was in the 50mg eltrombopag treatment group. Post study the subject was determined to have had decompensated liver disease at baseline. During Part 2 (antiviral phase) on Day 36, this subject experienced an adverse event of hyperbilirubinemia (83.79 $\mu\text{mol/L}$). The event was a non serious, Grade 1 event that did not resolve and was not considered to be related to study medication by the investigator. The event occurred 8 days after interrupting eltrombopag treatment and while receiving antiviral medication. Her bilirubin values were high and of potential clinical concern throughout the study. Her baseline value was 54.72 $\mu\text{mol/L}$ and the range throughout the study was 25.31 to 104.3 $\mu\text{mol/L}$.

No patterns of concern regarding other clinical chemistry laboratory evaluations were identified based on dosing with eltrombopag. One diabetic subject had a Grade 4 glucose value and one subject had a Grade 4 hyperkalemia value during the post-treatment phase.

As expected for this population, most subjects enrolled into TPL102357 had elevated ALT, AST and bilirubin at baseline. Scatter plots of hepatobiliary tests, with individual subject's maximum value as a function of their baseline value both expressed as ULN, were produced to identify subjects who experienced a change from baseline.

Based on the scatter plots of liver function tests, 2 subjects were identified with liver function tests (ALT) considered to be outliers. No subjects were considered to be outliers with respect to AST or total bilirubin. The results are consistent with this subject population. These subjects are highlighted below.

Subject 356, a 47-year-old white male, was receiving eltrombopag 75 mg. The subject completed 16 weeks treatment with eltrombopag and was continuing with peginterferon therapy at the 20-week follow up visit. This subject had a screening ALT of 7.73x ULN with a peak at Day 113 of 10.15x ULN (1.3X baseline). By the 20 week follow-up, the ALT was 3.84x ULN.

Subject 25, a 49-year-old hispanic male, was receiving eltrombopag 75 mg. The subject completed 12 weeks treatment with eltrombopag and was continuing with peginterferon therapy at the 20-week follow up visit. He had a Day 1 ALT of 3.39x ULN with a peak at Day 22 of 10.9x ULN (3.2X baseline). By the 20 week follow-up visit, the ALT was 2.48x ULN.

No important adverse events related to the hepatobiliary system were observed during the study, and no signal of drug-induced liver injury was detected.

6.6.2. Subjects with Cancer – SB497115/003

Study SB497115/003 was a randomized, double-blind, four-arm, parallel group, placebo-controlled, multi-center phase II study to evaluate the efficacy, safety, and pharmacokinetics of oral eltrombopag in cancer subjects with an advanced solid tumor who were receiving multiple cycles of carboplatin/paclitaxel (21 days per cycle), and evaluate the effects of eltrombopag on chemotherapy induced thrombocytopenia. The study was designed to allow efficient identification of doses which were efficacious, while minimizing the risk of exposing subjects to doses that were ineffective, or presented safety concerns.

Subjects with an advanced solid tumors, received multiple cycles of carboplatin/paclitaxel chemotherapy every 21 days, and were randomized in equal proportions to one of four groups: eltrombopag 50 mg, 75 mg, 100 mg, or placebo. Subjects were chemotherapy naïve, with histologically or cytologically confirmed advanced solid tumors. Carboplatin and paclitaxel were administered on day 1 and eltrombopag or placebo was administered orally on days 2 through 11 of each 21 day cycle. Eltrombopag/placebo was administered for at least 2 cycles, and additional cycles of eltrombopag/placebo were permitted if chemotherapy was continued, the subject appeared to benefit from the study drug, and the subject had not encountered greater than Grade 2 toxicity associated with the study drug. Subjects were permitted to receive a maximum of eight cycles of chemotherapy plus eltrombopag/placebo.

The overall incidence of AEs and AEs related to study medication was similar across each treatment group. Overall, 87% of subjects experienced at least one AE during the study (Table 33).

Table 33 Overall Incidence of Adverse Events in Study SB497115/003

During Entire Study	Treatment Group, n (%)			
	Placebo N=46	50mg N=44	75mg N=44	100 mg N=46
Any AE	39 (85)	38 (86)	38 (86)	42 (91)
Any SAE	9 (20)	4 (9)	7 (16)	10 (22)
AEs related to study medication	15 (33)	8 (18)	13 (30)	16 (35)
AEs leading to withdrawal	8 (17)	3 (7)	8 (18)	13 (28)

AEs were subcategorized using the categories of “Hematologic AEs” and “Non-hematologic AEs”. Hematologic AEs include any adverse event that falls into the NCI CTCAE category of Blood/Bone Marrow. Non-hematologic AEs include all other AEs.

Neutropenia was the most common hematologic AE reported, where nausea and alopecia were the most common non-hematologic AEs reported. Neutropenia was reported more frequently in the placebo group while alopecia and arthralgia were reported more frequently in the 50 mg group. Vomiting was reported more frequently in the placebo and 100 mg groups. Overall, the pattern of AEs among the different study treatment groups was similar. This safety profile is as expected for subjects receiving carboplatin and paclitaxel.

A total of 28 subjects experienced on-therapy SAEs during the study: 7 subjects in the placebo treatment group, 4 subjects in the 50 mg treatment group, 7 subjects in the 75 mg treatment group, and 10 subjects in the 100 mg treatment group. Ten of these subjects had fatal events during the study: three subjects in the placebo group, one subject in the 50 mg group, three subjects in the 75 mg group, and three subjects in the 100 mg group.

When clinical laboratory evaluations were summarized by visit for all four treatment groups, the treatment groups had similar results and there were no obvious patterns of concern based on dosing with eltrombopag for both hematology and clinical chemistry data.

In summary, the toxicities observed across all treatment groups were consistent with that expected with administration of carboplatin and paclitaxel.

6.7. Safety Conclusions

- A total of 495 patients with chronic ITP have been enrolled in eltrombopag clinical trials. Of these, 330 patients with ITP have received eltrombopag and 81, 39 and 12 patients have been exposed for at least 6, 12 and 15 months respectively (excluding subjects from the currently blinded RAISE study).
- Including an estimated two-thirds of blinded RAISE subjects who would have received eltrombopag, a total of 460 subjects with chronic ITP have been exposed to eltrombopag and >150 subjects have been exposed for at least 6 months.

Pivotal Short-term Dosing (TRA100773A, TRA100773B)

- Eltrombopag had a well-defined safety profile in 231 subjects in the 2 pivotal trials. No clinically meaningful differences in incidence or severity of the most common ($\geq 5\%$) adverse events (AEs) were observed between subjects treated with eltrombopag 50 mg compared to placebo.
- Headache was the most commonly reported AE (eltrombopag 50mg: 8%; placebo: 15%), followed by nasopharyngitis, nausea, fatigue and arthralgia. Nausea was the only AE with an incidence in eltrombopag-treated subjects $\geq 5\%$ higher than for placebo-treated subjects.
- Similar incidences of SAEs (12% and 11%) and discontinuations due to AEs (7% and 5%) were observed in the placebo and eltrombopag 50mg treatment groups, respectively.
- No dose-dependent pattern of AEs was observed across the eltrombopag 30 mg, 50 mg, and 75 mg treatment groups in TRA100773A.
- Preclinical findings that indicated potential for phototoxicity, cataracts and renal tubular toxicity do not appear to translate to clinical consequences during short-term use.
- Increases in hepatobiliary values (ALT or AST $\geq 3x$ ULN; or bilirubin or alkaline phosphatase [AP] $> 1.5x$ ULN) were observed in 10% of patients who received eltrombopag, compared to 8% of patients who received placebo.

Entire ITP Safety Database

- Across the entire program (excluding RAISE), the incidence of hepatobiliary laboratory abnormalities as defined in the draft FDA Guidance document is 9% (29/330). In the blinded RAISE study, the incidence is 10% (20/196).
- Thromboembolic events were reported during the clinical trials in patients with chronic ITP. However, the frequency (2.6%) was similar or less than that reported in the literature (3%) [[Aledort](#), 2004], in epidemiology studies (6.9 %) [Study [WEUKSTV1116](#)] and in observed with other thrombopoietic agents (4.4 %) [[Romiplostim](#) briefing document].
- As expected following discontinuation of eltrombopag, platelet counts returned to near baseline levels. In the pivotal studies, a transient decrease in platelet counts < 10 Gi/L and 10 Gi/L less than baseline was observed in patients treated with eltrombopag (10%) and those treated with placebo (6%). However, this numerical decrease was not associated with a clinically significant increase in bleeding.
- Similarly, in REPEAT and EXTEND, although some subjects had this numerical decrease in platelet counts < 10 Gi/L and 10 Gi/L less than baseline following discontinuation (10% and 3%, respectively) or interruption of eltrombopag (8% in EXTEND), these decreases were not accompanied by clinically meaningful increases in bleeding symptoms or need for rescue medication.

- In the intermittent and long-term studies, evidence of potentially abnormal cells upon examination of WBC differentials prompted a peripheral blood smear. No subject had peripheral blood smear findings of clinical relevance upon re-testing.
- Bone marrow biopsies were collected from 19 patients in EXTEND patients treated with eltrombopag for >12 months. Reticulin or collagen fibers were detected in 7 patients (including one patient with pre-treatment biopsy showing reticulin fibers). There were no AE reports, clinical consequences, laboratory abnormalities or withdrawal from treatment as of 12 April 2008.
- Preclinical findings that indicated potential for phototoxicity, cataracts and renal tubular toxicity do not appear to translate into clinical consequences.

7. RISK MANAGEMENT

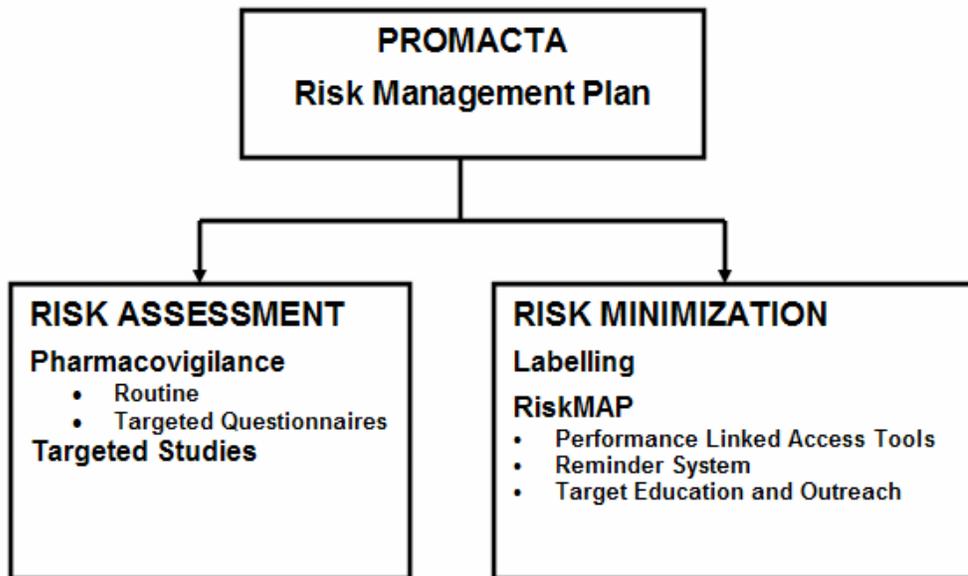
7.1. Overview

The purpose of the Risk Management Plan is to address each significant identified and potential risk of eltrombopag and the proposed risk management approach. The plan outlined below represents GSK's current proposal about the risk management approach for eltrombopag, which is based on recent interactions with the FDA. GSK is committed to developing a risk management program that maximizes the safety of patients exposed to the drug after approval while preserving the clinical benefit of the drug without placing an undue administrative burden on physicians and patients.

GSK has identified eight known or potential safety risks based on the available pre-clinical and clinical safety database for eltrombopag and the potential risks identified for romiplostim at the March 12, 2008 ODAC meeting. The risks identified based on the clinical findings in the clinical studies include hepatobiliary laboratory abnormalities and post-therapy transient decrease in platelet counts. Non-clinical data point to other potential risks, namely the development of cataracts, renal tubular toxicity and phototoxicity. Based on theoretical concerns, the potential risks of clinically relevant increases in thromboembolic events, bone marrow reticulin and the development of hematologic malignancies also need to be addressed. As with many other drugs, the possibility of off-label use needs to be considered based on the broad differential diagnosis of thrombocytopenia. A detailed summary of the action plan for each risk is presented in Appendix 1.

The Risk Management Plan for eltrombopag includes iterative risk assessment (active pharmacovigilance and targeted studies) and risk minimization (labeling, RiskMAP) (Figure 8).

Figure 8 Eltrombopag Risk Management Plan



7.2. Risk Minimization Action Plan

GSK is committed to maximizing the safety of patients treated with eltrombopag. There are several factors that suggest it would be appropriate to implement a RiskMAP for eltrombopag. They include the following:

- Eltrombopag is a new chemical entity and may be the first marketed product of a new therapeutic class of drugs used to treat chronic Idiopathic Thrombocytopenic Purpura (ITP).
- Chronic ITP is an orphan indication and therefore, the size of the patient population and the current clinical database for eltrombopag is relatively small compared to non-orphan indications.
- There are no long-term, placebo-controlled data available within the current database.
- Eltrombopag is a drug that increases the platelet count. There is a risk of the use of eltrombopag in other thrombocytopenia disorders in which it has not yet been fully investigated.

The FDA state in their guidance that “RiskMap” means a strategic safety program designed to meet specific goals and objectives in minimizing known risks for a product while preserving its benefits” (*Guidance for Industry entitled: Development and Use of Risk Minimization Action Plans*). In the case of eltrombopag, the situation is complicated by the several factors.

While several of the potential risks have a higher background rate in chronic ITP than the general population (thromboembolic events, hematologic malignancies, and cataract

development associated with long-term corticosteroid use), the currently available data have not identified specific individual patient risk factors that appear to predict the occurrence or development of any of the identified or potential risks of eltrombopag. Two of the risks appear to be preventable: 1) the identified risk of severe liver injury (by the recommended liver monitoring and liver stopping criteria) and 2) the potential risk for phototoxicity (by adherence to the appropriate patient behavior).

Due to these considerations, the focus of the proposed RiskMAP is on 1) communicating benefit-risk information to prescribers and patients, and 2) additional long-term safety data via active surveillance.

The eltrombopag RiskMAP proposed below will use restricted access, reminder systems, active surveillance and targeted education and outreach as the main tools to supplement the eltrombopag labeling and routine pharmacovigilance. The effectiveness of the proposed RiskMAP will be evaluated on a regular basis, and when appropriate, revisions to the RiskMAP will be made following discussions between the FDA and GSK.

7.2.1. RiskMAP Goals

The goals of the RiskMAP program are:

- To ensure the education of prescribers and patients on the safe and appropriate use of eltrombopag prior to initiation of therapy;
- To promote informed benefit risk decisions regarding the use of eltrombopag;
- To determine the incidence and risk factors for the identified and potential risks of eltrombopag use; and
- To further assess the overall safety profile of eltrombopag.

7.2.2. RiskMAP Objectives

The objectives of the RiskMAP program are:

- To enroll all patients and prescribers into the RiskMAP program;
- To assure that patients and prescribers make informed benefit risk decisions regarding the use of eltrombopag;
- To provide long-term monitoring and active surveillance of all patients receiving eltrombopag;
- To provide quantitative data on the incidence and risk factors for the identified, potential and theoretical risks of eltrombopag; and
- To monitor and assess off-label use of eltrombopag.

The key features of the RiskMAP include mandatory enrollment of prescribers and patients in the plan, controlled distribution, monitoring and follow-up of patients, and targeted education directed at healthcare professionals and patients.

7.2.3. Targeted Education and Outreach

GSK will use targeted education and outreach to complement the prescriber reminders and monitored distribution aspects of the RiskMAP. Each of the education and outreach tools listed below will emphasize the following content to ensure that patients and healthcare providers are educated about the appropriate use of eltrombopag:

- Benefits and risks associated with the use eltrombopag;
- Eltrombopag is indicated only for patients with chronic ITP; and
- Efficacy and safety data beyond 6 weeks from randomized, placebo-controlled trials are not yet available.

The proposed label for eltrombopag addresses identified and potential risks associated with the use of eltrombopag. Risks are addressed in the Prescribing Information and the Patient Information Leaflet (Table 34).

Table 34 Eltrombopag Risk Minimization Labeling

Identified Risks with eltrombopag	Prescribing Information (PI)	Patient Information Leaflet (PIL)
Hepatobiliary laboratory abnormalities	Warning and Precautions – monitoring and stopping criteria	✓
Post-treatment transient decrease of platelet counts	Warning and Precautions – monitoring after discontinuation of therapy	✓
Potential Risks with eltrombopag		
Thromboembolic events	Warnings and Precautions	✓
Cataracts	Warnings and Precautions	✓
Renal tubular toxicity	Nonclinical Toxicology	
Phototoxicity	Warnings and Precautions	✓
Bone marrow reticulin/fibrosis	Theoretical risk	✓
Malignancy	Theoretical risk – not described in the label	
Use > 6 weeks in chronic ITP	Limitations of Use placebo-controlled data for beyond 6 weeks are currently not available	✓
Use in other indications (e.g. MDS or CIT)	Limitations of Use ITP only indication	✓

Healthcare Provider Education and Outreach Tools (Physicians, Nurses, Pharmacists)

Healthcare Provider Education and Outreach tools will include the use of prescribing information (PI) and patient information leaflet (PIL), Patient Education Booklet, publication of safety data, eltrombopag.com web site, scientific/professional meetings, Healthcare Provider Education, among other tools.

Patient Education and Outreach Tools

Patient Education and Outreach tools will include the use of PIL, Patient Education Booklet, and the PROMACTA.com web site

Patients will have the opportunity to receive a healthcare provider phone call, Patient Starter Kit, and Patient Education e-mails.

There will be no Direct-to-Consumer television or radio advertising.

All clinical trials will be posted to clinicaltrials.gov and Patient Advocacy Groups will be notified about new and ongoing clinical trials.

7.2.4. Reminder Systems

Prescriber/ Patient Acknowledgement—The prescriber and patients are required to acknowledge that the key benefits and risks of eltrombopag therapy, as described in the PI and PIL, have been reviewed with the patient.

Drug supply will be limited with each prescription. A maximum of 42 days worth of medication will be dispensed with each prescription. This puts in place a mechanism to help facilitate interaction between the patient and a healthcare professional (prescriber, pharmacist, etc.).

Active surveillance (every 6 months) — Questionnaires to physicians will be sent regarding the occurrence of liver laboratory abnormalities, thromboembolic events, increase in bone marrow reticulin, and development of malignancies.

7.2.5. Performance-linked Access Tools

Mandatory Enrollment of Prescribers and Patients. The RiskMAP requires mandatory enrollment of all patients and prescribers in the RiskMAP program^a.

Controlled Distribution – Only authorized pharmacies will be able to dispense eltrombopag. Eltrombopag will not be available to retail pharmacies.

7.3. RiskMAP Evaluations

GSK will measure the effectiveness of the RiskMAP program and will provide a RiskMAP progress report to the FDA every 6 months for 2 years after the approval and launch of eltrombopag.

^a In rare cases there may be an exception to the mandatory enrollment requirement.

7.4. Additional Pharmacovigilance Activities and Targeted Studies

7.4.1. Pharmacovigilance (Routine and Active Surveillance)

Routine pharmacovigilance practices will take place through adverse event collection, single case processing, aggregate reports, and ongoing signal management. GSK has in place a robust and proactive signal management in place for signal detection and evaluation.

Targeted follow-up questionnaires for specific adverse events will be utilized to maximize the collection of essential safety information for reports of thromboembolic events, hepatobiliary abnormalities, cataracts, malignancies, and reports with increased bone marrow reticulin. These follow-up questionnaires are being used in the clinical studies, and will be developed for the spontaneous reports and for use in the active surveillance component of the RiskMAP program.

7.4.2. Targeted Studies

GSK has designed a comprehensive series of treatment (clinical trials) and non-treatment studies (observational clinical trials, epidemiologic, pharmacogenetic and pre-clinical studies) to further evaluate identified and potential risks associated with the use of eltrombopag. Details of these studies are presented below.

Ongoing Treatment Studies

There are four ongoing eltrombopag clinical trials in patients with chronic ITP: REPEAT (open-label repeat dosing study), EXTEND (open-label extension study), RAISE (placebo-controlled, Phase III study) and TRA108109 (a placebo-controlled study in Japan with planned enrollment of approximately 20 patients).

- RAISE and REPEAT will provide additional data to demonstrate the long-term efficacy and safety of PROMACTA and the efficacy and safety of repeated use of PROMACTA, respectively.
- The EXTEND study will offer additional data to support the long-term safety and efficacy in the majority of patients treated with eltrombopag.
- TRA108109 is a placebo-controlled, randomized trial examining the efficacy and safety of eltrombopag 12.5 mg and 25 mg in Japanese subjects.

Ongoing treatment studies outside of chronic ITP include 2 phase III clinical trials in patients with Hepatitis C associated thrombocytopenia, with a planned enrollment of 750 patients in each study.

Planned Treatment Studies

- A phase I photoirritancy study in healthy volunteers is planned to better understand the clinical implications of the preclinical phototoxicity findings.

- An additional Phase II study is planned in patients with chronic ITP called the ESCALATE study. The main goals of this study are:
 - To examine the potential effect on transient decrease of platelet counts following the end of therapy by tapering the dose of eltrombopag instead of a sudden stop; and
 - To enhance the pharmacokinetic/pharmacodynamic data in patients with chronic ITP (including Asian subjects).
- A Phase II study to evaluate safety, tolerability and PK and platelet response in pediatric patients with chronic ITP.

Ongoing/Completed Non-treatment Studies

Long-term Eltrombopag ObservatioNal Study (LENS): an observational long-term follow-up study to evaluate the risk of cataracts in subjects previously treated with eltrombopag or placebo (current N=54).

Epidemiology studies:

- A retrospective database analysis using eligibility and medical claims data from a large U.S. health plan was performed to evaluate the relative risk, incidence and prevalence of the following outcomes in patients with chronic ITP: thromboembolic events, hematological malignancies, cataracts, diabetes and acute/chronic renal failure. A sub-analysis to estimate the incidence and prevalence of arterial and venous thromboembolic events is ongoing.
- A retrospective database analysis is ongoing using eligibility and medical claims data from a large U.S. health plan to evaluate the relative risk and the incidence and prevalence of hepatobiliary laboratory abnormalities in patients with chronic ITP.
- A retrospective analysis using medical records of anonymous patients from the large computerized General Practice Research Database (GPRD) in the UK was performed to evaluate the risks and the incidence and prevalence of thromboembolic events in patients with ITP.
- UK ITP Registry: A disease registry and database in the United Kingdom is being established to understand the natural disease progression, treatment effectiveness, and burden of co-morbidities in ITP patients.
- Pediatric and Adult Intercontinental Registry of Chronic ITP (PARC- ITP): Prospective and retrospective analyses of thromboembolic events is planned and under discussion with the PARC- ITP collaborators.

Pharmacogenetic studies (data collection included in all clinical trials):

- To examine gene polymorphisms associated with drug induced liver injury (DILI) in chronic ITP patients with hepatobiliary laboratory abnormalities (HBLA) and those without HBLA.

- To examine the presence of mutations, polymorphisms and molecular markers associated with thrombophilia in chronic ITP patients with thromboembolic events and those without thromboembolic events.
- Follow-up pharmacogenetic studies are planned to identify reasons for PK differences observed between East Asians and non-East Asians.

In vitro / ex vivo studies

Further in vitro/ex vivo studies of leukemia cell lines and primary leukemia cells following exposure to eltrombopag (including proliferation, differentiation and apoptosis assays) and thrombopoietin to confirm the findings submitted in the NDA that eltrombopag does not stimulate leukemic cells in vitro.

7.5. Summary of the Risk Management Plan

The safety profile of eltrombopag will continue to be monitored in accordance with GSK's pharmacovigilance activities. Risk management will take place employing pharmacovigilance, active surveillance via targeted questionnaires, targeted studies and the RiskMAP program. GSK will pay specific attention to specific risks addressed in the RiskMAP.

The key features of the eltrombopag RiskMAP include:

- Targeted education directed at patients, healthcare professionals, and pharmacies.
- Acknowledgement by patient and physician that they are aware of information in the PIL and PI, respectively.
- Limits on drug supply to a maximum of 42 days worth of medication with each prescription.
- Mandatory enrollment of prescribers and patients in the RiskMAP.
- Controlled distribution by only authorized pharmacies.
- Active surveillance by collection and analysis of safety information.

GSK is committed to the safety of all subjects in the eltrombopag clinical development program and will continue to conduct studies and monitor all events to better understand the safety profile of eltrombopag. GSK believes that the potential benefits for the treatment of patients with chronic ITP with eltrombopag outweigh the potential risks and that therefore the drug should be made available for patients with chronic ITP.

8. BENEFIT RISK ASSESSMENT AND CONCLUSIONS

“Hematologists everywhere are thwarted by patients with ITP in whom every available treatment has failed to improve the platelet count” [[Schwartz, 2007](#)].

Benefit Risk Assessment

- Eltrombopag effectively and consistently raised platelet levels during short-term, intermittent and long-term treatment of patients with previously-treated chronic ITP. Clinically meaningful increases in platelet counts were observed, regardless of baseline platelet counts, use of concomitant medication and splenectomy status.
- Eltrombopag raises platelet counts relatively quickly: in all trials, >30% of subjects responded with an increase of platelet counts ≥ 50 Gi/L by Day 8, 50% of subjects by Day 15, following 50 mg eltrombopag. The maximal response can be expected to occur within 3 weeks of daily administration. Platelet levels remained elevated for approximately 1 week after stop of medication.
- Eltrombopag could be an excellent option from a clinical perspective to plan invasive procedures or operations with a lead time of 2 to 3 weeks.
- Consistent response to eltrombopag was observed following 3 intermittent treatment cycles: 88% of subjects who responded in Cycle 1, responded again in Cycle 2 or 3 (Exact 95% CI: 72%, 97%).
- During long-term treatment, the majority of subjects (54%) had clinically meaningful periods of continuous uninterrupted platelet counts ≥ 50 Gi/L for at least 10 consecutive weeks, with 24% achieving continuous, consecutive elevation of platelet counts ≥ 50 Gi/L for more than 6 months.
- In all studies, improvements in platelet counts, as measured by the WHO Bleeding Scale, were accompanied with a decrease in bleeding symptoms and subjects treated with eltrombopag were able to effectively master hemostatic challenges without additional treatments to elevate their platelet counts.
- The following are considered identified risks of eltrombopag: hepatobiliary laboratory abnormalities and transient decreases in platelet counts following discontinuation of treatment.
- Potential risks of eltrombopag are: thromboembolic events; cataracts; photosensitivity; and renal tubular toxicity.
- The potential for off-label use in indications where the risk benefit ratio of eltrombopag has not been adequately studied, especially given the effectiveness of eltrombopag and the oral formulation.
- Potential risks of other thrombopoietic agents include bone marrow fibrosis; and hematologic malignancies.
- GSK has proposed a comprehensive risk management plan to both assess and mitigate identified and potential risks of short- and long-term treatment with eltrombopag. The key features of the eltrombopag RiskMAP include:
 - Targeted education for patients, healthcare professionals, and pharmacies;
 - Acknowledgement by patient and physician of information in the patient information leaflet and prescribing information, respectively;
 - Limits on drug supply with each prescription;

- Mandatory enrollment of prescribers and patients into a safety tracking database;
- Controlled distribution by only authorized pharmacies; and
- Active surveillance by collection and analysis of safety information.

Conclusions

Eltrombopag is a new therapeutic option for the most difficult to treat ITP population, which are those with the greatest unmet medical need both for rapid, predictable and safe short-term platelet count elevations and for long-term chronic treatment in patients with platelet counts consistently $<30\text{Gi/L}$. Based on the data from the ITP clinical development program, the clear clinical benefit (as indicated by increases in platelet count, reduction in bleeding and successful mastering of homeostatic challenges) of eltrombopag has been demonstrated. A positive risk benefit relationship exists supporting the approval of eltrombopag for the treatment of subjects with chronic ITP.

GSK believes that eltrombopag can address the unmet medical need for the short-term treatment of patients with chronic ITP. TRA100773A and TRA100773B are the two largest randomized, placebo-controlled studies performed to date in adults with chronic ITP and platelet levels $<30\text{Gi/L}$. The REPEAT study has provided efficacy and safety data supporting the use of eltrombopag as an intermittent, short-term treatment of patients with chronic ITP. The results from these 3 studies have clearly demonstrated the efficacy and safety of eltrombopag as a short-term therapeutic option for previously treated chronic ITP, justifying the indication statement proposed in the NDA:

"PROMACTA 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."

In close collaboration with the FDA, GSK has implemented 2 additional trials that focus on the long-term treatment of patients with chronic ITP. The randomized, double-blind, placebo-controlled RAISE trial is currently ongoing; unblinded efficacy data for the trial will be available within the next 12 months. No new safety signal has been found in the blinded review of safety data for 196 subjects to date.

In the large, open-label extension study, EXTEND, safety and efficacy data from over 200 and 100 patients, respectively, have been analyzed. The data from the EXTEND study clearly demonstrate the long-term and durable effect of eltrombopag on platelet counts and reduction in bleeding, addressing the unmet medical need for a new long-term treatment option for patients with chronic ITP. These data, and the data from REPEAT, support the chronic use of eltrombopag. Although the short-term indication was the indication sought in the initial application, the FDA stated during the review process that a general or chronic indication may be considered. As such, GSK has tailored the risk management plan to encompass chronic administration of eltrombopag. Therefore, the indication for consideration could be:

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

The efficacy of PROMACTA for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) was established in short-term (6-week) controlled trials.

The effectiveness of PROMACTA in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials.”

9. REFERENCES

- Aharon A, Levy Y, Bar-Dayana Y, Afek A, et al. Successful treatment of early secondary myelofibrosis in SLE with IVIG. *Lupus* 1997;6:408-11.
- Aledort LM, Hayward CP, Chen MG, Nichol JL, Bussel J: ITP Study Group. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *Am J Hematol* 2004;76(3):205-213.
- Andres E, Zimmer J, Noel E, Kaltenbaach G, Koumariou A, Maloisel F. Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of the influence of age on the response to corticosteroids, splenectomy and danazol. *Drugs Aging* 2003;20:841-846.
- BCSH (British Society for Haematology). Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 2003;120:574-596.
- Beckman EN, Brown AW Jr. Normal reticulon level in iliac bone marrow. *Arch Pathol Lab Med* 1990;114:1241-3.
- Bellucci S, Han ZC and Caen JP. Studies of in vitro megakaryopoiesis in adult immune thrombocytopenic purpura. *Eur J Haematol* 1991;47:86-90.
- Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity and mechanism of effect. *Blood* 1991;77:1884-1893.
- Bussel J, Kuter DJ, Phil D, et al. AMG531, a thrombopoiesis-stimulation protein, for chronic ITP. *N Engl J Med* 2006;355:1672-1681.
- Bussel J, Cheng G, Saleh M, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007;357:2237-2247.
- Campbell SD, de Morais SM, Xu JJ. Inhibition of human organic anion transporting polypeptide OATP1B1 as a mechanism of drug-induced hyperbilirubinemia. *Chemico-Biological Interactions* 2004;150:179-187.
- Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002;346:995-1008.
- Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura. *Blood* 2005;106:2244-2241.
- Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med* 2000;160:1630-1638.

Cooper N and Bussel J. the pathogenesis of immune thrombocytopaenic purpura. *Br J Haematology* 2006;133:364-374.

Cui Y, Koenig J, Leier I, Buchholz U, Keppler D. Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. *J Bio Chem* 2001;276:9626-9630.

Deitz AC, St. Laurent SA, Kobayashi MG, Hall SA, Feudjo-Tepie MA. Prevalence Estimate of Idiopathic Thrombocytopenic Purpura (ITP) in the United States. *Blood (ASH Annual Meeting Abstracts)* 2006;108: 3955.

Feudjo-Tepie MA, et al. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. *J Thromb Haemost* 2008;6:711-2

Frisch B, Bartl R, Burkhardt R. Bone marrow biopsy in clinical medicine: an overview. *Haematologia* 1982;15:245-85.

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

George JN, Vesely SK. How can we provide the best care for our patients with immune thrombocytopenic purpura? *Mayo Clinic Proc* 2004;79:456-457.

Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. *Eur J Clin Pharmacol* 2007;63:537-546.

Heyns AdP, Badenhorst PN, Loetter MG et al. Platelet turnover and kinetics in immune thrombocytopenic purpura: results with autologous 111-In-labeled platelets and homologous 51-Cr-labeled platelets differ. *Blood* 1986;67:86-92.

Houwerzijl EJ, Blom NR, van der Want JJJ, Esselink MT et al. Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood* 2004;103:500506.

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

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

Marie I, Maurey G, Herve F, Hellot MF, Levesque H. Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. *Brit J Derm* 2006;155:714-721.

McCrae KR, Bussel JB, Mannucci PM, Remuzzi G and Cines DB. Platelets: an update on diagnosis and management of thrombocytopenic disorders. *Hematology* 2001;

McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J of Med* 2007;357:2227-36.

McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997;126:307-314.

McMillan R, Nugent D. The effect of antiplatelet autoantibodies on megakaryocytopoiesis. *Int J Hematol* 2005;8(2):94-99.

Mueller-Eckhardt C. Idiopathic thrombocytopenic purpura: clinical and immunologic considerations. *Seminars in Thrombosis and Hemostasis* 1977;3:125-159.

Mufti G, Bagg A, Hasserjian R, Bain B et al. Bone marrow reticulin in patients with immune thrombocytopenic purpura. *J Supportive Oncol* 2007;5:80-81.

Newland A, Chen G, Saleh L, et al. Eltrombopag increases platelets during 6-week treatment of ITP: results of a randomised, double-blind, placebo-controlled phase II study. *Haematologica/The Hematol J* 2006;91:375.

Neylon AJ, Saunders WG, Howard MR, et al. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br J Haematol* 2003;112:966-974.

Park AE, Birgisson G, Mastrangelo MJ, Marcaccio MJ, Witzke DB. Laparoscopic splenectomy: outcomes and lessons learned from over 200 cases. *Surgery* 2000;128:660-667.

Parker RI, Siegel RS, Ratajczak MZ and Gewirtz AM. Deficient in vitro megakaryocytopoiesis and decreased in vivo platelet turnover in children and young adults with chronic thrombocytopenia. *J Ped Hematology/Oncology* 1998;20:196-201.

Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001;97:2549-2554.

Romiplostim briefing document from Amgen, 12 Mar 2008 ODAC meeting.

Satia J, Acquavella J, Hollowell J, Rutstein M. Descriptive epidemiology of immune thrombocytopenic purpura in three European countries. The 11th Congress of the European Hematology Association. Amsterdam: [poster presentation]; 2006.

Schwartz R. Immune thrombocytopenic purpura – from agony to agonist. *New England J Med* 2007;357:2299-2301.

Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analysis of administrative data. *J Thromb Haemost* 2006;4:2377-2383.

Soederberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. *Eur J Cancer* 2006;42:3028-3033.

Stern M, Buser AS, Lohri A, Tichelli A, Nissen-Druey C. Autoimmunity and malignancy in hematology – more than an association. *Crit Rev Oncol/Hemat* 2007;63:100-110.

Stevens W, Koene H, Zwaginga JJ and Vreugdenhil G. Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights. *The Netherlands J of Med* 2006;64:356-363.

Study 002, GM2005/00070/00, A single-blind, randomised (with respect to placebo), placebocontrolled, parallel group, dose rising study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and repeat oral doses of SB-497115-GR, a thrombopoietin receptor agonist, in healthy adult subjects. November, 2005.

Study WEUKSTV1116, Descriptive study of selected comorbidities among persons with Idiopathic Thrombocytopenic Purpura, Hepatitis C and Cirrhosis, 2008.

ATTACHMENTS

ATTACHMENT 1: ACTIONS PROPOSED FOR RISKMAP

Identified Risk	Hepatobiliary Abnormalities
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Use of targeted follow up questionnaires for adverse events reports to identify risk factors, (including correlation with PK in clinical studies) • Adjudication on reports of hepatobiliary abnormalities <p>Studies</p> <ul style="list-style-type: none"> • Analysis of additional safety data from ongoing studies • Pharmacogenetics studies planned to examine gene polymorphisms from drug induced liver injury (DILI) • Epidemiology study to examine the background rate of hepatobiliary abnormalities in the ITP population <p>PROMACTA RiskMAP program</p> <ul style="list-style-type: none"> • Targeted Education • Reminder systems • Performance-linked access • Active surveillance for safety data on reports of hepatobiliary abnormalities for analysis <p>Proposed Label</p> <ul style="list-style-type: none"> • Include appropriate information relevant to hepatotoxicity abnormalities in Prescriber Information, Patient Information Leaflet and proposed educational information for physician, patient and pharmacy <ul style="list-style-type: none"> ○ Warning and Precaution statement for monitoring and management of patient with hepatobiliary abnormalities ○ Adverse Reactions section lists hepatobiliary abnormalities <p>Specify liver testing as recommended by the FDA guidance document on DILI. For the first 3 months, measure hepatobiliary laboratory values every 2 weeks. Thereafter, measure hepatobiliary laboratory values monthly.</p> <p>Liver stopping criteria: Specific instructions for discontinuation of PROMACTA to avoid further elevations of hepatobiliary laboratory values.</p>

Identified Risk	Post therapy transient decrease in platelet counts
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Analysis of additional safety data from ongoing and planned studies <p>Proposed Label</p> <ul style="list-style-type: none"> • Include appropriate information relevant to post therapy decrease in platelet counts in Prescriber Information, Patient Information Leaflet and proposed educational information for physician, patient and pharmacy <ul style="list-style-type: none"> ○ Adverse Reactions Clinical Trial Experience includes information on transient decrease in platelet counts <p>Ensure platelet counts are monitored after discontinuation of PROMACTA.</p>

Potential Risk	Thromboembolic Events
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Use of targeted follow up questionnaires for adverse events reports of thromboembolic events • Adjudication on reports of thromboembolic events <p>Studies</p> <ul style="list-style-type: none"> • Analysis of additional safety data from ongoing studies • Pharmacogenetics studies planned to assess the effect polymorphisms and mutations • Epidemiology studies of thromboembolic events in ITP patients to better define the baseline risk <p>PROMACTA RiskMAP program</p> <ul style="list-style-type: none"> • Targeted Education • Reminder systems • Performance-linked access • Active surveillance for safety data on reports of thromboembolic events for analysis <p>Proposed Label</p> <ul style="list-style-type: none"> • Include appropriate information relevant to thromboembolic events in Prescriber Information, Patient Information Leaflet and proposed educational information for physician, patient and pharmacy <ul style="list-style-type: none"> ○ Dosage and Administration statement for discontinuation if platelets increase to >200,000/μL ○ Warning and Precautions statement of potential for thromboembolic events in chronic ITP patients and those with history of thromboembolic events

Potential Risk	Cataracts
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Use of targeted follow up questionnaires for adverse events reports of cataracts • Adjudication on reports of cataract by external Clinical Event Committee <p>Studies</p> <ul style="list-style-type: none"> • Analysis of additional cataract safety data from ongoing studies • Ongoing Long term Safety Study (LENS) for 2-3 years following study discontinuation • 2 Epidemiologic studies of cataract events in ITP patients (US and UK based) <p>Proposed Label</p> <ul style="list-style-type: none"> • Include appropriate information relevant to phototoxicity in Prescriber Information, Patient Information Leaflet and proposed educational information for physician, patient and pharmacy • Warnings and Precautions recommends monitoring cataract as part of routine eye exam

Potential Risk	Phototoxicity
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Analysis of additional safety data from ongoing studies • Phase I clinical photoirritancy (MED) study planned Proposed Label <ul style="list-style-type: none"> • Include appropriate information relevant to phototoxicity in Prescriber Information, Patient Information Leaflet and proposed educational information for physician, patient and pharmacy <ul style="list-style-type: none"> ○ Warning and Precaution statement includes photosensitivity precaution including the use of protective clothing, sunscreen, and sunglasses.

Potential Risk	Increase of Bone Marrow Reticulin
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Targeted Follow up Studies <ul style="list-style-type: none"> • Continue to actively collect bone marrow reports after 12 months of treatment in the EXTEND study • Analysis of additional safety data from ongoing studies PROMACTA RiskMAP program <ul style="list-style-type: none"> • Targeted Education • Reminder systems • Performance-linked access <ul style="list-style-type: none"> • Active surveillance for safety data on reports of bone marrow reticulin accumulation

Potential Risk	Malignancies
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance • Targeted Follow up Studies <ul style="list-style-type: none"> • Analysis of additional safety data from ongoing studies • Ongoing in vitro and ex vivo research to understand the impact of PROMACTA on the biology of malignant cells PROMACTA RiskMAP program <ul style="list-style-type: none"> • Targeted Education • Reminder systems • Performance-linked access <ul style="list-style-type: none"> • Active surveillance for safety data on reports of malignancies for analysis

Potential Risk	Off- Label Use
Action proposed	<ul style="list-style-type: none"> • Routine pharmacovigilance <p>Studies</p> <ul style="list-style-type: none"> • Analysis of additional safety data from ongoing studies including indications other than chronic ITP <p>PROMACTA RiskMAP program</p> <ul style="list-style-type: none"> • Targeted Education • Reminder systems • Performance-linked access • Active collection of data on indication for which PROMACTA is prescribed <p>Proposed Label</p> <ul style="list-style-type: none"> • Include appropriate information relevant to PROMACTA indication in Prescriber Information, Patient Information Leaflet and proposed educational information for physician, patient and pharmacy <ul style="list-style-type: none"> ○ Indications and Usage states that PROMACTA is indicated for the treatment of patients with chronic ITP <p>: Inclusion of "Important Limitation of Use"</p> <ul style="list-style-type: none"> • 1) that controlled data for beyond 6 weeks is currently not available • 2) that PROMACTA has not been studied/indicated for other conditions characterized by thrombocytopenia such as chemotherapy-induced thrombocytopenia and myelodysplastic syndrome.