

Proportion of Responders by Race (Efficacy Population)

Race Category	Treatment Group	
	PBO N=36	Eltrombopag N=74
<b>African American/African</b>		
n	0	1
Responders, n (%)	0	1 (100)
Responders with platelets >200 GiL, n (%)	0	1 (100)
<b>American Indian or Alaskan Native</b>		
n	2	4
Responders, n (%)	0	3 (75.0)
Responders with platelets >200 GiL, n (%)	0	1 (25.0)
<b>Asian - Central/South</b>		
n	4	5
Responders, n (%)	1 (25.0)	2 (40.0)
Responders with platelets >200 GiL, n (%)	0	0
<b>Asian - East Asian</b>		
n	1	0
Responders, n (%)	0	0
Responders with platelets >200 GiL, n (%)	0	0
<b>Asian - Southeast Asian</b>		
n	3	7
Responders, n (%)	1 (33.3)	3 (42.9)
Responders with platelets >200 GiL, n (%)	0	3 (42.9)
<b>Arabic/North African</b>		
n	3	4
Responders, n (%)	1 (33.3)	2 (50.0)
Responders with platelets >200 GiL, n (%)	0	1 (25.0)
<b>White/Caucasian/European</b>		
n	22	51
Responders, n (%)	3 (13.6)	32 (62.8)
Responders with platelets >200 GiL, n (%)	1 (4.6)	12 (23.5)
<b>Other/Mixed</b>		
n	2	1
Responders, n (%)	0	0
Responders with platelets >200 GiL, n (%)	0	0

Data Source: Table 7.36, Table 7.44

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A posthoc analysis of the maximum number of weeks of continuous platelet response during days at 1-43 was performed by the sponsor. The eltrombopag treatment group showed a higher proportion of patients with  $\geq 5$  continuous weeks of response up to day 43. Durability of platelet response to study medication in the intent to treat population is shown in the table below.

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

Weeks of Continuous Response	Treatment Group, n (%) <sup>a</sup>	
	PBO N=36	Eltrombopag N=76
<b>Subjects in study <math>\geq 3</math> weeks</b>	<b>34</b>	<b>61</b>
$\geq 5$ weeks	2 (6)	15 (25)
$\geq 4$ weeks	3 (9)	18 (31)
$\geq 3$ weeks	4 (12)	27 (46)

Data Source: Table 7.123

a. Percentages based on subjects in study  $\geq 3$  weeks

In this study the sponsor prospectively collected information regarding hemostatic challenges. Three patients (two placebo treated patients and one eltrombopag treated patient) had such a

challenge during the six weeks of the treatment or six weeks of follow-up. The narratives for the hemostatic challenges are as follows:

- Patient 1659: this patient was a 69-year-old Caucasian male who was randomized to the placebo treatment arm. Prior treatment for ITP in this patient included corticosteroids, WinRho and a previous investigational compound. The patient's screening baseline platelet count was 18,000/mcl and he was noted to have a grade 1 WHO bleeding. On day 7, 14 and 21 the patient's platelet counts were all 25,000/mcl and grade 0 WHO was noted. On day 21 study treatment was discontinued and the patient received two days of intravenous immunoglobulin therapy in preparation for an elective total hip replacement. On the day of surgery the patient received three units of platelets. The patient underwent surgery and subsequently had 10 days of enoxaparin postoperatively for deep vein thrombosis prophylaxis. The patient received one unit of packed red blood cells four days after the surgery. The patient's platelet counts three weeks and seven weeks post study treatment were 86,000/mcl and 80 9000/mcl. No perioperative or postoperative complications were noted.
- Patient 1468: this patient was a 27 year old female who was randomized to the placebo treatment arm. Concomitant treatment for ITP included splenectomy, corticosteroids and intravenous immunoglobulin. Her baseline platelet count was 27,000/mcl and she was noted to have no bleeding. The patient's day 8-22 platelet counts ranged from 50,000/mcl-35,000/mcl. The patient underwent throat surgery without medication interruption. The patient's platelet counts for study days of 43-85 ranged between 9000/mcl-41,000/mcl and WHO bleeding grade ranged between 0-1. No perioperative or postoperative complications were noted.
- Patient 1878: this patient was a 68-year-old Native American female who was randomized to the eltrombopag treatment arm. The patient's prior ITP therapy included corticosteroids, splenectomy, cyclophosphamide and danazol. Her baseline platelet count was 26,000/mcl with a WHO bleeding grade ranging between 1-3 prior to study entry. The patient maintained prednisone therapy 25 mg once daily and was also on eltrombopag treatment for six weeks. The patient's platelet count responded to levels ranging between 100,000/mcl-129,000/mcl from days 15-43. Her WHO bleeding grade ranged between 0-1. On day 50 her platelet count was 80,000/mcl and she had teeth extracted. On day 57 her platelet count was 82,000/mcl and 30,000/mcl on day 85. The patient was noted to have a grade 1 WHO bleeding on follow-up days 71 and 85 but no perioperative complications.

*Reviewer comment: In study TRA 100773B (part B) the primary endpoint was achieved by 16% of patients in the placebo group compared to 59% of patients in the eltrombopag treatment group. The odds ratio of treatment response was statistically significant ( $P < 0.001$ ). These results confirm and are consistent with the results of TRA 100773A. The results of the two pivotal trials (TRA 100773 A and B) provide evidence demonstrating a predictable, and significant elevation of platelet counts to safe platelet levels in this disease setting.*

*The statistical reviewer, Dr. Qing Xu in her review (ODAC Briefing Document; April 19, 2008) stated that there were several issues discovered in the statistical review of the pivotal studies. One of the conclusions the sponsor made was that eltrombopag in the treatment of ITP patients decreases the incidence and severity of bleeding in subjects with relapsed or refractory chronic*

*ITP. The sponsor conducted logistic regression analysis of the bleeding events, adjusting for the covariates of use of concomitant medication at randomization, splenectomy status, and baseline platelet count. However, it is obvious that the bleeding event is time dependent with multiple observations per subject. It is more appropriate to use survival analysis models based on time-to-event in multiple event setting. In her review Dr. Xu used the Andersen-Gill (AG) formulation of proportional hazards model as a counting process is performed for assessment of bleeding, using the Schoefeld residuals to test the basic assumptions of a Cox model. The proportional hazard and the functional form of the covariates are also included in her review. The results of Dr. Xu's analyses are show in the tables below.*

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

	<i>Exp(coef)</i>	<i>Robust se</i>	<i>P-value</i>
<i>TRTCD</i>	1.928	0.314	0.121
<i>Baseline Platelet</i>	0.821	0.306	0.3800
<i>ITP medication use</i>	0.350	0.276	0.2800
<i>Splenctomy</i>	0.305	0.219	0.0040

*From the table above a P-value of 0.121 suggests that there is no statistically significant difference in WHO bleeding grade between the two groups.*

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

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

	<i>Exp (coef)</i>	<i>Robust se</i>	<i>P-value</i>
<i>TRTCD</i>	0.781	0.135	0.067

*The P-value is 0.067 suggests that there is no statistically significant difference between the two groups.*

### Clinical Microbiology

Not applicable.

### Reviewer's Efficacy Conclusions

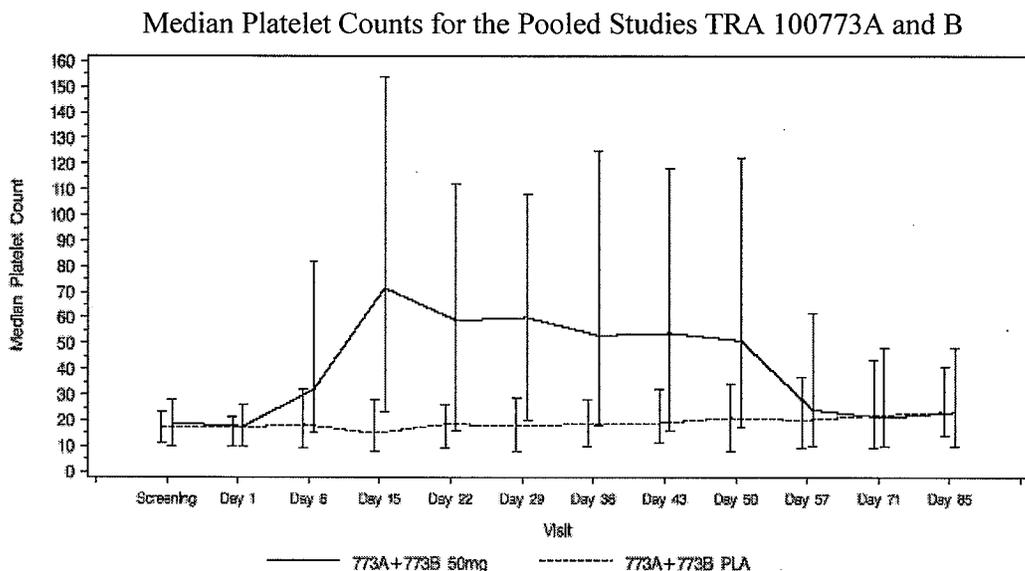
In study TRA 100773A analysis of the primary endpoint showed that eltrombopag increased the proportion of patients with chronic ITP who achieved a platelet count of  $\geq 50,000/\text{mcl}$  on day 43 starting from a baseline platelet count  $< 30,000/\text{mcl}$  compared to placebo: 11% (3/27) of patients on placebo, 28% (8/29) of patients on 30 mg of eltrombopag, 70% (9/27) of patients on 50 mg of eltrombopag and 81% (21/26) of patients on 75 mg of eltrombopag. Patients treated with eltrombopag 50 mg or 75 mg had statistically significant greater odds of responding at day 43 compared to patients treated with placebo ( $p < 0.001$ ). Median platelet counts for patients treated with eltrombopag 50 mg or 75 mg were higher than for patients treated with placebo at each on therapy visit. Median platelet counts in all eltrombopag treatment groups returned to baseline

within two weeks of discontinuation of therapy. There was a statistically significant decrease in the percentage of eltrombopag 50 mg and 75 mg treated patients (16/27 and 12/26 patients, respectively) with any bleeding observed during the on therapy phase of the trial compared to placebo (22/27 patients). The percentage of patients with any bleeding returned to baseline levels during the off therapy phase (26/27 in the 50 mg treatment group and 26/26 in the 75 mg treatment group compared to 25/27 in the placebo treatment group). WHO grade 2-4 bleeding occurred in 5/26 (19%) of placebo treated patients and 9/39 (23%) of eltrombopag treated patients who were nonresponders compared to 3/48 (6%) of eltrombopag treated patients who were considered responders but the bleeding difference between the treatment groups was not statistically significant by FDA statistical analysis. Statistically significant interactions were observed between study medication and the use or non-use of concomitant ITP medication at the time of randomization. Logistic regression analysis showed an interaction at the 10% level of significance between the response to treatment and the use of ITP medication at randomization ( $p=0.093$ ). In the subgroup of patients who did not report the use of concomitant ITP medication, a dose-dependent increase in the proportion of responders was observed. A similar dose response was observed in the subgroup of patients who did report concomitant use of the ITP medications; however, the proportion of responders in the 75 mg treatment group (6/26) did not increase to the same degree as in the 50 mg treatment group (8/27). A statistically significant interaction was also observed between the study medication and baseline platelet count at randomization. For study TRA 100773A logistic regression analysis showed an interaction at the 10% level of significance between the response to treatment and baseline platelet count at randomization ( $p=0.042$ ). In both subgroups ( $\leq 15,000/\text{mcl}$  and  $> 15,000/\text{mcl}$ ) the proportion of responders increased in a dose-dependent manner. However the proportion of responders was higher for the 50 mg and 75 mg treatment groups with baseline platelet counts  $> 15,000/\text{mcl}$  (13/16 and 12/12 patients respectively) compared to the subgroup with platelet counts  $\leq 15,000/\text{mcl}$  (6/11 of patients and 9/14 patients respectively). The interaction between treatment and splenectomy status was not statistically significant. There was no statistically significant difference in the response to treatment when assessed for subgroups by age, sex and race. However, data interpretation is limited due to the small number of patients in the race subgroup.

In study TRA 100773B, 16.2% (6/37) of patients on the placebo treatment arm compared to 58.9% (43/73) of patients on the eltrombopag treatment arm achieved a platelet count  $\geq 50,000/\text{mcl}$  on day 43 from a baseline platelet count  $< 30,000/\text{mcl}$ . Patients treated with eltrombopag had statistically significant greater odds of responding at day 43 compared to patients treated with placebo ( $p < 0.001$ ). Median platelet counts for patients treated with eltrombopag were higher than for patients treated with placebo at each on therapy visit. Median platelet counts in eltrombopag treated patients remained elevated one week after discontinuation of eltrombopag and returned to baseline within two weeks after discontinuation of eltrombopag. More patients (69%) in the placebo treatment group required a dose increase at the day 22 visit compared to the eltrombopag treatment group (39%). More patients in the eltrombopag treatment group (11/35, 31%) responded after having their dose increased compared to the placebo treatment group (3/28, 11%). A statistically significant lower percentage of patients treated with eltrombopag experienced WHO bleeding grade 1-4 at day 43 ( $p=0.029$ ) according to the sponsor's analysis. However, the bleeding difference between treatment groups was not statistically significant by FDA statistical analysis. The interactions between treatment and each

of the randomization strata were not statistically significant, which suggests that patients respond to eltrombopag similarly irrespective of their randomization strata. In addition there were no significant differences in the response to treatment when assessed for age and sex. The response to treatment based on race could not be estimated. Analyses of responders defined as patients with platelet counts  $\geq 50,000/\text{mcl}$  and at least two times baseline were similar to the analyses of the primary endpoint.

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



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- Eltrombopag appears to effectively raise platelet counts during the short term ( $\leq$  six weeks) treatment in patients with previously treated chronic ITP. In the pooled analysis the primary endpoint (i.e., a shift from baseline platelets  $< 30,000/\text{mcl}$  to platelet counts  $\geq 50,000/\text{mcl}$ ) was achieved by 62% of patients treated with 50 mg of eltrombopag compared to only 14% of patients on placebo. The odds of treatment response in the eltrombopag group relative to placebo (OR, 95% confidence intervals: 12.4, 5.18-29.72) was statistically significant ( $p < 0.001$ ).
- In both studies more than 50% of patients responded with clinically meaningful increases in platelet counts regardless of the baseline platelet counts, use of concomitant medication or splenectomy status.
- Eltrombopag was able to raise platelet counts relatively quickly in both trials,  $> 30\%$  of patients responded with an increase of platelet counts  $\geq 50,000/\text{mcl}$  by day eight and 50%

of patients responded by day 15 following treatment with eltrombopag 50 mg. Platelet levels remained elevated approximately 1 week after discontinuing eltrombopag.

- Rationale for short-term use of eltrombopag was stated in the protocols for study TRA 100773. Specifically, it was stated in the protocol that short-term treatment of eltrombopag may increase platelet counts in patients with chronic ITP scheduled for surgical or dental procedures where a low platelet count can be a hindrance or even prohibitive of the procedure due to the risk of excessive bleeding. However, the clinical study was not designed to assess clinical benefits in a peri-procedural setting. The study assessed changes from baseline bleeding status in each patient using a five component leading scale. The WHO bleeding scale characterizes bleeding as follows: grade 0 - no bleeding; grade 1- petechiae; grade 2- mild blood loss; grade 3- gross blood loss; grade 4 -debilitating blood loss. WHO bleeding scale grades 2-4 are considered clinically significant. WHO bleeding grade 2-4 was evaluated posthoc. No patients had grade four bleeding at any time during the study.
- The clinical meaningfulness of change in bleeding based on the WHO bleeding scoring system is not clear. In particular, incremental changes in score from two to one has little clinical utility. In addition, the protocols provided few criteria or definitions with regard to how investigators were to assign scores. Also, the scores could have been assigned with knowledge of the platelet count results by the investigators. These data may have biased the score assessment.
- In terms of bleeding, a statistically significant reduction in the proportion of patients with any bleeding at day 43 in the eltrombopag treatment group compared to patients in the placebo treatment group (OR= 0.34, p = 0.018) was observed in the pooled pivotal studies by logistic regression analysis adjusted for use of ITP medication at baseline, splenectomy status, baseline platelet count and WHO bleeding grade at baseline. However, the bleeding difference between treatment groups was not statistically significant by FDA statistical analysis. At the baseline visit 62% of patients treated with eltrombopag 50 mg and 59% of patients treated with placebo reported any bleeding. At the day 43 visit, 37% of patients treated with eltrombopag reported any bleeding compared to 55% of patients treated with placebo. In the pooled pivotal study analysis 35/39 patients in the eltrombopag group compared to 20/26 patients in the placebo group had a baseline WHO bleeding score of zero and a WHO bleeding score of zero at the end of therapy. In the pooled analysis of patients treated with 50 mg of eltrombopag or placebo, 26/44 patients treated with eltrombopag compared to 9/26 patients treated with placebo had a bleeding score of one at baseline and zero at the end of therapy. In the pooled pivotal analysis 4/17 patients treated with eltrombopag and 3/9 patients treated with placebo had baseline WHO bleeding scores of two at baseline and zero at the end of therapy. In the pooled analysis 2/2 patients treated with eltrombopag and 1/3 patients treated with placebo had a baseline bleeding score of three and a WHO bleeding score of zero at the end of therapy. There was no grade four bleeding in the pivotal trials. The clinical meaningfulness of the WHO bleeding score in terms of incremental changes (e.g., going from WHO bleeding score one to zero) is unclear. In addition, the investigators subjectively assigned bleeding scores and were aware of patient platelet counts at the time of bleeding assessments. These factors confound the analysis of eltrombopag's effect on bleeding.

- In the pivotal trials only 7/173 patients faced a hemostatic challenge during the observation period. In these trials, four patients received eltrombopag (three patients received eltrombopag 50 mg with baseline platelet counts of 10,000-25,000/mcl and one patient received eltrombopag 75 mg with a baseline platelet count of 10,000/mcl). The three placebo treated patients had platelet counts ranging from 12,000-36,000/mcl. The four patients treated with eltrombopag underwent hemostatic challenges consisting of cholecystectomy (two patients), dental extraction and motor vehicle accident. The patients treated with placebo had hemostatic challenges consisting of eye surgery, hip replacement and papilloma surgery of the throat. After treatment with eltrombopag but before the procedure the platelet counts ranged from 82,000-557,000/mcl. After placebo treatment but before the procedure the platelet counts ranged from 26,000-86,000/mcl. None of the patients treated with eltrombopag required rescue treatment. However all three placebo treated patients received other ITP therapy prior to surgery with IVIg or tranexamic acid. No bleeding complications were reported in any of these patients. The limited number of patients who underwent hemostatic challenge does not allow for a conclusion to be drawn with regard to eltrombopag's effectiveness in preventing bleeding in patients who have undergone hemostatic challenge.

## 6 INTEGRATED REVIEW OF SAFETY

### 6.1 Methods and Findings

Descriptive statistics were used by the sponsor in summarizing the safety results for all studies. In the two pivotal trials, TRA 100773A and TRA 100773B, all patients who were randomized and received at least one dose of study medication were included in the evaluation of safety and comprised the safety population. For study TRA 100773A the safety population included 29 patients treated with placebo, 30 patients each into 30 mg and 50 mg eltrombopag treatment cohorts and 28 patients in the 75 mg eltrombopag treatment cohort. For study TRA 100773B there were 38 patients in the safety population treated with placebo and 76 patients in the safety population treated with eltrombopag. In addition to the safety populations evaluated in the two pivotal trials, the analysis of the safety of eltrombopag in this review incorporates three other important ongoing supportive studies in ITP patients: REPEAT, RAISE and EXTEND with data provided as of the 120 day safety update. The three trials, REPEAT, RAISE and EXTEND, are ongoing.

REPEAT is a multicenter, open label, single group, repeat dose, phase 2 study designed to evaluate the efficacy, safety and tolerability of eltrombopag 50 mg once daily over three cycles in adult patients with previously treated chronic ITP. A cycle is defined as eltrombopag on therapy up to six weeks and off therapy up to four weeks. In REPEAT, patients with chronic ITP are eligible provided they have received at least one prior ITP therapy and have platelet counts of  $\geq 20,000/\text{mcl}$  and  $\leq 50,000/\text{mcl}$ . A placebo control arm is not included in this study because few patients who received placebo would respond and proceed beyond cycle one of the study, making comparisons on efficacy and safety of eltrombopag versus placebo over repeated cycles on administration impossible. RAISE is a randomized, double-blind, placebo-controlled, phase 3

study in adults with chronic ITP and baseline platelet counts <30,000/mcl. This study is designed to assess the efficacy and safety of eltrombopag in adults with chronic ITP dosed for up to six months. EXTEND is a single arm, open label, dose adjustment study designed to evaluate the safety and efficacy of eltrombopag treatment for patients with ITP who previously had been enrolled in eltrombopag trial. The study allows dosing eltrombopag at an individualized dose for each subject to maintain platelet counts  $\geq 50,000/mcl$ . The ability to reduce the dose of concomitant ITP medication in the presence of eltrombopag while maintaining platelet counts  $\geq 50,000/mcl$  is assessed. This study also examines retreatment with eltrombopag in patients who received eltrombopag in their previous study.

The disposition of patients after treatment in the two pivotal trials along with the REPEAT and RAISE studies is shown in the table below. In addition to the information presented below there were three patients and seven patients in the placebo and eltrombopag treatment groups, respectively, that failed screening criteria for entry into EXTEND from the pivotal trial TRA 100773A. There were 10 and 13 patients in the placebo and eltrombopag treatment groups, respectively, that failed screening criteria for entry into EXTEND from the pivotal trial TRA 100773B. There were 18 and 41 patients treated with eltrombopag that failed screening criteria for entry into EXTEND from the REPEAT and RAISE trials, respectively.

Disposition of Patients in Pivotal Trials, RAISE and REPEAT

Clinical Cut-off 7 January 2007	TRA100773A (N=118)		TRA100773B (N=114)		REPEAT (N=66)	RAISE (N=197)
	Placebo N=29	Promacta N=88 <sup>a</sup>	Placebo N=38	Promacta N=76	Promacta N=66	Blinded N=196 <sup>a</sup>
Patients Not Able to Enter EXTEND	12	46	9	22	11	72
Ongoing in Previous Study	0	0	0	0	8	53
Study center not participating in EXTEND	6	21	5	11	0	4
Subject decided not to participate	2	6	1	3	1	6
Did not complete 773 6m ocular follow-up	3	9	1	3	NA	NA
Change in diagnosis (no longer ITP)	0	3	0	0	NA	NA
Related AEs in prior study	0	1	0	2	0	0
Protocol violator in prior study	0	0	0	1	0	0
Lost to follow-up	0	2	0	0	2	5
High platelet counts (treatment not needed)	1	2	2	1	0	3
Investigator decision	0	1	0	0	0	0
Patient died	0	1	0	1	0	1
Potential Patients Eligible for EXTEND <sup>b</sup>	17	42	29	54	55	124
Subjects Who Entered EXTEND	14	35	19	41	37	83 <sup>a</sup>
Subjects who didn't enter EXTEND (as of clinical cut-off)	15	53	19	35	28	113

<sup>a</sup> In studies TRA 100773A and RAISE, one subject randomized and not treated and excluded from the N  
<sup>b</sup> Exclude patients that were ongoing in the previous study at the time of the clinical cut-off and subjects who were not screened for EXTEND  
<sup>c</sup> One RAISE subject (#834) was identified as a screen failure after the clinical cut-off for EXTEND

In addition to the data presented in the original NDA submission, data from the 120 day safety update that supports the safety evaluation for this NDA was reviewed. The sponsor states that in this 120 day safety update 330 ITP patients were exposed to eltrombopag. Therefore 61 more patients were included in the safety population compared to the 269 patients in the safety

population presented in the original NDA. The sponsor estimates that approximately 150 patients were exposed to eltrombopag for  $\geq 6$  months as of the cut off date for the 120 day safety update.

The exposure to study medication in study TRA 100773A is summarized by the number of days on treatment and cumulative dose in the table below.

Exposure to Eltrombopag TRA 100773A

	Treatment Group			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>Cumulative Dose, mg</b>				
n	29	30	29	28
Mean (SD)	0	1094.7 (348.34)	1634.5 (621.07)	1856.3 (1159.31)
Median	0	1260.0	2100.0	1650.0
Min - Max	0	240 - 1290	400 - 2150	225 - 3225
<b>Days on Study Drug</b>				
n	29	30	30	28
Mean (SD)	36.4 (12.19)	37.0 (11.53)	32.7 (12.53)	25.1 (15.72)
Median	42.0	42.0	42.0	22.5
Min - Max	7 - 43	8 - 46	10 - 44	3 - 43

Data Source: Table 8.1

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In study TRA 100773B the median duration of treatment in both treatment arms was 43 days. The table below summarizes by number of days on treatment and cumulative dose the exposure to study medication. The sponsor states that 35 patients in the eltrombopag treatment group had a dose increased to 75 mg on or after the day 22 visit. As a result the median cumulative dose for eltrombopag was higher than predicted (2262.5 mg compared to the predicted six-week exposure total for eltrombopag at 50 mg, i.e., 2100 mg).

Exposure to Eltrombopag TRA 100773B

	Treatment Group	
	PBO N=38	Eltrombopag N=76
<b>Cumulative Dose, mg</b>		
n	38	76
Mean (SD)	0.0 (0.00)	1958.2 (764.21)
Median	0.0	2262.5
Min - Max	0 - 0	350 - 2700
<b>Days on Study Drug</b>		
n	38	76
Mean (SD)	38.7 (10.94)	35.7 (12.63)
Median	43.0	43.0
Min - Max	5 - 49	8 - 51 <sup>a</sup>

Data Source: Table 8.1

- a. Subjects were dispensed 50 tablets per bottle (see Section 5.4.2, Dosages and Administration). Subjects 1730 and 1731 (both in the eltrombopag group) are recorded as having taken all tablets (none returned) over a 51 day period

## Deaths

At the time of the NDA submission there were four deaths reported in the ITP program and as of the safety update six deaths were reported. In study TRA 100773A there was one fatal serious adverse event (patient 144). This patient was a 66 year old male with ITP and a history of chronic obstructive pulmonary disease and lung cancer. His platelet counts at entry were 3000/mcl and his hemoglobin was 10.6g/dl. This patient had pulmonary embolism, renal insufficiency and hepatitis which were considered to be related to study medication. The patient was randomized to 50 mg of eltrombopag once daily. Approximately 2 weeks after starting study drug the patient was admitted to hospital with exacerbation of chronic obstructive pulmonary disease and grade 4 elevation in liver transaminases. The platelet count was a 44,000/mcl. One week later the patient's eltrombopag was stopped and his platelet count at that time was 108,000/mcl. The patient died 11 days after admission with the cause of death listed as embolism/pulmonary embolism, renal insufficiency, hepatitis. The patient's autopsy showed multiple thromboembolic events. Liver examination showed focal ischemic necrosis which was consistent with terminal low flow due to severe heart failure with no inflammatory changes noted in the liver. The findings were consistent with multiple organ failure arising from cardiorespiratory insufficiency which may have been initiated by pulmonary sepsis which may have been the etiology for his chronic obstructive pulmonary disease exacerbation. The thromboembolic events noted in the initial report were assessed as being near terminal and thence resulting from low cardiac output.

In study TRA 100773B no deaths occurred during the study. The sponsor reported in the 120 day safety update that five patients died in the supportive trials. There were four patients who died in the EXTEND trial thus far. The causes of death are listed below:

- Passenger in a motor vehicle accident.
- Hypovolemic shock due to gastrointestinal hemorrhage 55 days after the last dose of eltrombopag. This patient was a nonresponder and had a platelet count < 10,000/mcl at the time of the event.
- Multiorgan failure secondary to septic shock of pulmonary origin, acute respiratory insufficiency and acute renal failure. Six weeks prior to this patient's death, the patient was hospitalized with a pulmonary infection and progressive acute respiratory insufficiency requiring treatment with a broad spectrum intravenous antibiotics, intravenous immunoglobulin and vasopressors. Twelve hours after admission the patient's condition deteriorated and she required intubation and ventilatory support. Her chest x-ray showed evidence of parenchymal involvement and thoracic CT scan demonstrated infected bronchiectasis 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 leg was diagnosed. The patient's clinical course was further complicated by renal failure, urinary tract infection and tachycardia. One week prior to her death, the patient developed symptoms of septic shock and a multiresistant *Pseudomonas aeruginosa* strain was cultured from her bronchial secretions. Multiorgan failure ensued.

- Sudden-death with no postmortem examination. The report provided by the sponsor stated that the patient had an acute bleed, acute hemorrhage versus acute myocardial infarction versus acute arrhythmia and cardiac arrest versus sepsis syndrome in a patient with fever on steroids. This patient's medical history was significant for splenectomy, basal cell carcinoma, breast cancer, obesity, anxiety, depression, prolonged QT syndrome, gastroesophageal reflux disease and bronchiolitis obliterans organizing pneumonia. The patient's concomitant and recent medications included two drugs known to prolong the QT interval (formoterol and venlafaxine).

There was one death in the RAISE trial which was attributed to a brainstem cerebro-vascular accident bleed. This patient did not respond to blinded study medication and had a platelet count < 10,000 /mcl at the time of the event.

### Other Serious Adverse Events

In the pivotal trials six patients treated with placebo and 11 patients treated with eltrombopag had serious adverse events. The table below shows the adverse event profile for eltrombopag during study TRA 100773A. There were four patients in the placebo arm compared to nine patients in the eltrombopag treatment arms that had serious adverse events.

Proportion of Patients with Adverse Events in TRA 100773A (Safety Population)

During Entire Study	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
Any AE	18 (62)	20 (67)	17 (57)	19 (68)
Any SAE	4 (14)	1 (3)	6 (20)	2 (7)
AEs related to study medication	11 (38)	10 (33)	8 (27)	10 (36)
AEs leading to withdrawal	3 (10)	0	2 (7)	1 (4)

Data Source: Table 8.2

The table below shows the adverse event profile for eltrombopag during study TRA 100773B. There were two patients in the placebo treatment group and two patients in the eltrombopag treatment group that had serious adverse events.

Proportion of Patients with Adverse Events in Study TRA 100773B (Safety Population)

AEs During Treatment Phase	Treatment Group, n (%)	
	PBO N=38	Eltrombopag N=76
Any AE	14 (37)	45 (59)
Any SAE	2 (5)	2 (3)
AEs related to study medication	4 (11)	20 (26)
AEs leading to withdrawal	2 (5)	3 (4)

Data Source: Table 8.3

The table below shows the serious adverse events on therapy for study TRA 100773A.

Best Possible Copy

Serious Adverse Events on Therapy for TRA 100773A

	Treatment Group			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>Any SAE, n (%)</b>	2 (7)	0	2 (7)	0
<b>Events by Subject</b>	Toxic hepatitis <sup>a</sup> (Subject 165)		Herpes zoster (Subject 414)	
	Ruptured varicose vein (Subject 171)		Embolism <sup>a</sup> , hepatitis <sup>a</sup> , renal failure <sup>a</sup> , pulmonary embolism <sup>a</sup> (Subject 144)	

Data Source: Table 8.9

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

Post therapy serious adverse events were defined as an event with onset one day or more after the last dose of study treatment. In study TRA 100773A two patients experienced serious adverse events within 24 hours of the last dose of their study medication. One patient had a convulsion (placebo patient 1372) and one patient developed urticaria (eltrombopag 75 mg patient 167). In addition a total of nine serious adverse events were reported in seven patients across the four treatment groups more than 24 hours after the last dose. The frequency of post therapy serious adverse events in study TRA 100773A is shown on the table below.

Post Therapy Serious Adverse Events in TRA 100773A

	Treatment Group			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>Any SAE, n (%)</b>	2 (7)	1 (3)	4 (13)	2 (7)
<b>Events by Subject</b>	Convulsion <sup>a</sup> (Subject 1372)	Pneumonitis <sup>a</sup> (Subject 1123)	Thrombocytopenia, Petechiae (Subject 1369)	Menorrhagia (Subject 61)
	Gastronenteritis salmonella (Subject 1069)		Cardiopulmonary Failure (Subject 144)	Urticaria <sup>a</sup> (Subject 167)
			Gallbladder empyema, Cholelithiasis (Subject 175)	
		Rectal hemorrhage (Subject 1085)		

Data source: Table 8.10

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

The table below shows the frequency of on therapy serious adverse events in study TRA 100773B.

Best Possible Copy

On Therapy Serious Adverse Events in TRA 100773B

	Treatment Group	
	PBO N=38	Eltrombopag N=76
Any SAE, n (%)	2 (5)	2 (3)
Events by Subject	Gastrointestinal hemorrhage <sup>a</sup> Cerebral hemorrhage <sup>a</sup> Hematuria <sup>a</sup> (Subject 1233)	Gastrointestinal hemorrhage (Subject 785)
	Face injury (Subject 1877)	Cerebral hemorrhage (Subject 1846)

Data Source: Table 8.9, Attachment 4 Listing 30

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

In study TRA 100773B a total of five patients experienced post therapy serious adverse events one patient in the placebo group experienced 10 serious adverse events and four patients in the eltrombopag treatment group reported a total of five post therapy serious adverse events. One patient in the eltrombopag treatment group developed a cataract which was considered to be related to study medication. The frequency of post therapy serious adverse events for study TRA 100773B is shown in the table below.

Post Therapy Serious Adverse Events in TRA 100773B

	Treatment Group	
	PBO N=38	Eltrombopag N=76
Any SAE, n (%)	1 (3)	4 (5)
Events by Subject	Anemia <sup>a</sup> Abdominal pain upper <sup>a</sup> Constipation <sup>a</sup> Mouth ulceration <sup>a</sup> Asthenia <sup>a</sup> Decrease Appetite <sup>a</sup> Lethargy <sup>a</sup> Pruritus generalized <sup>a</sup> Abdominal tenderness <sup>a</sup> Hyperglycemia <sup>a</sup> (Subject 1577)	Typhoid fever Subarachnoid hemorrhage <sup>b</sup> (Subject 1562)
		Epistaxis <sup>b</sup> (Subject 1313)
		Cataract <sup>a</sup> (Subject 77)
		Epilepsy (Subject 1364)

Data source: Table 8.10, Attachment 4 Listing 30

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

b. Subarachnoid hemorrhage in Subject 1562 occurred 39 days after last dose of study medication; epistaxis in Subject 1313 occurred 32 days after last dose of study medication. Both subjects had platelet counts less than 12GiL proximate to when the bleeding SAEs occurred.

### Dropouts and Other Significant Adverse Events

A total of nine adverse events were reported as leading to withdrawal of six patients from the study medication in study TRA 100773A. The table below shows the adverse events leading to withdrawal from study medication in this pivotal trial.

Adverse Events Leading to Patient Withdrawal from TRA 100773A

	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>Any AE, n (%)</b>	3 (10)	0	2 (7)	1 (4)
<b>Events by Subject</b>	Toxic hepatitis <sup>a</sup> (Subject 165)		Menorrhagia (Subject 1070)	Tonsillitis <sup>a</sup> , urticaria <sup>a</sup> (Subject 167)
	Bilirubin increase <sup>a</sup> (Subject 179)		Embolism <sup>a</sup> , hepatitis <sup>a</sup> , pulmonary embolism <sup>a</sup> (Subject 144)	
	Convulsion <sup>a</sup> (Subject 1372)			

Data Source: Table 8.11

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

The number of patients and reasons for withdrawal from study medication are listed in the table below for study TRA 100773B.

Adverse Events Leading to Withdrawal of Patients from TRA 100773B

	Treatment Group	
	PBO N=38	Eltrombopag N=76
<b>Any AE Leading to Withdrawal, n (%)</b>	2 (5)	3 (4)
<b>Events by Subject</b>	Gastrointestinal hemorrhage <sup>a</sup> Cerebral hemorrhage <sup>a</sup> Hematuria <sup>a</sup> (Subject 1233)	Gastrointestinal hemorrhage (Subject 785) <sup>b</sup>
	Face injury (Subject 1877)	Cerebral hemorrhage (Subject 1846) <sup>b</sup>
		Hepatic function abnormal <sup>a,c</sup> (Subject 430)

Data Source: Table 8.11

a. AEs considered by the investigator to be related to study medication. For subject 430, no relationship status was reported for hepatic function abnormal, and was thus considered related.

b. Subjects 785 and 1846 were non-responders.

c. Subject 430 was receiving concomitant dexamethasone.

### Overall profile of dropouts

The overall number of adverse events between placebo and eltrombopag treated patients was similar (five patients in the placebo treated group compared to six patients in the eltrombopag treated group) when both pivotal trials are combined. Bleeding and abnormal hepatic function

were the most common adverse events in patients that were withdrawn either from placebo or eltrombopag when both pivotal trials are combined.

Adverse events associated with dropouts

The adverse events associated with dropouts in the two pivotal trials was discussed in section 7.1.3.1 Overall profile of dropouts in this review.

Other significant adverse events

In study TRA 100773A there were 13 adverse events reported on therapy for 12 patients. On therapy bleeding adverse events were more frequent in the placebo and 30 mg treatment groups (four adverse events and six adverse events respectively) compared to the 50 mg and 75 mg treatment groups (two adverse events and one adverse event respectively). In all but one case the patient was not responding to therapy according to the sponsor. The table below shows the on therapy bleeding and thrombocytopenia adverse events.

TRA 100773A on Therapy Bleeding Adverse Events

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Platelet Count Proximal to AE <sup>a</sup>	Days Since 1 <sup>st</sup> Dose	Duration (days)	Treatment -related	Study Medication
<b>PBO Treatment Group</b>										
1215	47	F	WC	Conjunctival hemorrhage	1	36Gi/L	35	8	No	NC
171	36	F	WC	Varicose vein ruptured (SAE)	3	13Gi/L	22	1	No	NC
70	39	F	WAN	Diarrhea hemorrhagic	1	5Gi/L	17	3	No	NC
1705	24	F	WAN	Contusion	2	41Gi/L	15	57	No	NC
<b>30mg Treatment Group</b>										
1084	67	M	WC	Epistaxis	2	10Gi/L	21	1	No	NC
644	70	M	WC	Epistaxis	1	6Gi/L	14	9	No	NC
645	71	F	WC	Gingival bleeding	1	12Gi/L	1	--	No	NC
				Epistaxis	1	13Gi/L	9	1	No	NC
623	42	M	AAA	Contusion	1	1Gi/L (D15&D22)	19	33	No	NC
1043	58	M	WC	Epistaxis	2	31Gi/L	13	1	No	NC
<b>50mg Treatment Group</b>										
1070	38	F	WC	Menorrhagia	2	1Gi/L	13	66	No	withdrawn
1642	44	F	WAN	Contusion	1	75Gi/L	8	8	No	NC
<b>75mg Treatment Group</b>										
282	55	F	WC	Contusion	1	7Gi/L	2	1	No	NC

a. Platelet counts were 22 days of the event, except as noted. Subject 623 had platelet counts of 1Gi/L on both Day 15 and Day 22. WC = White-Caucasian/European; WAN = White-Arabic/North African; AAA = African American/African; NC = no change.

During the post therapy follow-up phase of study TRA 100773A bleeding adverse events occurred similarly a cross the treatment groups. The table below shows the post therapy bleeding adverse events and thrombocytopenia.

Best Possible Copy

TRA 100773A Post Therapy Bleeding Adverse Events

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Platelet Count Proximal to AE	Days Since 1 <sup>st</sup> Dose/Last Dose	Duration (days)	Treatment-related
<b>PBO Treatment Group</b>									
1215	47	F	WC	Hemorrhoidal hemorrhage	1	27 Gi/L	70/28	8	No
166	49	F	WC	Epistaxis	1	16 Gi/L	35/27	1	No
70	39	F	WAN	Menometrorrhagia	1	5 Gi/L (D67) <sup>a</sup>	54/11	4	No
1705	24	F	WAN	Menorrhagia	1	39 Gi/L	57/14	--	No
<b>30mg Treatment Group</b>									
162	48	F	WC	Cortusion	1	8 Gi/L	56/13	11	No
				Epistaxis	1	8 Gi/L	56/13	1	No
163	49	M	WC	Gingival bleeding	1	10 Gi/L (D71) <sup>a</sup>	67/24	1	No
				Cortusion	1	9 Gi/L (D85) <sup>a</sup>	80/37	--	No
172	51	F	WC	Epistaxis	2	17 Gi/L	21/13	1	No
1123	72	M	WC	Platelet count decreased	2	54 Gi/L	36/26	--	No
1043	58	M	WC	Conjunctival hemorrhage	1	27 Gi/L	57/15	15	No
				Epistaxis	1	38 Gi/L (D71) <sup>a</sup>	67/25	1	No
<b>50mg Treatment Group</b>									
1070	38	F	WC	Menstrual disorder	1	4 Gi/L	78/43	--	No
1085	60	F	WC	Rectal hemorrhage (SAE)	3	4 Gi/L (D43) <sup>a</sup>	51/9	9	No
1369	27	F	WC	Petechiae (SAE)	2	4 Gi/L <sup>b</sup>	65/22	2	No
				Thrombocytopenia (SAE)	4	4 Gi/L <sup>b</sup>	65/22	25	No
<b>75mg Treatment Group</b>									
703	77	M	WC	Petechiae	2	13 Gi/L (D64)	71/49	--	No
61	44	F	WAN	Menorrhagia (SAE)	3	4 Gi/L	59/16	3	No
				Petechiae	2	4 Gi/L	59/16	2	No
				Ulorrhagia (gum bleeding)	2	4 Gi/L	59/16	2	No

a. Platelet counts were  $\pm 2$  days of the event, except as noted. Subject 163 had platelet counts of 13 Gi/L on Day 57, 10 Gi/L on Day 71 and 9 Gi/L on Day 85. Subject 1085 had platelet counts of 4 Gi/L on Day 43 and 2 Gi/L on Day 71.  
 b. Platelet count data for Subject 1369 was based on information from the SAE narrative.  
 WC = White-Caucasian/European; WAN = White-Arabic/North African.

The mean and median platelet counts at the six-week follow-up phase after discontinuation of study medication in each treatment group were compared to the mean and median baseline platelet counts in each treatment group for study TRA 100773A. The baseline and lowest post-treatment platelet counts are shown in the table below. There does not appear to be a trend in any treatment group following discontinuation of study medication with regard to the lowest platelet count post therapy during the six-week follow-up phase.

Post-treatment Platelet Counts TRA 100773A

	Treatment Group			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>n</b>	28	28	29	28
<b>Baseline Platelet Count (Gi/L)</b>				
Mean (SD)	16 (7.9)	16 (7.1)	17 (9.6)	16 (10.1)
Median	16	16	19	14
Min - Max	4 - 30	4 - 34	2 - 40	1 - 33
<b>Lowest Post-Therapy Platelet Count<sup>a</sup> (Gi/L)</b>				
Mean (SD)	27 (41.9)	17 (11.7)	28 (38.2)	12 (10.4)
Median	16	16	14	10
Min - Max	1 - 228	4 - 54	0 - 181	0 - 51

Data Source: Table 7.125

a. Lowest platelet count from >3 days post-dosing.

In study TRA 100773A and in study TRA 100773B there appeared to be a trend for transient thrombocytopenia observed within four weeks of discontinuation of eltrombopag therapy. In study TRA 100773A six patients, one in the placebo arm, none in the 30 mg eltrombopag group, three in the 50 mg eltrombopag group and two in the 75 mg eltrombopag group had platelet counts < 10,000/mcl and a decrease in platelet count of at least 10,000/mcl compared to baseline within four weeks after discontinuation of study medication. All five patients who received eltrombopag were defined as responders and three patients achieved platelet counts  $\geq$  200,000/mcl. The table below shows platelet counts for the patients with platelet counts < 10,000/mcl and decreased by at least 10,000/mcl within four weeks of study medication discontinuation in study TRA 100773A.

TRA 100773A: Platelet Counts < 10,000/mcl and Decreased by at Least 10,000/mcl within 4 Weeks of Treatment Discontinuation

Treatment Group	Subject Number	Platelet Counts (Gi/L)		
		Baseline	Day 57 Visit <sup>a</sup>	Day 71 Visit <sup>b</sup>
PBO	763	13	3	ND
50mg	71	28	5	238
	1067	19	8	52
	1642	17	30	5
75mg	292	28	49	9
	294	13	4	2

Data Source: Listing 86, Attachment 4.

- Subject 253 (PBO) had baseline platelet count 14Gi/L and a platelet count of 4Gi/L on Day 43 Visit. Subject 300 (30mg) had baseline platelet count 16Gi/L and a post-therapy platelet count of 4Gi/L only at the Day 85 Visit.
- Day 57 = 14 days after discontinuation of study medication; Day 71 = 28 days after discontinuation of study medication.

To analyze the clinical consequences of potential transient worsening of platelet counts in the six subjects baseline WHO bleeding scores were compared to post therapy WHO bleeding scores and the use of rescue therapy were evaluated. The bleeding scores for these six patients and use of rescue medication are shown in the table below. In three patients bleeding score increased from baseline. However, the number of patients included in this analysis is very small.

WHO Bleeding Score for 6 Patients with Platelet Counts < 10,000/mcl and Decreased by at Least 10,000/mcl within 4 Weeks of Treatment Discontinuation

Treatment Group	Subject Number	WHO Bleeding Score		
		Baseline	Day 57 Visit	Day 71 Visit
PBO	763	0	0	0
50mg	71	0	2 <sup>a</sup>	0
	1067	0	0 <sup>a</sup>	0
	1642	0	1	1
75mg	292	1	0	1
	294	1	1	3 <sup>a</sup>

Data Source: Attachment 4 Listing 46

- Rescue therapy: 50mg group – Subject 71 received a cyclophosphamide (1g) infusion and initiated a 4-week course of danazol 400mg (Attachment 5 Data Clarifications Received Post-Analysis); Subject 1067 initiated prednisone 80mg; 75mg group – Subject 294 increased daily dose of prednisone from 10mg to 15mg.

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In terms of thromboembolic events in study TRA 100773A patient 144 had a serious adverse event of pulmonary embolism and thromboemboli and was discussed in section 7.1.1 Deaths in this review. No other thromboembolic events were reported in any other study patient during the treatment or post therapy phases of this study. Of the 12 patients who achieved a platelet count > 400,000/mcl during treatment, only two patients (both in the 50 mg treatment group) received medication for prophylaxis of thrombosis in response to their increase in platelets. These patients achieved platelet counts in the range >400,000/mcl-<1,000,000/mcl by day 15 and were discontinued from study medication and received aspirin therapy along with antacid therapy for three days. No adverse events were reported in either of these patients. The other 10 patients did not receive thrombosis prophylaxis and did not have thromboembolic events with platelet counts in a similar range to those above. In study TRA 100773B patients were to have their study medication discontinued and either aspirin or platelet pheresis therapy for platelet counts > 800,000/mcl.

The table below shows the on therapy hepatobiliary adverse events reported in the original NDA submission for study TRA 100773A. The number and severity of hepatobiliary adverse events appear to be low and comparable between the active treatment groups and placebo.

On Therapy Hepatobiliary Adverse Events TRA 100773A

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Days Since 1 <sup>st</sup> dose	Duration (days)	Treatment-related	Study Medication
<b>PBO Treatment Group</b>									
165	49	F	WC	Hepatitis toxic (SAE)	3	7	9	yes	withdrawn
179	28	M	WC	Blood bilirubin increased	2	8	--	Yes	withdrawn
<b>30mg Treatment Group</b>									
293	48	F	WC	ALT increased	1	29	8	No	NC
				AST increased	1	29	8	No	NC
173	23	M	WC	Blood bilirubin increased	1	15	57	Yes	NC
<b>50mg Treatment Group</b>									
144	66	M	WC	Hepatitis (SAE)	3	15	--	Yes	withdrawn
<b>75mg Treatment Group</b>									
381	63	M	WC	AST increased	1	29	--	No	NC
383	66	F	WC	ALT increased	1	36	26	Yes	NC
				AST increased	1	36	26	Yes	NC

WC = White/Caucasian/Euro pean; NC = no change.

Post therapy, in study TRA 100773A, two hepatobiliary adverse events occurred in one patient (patient 175) and are listed below.

Post Therapy Hepatobiliary Adverse Events TRA 100773A

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Days Since 1 <sup>st</sup> Dose/Last Dose	Duration (days)	Treatment-related
<b>50mg Treatment Group</b>								
175	53	F	WC	Cholelithiasis (SAE)	--	22/7	2	No
				Gallbladder empyema (SAE)	--	23/8	1	No

WC = White/Caucasian/Euro pean.

In study TRA 100773B there were no patients in the placebo treatment group who experienced a hepatobiliary adverse event either on therapy or post therapy. In the eltrombopag treatment group there were five patients who had seven hepatobiliary adverse events. No eltrombopag

treated patients experienced a hepatobiliary adverse event post therapy. The on therapy hepatobiliary adverse events experienced by those patients in study TRA 100773B are shown in the table below.

TRA 100773B on Therapy Hepatobiliary Adverse Events

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Days Since 1 <sup>st</sup> Dose	Duration (days)	Treatment-related	Study Medication
<b>Eltrombopag Treatment Group</b>									
430	38	M	Asian	Hepatic function abnormal	2	15	-	Y	Withdrawn
386	64	F	White	AST increased	2	29	43	Y	NC
				ALT increased	2	36	36	Y	NC
1562	38	M	Asian	Hepatic enzyme increased	1	24	18	N	NC
1578	28	M	Asian	AST increased	1	43	8	Y	NC
				ALT increased	1	43	8	Y	NC
1373	61	M	White	Hepatic steatosis	1	22	-	N	NC

NC = no change

In study TRA 100773A while on therapy there were two patients in the placebo group, three patients in the 30 mg treatment group, three patients in the 50 mg treatment group and four patients in the 75 mg treatment group that had skin disorders characterized as rash, erythema, pruritis, hyperhidrosis, hot flush, urticaria and flushing.

In study TRA 100773B bleeding adverse events were reported on therapy for five placebo treated patients who experienced nine events and seven eltrombopag treated patients who experienced nine events. On therapy bleeding adverse events were reported more frequently in placebo treated patients (13%) compared to eltrombopag treated patients (9%). All bleeding events occurred in patients who had platelet counts < 30,000/mcl around the time of their adverse event. The table below shows the on therapy bleeding adverse events for study TRA 100773B.

On Therapy Bleeding Adverse Events TRA 100773B

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Baseline Platelet Count <sup>a</sup>	Platelet Count Proximal to AE <sup>b</sup>	Days Since 1 <sup>st</sup> Dose	Duration (days)	Treatment-related	Study Medication
<b>PBO Treatment Group</b>											
1233	50	F	White	Gastrointestinal hemorrhage	2	11Gi/L	5Gi/L	15	7	Yes	Withdrawn
				Cerebral hemorrhage	2	11Gi/L	5Gi/L	15	9	Yes	Withdrawn
				Hematuria	2	11Gi/L	5Gi/L	15	9	Yes	Withdrawn
78	21	F	W/A	Gingival bleeding	3	3Gi/L	3Gi/L	1	43	No	NC
192	38	M	White	Contusion	1	2Gi/L <sup>a</sup>	2Gi/L	12	6	No	NC
				Contusion	1	2Gi/L <sup>a</sup>	4Gi/L	20	10	No	NC
1867	35	F	Asian	Gingival bleeding	1	26Gi/L	29Gi/L	8	1	No	NC
1335	41	M	White	Gingival bleeding	1	23Gi/L	23Gi/L to 13Gi/L <sup>b</sup>	6	7	No	NC
				Epistaxis	1	23Gi/L	13Gi/L	12	11	No	NC
<b>Eltrombopag Treatment Group</b>											
785	79	M	White	Gastrointestinal hemorrhage	4	26Gi/L	12Gi/L	16	-	No	Withdrawn
77	47	F	W/A	Ulorrhagia (gum bleeding)	1	30Gi/L	58Gi/L to 3Gi/L <sup>b</sup>	19	9	No	NC
1846	59	F	W/A	Cerebral hemorrhage	-	13Gi/L	2Gi/L <sup>b</sup>	12	12	No	Withdrawn
1221	45	F	White	Menorrhagia	2	9Gi/L	20Gi/L	15	6	No	NC
				Blood blisters mouth	2	9Gi/L	9Gi/L <sup>b</sup>	5	4	No	NC
1475	61	F	White	Hematochezia	1	10Gi/L	9Gi/L	44/1	-	No	NC
				Epistaxis	2	10Gi/L	9Gi/L	44/1	-	No	NC
1576	34	F	Asian	Menorrhagia	1	6Gi/L	4Gi/L <sup>b</sup>	11	9	No	NC
1873	37	F	A/AN	Ecchymosis (accidental traumatic)	1	10Gi/L	12Gi/L <sup>b</sup>	11	-	No	NC

a. Platelet counts were from Day 1, except as noted. Subject 192 baseline platelet count from Screening.

b. Platelet counts were ±2 days of the event, except as noted. Subject 1335: platelet count was 23Gi/L 5 days prior and 13Gi/L 5 days after the onset of gingival bleeding; Subject 1221: platelet count was 5 days prior to the event of 'blood blisters mouth'; Subject 77: platelet count was 58Gi/L 4 days prior and 3Gi/L 3 days post-onset of ulorrhagia; Subject 1873: platelet count was 3 days prior to the event.; Subject 1576: platelet count was 3 days prior to the event; Subject 1846: platelet count was 2Gi/L 4 days prior to onset of the event.

W/A = White-Arabic; A/AN = American Indian-Alaskan Native; NC = no change.

Best Possible Copy

In study TRA 100773B the post therapy treatment phase was defined as >1 day after discontinuation of study medication until day 85 (six weeks after discontinuation of study medication). The table below shows the post therapy bleeding adverse events and thrombocytopenia that occurred in patients in study TRA 100773B.

Post Therapy Bleeding Adverse Events TRA 100773B

Subject No.	Age (yr)	Sex	Race	AE, Preferred term	CTCAE Grade	Baseline Platelet Count <sup>a</sup>	Platelet Count Proximal to AE <sup>b</sup>	Days Since 1 <sup>st</sup> Dose/Last Dose	Duration (days)	Treatment-related
<b>PBO Treatment Group</b>										
75	42	F	W/A	Ecchymosis Petechiae	2 2	10Gi/L 10Gi/L	4Gi/L 4Gi/L	50/7 50/7	8 8	No No
<b>Eltrombopag Treatment Group</b>										
1562	38	M	Asian	Subarachnoid hemorrhage	4	5Gi/L	11Gi/L <sup>b</sup>	80/39	15	No
77	47	F	W/A	Ulorrhagia (gum bleeding)	1	30Gi/L	2Gi/L	45/0	5	No
79	28	F	W/A	Gingival bleeding	1	29Gi/L	23Gi/L	22/14	3	No
406	70	F	Asian	Conjunctival hemorrhage	2	23Gi/L	17Gi/L	42/26	13	No
430	38	M	Asian	Conjunctival hemorrhage	2	28Gi/L	22Gi/L <sup>b</sup>	36/21	77	No
407	37	F	Asian	Menorrhagia	3	28Gi/L	16Gi/L <sup>b</sup>	41/20	19	No
1404	43	M	White	Traumatic hematoma	2	11Gi/L	7Gi/L to 21Gi/L <sup>b</sup>	80/37	-	No
1313	60	F	White	Epistaxis	3	10Gi/L	10Gi/L <sup>b</sup>	74/32	2	No
964	83	F	White	Ecchymosis	2	18Gi/L	31Gi/L	69/26	-	No
1448	75	F	White	Thrombocytopenia	4	29Gi/L	23Gi/L	57/14	8	No

a. Platelet counts were from Day 1.

b. Platelet counts were  $\pm 2$  days of the event, except as noted. Subject 1562 platelet count 8 days prior to the onset of the event (platelets were 39Gi/L 8 days after the event during the recovery period, after receiving IV steroids and 6 units of platelets); Subject 430 platelet count 9 days prior to event; Subject 407 platelet count 7 days prior to onset of the event, platelet count on day 10 of the event was 5Gi/L; Subject 1404 platelet count 9 days prior to the event were 7Gi/L and 21Gi/L 5 days after the onset of the event; Subject 1313 platelet count 3 days prior to the event.

W/A = White-Arabic

Platelet counts declined after discontinuation of Eltrombopag. In study TRA 100773B the median lowest platelet counts in the six weeks following discontinuation of study medication in each treatment group were compared to the median baseline platelet counts in each treatment group. The baseline and lowest off treatment platelet counts regardless of whether rescue medication was utilized are summarized in the table below across the entire six-week post therapy phase.

Lowest off Therapy Platelet Counts TRA 100773B

	Treatment Group	
	PBO N=38	Eltrombopag N=76
<b>Baseline Platelet Count (Gi/L)</b>		
n	36	75
Mean (SD)	16.3 (8.71)	17.7 (9.49)
Median	17	16
Min - Max	2 - 29	0 - 42
<b>Lowest Post-therapy Platelet Count<sup>a</sup> (Gi/L)</b>		
n	36	75
Mean (SD)	20.9 (25.64)	22.1 (26.94)
Median	11.5	12
Min - Max	0 - 95	0 - 161

Data source: Table 7.125

a. Lowest platelet count from >3 days post-dosing.

In study TRA 100773A and in study TRA 100773B there appeared to be a trend for transient thrombocytopenia observed within four weeks of discontinuation of eltrombopag therapy. In study TRA 100773B a total of eight patients treated with eltrombopag and three patients treated with placebo had platelet counts < 10,000/mcl and at least 10,000/mcl less than baseline platelet count within four weeks after discontinuation of study medication. The table below shows these patients.

TRA 100773B Patients with Platelet Counts < 10,000/mcl and at Least 10,000/mcl Less than Baseline Within Four Weeks of Treatment Discontinuation

Treatment Group	Subject Number	Platelet Counts (G/L)			
		Baseline	Visit Day 50	Visit Day 57	Visit Day 71
PBO N=38	333	11	6	0	-
	1577	20	9	51	28
	1870	29	5	240	67
Eltrombopag N=76	77	30	2	38	385
	331	13	0	2	0
	332	19	36	5	19
	407	28	98	16	5
	1578	29	21	-	5
	1708	19	5	3	3
	1858	14	3	2	3
	1868	29	24	3	3

Source Data: Attachment 4 Listing 83

To analyze the clinical consequences of potential transient worsening of platelet counts in the 11 subjects the sponsor compared baseline WHO bleeding scores to post therapy WHO bleeding scores and the use of rescue therapy. The bleeding scores for these six patients and use of rescue medication are shown in the table below. In three patients (in the eltrombopag group) bleeding score increased from baseline.

TRA 100773B Patients WHO Bleeding Scores at Baseline and Post-Therapy

Treatment Group	Subject Number	WHO Bleeding Score			
		Baseline	Day 50 Visit	Day 57 Visit	Day 71 Visit
PBO N=38	333	3	2	1	ND
	1577	1	1	1	0
	1870	2	1	0	0
Eltrombopag N=76	77	0	1	1	0
	331	1	2	1	2
	332	1	0	0	0
	407	1	0	1	3
	1578	1	1	0	1
	1708	2	1	2	2
	1858	2	0	1	0
	1868	2	0	2	1

Data Source: Attachment 4 Listing 77

There were no thromboembolic adverse events reported in either treatment group in study TRA 100773B.

In study TRA 100773B there were six patients who reported skin related adverse events and all but two were graded as grade 1 while on therapy with either placebo or eltrombopag. One patient in the placebo group developed pruritis. Six patients in the eltrombopag treatment group developed alopecia, night sweats, photosensitivity, infection of a surgical scar and rash. No ocular adverse were reported in the placebo group. While on therapy two patients treated with eltrombopag had ocular adverse events but none were determined to be cataracts. Post-therapy one placebo treated patient compared to three eltrombopag treated patients developed cataracts.

#### Other Search Strategies

Included in this analysis are adverse events and safety assessments of special interest. Hepatobiliary adverse events was analyzed because of the evidence of liver toxicity and toxicology studies at non-tolerated doses and rats and dogs and because the predominant route of excretion for eltrombopag in humans is hepatic (approximately 60%). Data across the ITP clinical program was analyzed according to a draft FDA guidance document on clinical evaluation of drug-induced liver injury issued in October of 2007. In the placebo-controlled trials 16/164 patients (10%) who receive any dose of eltrombopag met at least one of the criteria listed in the guidance compared to 5/67 patients (8%) in the placebo group. Additional hepatobiliary laboratory data showed that more subjects receiving eltrombopag treatment (n= 11, 7%) had pre-existing elevations of hepatobiliary laboratory values as compared to patients in the placebo treatment group (n= 3, 5%). Across the entire ITP program the incidence of hepatobiliary abnormalities meeting the criteria listed in the guidance was 9% (29/330 which does not include patients from the blinded RAISE study).

Thromboembolic events were reported during treatment with eltrombopag in 11 patients. These thromboembolic events were in patients treated in the EXTEND and RAISE studies. Platelet counts obtained approximately at the time of the event range between 14,000 /mcl-407,000 /mcl and 6/11 patients had platelet counts below 100,000 /mcl at the time of the event. All patients had at least one risk factor for thromboembolic events. The most frequent risk factor was hospitalization prior to the thromboembolic event without prophylactic anticoagulation in four patients with venous thromboembolism. The thromboembolic events that occurred were pulmonary embolism in five patients and deep vein thrombosis in five patients. One patient had a transient ischemic attack. Two patients that had thromboembolic events died due to sepsis. Thromboembolic events in the remaining patients either resolved or were improving.

Data from other thrombopoietic agent studies (romiplostim) suggests that there is a potential risk that chronic stimulation of megakaryocytes with thrombopoietin receptor agonists might lead to a pathological increase of reticulin or collagen fibers in the bone marrow which may lead to a clinical situation similar to that of myelofibrosis. Collected peripheral blood smear data was analyzed for the occurrence of the immature cells which would be suggestive of bone marrow replacement with fibrosis and which would not be typical of chronic ITP. Sponsor reports that 9149 white blood cell count differentials were performed and prompted a total of 97 blood smears from 51 patients across three studies (REPEAT, EXTEND and RAISE). Thirteen patients had in mature or dysplastic findings that were nonspecific or compatible with ITP. Five

patients had peripheral blood smear findings of potential clinical relevance (1% nucleated red blood cells or 1% peripheral blast). These findings were found on a single blood smear for each subject. The findings were not reproducible according to the sponsor upon retesting and therefore did not prompt bone marrow biopsies. No subject had peripheral blood smear findings of potential clinical relevance upon retesting. Bone marrow biopsies were collected from 19 of 56 eligible patients in the EXTEND study and 17 of these patients had been treated for > 12 months. The median age of the patients with bone marrow biopsies was 58 years (range: 35-82). Bone marrow cellularity was available from 17/19 patients with a bone marrow biopsy. No patient had a significant decrease in cellularity documented on their bone marrow report. Cytogenetics was available for five patients and none of these patients showed an abnormal karyotype. Reticulin was described as none, focal, mild, moderate or by grade. Reticulin or collagen fibers were detected in seven patients (including one patient with a pretreatment biopsy showing reticulin fibers). Mild or focal mild reticulin formation was reported in 5/7 patients. Collagen formation was reported in 2/7 patients and was reported as moderate increase/moderate fibrosis in one patient and myelofibrosis grade 2/3 in one patient.

Based on preclinical findings in rodents there was concern for the development of cataracts in patients treated with eltrombopag. Chronic use of corticosteroids in patients with chronic ITP increases the incidence of cataracts in this patient population. In the pivotal trials (TRA 100773A and TRA 100773B) 8/161 patients 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 patients received placebo and six received eltrombopag (five patients received 50 mg of eltrombopag and one patient received 75 mg of eltrombopag). While on study or in follow-up five patients had an incident report of cataract that was not observed at baseline. The progression of a pre-existing cataract while on study or in follow-up was reported in 3/5 patients. All but one of these patients reported risk factors for cataract formation at the first ocular exam on study. All of the patients had used corticosteroids prior to beginning treatment on study.

Based on interim results from a two-year carcinogenicity study in mice that showed dose related renal tubular toxicity, patient safety data that was analyzed for compromised renal function or renal toxicity. Serum creatinine values were evaluated for moderate changes from baseline (defined as the average of day one creatinine values) of approximately 0.3 mg/dL and for two or more consecutive elevations of approximately 0.3 mg/dl. In the placebo controlled pivotal, short-term trials a similar incidence of potentially on therapy renal related adverse events was observed in patients treated with eltrombopag (8/164, 5%) and patients treated with placebo (4/67, 6%). These events were generally mild and did not lead to withdrawal from study medication. In the intermittent and long-term studies renal related adverse events were mild-moderate and none lead to withdrawal from study medication. In these studies >95% of patients had serum creatinine values within normal ranges during the study. In these studies < 1% of patients had  $\geq 0.3$  mg/dL change from baseline at two or more consecutive assessments. There was no clear relationship to study drug treatment.

Based on preclinical *in vitro* phototoxicity studies, skin and subcutaneous related adverse events were analyzed. The skin adverse events that were reported included rash, pruritus, itching, exfoliation, discoloration, ulcer, dermatitis and urticaria. In the placebo controlled pivotal trials

15/164 (9%) patients treated with eltrombopag and 3/67 (4%) patients treated with placebo had adverse events classified under the system organ class of skin. Most of the adverse events were grade 1 and considered related to study treatment. There was no pattern in the type of skin or subcutaneous adverse event reported across treatment arms. One patient who received 50 mg of eltrombopag developed a grade 2 photosensitivity reaction after visiting a solar tanning salon. The event resolved that was considered by the investigator to be unrelated to study medication. Two patients who received 75 mg of eltrombopag experienced grade 3 rash (one patient) and grade 2 urticaria (one patient). These events were considered to be related to the study medication. In the pivotal studies one adverse event of urticaria led to a permanent withdrawal from study medication. In the REPEAT, EXTEND and RAISE studies grade 1-grade 2 severity skin reactions were reported. In the REPEAT study eight skin and subcutaneous related adverse events were reported in seven patients (11%). In the EXTEND study 40 events were reported in 28 patients (14%) and in the RAISE study 38 patients (19%) experienced 64 events. Two patients who were treated with eltrombopag temporarily interrupted their treatment due to skin or subcutaneous adverse events (grade 2 urticaria, grade 3 cellulitis which was characterized as a serious adverse event). Two patients were withdrawn from treatment as a result of skin related adverse events (grade 1 rash, grade 2 urticaria); however these were not considered to be related to study medication by the investigator.

*Reviewer comment: Based on the guidance for drug-induced liver injury of October 2007 an analysis was undertaken to determine if there was a potential for eltrombopag to cause hepatobiliary adverse events. In the placebo-controlled trials 16/164 patients (10%) who received any dose of eltrombopag met at least one of the criteria listed in the guidance compared to 5/67 patients (8%) in the placebo group. Additional hepatobiliary laboratory data showed that more subjects receiving eltrombopag treatment (n= 11, 7%) had pre-existing elevations of hepatobiliary laboratory values as compared to patients in the placebo treatment group (n= 3, 5%). Across the entire ITP program the incidence of hepatobiliary abnormalities among eltrombopag treated patients meeting the criteria listed in the guidance was 9% (29/330 which does not include patients from the blinded RAISE study). Therefore, due to the small safety database available, the fact that the long-term studies for the chronic treatment of ITP with eltrombopag are still ongoing there is concern that eltrombopag may be related to serious hepatobiliary adverse events. Labeling of the drug should warn prescribers about this potential for hepatobiliary adverse events with eltrombopag treatment of ITP and monitoring of liver function tests should be included in the labeling as well.*

*Bone marrow biopsies were collected from 19 of 56 eligible patients in the EXTEND study and 17 of these patients had been treated for > 12 months. The median age of the patients with bone marrow biopsies was 58 years (range: 35-82). Reticulin or collagen fibers were detected in seven patients (including one patient with a pretreatment biopsy showing reticulin fibers). Mild or focal mild reticulin information was reported in 5/7 patients. Collagen formation was reported in 2/7 patients and was reported as moderate increase/moderate fibrosis in one patient and myelofibrosis grade 2/3 in one patient. Findings of myelofibrosis was also observed with romiplostim. Therefore, labeling should include a warning that eltrombopag may be related to the adverse event of bone marrow fibrosis.*

*The analysis for thromboembolic events indicates that thromboembolic adverse events may occur in patients treated with eltrombopag for chronic ITP. The labeling should include a warning for this potential adverse event.*

*The remainder of the adverse events of special interest do not appear to correlate to treatment with eltrombopag.*

### Common Adverse Events

The pooled adverse events occurring in  $\geq 5\%$  of patients on either treatment in study TRA 100773A and TRA 100773B are shown in the table below.

Pooled Adverse Events from TRA 100773A and B in  $\geq 5\%$  of Patients

AE (preferred term)	PBO n = 67	Eltrombopag n =106
Any AE	35	70
Headache	11	12
Nasopharyngitis	3	7
Anemia	4	6
Nausea	3	6
Fatigue	6	5
Diarrhea	5	5
Arthralgia	4	3
Constipation	4	3
Abdominal pain	4	1
Abdominal Distention	4	0

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

### Eliciting adverse events data in the development program

Patients underwent physical examination, clinical laboratory tests were drawn according to the schedule of events and patients had routine follow-up visits according to the schedule of events previously listed in this review.

Appropriateness of adverse event categorization and preferred terms

The sponsor's characterization of adverse events is appropriate and based on MedRA preferred terms.

Incidence of common adverse events

The common adverse events for the pivotal trials were discussed in section 7.1 .5 Common adverse events of this review.

Common adverse event tables

See section 7.1.5 Common adverse events in this review for a discussion of common adverse events.

Identifying common and drug-related adverse events

See section 7.1.5.

Additional analyses and explorations

The table below shows the hepatobiliary adverse events for patients in the pooled pivotal study analysis for placebo compared to 50 mg of eltrombopag treatment. There were three patients who were treated with placebo and six patients who were treated with 50 mg of eltrombopag as their starting dose who had a hepatobiliary adverse events while on therapy.

Hepatobiliary Adverse Events Pooled Pivotal Analysis

Dose Group, N, n(%)	773A + 773B		
	Subject Number	Event	Grade
Placebo, N=67, 3(4)	75	Hepatitis <sup>a</sup>	
	165	Toxic Hepatitis <sup>b,c,d</sup>	3
	179	Blood bilirubin increase <sup>b,d</sup>	2
50mg, N=106, 6(6)	144	Hepatitis <sup>b,c,d</sup>	3
	386	ALT increased <sup>b</sup>	2
		AST increased <sup>b</sup>	2
	430	Hepatic function abnormal <sup>b,d</sup>	2
	1373	Hepatic steatosis	1
	1562	Hepatic enzyme increased	1
	1578	ALT increased <sup>b</sup>	1
	ALT increased	1	

Data Source: TRA100773A CSR Section 8.5.3, TRA100773B CSR Section 8.5.3

- a. The event for Subject 75 was reported pre-therapy. The Screening Visit occurred on 27 March 2006, Hepatitis was reported 06 April 2006, and Visit 1 Day 1 occurred on 21 April 2006. Subject had no LFTs of concern throughout the study.
- b. AEs considered by the investigator to be related to study medication.
- c. SAE
- d. Led to withdrawal of study medication

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Most of the hepatobiliary adverse events were grade 0-1 during treatment. In the 50 mg treatment group a higher percentage of grade 1 values (21%) for alkaline phosphatase was observed compared to placebo (13%). The incidence of grade 2-4 ALT elevations was 8% in the 50 mg treatment group compared to 3% in the placebo treatment group. Grade 3-4 ALT elevations were 3% and 2% in the 50 mg treatment group and placebo group respectively. The incidence of grade 2-4 AST elevations was 3% in the 50 mg treatment group compared to 2% in the placebo treatment group. Grade 3-4 AST elevations were 2% in each treatment group (50 mg eltrombopag group and placebo group). In the 50 mg treatment group a higher percentage of grade 1 values (14%) for bilirubin was observed compared to placebo (8%). The table below shows a summary of the hepatobiliary laboratory values by maximum toxicity grade in the pooled pivotal studies.

Hepatobiliary Laboratory Values by Toxicity Grade Pooled Pivotal Studies

Parameter and Toxicity Grade <sup>a</sup>	773A + 773B	
	Placebo N=67	50mg N=106
<b>Albumin, n (%)</b>	66	106
Grade 0	49 (74)	77 (73)
Grade 1	16 (24)	26 (25)
Grade 2	1 (2)	3 (3)
Grade 3	0	0
Grade 4	0	0
<b>Alkaline Phosphatase, n (%)</b>	48	85
Grade 0	42 (88)	67 (79)
Grade 1	6 (13)	18 (21)
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
<b>Alanine aminotransferase, n (%)</b>	66	106
Grade 0	47 (71)	76 (72)
Grade 1	17 (26)	22 (21)
Grade 2	1 (2)	5 (5)
Grade 3	1 (2)	2 (2)
Grade 4	0	1 (<1)
<b>Aspartate aminotransferase, n (%)</b>	66	104
Grade 0	53 (80)	74 (71)
Grade 1	12 (18)	27 (26)
Grade 2	0	1 (<1)
Grade 3	1 (2)	2 (2)
Grade 4	0	0
<b>Total Bilirubin, n (%)</b>	66	106
Grade 0	58 (88)	87 (82)
Grade 1	5 (8)	15 (14)
Grade 2	2 (3)	3 (3)
Grade 3	1 (2)	1 (<1)
Grade 4	0	0

Data Source: SDAP Table 8.145

a Maximum toxicity Grade at any scheduled or unscheduled post-baseline visit.

An analysis of potential drug-induced liver injury based on the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation<sup>7</sup> demonstrated that 16/164 patients (9.7%) who received any dose of eltrombopag in the pivotal trials met the FDA criteria for having hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. Hy's Law is summarized as follows:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

Of the 16 eltrombopag treated patients with hepatobiliary toxicity, three received 30 mg, 11 received 50 mg (three increased to 75 mg in TR 8100773B) and two received 75 mg as a starting dose. These patients ranged in age from 19-75 years. There were 9/16 patients who were female and the majority were Caucasian (10 patients) followed by Asian (five patients). The table below shows a summary of the hepatobiliary laboratory adverse events based on the criteria for assessment of hepatobiliary toxicity for the pooled pivotal studies.

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Hepatobiliary Adverse Events Based on the Criteria for Assessment of Hepatobiliary Toxicity  
 for the Pooled Pivotal Studies

Laboratory Criteria	773A + 773B	
	Placebo N=67	Eltrombopag All doses N=164
Subjects, n(%)	5 (7)	16 (10)
>3x ULN AT and >2.0x ULN Total Bilirubin	0 (0)	1 (<1)
>3x ULN AT and >1.5x ULN Total Bilirubin	0 (0)	1 (<1)
≥20x ULN ALT and AST	0 (0)	0 (0)
≥10x ULN ALT and AST	1 (2)	2 (1)
≥5x ULN ALT and AST	1 (2)	2 (1)
≥3x ULN ALT and AST	1 (2)	4 (2)
≥20x ULN ALT	0 (0)	1 (<1)
≥10x ULN ALT	1 (2)	2 (1)
≥5x ULN ALT	1 (2)	4 (2)
≥3x ULN ALT	1 (2)	7 (4)
≥20x ULN AST	0 (0)	0 (0)
≥10x ULN AST	1 (2)	2 (1)
≥5x ULN AST	1 (2)	2 (1)
≥3x ULN AST	1 (2)	5 (3)
≥2x ULN Total Bilirubin	2 (3)	5 (3)
≥1.5x ULN Total Bilirubin	4 (6)	6 (4)
≥1.5x ULN Alkaline Phosphatase	0 (0)	3 (2)

Data Source: TR A100773 A CSR and TR A100773B CSR  
 Based on the FDA Draft Guidance for Drug-Induced Liver Injury: Premarketing Clinical Evaluation (October 2007)  
 ULN = upper limit of normal  
 AT = Aminotransferase (alanine or aspartate aminotransferase)  
 Subjects are counted in more than one category if they fulfill multiple criteria.

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One patient (patient 144) who was treated with eltrombopag 50 mg had elevated aminotransferase is about three times the upper limit of normal in conjunction with total bilirubin above two times the upper limit of normal. This patient died from cardiopulmonary failure and possible sepsis of pulmonary origin and was discussed previously in section 7.1.1 Deaths of this review. Sponsor states that this patient is not a Hy's Rule case due to the confounding factors previously discussed. The sponsor states that except for this subject all other hepatobiliary laboratory abnormalities on the studies resolved after study drug discontinuation. Elevations of both AST and ALT of at least three times the upper limit of normal were observed in four patients in the eltrombopag treatment group and in one patient in the placebo treatment group. Elevations of ALT alone of at least three times the upper limit of normal was observed in seven eltrombopag treated patients and one placebo treated patient. Elevations of AST alone of at least three times the upper limit of normal was observed in five patients treated with eltrombopag and one patient treated with placebo. Elevation of total bilirubin alone above 1.5 times the upper limit of normal was observed in six patients in the eltrombopag treatment group and four patients in the placebo treatment group. Elevation in alkaline phosphatase alone above 1.5 times the

upper limit of normal was observed in three patients in the eltrombopag treatment group and zero patients in the placebo treatment group.

*Reviewer comment: These results evaluating for hepatobiliary adverse events and toxicity indicate that there is a potential signal for hepatobiliary toxicity with eltrombopag treatment in patients with chronic ITP.*

### Less Common Adverse Events

*Reviewer comment: As of the 120 day safety update among patients who were treated for at least 13 months with eltrombopag in the EXTEND trial there were 19 bone marrow biopsies. The sponsor reports that reticulin/collagen was observed in 9/19 bone marrow biopsies. In 2/9 of the bone marrow biopsies reticulin deposition was graded as grade 2.*

*In preclinical studies phototoxicity was a recognized adverse event. In the pivotal trial TRA 100773A there were 17 adverse events listed for skin disorder. In the placebo treatment group there were two patients who developed rash, hot flush. In the 30 mg treatment group 3 patients developed rash, pruritus and hyperhidrosis. In the 50 mg treatment group 3 patients developed pigmentation disorder, erythema, pruritis. In the 75 mg treatment group four patients developed rash, urticaria and flushing while on therapy. In addition, cardiac related adverse events occurred in two patients during treatment with 30 mg of eltrombopag in this study. One patient had a grade two prolonged QTc interval on EKG evaluation. One patient had a grade 1 left atrial repolarization abnormality. It is noted that both patients had previous EKG abnormalities at baseline with abnormal cardiovascular histories. In addition, in preclinical models cataract development was observed. In this study 49/117 patients had ocular assessments in the safety population. In these 49 patients there were 14 reports of cataracts. Three patients had a cataract observed at baseline but none of these patients had cataract progression over the course of the study. There were 10 patients who had cataract observed at the time of treatment discontinuation or at the day 43 visit. One patient was observed to have a cataract formation during the follow-up phase of the study.*

*In the pivotal trial TRA 100773B there were six patients (five eltrombopag treated patients and one placebo treated patient) who developed skin related adverse events. There was one report of photosensitivity in an eltrombopag treated patient which was characterized as a grade 2 adverse event. The remaining eltrombopag treated patients had adverse events listed as alopecia, night sweats, skin infection of a surgical scar and rash. There was one patient in the placebo treatment group that developed pruritus. In addition, cardiac related adverse events occurred in one patient in the eltrombopag treatment group and no patients in the placebo treatment group. The one patient in the eltrombopag treatment group developed a grade 1 sinus tachycardia which was considered to be related to study medication while on therapy. In this study 112/114 patients in the safety population had ocular assessments for cataracts. Cataracts were observed at baseline in nine patients of which three patients had progression of their cataracts. There were 101 patients who had no evidence of cataract observed at baseline. Of these 101 patients, four patients subsequently developed cataracts and none progressed after treatment was discontinued.*

Laboratory Findings

In study TRA 100773A hematology data outside the threshold range in any post baseline visit is shown on the table below. The table shows that there is no clear hematologic abnormality related to study drug therapy and study TRA 100773A.

TRA 100773A Hematology Results Outside Threshold Range

Parameter and Threshold			Treatment Group, n (%)			
			PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>Hemoglobin</b>	n		29	30	30	28
	Below threshold	≤0.8xLLN	1 (3)	1 (3)	3 (10)	1 (4)
	Above threshold	≥1.10xULN	0	0	1 (3)	0
<b>Hematocrit</b>	n		29	30	29	28
	Below threshold	≤30%	1 (3) <sup>a</sup>	1 (3) <sup>a</sup>	1 (3) <sup>a</sup>	1 (4) <sup>a</sup>
	Above threshold	≥60%	0	0	0	0
<b>Neutrophils</b>	n		29	30	30	28
	Below threshold	≤1.5G/L	0	3 (10)	1 (3) <sup>a</sup>	1 (4)
	Above threshold	≥15G/L	1 (3)	2 (7)	0	1 (4)
<b>WBCs</b>	n		29	30	30	28
	Below threshold	<3G/L	0	2 (7)	0 <sup>a</sup>	1 (4)
	Above threshold	≥20G/L	1 (3)	1 (3)	0	0

Data Source: Table 8.18 and Attachment 5 Data Clarifications Received Post-analysis  
 a. Value was corrected based on data clarifications received post-analysis.

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Clinical chemistry data outside the threshold range at any post baseline visit for study TRA 100773A are shown in the table below.

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Chemistry Data Outside Threshold Range TRA 100773A

Parameter and Threshold			Treatment Group, n (%)			
			PBO N=29	30mg N=30	50mg N=30	75mg N=28
Alkaline Phosphatase	n		12	11	10	11
	Above threshold	≥1.5xULN	0	0	0	1 (9)
ALT	n		29	30	30	28
	Above threshold	≥2xULN	3 (10)	1 (3)	3 (10)	1 (4)
AST	n		29	30	30	28
	Above threshold	≥2xULN	1 (3)	2 (7)	3 (10)	2 (7)
Total bilirubin	n		29	30	30	28
	Above threshold	≥1.5xULN	2 (7)	2 (7)	2 (7)	1 (4)
BUN	n		6	6	7	6
	Above threshold	≥1.3xULN	0	0	0	1 (17)
Chloride	n		29	29	29	28
	Above threshold	≥115mM	2 (7)	0	0	0
Creatinine	n		29	30	30	28
	Above threshold	>1.3xULN	0	0	2 (7)	0
Glucose	n		29	30	30	28
	Below threshold	<3.33mM	3 (10)	0	2 (7)	0
	Above threshold	≥7.22mM	3 (10)	7 (23)	8 (27)	6 (21)
Potassium	n		29	30	30	28
	Below threshold	≤3.0mM	0	2 (7)	0	0
	Above threshold	≥5.5mM	0	0	1 (3)	0
Sodium	n		29	30	30	28
	Below threshold	≤130mM	0	3 (10)	0	1 (4)
	Above threshold	≥150mM	2 (7)	1 (3)	1 (3)	0

Data Source: Table 8.13

In study TRA 100773B hematology data outside the threshold range in any post baseline visit is shown on the table below. The table shows that there is no clear hematologic abnormality related to study drug therapy and study TRA 100773B.

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TRA 100773B Hematology Data Outside Threshold Range

Parameter and Threshold			Treatment Group, n (%)	
			PBO N=38	Eltrombopag N=76
<b>Eosinophils</b>	n		37	74
	Above threshold	>2.5xULN	1 (3)	2 (3)
<b>Hemoglobin</b>	n		37	76
	Below threshold	≤0.8xLLN	5 (13) <sup>a</sup>	10 (13)
	Above threshold	≥1.10xULN	0	0
<b>Hematocrit</b>	n		37	76
	Below threshold	≤30%	5 (14)	11 (14)
	Above threshold	≥60%	0	0
<b>Neutrophils</b>	n		37	76
	Below threshold	≤1.5 Gi/L	5 (14)	0 <sup>b</sup>
	Above threshold	≥15 Gi/L	3 (8)	5 (7)
<b>RBCs</b>	n		37	76
	Below threshold	≤0.8xLLN	5 (14)	4 (5) <sup>c</sup>
	Above threshold	≥1.20xULN	0	1 (1)
<b>WBCs</b>	n		37	76
	Below threshold	<3 Gi/L	4 (11)	1 (1)
	Above threshold	≥20 Gi/L	1 (3)	4 (5)

Data Source: Table 8.18

- Subject 1577 (PBO group) had a hemoglobin value of 75g/L at an unscheduled post-therapy visit that was not included in Table 8.18
- An erroneous neutrophil count of 0.3Gi/L at the 2-week post-therapy visit (Day 57) was reported for Subject 652. The actual neutrophil count was 4.7Gi/L (Attachment 5, Post-analysis Data Clarifications).
- Subject 1578 (eltrombopag group) had an RBC value of 3.12Ti/L at an unscheduled post-therapy visit that was not included in the summary table.

Clinical chemistry data outside the threshold range at any post baseline visit for study TRA 100773B are shown in the table below.

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Chemistry Data Outside Threshold Range TRA 100773B

Parameter and Threshold			Treatment Group, n (%)	
			PBO N=38	Eltrombopag N=76
<b>Albumin</b>	n		37	76
	Below threshold	LLN - 5g/L	1 (3)	5 (7) <sup>a</sup>
	Above threshold	ULN +5g/L	1 (3)	1 (1)
<b>AP</b>	n		37	75
	Above threshold	≥1.5xULN	0	2 (3)
<b>ALT</b>	n		37	76
	Above threshold	≥2xULN	1 (3)	6 (8)
<b>AST</b>	n		37	74
	Above threshold	≥2xULN	0	3 (4)
<b>Total bilirubin</b>	n		37	76
	Above threshold	≥1.5xULN	2 (5) <sup>b</sup>	2 (3)
<b>BUN</b>	n		15	28
	Above threshold	≥1.3xULN	0	2 (7)
<b>Chloride</b>	n		34	75
	Above threshold	≥115mmol/L	0	1 (1)
<b>Creatinine</b>	n		37	76
	Above threshold	>1.3xULN	1 (3)	2 (3)
<b>CPK</b>	n		22	45
	Above threshold	≥2xULN	3 (14)	3 (7)
<b>Glucose</b>	n		37	74
	Below threshold	<3.33mmol/L	1 (3)	10 (14)
	Above threshold	≥7.22mmol/L	12 (32) <sup>c</sup>	22 (30)
<b>Potassium</b>	n		37	76
	Below threshold	≤3.0mmol/L	4 (11)	2 (3) <sup>e</sup>
	Above threshold	≥5.5mmol/L	0	2 (3)
<b>Total Protein</b>	n		37	76
	Above threshold	≥100g/L	0	1 (1) <sup>d</sup>
<b>Sodium</b>	n		37	76
	Below threshold	≤130mmol/L	2 (5)	0
	Above threshold	≥150mmol/L	0	2 (3)

Data Source: Table 8.13

- Subject 1382 (eltrombopag group) was not included in the table as albumin levels were incorrectly flagged as low due to a unit conversion error.
- Subject 1877 had a laboratory assessment 4 days after stopping treatment that was not included in the summary table. This subject had values above threshold for total bilirubin and glucose, which are summarized in Section 13.4.
- Subject 1578 (eltrombopag group) had a low potassium value (2.9mmol/L) at an unscheduled post-therapy visit that was not included in the summary table.
- Subject 334 had an elevation in total protein recorded as 106g/L on Day 22 that was reported as an AE. When queried the investigator later commented that a temporary failure in calibration of the lab equipment could have been responsible for this value and other total protein elevations reported in subjects at Center 010225 (see explanation in Section 8.2, AEs related to Study Medication)

*Reviewer comment: In studying TRA 100773B slightly more patients 6/76 and 3/74 had an increase in liver function tests ≥ two times the upper limit of normal in terms of ALT and AST abnormalities compared to 1/37 and 0/37 for patients treated with placebo. Other laboratories showed minimal difference between the eltrombopag group and the placebo group. Minimal differences in other laboratories in terms of treatment group are of questionable clinical significance.*

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### Vital Signs

In study TRA 100773A and TRA 100773B no clear differences between treatment groups were observed during the study in terms of vital sign assessments.

### Electrocardiograms (ECGs)

The result of ECG analysis showed no clear difference difference between the two treatment groups in study TRA 100773A or TRA 100773B. The results of ECG evaluation in study TRA 100773A are shown in the table below.

ECG Evaluation in Study TRA 100773A

	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
<b>Any Post-baseline ECG Assessment</b>				
Normal	28 (97)	22 (73)	25 (83)	23 (82)
Abnormal, not clinically significant	14 (48)	16 (53)	11 (37)	14 (50)
Abnormal, clinically significant	1 (3)	2 (7)	0	0
No result	0	3 (10)	0	4 (14)
Missing	0	1 (3)	0	2 (7)
<b>ECG Shift from Baseline</b>				
No change	18 (62)	21 (70)	19 (63)	13 (46)
To normal	11 (38)	7 (23)	12 (40)	15 (54)
To Abnormal, not clinically significant	9 (31)	8 (27)	2 (7)	6 (21)
To Abnormal, clinically significant	1 (3)	2 (7)	0	0
To no result	0	1 (3)	0	2 (7)
To Missing	0	0	0	1 (4)

Data Source: Table 8.25, Table 8.26

The result of ECG evaluation in study TRA 100773B are shown in the table below.

ECG evaluation in study TRA 100773B

	Treatment Group, n (%)	
	PBO N=38	Eltrombopag N=76
<b>Any Post-baseline ECG Assessment</b>		
Normal	38	76
Abnormal, not clinically significant	36 (95)	63 (83)
Abnormal, clinically significant	14 (37)	32 (42)
Missing	0	2 (3)
<b>ECG Shift from Baseline</b>		
No change	38	75
To normal	16 (42)	30 (39)
To Abnormal, not clinically significant	23 (61)	45 (59)
To Abnormal, clinically significant	11 (29)	15 (20)
To Missing	0	2 (3)

Data Source: Table 8.25, Table 8.26

### Immunogenicity

No immunogenic responses were reported in any of the clinical trials.

### Human Carcinogenicity

Not applicable.

### Special Safety Studies

Study TRA 102860 evaluated the potential effects of eltrombopag on cardiac repolarization in healthy volunteers in a randomized, crossover, placebo and active controlled (moxifloxacin 400 mg single-dose) study design. Doses of 50 mg and 150 mg of eltrombopag were given once daily for five days. Eltrombopag demonstrated a lack of effect on cardiac repolarization. The upper limits of the 90% confidence interval for the mean difference in the QTc change from baseline between eltrombopag and placebo were below 10 msec at all time-points for both 50 mg once daily and 150 mg once daily doses of eltrombopag. The sponsor reports that the study was sensitive enough to detect the effect of moxifloxacin (positive control) on QT prolongation as the lower limit of the 90% confidence interval of the control QTc and was greater than 5 msec for at least one time point. In addition, based on a PK/PD model simulation for eltrombopag 150 mg and 300 mg the sponsor predicts that plasma eltrombopag exposures up to 3.5 times higher than those achieved in ITP patients will not have a clinically significant affect on QT interval. The FDA review of the TQT study stated that there was no significant QT prolongation (Dr. Joanne Zhang, QT-IRT review May 15, 2008).

### Withdrawal Phenomena and/or Abuse Potential

Fluctuations in platelet counts in ITP are common.<sup>8</sup> In the pivotal trials there was a 6% incidence of transient decreases of platelet counts below baseline with absolute platelet counts below 10,000/mcl and more than 10,000/mcl lower than their baseline level. In patients treated with eltrombopag 50 mg 11/106 (10%) compared to 4/67 (6%) placebo treated patients had thrombocytopenia within four weeks after discontinuation of eltrombopag with platelet counts < 10,000/mcl.

### Human Reproduction and Pregnancy Data

There have been no studies of eltrombopag in pregnant women. In the 120 day safety update the sponsor reported that one patient became pregnant while taking eltrombopag. The outcome of this pregnancy was not reported with the 120 day safety update. The sponsor stated that they will provide an update to this pregnancy as soon as it becomes available.

In preclinical studies of Eltrombopag at 10, 20, or 60 mg/kg/day (0.8, 2.3, and 5.3 times the human clinical exposure, respectively, based on AUC) administered orally to pregnant rats in an embryofetal development study. Decreases in maternal body weight gain and food consumption occurred in the 60 mg/kg/day dose group. At this maternally toxic dose, male and female fetal

weights were significantly reduced (6% to 7%) and there was a slight increase in the presence of cervical ribs, a fetal variation. There was no evidence of teratogenicity. In an embryofetal development study in mated female rabbits, eltrombopag at 30, 80, or 150 mg/kg/day (0.1, 0.3, and 0.6 times the human clinical exposure, respectively, based on AUC) was administered orally. There was no evidence of fetotoxicity, embryoletality, or teratogenicity at any dose. There are no adequate and well-controlled studies in pregnant women. The sponsor proposes that Eltrombopag should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether eltrombopag is excreted in human milk. Because many drugs are excreted in human milk,

b(4)

*Reviewer comment: The sponsor's analysis and proposed wording with regard to human reproduction and pregnancy data appears to be reasonable given that no studies of eltrombopag have been specifically conducted in pregnant women. The pharmacology and toxicology review is pending.*

### Overdose Experience

There is no known antidote for overdose of eltrombopag. The sponsor states that in case of an overdose, administration of a calcium-containing antacid should be considered to limit absorption, if overdose has occurred. The maximum oral doses of eltrombopag that have been administered in clinical trials are 200 mg once daily for up to 5 days. Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

There is one report of overdose as an apparent suicide attempt in which a female subject ingested 5,000 mg of eltrombopag and was treated with gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium, dexamethasone, and plasmapheresis. The patient's platelet count responded to levels between 1,000,000/mcl-1,500,000/mcl. Reported adverse events included mild rash, transient bradycardia, transient ALT/AST elevation to levels less than 3 times the upper limit of normal, and fatigue. The patient did not have any evidence of thrombosis based on physical exam. The patient's platelet count returned to normal levels within 3-4 weeks. After 2 months of follow up, all events were resolved without sequelae and the subject remained otherwise asymptomatic.

### Postmarketing Experience

Eltrombopag is currently not marketed or withdrawn in the United States or elsewhere.

## **6.2 Adequacy of Patient Exposure and Safety Assessments**

### Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The sponsor has presented a complete safety profile from the two pivotal trials TRA 100773A and TRA 100773B. The median number of days of exposure to placebo in these trials was 42. The median number of days of exposure to 50 mg eltrombopag was 43. In addition, additional safety information was presented with the 120 day safety update for the REPEAT and the EXTEND studies. The RAISE study remains blinded to treatment allocation. Overall, excluding the RAISE study, 330 patients have been exposed to eltrombopag. Of these, 81 patients have been exposed for  $\geq 6$  months and 12 patients have been exposed for  $\geq 15$  months. The median duration of exposure based on the number of days exposed to eltrombopag in the REPEAT study was 81 days. The median number of days of eltrombopag exposure in the EXTEND study was 98. The sponsor should complete the supportive studies and submit them for review. The sponsor provided narratives for patient deaths and other adverse events related to treatment with eltrombopag or placebo for the pivotal trials and supportive studies.

### Description of Secondary Clinical Data Sources Used to Evaluate Safety

The safety database was evaluated for all ITP patients listed in section 4.1 of this review and was also discussed in section 7.1.7.1 of this review. All data are from the sponsor's studies. No postmarketing or other experience is available for review.

### Other studies

As noted in the safety section of this review other studies have been evaluated for safety including supportive studies performed in patients with chronic ITP.

### Postmarketing experience

Eltrombopag has not been marketed in the United States or any other country previously.

### Literature

The results of study TRA 100773 A have been previously published.<sup>9</sup> The article concludes that eltrombopag increased platelet counts in a dose-dependent manner in patients with relapsed or refractory ITP.

### Adequacy of Overall Clinical Experience

Overall only 330 patients have been exposed to eltrombopag in the ITP development program as of the 120 day safety update for this NDA. The pivotal trials were able to show that eltrombopag can increase platelet counts in patients with chronic ITP. However, the pivotal trials were not

able to show that eltrombopag can decrease the incidence of bleeding. The sponsor used the WHO bleeding scale and it is unclear whether incremental changes in assessed bleeding e.g., going from WHO bleeding grade 1 to 0 is clinically meaningful. Furthermore, investigators were not blinded to patient platelet counts at the time of assessment of bleeding. In addition, in the pivotal trials only seven patients underwent a hemostatic challenge so the utility of the short-term use is unproven. In terms of safety, there appears to be a potential for liver toxicity after treatment with eltrombopag in patients treated with chronic ITP. One patient treated with 50 mg of eltrombopag developed hepatotoxicity consistent with Hy's Law criteria. Although this patient had underlying comorbidities and appears to have died due to causes other than liver toxicity based on his autopsy report, the patient's liver function tests increased within two weeks of starting eltrombopag. It would be unexpected that his liver function tests would be abnormal due to the underlying condition which ultimately caused him to require hospital care i.e., chronic obstructive pulmonary disease exacerbation. There may be a potential toxic effect of eltrombopag on bone marrow. Only 19 bone marrow reports are available as of the 120 day safety update for this NDA. Investigators were not required to perform bone marrow biopsies according to the pivotal trial protocols. There are two bone marrow reports which suggest that there may be an increased risk for reticulin/collagen deposition. There is a strong potential for off label chronic use of eltrombopag for a long-term duration due to the chronic nature of the disease and the fact that platelet counts returned to baseline levels within two weeks after discontinuation of eltrombopag therapy. The pivotal trials did not assist in any way in terms of determining the long-term dosing of eltrombopag or dose adjustment that may be needed with other concomitant ITP medications. The potential chronic use of eltrombopag may increase the risk for liver toxicity, bone marrow toxicity as well as other adverse events. Analysis of the long-term treatment studies RAISE, REPEAT and EXTEND studies when they are completed may clarify these concerns.

#### Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

#### Adequacy of Routine Clinical Testing

The pivotal trials analyzed the appropriate endpoints and safety data except for bone marrow toxicity. The supportive studies allowed for additional analyses of the safety profile of the eltrombopag.

#### Adequacy of Metabolic, Clearance, and Interaction Workup

No formal drug interaction was performed in the pivotal trials. However, patients in the pivotal trials were treated with a number of concomitant medications and other concomitant ITP medications.



### Additional Submissions, Including Safety Update

The sponsor submitted the 120 day safety update as is required to support the NDA and is reviewed in section 7.1.7.1

### **6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

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

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

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

An analysis of potential drug-induced liver injury based on the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation<sup>10</sup> demonstrated that 16/164

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

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

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

*Reviewer comment: The eltrombopag safety database consists of 330 ITP patients who were exposed to at least one dose of eltrombopag. Of these, 81 patients have been exposed for  $\geq 6$  months and 12 patients have been exposed for  $\geq 15$  months. Therefore, the safety profile for eltrombopag is limited with regard to long-term exposure. It is expected that patients who have chronic ITP will need to take this drug chronically. Prolonged exposure to eltrombopag may increase the risk for certain potentially fatal adverse events. In the pivotal trials 16/164 patients (9.7%) who received any dose of eltrombopag met the FDA criteria for assessment of hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. Of the 16 eltrombopag treated patients three received 30 mg, 11 received 50 mg (three increased to 75 mg in TRA 100773B) and two received 75 mg as a starting dose. One patient treated with eltrombopag 50 mg once daily with a history of chronic obstructive pulmonary disease developed marked liver and renal abnormalities beginning on the 15th day of eltrombopag treatment and died on day 26. By day 15 the patient had a tenfold increase in ALT compared to baseline. Although this patient's autopsy revealed thromboemboli and biventricular cardiac hypertrophy which may have ultimately led to pulmonary failure, elevated liver enzymes are not typically a hallmark characteristic of chronic obstructive pulmonary disease. Therefore, patients who are taking eltrombopag for chronic ITP therapy should liver function tests in order to minimize the risk of hepatobiliary adverse events.*

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*Six deaths were reported in the ITP program as of the 120 day safety update. In study TRA 100773A any adverse events were generally evenly distributed between the treatment groups. However patients with any serious adverse event were numerically higher the 50 mg eltrombopag group (6/30, 20%) compared to placebo (4/29, 14%). However, 2/28 (7%) of patients treated with 75 mg of eltrombopag once daily reported any serious adverse event. In study TRA 100773B 45/76 (59%) patients treated with eltrombopag 50 mg once daily compared to 14/38 (37%) of patients treated with placebo reported any adverse event. In this study similar numbers of patients reported serious adverse events (eltrombopag 2/76, 3% compared to placebo 2/38, 5%).*

*Bone marrow biopsies were collected from 19 of 56 eligible patients in the EXTEND study and 17 of these patients had been treated for > 12 months. Mild or focal mild reticulin information was reported in 5/7 patients. Collagen formation was reported in 2/7 patients and was reported as moderate increase/moderate fibrosis in one patient and myelofibrosis grade 2/3 in one patient. Findings of myelofibrosis were also observed with romiplostim, another TPO receptor agonist, in this class. Therefore, labeling should include a warning that eltrombopag may be related to the adverse event of bone marrow fibrosis.*

*The analysis for thromboembolic events indicates that thromboembolic adverse events may occur in patients treated with eltrombopag for chronic ITP. The labeling should include a warning for this potential adverse event.*

*Following discontinuation of eltrombopag, platelet counts returned to near baseline levels within approximately 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 < 10,000/mcl and 10,000/mcl less than baseline. The decrease in platelet counts was not associated with a significant increase in bleeding. There is currently little evidence of transient decreases in platelet counts following discontinuation or interruption of Eltrombopag in the EXTEND study.*

*The remainder of the adverse events of special interest do not appear to correlate to treatment with eltrombopag.*

## **6.4 General Methodology**

### Pooling Data Across Studies to Estimate and Compare Incidence

The table below shows the incidence of adverse events across both pivotal trials. Headache was the most common adverse event during the entire study in the pivotal trials observed in 16% of placebo treated patients and 11% of eltrombopag treated patients who received 50 mg of eltrombopag once daily as a starting dose.

Preferred Term	773A+ 773B	
	Placebo N=67	30mg N=106
Any AE, n (%)	35 (52)	70 (66)
Headache	11 (16)	12 (11)
Nasopharyngitis	3 (4)	7 (7)
Anemia	4 (6)	6 (6)
Nausea	3 (4)	6 (6)
Fatigue	6 (9)	5 (5)
Diarhea	5 (7)	5 (5)
Arthralgia	4 (6)	3 (3)
Constipation	4 (6)	3 (3)
Abdominal pain upper	4 (6)	2 (2)
Abdominal distension	4 (6)	1 (<1)

Data Source: SDAP Table 8.59  
 Note: on-therapy (+1 day) and post-therapy

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### Causality Determination

Eltrombopag may cause liver injury based on the fact that an analysis of potential drug-induced liver injury based on the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation<sup>11</sup> demonstrated that 16/164 patients (9.7%) who received any dose of eltrombopag met the FDA criteria for assessment of hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. The sponsor states that for the one patient that had chronic obstructive pulmonary disease and ITP who was treated with eltrombopag the elevation in liver function tests does not fit Hy's law criteria due to the fact that the patient had underlying Alt chronic obstructive pulmonary disease. However, this patient's liver function abnormalities began 15 days after starting eltrombopag therapy with an ALT 10 times the baseline level. Liver function test abnormalities are not a hallmark of the clinical presentation of chronic obstructive pulmonary disease. Therefore it is possible that this case demonstrates liver toxicity directly related to eltrombopag therapy.

*Reviewer comment: With regard to other adverse events of special interest the findings of myelofibrosis were also observed with romiplostim. It is possible that a class effect of myelofibrosis may be present with thrombopoietic agents. The analysis for thromboembolic events indicates that thromboembolic adverse events may occur in patients treated with eltrombopag for chronic ITP. The remainder of the adverse events of special interest do not appear to correlate to treatment with eltrombopag.*

## 7 ADDITIONAL CLINICAL ISSUES

### 7.1 Dosing Regimen and Administration

The dosing of eltrombopag in patients with ITP has been evaluated in two pivotal trials TRA 100773A and TRA 100773B. The pivotal trial TRA 100773A shows that there is a dose-dependent increase in platelet count after treatment with Eltrombopag with significant rise in

platelets with eltrombopag doses of 50mg and 75mg daily. There was no dose adjustment in this study. Study TRA 100773B demonstrates that, eltrombopag 50mg administered once daily for six weeks to previously treated adult patients with chronic ITP was able to increase platelet counts to levels  $\geq 50,000/\text{mcl}$  in a greater proportion of patients compared to placebo. The sponsor proposes that patients with ITP be treated with 50 mg of eltrombopag orally once daily. If the platelet count is less than 50,000/mcl after 3 weeks the dose should be increased to 75 mg orally once daily. Treatment should be continued for six weeks. Treatment with eltrombopag should be discontinued if the platelet count is above 200,000/mcl. The sponsor proposes that 25 mg orally once daily for patients of the East Asian ancestry. The dose may be increased in this patient population to 50 mg orally once daily if the platelet count is below 50,000/mcl after 2 weeks.

b(4)

*Reviewer comment: The dosing of eltrombopag is based on the clinical studies and TRA 100773A and TRA 100773B. The dosing regimen of 50 mg once daily with increased to 75 mg once daily after three weeks of therapy should the platelet count remained below 50,000 /mcl appears to be reasonable. The pharmacology review by Dr. Joe Grillo (August 8, 2008) stated that based on non-compartment analysis and population pharmacokinetic analysis, plasma eltrombopag exposure was approximately 70% higher in some East Asian (i.e., Japanese, Chinese, Taiwanese, and Korean) subjects with ITP as compared to non-East Asian subjects who were predominantly Caucasian. The proposed dosing regimen for patients of East Asian ancestry appears to be reasonable based on this analysis.*

## 7.2 Drug-Drug Interactions

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

Administration of eltrombopag 75 mg once daily for five days with a single dose of rosuvastatin 10 mg increased plasma rosuvastatin Cmax by 2.03 fold and AUC by 55%. Therefore when coadministered with eltrombopag a reduced dose of rosuvastatin should be considered and careful monitoring for rosuvastatin adverse effects should be undertaken. eltrombopag is an inhibitor of the anion transporting polypeptide OATP1B1. Therefore concomitant administration of eltrombopag and other OATP1B1 substrates should be used with caution.

### 7.3 Special Populations

The sponsor proposes that 25 mg orally once daily ~~\_\_\_\_\_~~ for patients of the East Asian ancestry. The dose may be increased in this patient population to 50 mg orally once daily if the platelet count is below 50,000/mcl after 2—weeks.

b(4)

*Reviewer comment: The proposed dosing for patients at East Asian ancestry appears to be reasonable based on the FDA Clinical Pharmacology review.*

### 7.4 Pediatrics

ITP is a common manifestation of autoimmune disease in children. Although patients often present with bruises, petechiae, and some mucosal bleeding, the incidence of life-threatening hemorrhage is rare (0.2–0.9%) but can be fatal when presenting in vital organs. A wide range of therapeutic regimens are currently in use, including observation alone, as the majority of children recover within 4–6 months regardless of treatment. A growing understanding of the pathophysiology of acute ITP in children has not impacted the controversy surrounding treatment, but has clarified the mechanism of action of the most frequently used agents in chronic ITP. Newer monoclonal antibodies such as rituximab have proved very useful in chronic or refractory ITP and studies are ongoing to determine the best regimens using this form of immune modulation. Splenectomy and newer agents to boost platelet production are also under study in chronic ITP. Neonates may also have a form of immune thrombocytopenia with extensive bruising and thrombocytopenia called neonatal alloimmune thrombocytopenic purpura (NATP). Rather than autoantibodies, the platelet destruction is secondary to transplacental maternal IgG alloantibodies. During pregnancy mothers may become sensitized to platelet membrane antigens present on fetal platelets. These antibodies may result in serious bleeding, including intracranial hemorrhage in the perinatal period. Once identified, these mothers may require treatment during future pregnancies to minimize serious bleeding in the fetus and neonate. Pediatric ITP is generally a self-limited disease.<sup>12</sup>

ITP in childhood can present with severe bleeding. However, in childhood ITP usually is not chronic. Childhood ITP may be a situation where short-term treatment may be of great utility. The sponsor requests a deferral of pediatric studies for this NDA. Because, eltrombopag has been granted orphan drug status (May 5, 2008) for this indication, pediatric studies may not be required.

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### 7.5 Advisory Committee Meeting

On May 30, 2008 a meeting of the Oncology Drug Advisory Committee was held in Chicago, Illinois to discuss eltrombopag for the short-term treatment of ITP. The results of this meeting are as follows:

The question 1 posed to the committee was as follows:

Eltrombopag is proposed for use in patients, such as those undergoing a surgical procedure, who have a specific need for short term therapy. The patients in the completed, controlled studies did not have this specific need and some experienced serious hemorrhage when eltrombopag was discontinued. Since ITP is generally a chronic condition, long term therapy is anticipated. Given these observations, should FDA delay marketing authorization until it has reviewed the final data from the on-going clinical studies (RAISE, EXTEND)?  
If no, please answer the next question. The committee did not vote on this question.

- *Committee members questioned the definition of short term in the proposed indication as members felt that eltrombopag could be used for multiple short terms.*
- *Committee members felt that if approved for short term use, there was a potential for eltrombopag to be used off label for recurrent short terms (multiple 42 day treatments)*
- *During the discussion of this question, it was decided that the committee would not vote on Question 1 and vote only on Question #2.*

Question 2 posed to the committee was as follows:

Do the current clinical data demonstrate a favorable risk-benefit profile for the use of eltrombopag in the "short term" treatment of patients with chronic ITP?

*Voted :*                      *Yes=16*                      *No = 0*                      *Abstain = 0*

- *Committee members were concerned that eltrombopag would be used for multiple short terms and were concerned with the lack of adverse event data for long term use.*
- *The committee agreed that to ensure safe use of the product a Risk Management Plan should be put in place that states that long term data is pending..*
- *The committee agreed that it was important for patients to have access to this drug and also agreed that they as physicians would be willing to register these patients as needed for the Risk Management Plan.*
- *Committee members noted that they felt that the drug was efficacious but would like more safety data in specific populations.*

## **7.6 Literature Review**

The results of study TRA 100773 A have been published.<sup>13</sup> The article concludes that eltrombopag increased platelet counts in a dose-dependent manner in patients with relapsed or refractory ITP.

## **7.7 Postmarketing Risk Management Plan**

The sponsor identified the following safety risks with eltrombopag:

- Thromboembolic events
- Increase in liver chemistries
- Bone marrow toxicity

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

In order to address these risks the sponsor should undertake the usual postmarketing monitoring and reporting. In addition, the sponsor proposes a risk minimization program

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*Reviewer comment: The current risk management plan*

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*The risk management plan should be revised to address the concerns listed under the final bullet of section 1.1 Recommendation on regulatory action above.*

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## 7.8 Other Relevant Materials

Not applicable.

## 8 OVERALL ASSESSMENT

### 8.1 Conclusions

#### Efficacy

- Eltrombopag appears to effectively raise platelet counts during the short term ( $\leq$  six weeks) treatment in patients with previously treated chronic ITP. In the pooled analysis the primary endpoint (i.e., a shift from baseline platelets  $< 30,000/\text{mcl}$  to platelet counts  $\geq 50,000/\text{mcl}$ ) was achieved by 62% of patients treated with 50 mg of eltrombopag compared to only 14% of patients on placebo. The odds of treatment response in the eltrombopag group relative to placebo (OR, 95% confidence intervals: 12.4, 5.18-29.72) was statistically significant ( $p < 0.001$ ).
- In both pivotal studies more than 50% of patients responded with clinically meaningful increases in platelet counts regardless of the baseline platelet counts, use of concomitant medication or splenectomy status.

- Eltrombopag was able to raise platelet counts relatively quickly in both trials, > 30% of patients responded with an increase of platelet counts  $\geq 50,000/\text{mcl}$  by day eight and 50% of patients responded by day 15 following treatment with eltrombopag 50 mg. Platelet levels remained elevated approximately 1 week after discontinuing eltrombopag.
- Rationale for short-term use of eltrombopag was stated in the protocols for study TRA 100773. Specifically, it was stated in the protocol that short-term treatment of eltrombopag may increase platelet counts in patients with chronic ITP scheduled for surgical or dental procedures where a low platelet count can be a hindrance or even prohibitive of the procedure due to the risk of excessive bleeding. However, the clinical study was not designed to assess clinical benefits in a peri-procedural setting. The study assessed changes from baseline bleeding status and each patient using a five component leading scale. The WHO bleeding scale characterizes bleeding as follows: grade 0 - no bleeding; grade 1- petechiae; grade 2- mild blood loss; grade 3- gross blood loss; grade 4 -debilitating blood loss. WHO bleeding scale grades 2-4 are considered clinically significant. WHO bleeding grade 2-4 was evaluated posthoc. No patients had grade four bleeding at any time during the study.
- The clinical meaningfulness of change in bleeding based on the WHO bleeding scoring system is not clear. In particular incremental changes in score from two to one has little clinical utility. In addition the protocols provided few criteria or definitions with regard to how investigators were to assign scores. Also, the scores could have been assigned with knowledge of the platelet count results by the investigators. These data may have biased the score assessment.
- In terms of bleeding, a statistically significant reduction in the proportion of patients with any bleeding at day 43 in the eltrombopag treatment group compared to patients in the placebo treatment group (OR= 0.34, p = 0.018) was observed in the pooled pivotal studies by logistic regression analysis adjusted for use of ITP medication at baseline, splenectomy status, baseline platelet count and WHO bleeding grade at baseline based on the sponsor's analysis. However, the FDA statistical analysis showed no difference between the two treatment groups in terms of bleeding. At the baseline visit 62% of patients treated with eltrombopag 50 mg and 59% of patients treated with placebo reported any bleeding. At the day 43 visit, 37% of patients treated with eltrombopag reported any bleeding compared to 55% of patients treated with placebo. In the pooled pivotal study analysis 35/39 patients in the eltrombopag group compared to 20/26 patients in the placebo group had a baseline WHO bleeding score of zero and a WHO bleeding score of zero at the end of therapy. In the pooled analysis of patients treated with 50 mg of eltrombopag or placebo, 26/44 patients treated with eltrombopag compared to 9/26 patients treated with placebo had a bleeding score of one at baseline and zero at the end of therapy. In the pooled pivotal analysis 4/17 patients treated with eltrombopag and 3/9 patients treated with placebo had baseline WHO bleeding scores of two at baseline and zero at the end of therapy. In the pooled analysis 2/2 patients treated with eltrombopag and 1/3 patients treated with placebo had a baseline bleeding score of three and a WHO bleeding score of zero at the end of therapy. There was no grade four bleeding in the pivotal trials. The clinical meaningfulness of the WHO bleeding score in terms of incremental changes (e.g., going from WHO bleeding score one to zero) is unclear. In addition, the investigators subjectively assigned bleeding scores and were

aware of patient platelet counts at the time of bleeding assessments. These factors confound the analysis of eltrombopag's effect on bleeding.

- In the pivotal trials only 7/173 patients faced a hemostatic challenge during the observation period. In these trials, four patients received eltrombopag (three patients received eltrombopag 50 mg with baseline platelet counts of 10,000-25,000/mcl and one patient received eltrombopag 75 mg with a baseline platelet count of 10,000/mcl). The three placebo treated patients had platelet counts ranging from 12,000-36,000/mcl. The four patients treated with eltrombopag underwent hemostatic challenges consisting of cholecystectomy (two patients), dental extraction and motor vehicle accident. The patients treated with placebo had hemostatic challenges consisting of eye surgery, hip replacement and papilloma surgery of the throat. After treatment with eltrombopag but before the procedure the platelet counts ranged from 82,000-557,000/mcl. After placebo treatment but before the procedure the platelet counts ranged from 26,000-86,000/mcl. None of the patients treated with eltrombopag required rescue treatment. However all three placebo treated patients received other ITP treatment prior to surgery with IVIg or tranexamic acid. No bleeding complications were reported in any of these patients. The limited number of patients who underwent hemostatic challenge does not allow for a conclusion to be drawn with regard to eltrombopag's effectiveness in preventing bleeding in patients who have undergone hemostatic challenge.

### Safety

- The eltrombopag safety database consists of 330 ITP patients who were exposed to at least one dose of eltrombopag. Of these, 81 patients have been exposed for  $\geq 6$  months and 12 patients have been exposed for  $\geq 15$  months. Therefore, the safety profile for eltrombopag is limited with regard to long-term exposure. It is expected that patients who have chronic ITP will need to take this drug chronically. Prolonged exposure to eltrombopag may increase the risk for certain potentially fatal adverse events. In the pivotal trials 16/164 patients (9.7%) who received any dose of eltrombopag met the FDA criteria for assessment of hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. Of the 16 eltrombopag treated patients three received 30 mg, 11 received 50 mg (three increased to 75 mg in TRA 100773B) and two received 75 mg as a starting dose. One patient treated with eltrombopag 50 mg once daily with a history of chronic obstructive pulmonary disease developed marked liver and renal abnormalities beginning on the 15th day of eltrombopag treatment and died on day 26. By day 15 the patient had a tenfold increase in ALT compared to baseline. Although this patient's autopsy revealed thromboemboli and biventricular cardiac hypertrophy which may have ultimately led to pulmonary failure, elevated liver enzymes are not typically a hallmark characteristic of chronic obstructive pulmonary disease. Therefore, patients who are taking eltrombopag for chronic ITP therapy should be monitored with liver function tests in order to minimize the risk of hepatobiliary adverse events.
- Six deaths were reported in the ITP program as of the 120 day safety update. In study TRA 100773A any adverse events were generally evenly distributed between the treatment groups. However patients with any serious adverse event were numerically

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higher the 50 mg eltrombopag group (6/30, 20%) compared to placebo (4/29, 14%). However, 2/28 (7%) of patients treated with 75 mg of eltrombopag once daily reported any serious adverse event. In study TRA 100773B 45/76 (59%) patients treated with eltrombopag 50 mg once daily compared to 14/38 (37%) of patients treated with placebo reported any adverse event. In this study similar numbers of patients reported serious adverse events (eltrombopag 2/76, 3% compared to placebo 2/38, 5%).

- Bone marrow biopsies were collected from 19 of 56 eligible patients in the EXTEND study and 17 of these patients had been treated for > 12 months. Mild or focal mild reticulin information was reported in 5/7 patients. Collagen formation was reported in 2/7 patients and was reported as moderate increase/moderate fibrosis in one patient and myelofibrosis grade 2/3 in one patient. Findings of myelofibrosis were also observed with romiplostim. Therefore, labeling should include a warning that eltrombopag may be related to the adverse event of bone marrow fibrosis.
- The analysis for thromboembolic events indicates that thromboembolic adverse events may occur in patients treated with eltrombopag for chronic ITP. The labeling should include a warning for this potential adverse event.
- The remainder of the adverse events of special interest do not appear to correlate to treatment with eltrombopag.
- Following discontinuation of eltrombopag, platelet counts returned to near baseline levels within approximately 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 < 10,000/mcl and 10,000/mcl less than baseline. The decrease in platelet counts was not associated with a significant increase in bleeding. There is currently little evidence of transient decreases in platelet counts following discontinuation or interruption of Eltrombopag in the EXTEND study. In REPEAT, no increase in the incidence or severity of transient thrombocytopenia has been observed.

## 8.2 Recommendation on Regulatory Action

Eltrombopag is approvable for

The pivotal trials were able to adequately demonstrate that Eltrombopag can raise platelet counts in patients with chronic refractory ITP. However, the sponsor should complete the ongoing studies and submit them for review. This recommendation is based on the data provided by the sponsor in this submission and is also based on the concerns listed below so that more safety information can be obtained.

The sponsor has not shown that eltrombopag is able to reduce or prevent bleeding and this wording should be removed from the proposed indication. The sponsor has shown that patients are able to increase their platelet count within approximately 2 weeks of starting 50 mg of eltrombopag therapy orally once daily. Patients who begin with platelet counts < 30,000/mcl are

able to increase their platelet count to levels  $\geq 50,000/\text{mcl}$  and maintain this level of platelet count for as long as they are taking eltrombopag. Once eltrombopag is discontinued within approximately 2 weeks platelet counts returned to baseline. However, patients may experience a transient thrombocytopenia below their baseline level which may put them at increased risk for bleeding

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Eltrombopag may be associated with myelofibrosis. Thus far in the safety database 19 bone marrow biopsies performed in patients with ITP to rule out other cause for the thrombocytopenia have shown reticulin/collagen deposition in 2 biopsies. The sponsor plans to perform bone marrow \_\_\_\_\_ in the supportive studies.

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In the pivotal trials, a hepatobiliary adverse event occurred in 1 patient that would appear to satisfy Hy's Law criteria for drug induced liver injury. Also there were numerically greater numbers of patients with elevated liver function tests in patients treated with Eltrombopag compared to patients treated with placebo. Further analysis of this adverse event in the ongoing supportive studies will enable a better understanding of this adverse event. There is a high potential for off label use because of the oral administration of this drug as well as the chronic nature of the disease being treated.

### 8.3 Recommendation on Postmarketing Actions

The sponsor proposes a risk management plan and continued monitoring of adverse events in the ongoing supportive studies.

#### Risk Management Activity

The sponsor proposes the following criteria to their risk management plan for eltrombopag:

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The Risk MAP submitted by the sponsor

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Required Phase 4 Commitments

The following should be required postmarketing:

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

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**8.4 Labeling Review**

The sponsor should commit to the draft labeling proposed in appendix 9.2.

**8.5 Comments to Applicant**

The indication sought by the sponsor is approvable. The sponsor should submit for review the completed supportive studies and should continue to report the safety and efficacy of eltrombopag in the ITP population as is required by 21 CFR § 314.50.

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## **9 APPENDICES**

### **9.1 Review of Individual Study Reports**

The studies used for this review are listed in section 6.0 Integrated review of efficacy and 7.0 Integrated review of safety.

### **9.2 Line-by-Line Labeling Review**

The proposed draft label incorporating my recommendations for edits is shown below.

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18 Page(s) Withheld

\_\_\_\_\_ Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

#### List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
Anti-D	Anti-immunoglobulin-D
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
AUC(0- $\tau$ )	Area under the concentration – time curve from time 0 to time $\tau$
AUC(0- $\infty$ )	Area under the concentration – time curve from time 0 to time $\infty$
C <sub>max</sub>	Maximum observed plasma concentration
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome P450
DVT	Deep vein thrombosis
ECG	Electrocardiogram
FDA	Food and Drug Administration
GEE	Generalized estimating equations
GI	Gastrointestinal
Gi/L 10 <sup>9</sup> (giga) units per liter	
GR	Bis-monoethanolamine salt form
GSK	GlaxoSmithKline
IHCIS	Integrated Healthcare Information Services h hours
IC <sub>50</sub>	Concentration producing 50% inhibition
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-Treat
IVIg	Intravenous immunoglobulin
NCI	National Cancer Institute
OATP1B1	Organic anion transporter protein 1B1
PBO	Placebo
PK	Pharmacokinetics
PP	Per Protocol
QC	Quality control
QD	once daily
QTc	Corrected QT interval between QRS complex and T wave
QTcF	QTc with Fridericia's correction
ddQTcF	Time-matched change from baseline in QTcF between active treatment and placebo
R&D	Research and Development
RBC	Red blood cells
SAE	Serious adverse event
t <sub>1/2</sub>	Half-life
TIA	Transient ischemic attack
TPO	Thrombopoietin
TPO-R	Thrombopoietin receptor
UK	United Kingdom
ULN	Upper limit of normal

## References

- <sup>1</sup> <http://www.fda.gov/cder/guidance/7507dft.htm>
- <sup>2</sup> Satia, J. et al.: Descriptive epidemiology of immune thrombocytopenic purpura in three European countries. The 11th Congress of the European hematology of association. Amsterdam: (poster presentation); 2006.
- <sup>3</sup> Ibid 2
- <sup>4</sup> Williams Hematology 6<sup>th</sup> edition.
- <sup>5</sup> Cohen, Y.C. et al.: The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch. Intern. Med. 2000; 160:1630-1638.
- <sup>6</sup> Ibid 3.
- <sup>7</sup> <http://www.fda.gov/cder/guidance/7507dft.htm>
- <sup>8</sup> Bussel, J. B. et al.: Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. NEJM. 2007; 357 (22): 2237-2247.
- <sup>9</sup> Ibid 6.
- <sup>10</sup> <http://www.fda.gov/cder/guidance/7507dft.htm>
- <sup>11</sup> <http://www.fda.gov/cder/guidance/7507dft.htm>
- <sup>12</sup> Nugent, D.J.: Immune Thrombocytopenic Purpura of Childhood. Hematology. 2006; ASH Program Education Book.
- <sup>13</sup> Ibid 6.

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Kathy Robie-Suh  
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MEDICAL OFFICER  
Exact wording of labeling and contents of REMS are  
being negotiated with the sponsor.

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	22,291
<b>Brand Name</b>	Promacta®
<b>Generic Name</b>	Eltrombopag olamine
<b>Sponsor</b>	GlaxoSmithKline
<b>Indication</b>	Short Term Idiopathic Thrombocytopenic Purpura (ITP)
<b>Dosage Form</b>	Film-coated tablet
<b>Drug Class</b>	TPO-R agonist
<b>Therapeutic Dose</b>	25 mg to 75 mg QD
<b>Duration of Therapeutic Use</b>	Acute
<b>Maximum Tolerated Dose</b>	Not established. Highest studied dose: 75 mg QD for 6 weeks in patients and 200 mg QD for 5 days in healthy subjects
<b>Application Submission Date</b>	19 December 2007
<b>Review Classification</b>	Priority NDA
<b>Date Consult Received</b>	26 March 2008
<b>Clinical Division</b>	DMIHP / HFD 160
<b>PDUFA Date</b>	June 19 2008

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

No significant QT prolongation effect of eltronbopag (50 mg QD and 150 mg QD) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between eltrombopag (50 mg and 150 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance.

This was a two-part study. Part 1 was a double-blind, placebo-controlled, randomized, parallel, repeat dose escalation study to investigate the safety, pharmacokinetics and pharmacodynamics of eltrombopag dosed as 100 mg, 150 mg, and 200 mg QD for 5 days. A total of 33 subjects were in Part 1. Part 2 was a double-blind, placebo and active (moxifloxacin) controlled, randomized, balanced crossover study to evaluate the effect of eltrombopag on cardiac repolarization when dosed at 50 mg and 150 mg QD for five days. A total of 87 subjects were in Part 2. Overall findings are summarized in the following table.

**FDA analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Eltrombopag (50 mg and 150 mg) and the Largest Lower Bound for Moxifloxacin**

Treatment	Time, h	$\Delta\Delta\text{QTcF}$ , ms	90% CI, ms
Eltrombopag 50 mg QD	6	1.58	(-2.98, 6.14)
Eltrombopag 150 mg QD	6	1.26	(-3.03, 5.56)
Moxifloxacin 400 mg*	3	10.62	(6.54, 14.70)

\* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment was 4.83 ms.

The suprathreshold dose of 150 mg QD covers the 2-fold increase in the exposures that can be achieved with the highest therapeutic dose of 75 mg QD. However, the suprathreshold dose might not fully cover the range of exposures that can be achieved with a 75 mg QD dose in HCV patients who are reported to have 2.3 fold increases in exposures.

There was no relationship between eltrombopag concentrations and  $\Delta\Delta\text{QTcF}$ .

## 2 PROPOSED LABEL

The sponsor did not include a description of study results in the proposed label. The following text is our suggestions for labeling. We defer all labeling decisions to the clinical review team.

There is no indication of a QT/QTc prolonging effect of Promacta in doses up to 150 mg QD for 5 days. The effects of Promacta at doses up to 150 mg QD for 5 days (suprathreshold doses) on the QT/QTc interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by moxifloxacin.

## 3 BACKGROUND

Promacta® is an orally bioavailable, small molecule, thrombopoietin receptor (TPO-R) agonist. Eltrombopag functions by inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Proposed Indication is for the short-term treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

### 3.1 MARKET APPROVAL STATUS

Promacta is not approved for marketing in the USA or elsewhere.

### 3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary

“A study was conducted to measure the effect of eltrombopag on hERG currents recorded from HEK293 cells stably transfected with hERG-1 cDNA [Report FD2004/00272/00, m4.2.1.3]. The maximum soluble concentration of eltrombopag (21.7  $\mu\text{M}$ , equivalent to 9.62  $\mu\text{g/ml}$ ) determined and the

concentration-dependent effect of eltrombopag on hERG tail current was subsequently studied at 0.00652, 0.0217, 0.0652, 0.217, 0.652 and 2.17  $\mu\text{M}$  (equivalent to 0.003, 0.010, 0.029, 0.096, 0.288 and 0.961  $\mu\text{g/ml}$ , respectively). E-4031 (0.1  $\mu\text{M}$ ), a known inhibitor of the IKr current, was used as a reference substance.

Eltrombopag was found to inhibit hERG channel tail current in a concentration-dependent manner. The nominal IC<sub>25</sub>, IC<sub>50</sub> and IC<sub>75</sub> values were estimated to be 0.09, 0.69 and 5.13  $\mu\text{M}$  (equivalent to 0.04, 0.31 and 2.27  $\mu\text{g/ml}$ ), respectively.

“The effects of eltrombopag (10 or 25  $\mu\text{M}$ ) on action potential duration at 30%, 60% and 90% repolarization (APD<sub>30</sub>, APD<sub>60</sub> and APD<sub>90</sub>, respectively), maximum rate of depolarization (MRD), upstroke amplitude (UA) and resting membrane potential (RMP) were investigated in isolated dog Purkinje fibers paced at stimulation frequencies of 1 and 0.5 Hz [Report FD2002/00064/00, m4.2.1.3]. In fibers paced at 3 Hz (control and 25  $\mu\text{M}$ ), only MRD was measured.

Eltrombopag had no effects on RMP or APD<sub>30</sub>. In fibers stimulated at 0.5 or 1 Hz, exposure to 10 and 25  $\mu\text{M}$  resulted in decreases in MRD (14% to 16% and 22% to 24%, respectively). In fibers stimulated at 1 Hz and exposed to 10 and 25  $\mu\text{M}$ , significant decreases in UA (3 and 5 mV, respectively), APD<sub>60</sub> (8% and 14%, respectively) and APD<sub>90</sub> (6% and 11%, respectively) were noted. At a stimulation frequency of 0.5 Hz, exposure to 10 and 25  $\mu\text{M}$  had no effect on UA whereas slightly larger decreases in APD<sub>60</sub> (12% and 18%, respectively) and APD<sub>90</sub> (10% and 16%, respectively) were found in comparison to stimulation at 1 Hz. When the stimulation frequency was increased from 1 to 3 Hz, MRD was reduced in both the control and 25  $\mu\text{M}$  samples (9% and 6%, respectively), and comparisons to results obtained at 1 Hz indicated no significant differences between the treated and control fibers. However, the effects on MRD at 1 and 0.5 Hz suggested that eltrombopag may produce a tonic (i.e., not use-dependent) inhibition of cardiac sodium channels.

“Conscious male beagle dogs (n=4) were administered eltrombopag at 3, 10 and 30 mg/kg orally in capsules on separate days in a crossover study design with 7 days between treatments [Report SB-497115/RSD-101TT9/1, m4.2.1.3]. The following parameters were measured continuously from ~2 hours prior to dosing to 48 hours post dose: mean arterial pressure, heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, ECG intervals (PR, QRS, QT, QTc) and ECG waveforms.

“Eltrombopag had no effect on arterial blood pressures, heart rate or ECG intervals during the 48 hours post dose. There was no evidence of ECG waveform abnormalities or arrhythmias in ECG tracings evaluated by a veterinary cardiologist at around the time of C<sub>max</sub> (~1 hour post dose) and at approximately 4, 24 and 48 hours post dose.

“Additionally, there was no evidence of ECG abnormalities (e.g., heart rate; PR, QRS, QT and RR intervals and QTc) when evaluated pre- and post dose in conscious dogs after repeated oral administration for 52 weeks at doses up to 30 mg/kg/day (C<sub>max</sub> of 34.5  $\mu\text{g/ml}$  and AUC<sub>0-t</sub> of 418  $\mu\text{g}\cdot\text{h/ml}$ ).”

*Reviewer's Comment: IC<sub>50</sub> for hERG current inhibition was estimated to be 0.69 μM. The effects in isolated canine Purkinje fibers suggested sodium channel inhibition. The in vivo studies showed no evidence of QT prolongation.*

### **3.3 PREVIOUS CLINICAL EXPERIENCE**

Source: Summary of Clinical Safety- Dec 17, 2007

“The safety profile of eltrombopag has been evaluated in 1035 subjects in 22 completed or ongoing GlaxoSmithKline (GSK) sponsored clinical studies globally. The doses of eltrombopag used in these studies ranged from 3 mg to 200 mg in healthy volunteers and in various clinical settings. The duration of treatment with eltrombopag ranged from 1 day in healthy volunteers to >52 weeks in subjects with idiopathic thrombocytopenic purpura (ITP).

This summary reviews the safety data from two double-blind pivotal studies (TRA100773A and TRA100773B) that investigated the use of eltrombopag in the short-term treatment of subjects with chronic ITP.

“One subject died of cardiopulmonary failure in Study TRA100773A (Subject 144, eltrombopag 50 mg). 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. On Day 25, Subject 144 suffered a fatal SAE cardiopulmonary failure which was assessed as not related to study treatment and the subject died 2 days later. Two additional fatal SAEs were reported: embolism and pulmonary embolism. These SAEs were considered drug-related and were identified upon autopsy.

“Cardiac-related AEs were analyzed because eltrombopag was a potent inhibitor of hERG channel tail current in vitro. With the exception of one subject in the eltrombopag 30 mg treatment group, no subjects in the pivotal short-term or supportive long-term studies experienced AEs related to QTc prolongation. Subject 607 (TRA100773A) in the eltrombopag 30 mg treatment group experienced a Grade 2 AE of prolonged QTc segment on ECG evaluation. This subject had ECG abnormalities at baseline and cardiovascular history.”

*Reviewer's Comment: There are no reports of increased adverse events related to QT prolongation: TdP, sudden cardiac death, seizure or significant ventricular arrhythmias.*

### **3.4 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of eltrombopag's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The sponsor submitted data from a two-part Phase I study to evaluate the effect of eltrombopag on cardiac conduction (repolarization). QT evaluation was performed in the Part 2 of Study TRA102860.

## **4.2 TQT STUDY**

### **4.2.1 Title**

A Two-Part, Randomized, Placebo-Controlled Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of Single, Oral Doses of the Thrombopoetin Receptor Agonist, Eltrombopag, and the Effect of Eltrombopag on Cardiac Conduction as Compared to Placebo and Single Oral Doses of Moxifloxacin in Healthy Adult Subjects

### **4.2.2 Protocol Number**

TRA 102860 (Part 1 & 2)

### **4.2.3 Study Dates**

13 March 2006 - 02 August 2007

### **4.2.4 Objectives**

To determine the effect of multiple daily doses of 50 mg and 150 mg eltrombopag on QTcF as compared to placebo and an active comparator.

### **4.2.5 Study Description**

#### **4.2.5.1 Design**

Part 2 was a double-blind, placebo and positive (moxifloxacin) controlled, randomized, balanced crossover study to evaluate the effect of eltrombopag on cardiac repolarization when dosed at 50 mg and 150 mg QD for five days.

#### **4.2.5.2 Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

#### **4.2.5.3 Blinding**

All treatments were administered blinded using a double-dummy approach.

### **4.2.6 Treatment Regimen**

#### **4.2.6.1 Treatment Arms**

The treatment arms are Placebo, 50 mg eltrombopag, 150 mg eltrombopag, 400 mg moxifloxacin. Subjects received each of four regimens in a randomized crossover fashion, using one Williams square, as summarized in the table below:

Sequence	Period 1	Period 2	Period 3	Period 4
1	D	C	A	B
2	A	D	B	C
3	B	A	C	D
4	C	B	D	A

A: 50mg eltrombopag QD for five days + Placebo for moxifloxacin on Day 5  
 B: 150mg eltrombopag QD for five days + Placebo for moxifloxacin on Day 5  
 C: placebo for eltrombopag QD for five days + Placebo for moxifloxacin on Day 5  
 D: placebo for eltrombopag QD for five days + 400 mg moxifloxacin on Day 5

There was a wash-out period of at least 14 days between each study period.

#### 4.2.6.2 Sponsor's Justification for Doses

The goal of the two-part study was to identify the highest safe dose of eltrombopag (not to exceed a mean observed platelet count of  $400 \times 10^6/L$ ), and to investigate the effects of this dose on the cardiac repolarization along with a therapeutic dosing regimen.

*Reviewer's Comment: The supratherapeutic dose of 150 mg QD covers the 2-fold increase in the exposures that can be achieved with the highest therapeutic dose of 75 mg QD. However, the supratherapeutic dose might not fully cover the range of exposures that can be achieved with a 75 mg QD dose in HCV patients who are reported to have 2.3 fold increased exposures.*

#### 4.2.6.3 Instructions with Regard to Meals

All study drugs were taken with 240 ml (8 fluid ounces) of water and at least two hours before or after food intake.

*Reviewer's Comment: Standard high fat breakfast/meal have been shown to decrease eltrombopag exposures. Hence, it is appropriate that the study drug was not administered with food.*

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#### 4.2.6.4 ECG and PK Assessments

**Table 1: Sampling Schedule**

Study Day	-1	1-4	5
<b>Intervention</b>	No treatment (Baseline)	Placebo (for Eltrombopag) Eltrombopag 50 mg Eltrombopag 150 mg	Placebo Eltrombopag 50 mg Eltrombopag 150mg Moxifloxacin 400mg Placebo (for Moxifloxacin)
<b>12-Lead ECGs</b>	Record ECGs <sup>####</sup>		Record ECGs <sup>####</sup>
<b>PK Samples for drug</b>	None collected		Collected <sup>++++</sup>

#### -0.5, 0.5, 1, 2, 3, 4, 6, 12 and 23.25 hours post-dose

++++ pre-dose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12, 24 hours post-dose

#### 4.2.6.5 Baseline

On Day -1, time-matched baseline ECGs were obtained using continuous 12-lead Holter monitor. In the analysis however, pre-dose ECG was used to adjust for baseline.

#### 4.2.7 ECG Collection (Source Protocol)

Continuous 12-Lead Holter monitoring will be performed during Part 2. On Day -1, subjects will be fitted with a H12+ Holter recording device. Holter monitoring will be performed over a 24 hr period on Day -1 and Day 5 of each treatment period. Subjects are to remain supine in a quiet environment for the first four hours post the planned dosing on Day -1 and post dose on Day 5 and will be allowed to freely ambulate except at least 10 – 15 minutes prior to each ECG collection timepoint when they should be resting in a supine position.

Time-matched ECGs (using the time of planned dosing as a starting point) will be collected in triplicate at the timepoints specified above. The core laboratory will store data collected on Day -1 and Day 5 using the Holter monitor and will extract ECGs at specified timepoints.

The mean QTc from 3 separate beats should be analyzed for each ECG timepoint. Analysis of Lead II will be conducted with V5 as a back-up, and V2 as an alternative when T waves are not well defined in leads II or V5. QTc for an individual beat will be calculated from the preceding RR interval as using the average heart rate (RR) intervals from the 12-lead ECG could result in inaccurate QTc calculations due to beat to beat variations in the RR intervals. Collection of critical ECG data shortly after meals or during sleep should be avoided since QT prolongation occurs at these times and a change in the QT-RR relationship occurs during sleep. ECGs should be recorded prior to phlebotomy. All ECGs should be digitally acquired and transmitted to a specified core lab for digital calliper analysis.

In order to further limit sources of electrocardiographic variability, a limited number of ECG over-readers should be used throughout the study. The ECG reader must be blinded to treatment and sequence. One reader must read all ECGs from one particular subject throughout the study.

12-lead ECGs for safety assessment will be obtained in triplicate or as a single reading as specified and after the subject has rested in the supine position for at least 15 minutes.

#### 4.2.8 Sponsor's Results

##### 4.2.8.1 Study Subjects

Eighty-seven healthy adult men and women, between 18-45 yrs of age with a normal baseline ECG and BMI between 19-30 kg/m<sup>2</sup> were enrolled in Part 2 of the study. 39 subjects were withdrawn from the study and 48 completed (See Table 2 below).

Twenty-six subjects were withdrawn from the study due to elevated platelet counts greater than 400 x 10<sup>9</sup>/L. Twenty-four of these subjects were withdrawn after the eltrombopag 150 mg treatment period, one subject after the 50 mg treatment and one subject after the placebo treatment.

**Table 2: Summary of Subject Withdrawals by Treatment for Part 2**

Number of Subjects:	Placebo	Eltrombopag		Moxifloxacin
		50 mg	150 mg	400 mg
Received treatment, N:	64	62	77	63
Completed, n (%)	62 (97)	57 (92)	49 (64)	59 (94)
Withdrawn (any reason), n (%)	2 (3)	5 (8)	28 (36)	4 (6)
Adverse event, n (%)	0	2 (3)	3 (4)	1 (2)
Protocol violation, n (%)	1 (2)	2 (3)	1 (1)	2 (3)
Other, <sup>1</sup> n (%)	1 (2)	1 (2)	24 (31)	1 (2)

1. 26 of 27 subject were withdrawn for platelet counts >400 X 10<sup>9</sup>/L on Day 14 of any treatment period that were still ≥350 X 10<sup>9</sup>/L on Day -2 of the next treatment period (stopping criteria); 1 subject was withdrawn for non-compliance. (Source Data: table 9.204)

Source Data: Table 9.203

##### 4.2.8.2 Statistical Analyses

###### 4.2.8.2.1 Primary Analysis

Eltrombopag had no effect on cardiac repolarization at either the therapeutic or supratherapeutic dose. The upper limit of the 90% CI for the mean difference in QTcF change from baseline between eltrombopag and placebo ( $\Delta\Delta$ QTcF) was below 10 ms at all time points for both doses. The study was sensitive enough to detect the effect of moxifloxacin on QT prolongation as the lower limit of the 90% CI of  $\Delta\Delta$ QTcF was greater than 5 ms for at least one timepoint. The Sponsor's results are provided in the tables below.

**Table 3: The Sponsor's  $\Delta$ QTcF analysis: Eltrombopag 50 mg versus Placebo (A vs. C)**

Day	Time	Treatment Difference: $\Delta\Delta$ QTcF		
		Estimate	S.E.	90% CI
	1	-0.03	1.22	(-2.04, 1.98)
	2	1.54	1.22	(-0.47, 3.55)

5	3	1.52	1.22	(-0.48, 3.53)
	4	0.23	1.23	(-1.79, 2.25)
	6	1.36	1.25	(-0.69, 3.41)
	24	-0.53	1.23	(-2.55, 1.49)

Source: this table is from the sponsor's report Table 12.207

**Table 4: The Sponsor's  $\Delta$ QTcF analysis: Eltrombopag 50 mg versus Placebo (B vs. C)**

Day	Time	Treatment Difference: $\Delta\Delta$ QTcF		
		Estimate	S.E.	90% CI
5	1	2.29	1.18	(0.341, 4.24)
	2	1.86	1.18	(-0.09, 3.81)
	3	0.79	1.19	(-1.16, 2.75)
	4	0.10	1.18	(-1.83, 2.04)
	6	1.95	1.20	(-0.02, 3.93)
	24	0.03	1.19	(-1.92, 1.99)

Source: this table is from the sponsor's report Table 12.207

**Table 5: The Sponsor's  $\Delta$ QTcF analysis: 400 mg Moxifloxacin versus Placebo (D vs. C)**

Day	Time	Treatment Difference: $\Delta\Delta$ QTcF		
		Estimate	S.E.	90% CI
5	1	9.85	1.21	(7.87, 11.84)
	2	10.63	1.20	(8.65, 12.60)
	3	11.16	1.21	(9.17, 13.15)
	4	11.64	1.21	(9.64, 13.64)
	6	8.07	1.22	(6.06, 10.07)
	24	5.25	1.23	(3.23, 7.26)

Source: this table is from the sponsor's report Table 12.207

Based on the sponsor's analysis:

1. None of the subjects experienced the change from baseline greater than 60 ms for any QTc.
2. All of the changes from baseline were less than 30 ms in QTcF.
3. Changes from baseline in QTcB that were greater than 30 ms, occurred in 2 subjects in the placebo group (3%) and 14 subjects in the moxifloxacin group (26%).
4. One subject (2%), administered with moxifloxacin experienced the QTcI change from baseline in the range of (30, 60).

#### 4.2.8.3 Safety Analysis

There were no deaths or serious adverse events. Twenty-six subjects were withdrawn from the study due to elevated platelet counts greater than  $400 \times 10^9/L$ . There were 6 withdrawals due to other adverse events.

**Table 6: Summary of Subjects Withdrawn Due to AEs in Part 2**

Preferred Term	Placebo N=64	Eltrombopag		Moxifloxacin 400 mg N=63
		50 mg N=62	150 mg N=77	
Ventricular extrasystoles	0	1 (2%)	0	1 (2%)
Ventricular tachycardia	0	0	1 (2%)	0
Gingival pain	0	1 (2%)	1 (2%)	0
Gingivitis	0	0	1 (2%)	0
Oral discharge	0	0	1 (2%)	0
Tooth Abscess	0	1 (2%)	0	0
Eosinophil count increased	0	1 (2%)	0	0

Source data: Table 10.209

Subject 5208 had completed Period 1 of the study (150 mg eltrombopag). On Day 1 of Period 2, after receiving one dose of 50 mg eltrombopag, 138 multifocal PVCs /ventricular extrasystoles were observed on telemetry over a 68 h time period. The subject was asymptomatic. Study drug was withdrawn the same day. The maximum intensity of these events was reported as mild. The events resolved and were considered by the investigator to be related to study drug. At the time these events were observed on telemetry (Period 2 Day 1) an abnormal ECG showed flat T-waves four hours after study drug administration. On the same day, pre-dose and one hour post dose, sinus bradycardia were also recorded on ECG. The following day sinus bradycardia was recorded on ECG at one hour after study drug administration (Table 10.214).

Subject 5218 had completed Period 1 (50 mg eltrombopag). On Day 3 of Period 2 (400 mg moxifloxacin) prior to receiving the moxifloxacin, multiple unifocal (87) PVCs/ventricular extrasystoles were observed on telemetry over a 66 h period. The maximum intensity of these events was reported as mild. The subject was withdrawn from the study on Day 3 of Period 2. The events resolved, and were considered by the investigator to be related to study drug. No abnormal findings were recorded on ECG for this subject on or around the time these events were observed on telemetry. (Table 10.214)

Subject 5023 had completed Period 1 (50 mg eltrombopag) and Period 2 (400 mg moxifloxacin). On Day 3 and 4 of Period 3, (150 mg eltrombopag) four-beat non-sustained ventricular tachycardia and five-beat non-sustained ventricular tachycardia, respectively were observed on telemetry. Both episodes lasted one minute. The subject was asymptomatic and was hemodynamically stable. The maximum intensity of these events was reported as mild. The events were considered by the investigator to be related to study drug and the subject was withdrawn from the study. No abnormal findings were recorded on ECG for this subject on or around the time these events were observed on telemetry.

Other abnormal ECG findings reported are summarized below.

**Table 7: Summary of Abnormal ECG Findings in Part 2**

Abnormal ECG Findings	Placebo N=64	Eltrombopag		Moxifloxacin
		50 mg N=62	150 mg N=77	400 mg N=63
Any	15 (23)	13 (21)	17 (22)	10 (16)
Sinus tachycardia	1 (2)	0	0	0
Ectopic supraventricular rhythm	0	0	0	1 (2)
Junctional rhythm ( $\leq 100$ /min)	0	0	0	1 (2)
First degree AV block (PR interval $> 200$ msec)	6 (9)	6 (10)	8 (10)	4 (6)
Non-specific intraventricular conduction delay ( $\geq 120$ msec)	2 (3)	3 (5)	2 (3)	2 (3)
T wave inversion	2 (3)	2 (3)	2 (3)	0
T waves flat	6 (9)	6 (10)	9 (12)	4 (6)
T waves biphasic	1 (2)	0	1 (1)	0
Other	1 (2)	0	0	0

Source Data: Table 10.214

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

Plasma eltrombopag PK parameters following repeat dose administration in Part 2 are summarized in table below. Plasma eltrombopag  $AUC_{(0-\tau)}$  and  $C_{max}$  values observed at the 150 mg dose level in Part 2) were consistent with those observed in Part 1.

**Table 8: Summary of Plasma Eltrombopag PK Parameters in Study TRA102860 Part 2**

Day	Dose (mg)	N	$AUC_{(0-\tau)}$ ( $\mu\text{g hr/mL}$ )	$C_{max}$ ( $\mu\text{g/mL}$ )	$C_{\tau}$ ( $\mu\text{g/mL}$ )	$t_{max}$ (h)
5	50	60	65.4 (59.7, 71.6) [36.4]	6.40 (5.87, 6.97) [34.2]	1.19 (1.05, 1.34) [51.2]	3.19 (2.17, 6.22)
	150	73	204 (186, 223) [39.3]	19.0 (17.4, 20.6) [37.5]	4.07 (3.64, 4.55) [50.3]	2.67 (1.67, 6.20)

Data presented as geometric mean (95% CI) [CVb%], except  $t_{max}$  presented as median (minimum, maximum)

Source Data: Table 29 of sponsor report tra102860-report-body.pdf

Following five days of repeat dosing, plasma eltrombopag  $C_{max}$  and  $AUC_{(0-\tau)}$  increased in a dose proportional manner between the 50 mg and 150 mg dose levels. The dose proportionality ratio estimate (90% CI) was 1.04 (0.987, 1.09) for  $AUC_{(0-\tau)}$  and 1.01 (0.942, 1.08) for  $C_{max}$  over a range of 50 mg QD to 150 mg QD

Plasma moxifloxacin PK parameters following single dose administration in Part 2 are summarized in

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**Table 9: Summary of Plasma Moxifloxacin PK Parameters in Study TRA102860 Part 2**

Dose (mg)	N	AUC(0-4) ( $\mu\text{g hr/mL}$ )	C <sub>max</sub> ( $\mu\text{g/mL}$ )	t <sub>max</sub> (h)
400	60	22.6 (21.4, 23.9) [21.1]	2.05 (1.93, 2.18) [23.7]	2.17 (0.63, 6.17)

Data presented as geometric mean (95% CI) [CVb%], except t<sub>max</sub> presented as median (minimum, maximum)

Source Data: Table 30 of sponsor report tra102860-report-body.pdf

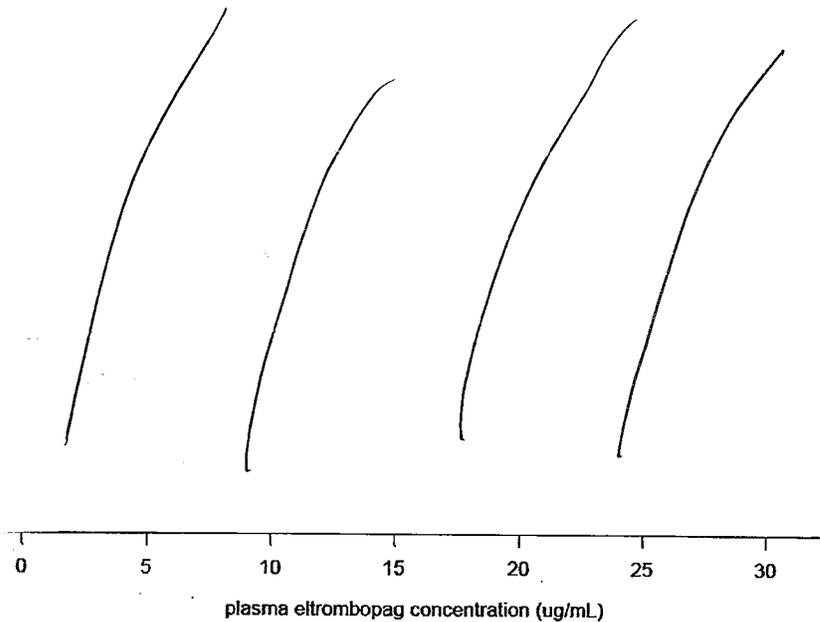
Plasma moxifloxacin C<sub>max</sub> values in this study were 2.05  $\mu\text{g/ml}$  on average, which is lower than the C<sub>max</sub> value of 3.1  $\mu\text{g/ml}$  in the moxifloxacin product label [Avelox, Package Insert, 2005].

#### 4.2.8.4.2 Exposure-Response Analysis

Change from baseline in the QTcF between active treatment and placebo ( $\Delta\Delta\text{QTcF}$ ) was selected as the PD measure. Specifically:  $\Delta\Delta\text{QTcF} = ([\text{mean QTcF of drug on Day 5 at time X} - \text{mean QTcF of drug on Day -1 at time X}] - [\text{mean QTcF of placebo on Day 5 at time X} - \text{mean QTcF of placebo on Day -1 at time X}])$ .

A plot of  $\Delta\Delta\text{QTcF}$  and plasma eltrombopag concentrations showed no relationship as shown in Figure 1.

**Figure 1:  $\Delta\Delta\text{QTcF}$  versus Plasma Concentration following Repeat Dose Administration of 50 mg QD and 150 mg QD Eltrombopag for Five Days**



Source Data: Figure 20 of sponsor report tra102860-report-body.pdf

The final Cp- $\Delta\Delta$ QTcF model for eltrombopag was a linear model with no delay in effect of concentration on  $\Delta\Delta$ QTcF; fixed effects for pre-dose  $\Delta\Delta$ QTcF on Day 5 (intercept,  $\Theta_1$ ) and the slope relating plasma eltrombopag concentration to  $\Delta\Delta$ QTcF ( $\Theta_2$ ) were included, along with inter-individual variability and inter-occasion variability (TRT1=50 mg and TRT2=150 mg) for both fixed effects, and additive random residual variability, as defined by the following equation:

$$ddQTcF = \Theta_1 + \eta_1 + TRT1 * \eta_3 + TRT2 * \eta_4 + (\Theta_2 + \eta_2 + TRT1 * \eta_5 + TRT2 * \eta_6) * Cp + \varepsilon_1$$

The slope of eltrombopag concentration effect on  $\Delta\Delta$ QTc was slight, with a model predicted value of 0.120 msec/ $\mu$ g/ml. The 90% CI obtained from the bootstrap analysis for the slope estimate (-0.014 to 0.244 msec/ $\mu$ g/ml) contained zero.

Based on the final Cp- $\Delta\Delta$ QTcF model, simulations were performed to predict the mean (90% CI)  $\Delta\Delta$ QTc at eltrombopag doses of 50 mg QD, 150 mg QD, and 300 mg QD. The results of these simulations suggest that eltrombopag will not have a clinically significant effect on  $\Delta\Delta$ QTcF at concentrations predicted for a dose of 300mg QD as shown in Table 10.

**Table 10: Summary of  $\Delta\Delta$ QTcF at C<sub>max</sub> for Therapeutic and Supratherapeutic Eltrombopag Doses**

Dose (mg) QD	Plasma eltrombopag C <sub>max</sub> ( $\mu$ g/mL) mean (95% CI)	Predicted ddQTcF (msec) mean (90% CI) <sup>1</sup>
50	6.72 (6.35, 7.10)	0.02 (-1.92, 2.42)
150	20.2 (19.0, 21.3)	1.60 (-0.50, 4.03)
300 <sup>2</sup>	40.3 (38.1, 42.6)	4.03 (1.55, 6.79)

1. Based on 1000 study simulations per dose level (n=60 subjects for 50 mg, n=73 subjects for 150 mg, n=81 subjects for 300 mg per simulation)
2. Simulations extrapolated beyond range of observed data; dose proportionality and constant coefficient of variation assumed

*Reviewer's Comment: The sponsor's analysis of the concentration-QT relationship is acceptable. The estimate of the slope and intercept were comparable to that obtained by the reviewer's independent analysis of the data.*

## 5 REVIEWERS' ASSESSMENT

### 5.1 STATISTICAL ASSESSMENTS

#### 5.1.1.1.1 Primary Analysis

The reviewer analyzed the Sponsor's SAS data set ecg.xpt using ANCOVA. The primary endpoint was the change from baseline in QTcF at each time point (average of three replicated ECGs). The eltrombopag 50 mg and eltrombopag 150 mg were compared with placebo. The primary analysis was performed on all time points using mixed-effect analysis of covariance model, including sequence, period, regimen as fixed effects covariates and subject as a random effect covariate. The moxifloxacin 400 mg was also compared with placebo using the same model.

As seen from Table 11 and Table 12, the upper limit of the 90% confidence interval for the mean difference in QTcF change from baseline between eltrombopag and placebo was below 10 ms at all time points for both 50 mg QD and 150 mg QD doses, which demonstrates that this is a negative TQT study using the proposed dose.

For 400 mg moxifloxacin, the largest lower 90% CI for the baseline adjusted mean difference of 400 mg moxifloxacin and placebo is 6.5 ms at hour 3 after dosing without multiple endpoint adjustment. If Bonferroni multiple endpoint correction method is applied (corrected 5 time points), the largest lower bound of  $\Delta\Delta\text{QTcF}$  between moxifloxacin and placebo is 4.83 ms. Since Bonferroni correction is the most conservative approach by assuming the independence of the data, we believe the assay sensitivity of the study has been established.

**Table 11: Summary of  $\Delta\text{QTcF}$  analysis: Eltrombopag 50 mg versus Placebo (A vs. C)**

Day	Time	Mean $\Delta\text{QTcF}$		Treatment Difference: $\Delta\Delta\text{QTcF}$		
		TRT: A	TRT: C	Estimate	S.E.	90% CI
5	1	-2.23	0.21	-2.4435	2.5885	(-6.7248, 1.8377)
	2	-1.88	-1.98	0.1053	2.5392	(-4.0943, 4.3050)
	3	-4.48	-1.40	-3.0815	2.5004	(-7.2170, 1.0540)
	4	-3.62	-2.21	-1.4172	2.4708	(-5.5037, 2.6693)
	6	-5.87	-7.45	1.5798	2.7552	(-2.9771, 6.1368)
	24	-5.68	-2.88	-2.8021	2.4692	(-6.8860, 1.2819)

**Table 12: Summary of  $\Delta\text{QTcF}$  analysis: Eltrombopag 150 mg versus Placebo (B vs. C)**

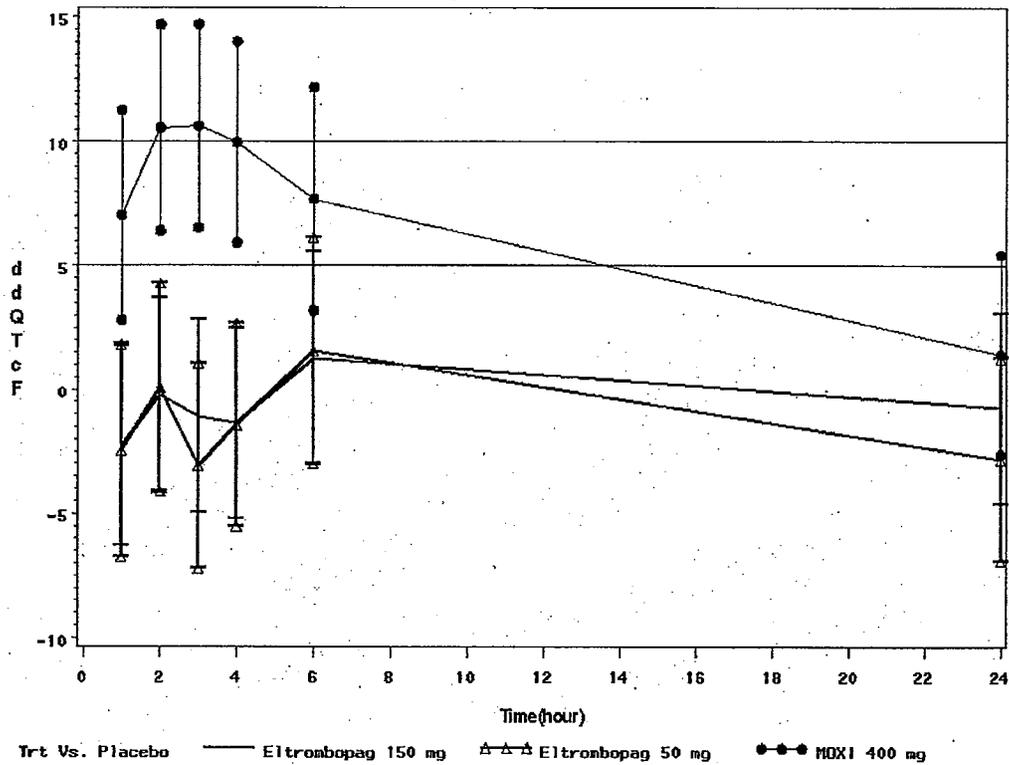
Day	Time	Mean $\Delta\text{QTcF}$		Treatment Difference: $\Delta\Delta\text{QTcF}$		
		TRT: B	TRT: C	Estimate	S.E.	90% CI
5	1	-2.06	0.21	-2.2653	2.4346	(-6.2920, 1.7614)
	2	-2.23	-1.98	-0.2478	2.3883	(-4.1978, 3.7022)
	3	-2.47	-1.40	-1.0682	2.3545	(-4.9624, 2.8261)
	4	-2.47	-2.21	-1.3683	2.3293	(-5.2208, 2.4842)
	6	-6.18	-7.45	1.2636	2.5977	(-3.0327, 5.5600)
	24	-3.62	-2.88	-0.7448	2.3224	(-4.5859, 3.0963)

**Table 13: Summary of  $\Delta\text{QTcF}$  analysis: Moxifloxacin 400 mg versus Placebo (D vs. C)**

Day	Time	$\Delta\text{QTcF}$		Treatment Difference: $\Delta\Delta\text{QTcF}$		
		TRT: D	TRT: C	Estimate	S.E.	90% CI
5	1	7.26	0.21	7.0481	2.5527	(2.8261, 11.2701)
	2	8.56	-1.98	10.5471	2.5041	(6.4055, 14.6886)
	3	9.22	-1.40	10.6215	2.4668	(6.5417, 14.7014)
	4	7.77	-2.21	9.9764	2.4383	(5.9436, 14.0092)
	6	0.25	-7.45	7.6967	2.5977	(3.1995, 12.1938)
	24	-1.45	-2.88	1.4309	2.4351	(-2.5965, 5.4583)

The time course of  $\Delta\Delta\text{QTcF}$  for the study drug Eltrombopag and moxifloxacin is displayed in Figure 2.

**Figure 2:  $\Delta\Delta\text{QTcF}$  for Eltrombopag and Moxifloxacin**



**5.1.1.1.2 Categorical Analysis**

Three subjects- 5102 (B), 5032 (D), and 5214 (C) had their QTcF over 450 ms. Maximum QTcF for all subjects was 459 ms. A total of 34 subjects experienced the QTcF change from baseline greater than 30 ms at least one time during the trial (See Table 14). None of the QTcF intervals change exceeded 60 ms.

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**Table 14: Subjects with  $\Delta$ QTcF over 30 ms (FDA)**

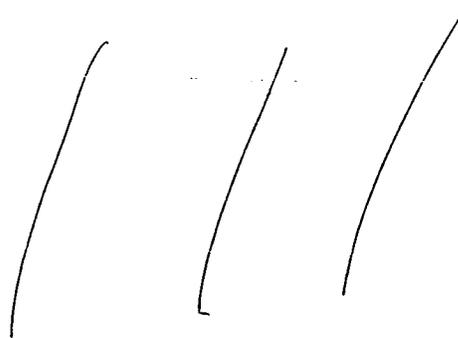
SUBJID	TREATMENT	dQTcF	SUBJID	TREATMENT	dQTcF
5001	C	32	5120	C	31
5019	B	41	5122	C	31
5022	B	41	5124	B	39
5023	D	37	5127	C	34
5025	A	36	5128	A	39
5026	D	34	5131	B	47
5030	B	33	5134	C	34
5031	C	40	5139	B	37
5032	D	40	5142	C	32
5102	D	40	5143	A	32
5105	C	33	5145	C	40
5106	A	40	5201	D	40
5108	D	32	5202	D	37
5110	D	37	5207	C	35
5111	D	35	5208	A	32
5112	D	33	5210	D	45
5113	D	36	5212	C	32

**5.2 CLINICAL PHARMACOLOGY ASSESSMENTS**

**5.2.1 QT Corrections**

The observed QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI). The Fridericia's correction seems reasonable.

**Figure 3. QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



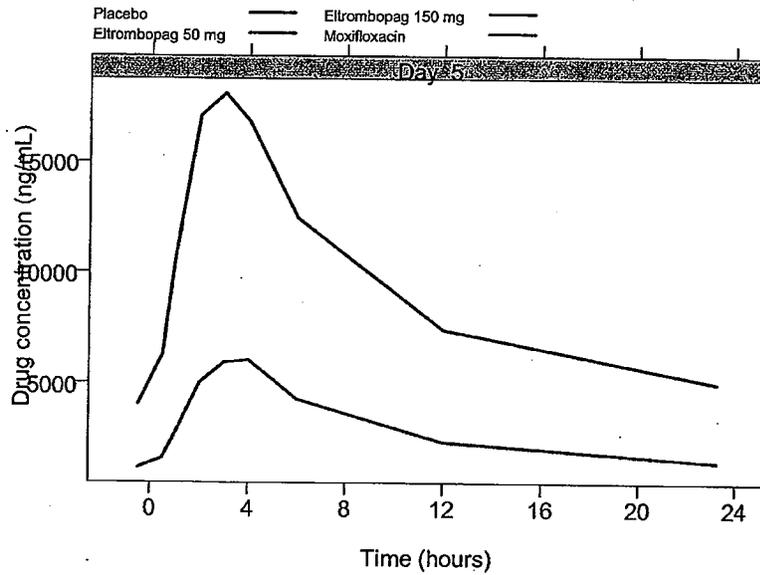
RR interval (ms)

**b(4)**

### 5.2.2 QTcF and Eltrombopag Concentration Time Profiles

Please refer to Figure 2 of the Reviewer's Statistical Assessment for time course of  $\Delta\Delta$ QTcF for eltrombopag and moxifloxacin.

**Figure 4. Mean Drug concentration - time profiles for Eltrombopag 50 mg (blue line), Eltrombopag 150 mg (red line),**

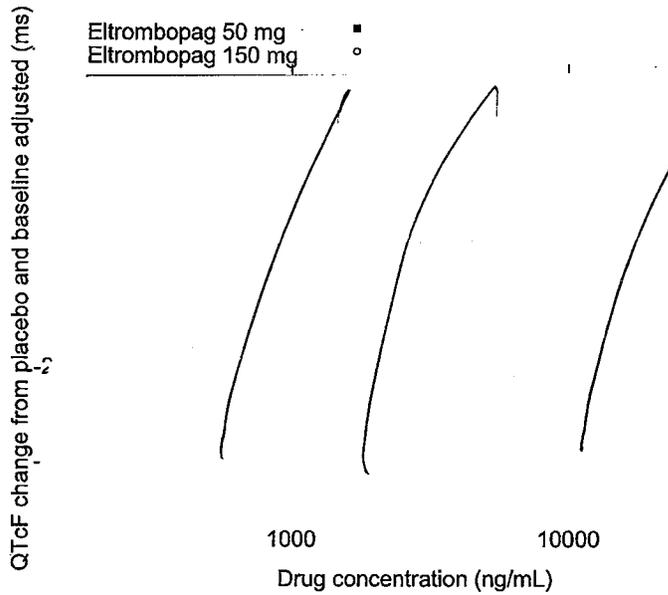


### 5.2.3 Eltrombopag Concentration-QTcF Analysis

The relationship between  $\Delta\Delta$  QTcF and eltrombopag concentrations is visualized in Figure 5 with no evident exposure-response relationship.

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**Figure 5.  $\Delta\Delta$  QTcF vs. Eltrombopag concentration**



b(4)

### 5.3 CLINICAL ASSESSMENTS

#### 5.3.1 Safety assessments

None of the events identified to be of clinical importance per ICH E14 guidelines i.e. sudden death, syncope and seizures and significant ventricular arrhythmias occurred in this study. One subject experienced runs of ventricular tachycardia but they were non sustained 4-5 beat runs and the subject was asymptomatic.

#### 5.3.2 ECG assessments

Waveforms submitted to the ECG warehouse were reviewed. ECGs were predominantly read in Lead II (96%) with V2 or V5 as alternate leads. Per QT analysis scores computed by the warehouse, there was no significant QT bias. Overall ECG acquisition and interpretation in this study appears acceptable.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	25mg to 75mg QD	
Maximum tolerated dose	<p><b>Healthy Adult Subjects:</b></p> <p>No dose-limiting toxicity occurred, but there was a high percentage of subjects who achieved high platelets, including 5 of 10 (50%) achieving platelets &gt;400Gi/L and 2 of 10 (20%) achieving platelets &gt;600Gi/L at the maximum dose, 200mg QD, tested in healthy adult subjects.</p> <p>At the NOAEL established in rats (28-week study), eltrombopag AUC was approximately 2.2-fold the AUC observed in healthy adult human subjects at the 200mg QD dose. At the NOAEL established in dogs (52-week study), eltrombopag AUC was approximately 1.2-1.6-fold the AUC observed in healthy adult human subjects at the 200mg QD dose.</p> <p><b>Patients with ITP:</b></p> <p>No dose-limiting toxicity occurred in patients with ITP, and the highest dose tested was 75mg QD.</p> <p>At the NOAEL established in rats (28-week study), eltrombopag AUC was approximately 4.5-fold the AUC observed in ITP patients at the 75mg QD dose. At the NOAEL established in dogs (52-week study), eltrombopag AUC was approximately 2.5-3.2-fold the AUC observed in ITP patients at the 75mg QD dose.</p>	
Principal adverse events	<p>The most common adverse events observed in healthy adult subjects enrolled in clinical pharmacology studies and receiving the targeted therapeutic dose of 50 to 75mg (N=104 across studies) were headache (7%), pharyngolaryngeal pain (2%), somnolence (&lt;1%), nausea (&lt;1%), fatigue (&lt;1%), nasal congestion (&lt;1%), epistaxis (&lt;1%) and cough (&lt;1%).</p> <p>The dose limiting event (it is an anticipated pharmacodynamic effect, not defined as an adverse event) in clinical pharmacology studies was elevated platelet counts. Of the 568 healthy subjects who received eltrombopag in the 13 clinical pharmacology studies, 101 subjects had platelet counts above 400Gi/L (upper limit normal range) for at least one time point during the study.</p>	
Maximum dose tested	Single Dose	Healthy Adult Subjects: 200mg
	Multiple Dose	Healthy Adult Subjects:

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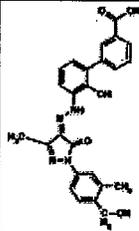
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		200mg QD for 5 days Patients with ITP: 75mg QD for 6 weeks
Exposures Achieved at Maximum Tested Dose	Single Dose	Healthy Adult Subjects geometric mean (%CV), N=7: C <sub>max</sub> : 18.3 µg/mL (52.3) AUC(0-τ): 167 µg·h/mL (36.2) (sampling not long enough to determine AUC(0-∞).
	Multiple Dose	Healthy Adult Subjects geometric mean (%CV), N=7: C <sub>max</sub> : 24.8 µg/mL (48.1) AUC(0-τ): 302 µg·h/mL (48.5) Patients with ITP geometric mean (95% CI), N=26: C <sub>max</sub> : 11.4 µg/mL (9.39, 13.9 µg/mL) AUC(0-τ): 146 µg·h/mL (122, 176 µg/mL)
Range of linear PK	Healthy Adult Subjects: dose proportional between 50mg and 200mg QD slightly greater than dose-proportional at lower doses.	
Accumulation at steady state	Healthy Adult Subjects geometric least squares mean ratio (90% CI) for Day 10 vs Day 1 AUC(0-τ): 50mg QD: 1.41 (1.20, 1.64) 75mg QD: 1.56 (1.23, 1.97)	
Metabolites	Eltrombopag metabolites have not been tested for activity because each circulating component accounted for <10% of total plasma radioactivity. Metabolites J and K have been identified in plasma. METABOLITE J (oxidative metabolite; 0.4% plasma radioactivity at 4 hours)	

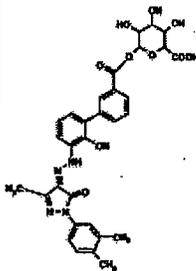
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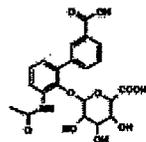


**METABOLITE K** (glucuronide metabolite; three isomers, together 0.6% plasma radioactivity at 4 hours)



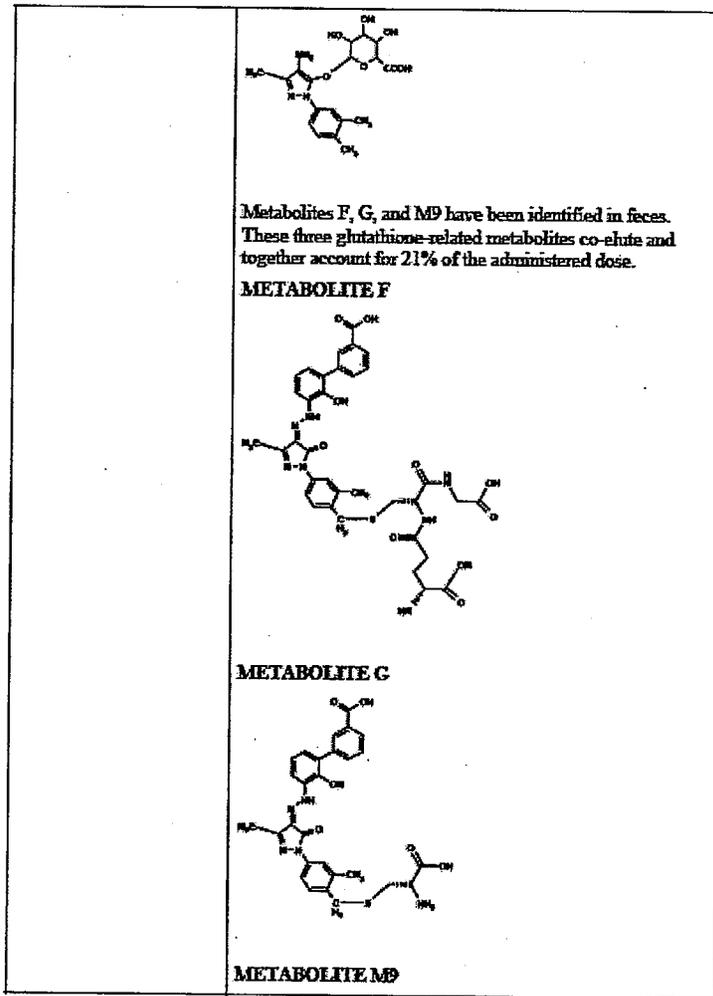
Metabolites M14 and AE have been identified in urine; representing the radiolabeled and unlabeled portion of the molecule following hydrazine cleavage, these glucuronide metabolites account for 20% of the administered dose.

**METABOLITE M14**



**METABOLITE AE**

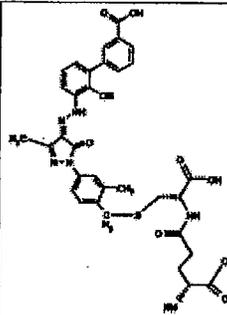
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Absorption	Absolute/Relative Bioavailability	<p>Absolute bioavailability data are not available due to inability to make IV formulation.</p> <p>Relative bioavailability of tablet compared to capsule formulation geometric least squares mean ratio (90% CI):</p> <p><math>C_{max}</math>: 0.82 (0.70, 0.96)</p> <p><math>AUC(0-\infty)</math>: 0.85 (0.75, 0.97)</p>
	$T_{max}$	<p>Healthy Adult Subjects:</p> <p>Parent (eltrombopag): median 3 to 4 hours range: 2 to 6 hours</p> <p>Metabolites: not determined.</p>
Distribution	$V_d/F$ or $V_d$	From the population PK analysis, the typical value for $V_c/F$ was 11L (inter-individual %CV of 41.8).
	% bound	>99%
Elimination	Route	<p>Primary route: feces, 59% of dose (20% of dose as parent drug in feces)</p> <p>Other route: urine, 31% of dose (no parent drug in urine)</p>
	Terminal $t_{1/2}$	<p>Parent: geometric mean ranged from 21 to 32 hours across four studies. %CVb ranged from 18 to 40%.</p> <p>Metabolites: not determined.</p>

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	CL/F or CL	<p>From the population PK analysis, the typical value for CL/F for a non-Japanese healthy subject was 0.794L/h (inter-individual %CV of 44.3).</p> <p>Separate typical values were estimated for Japanese healthy subjects: 0.490L/h, ITP patients taking corticosteroids: 0.458L/h, and ITP patients not taking corticosteroids: 0.607L/h.</p>
Intrinsic Factors	Age	Age was not identified as having a significant influence on eltrombopag PK.
	Sex	From the population PK analysis, the typical value for sex effect was that males had 27% higher CL/F than females.
	Race	<p>From the population PK analysis, the typical value for CL/F was 62% higher in non-Japanese compared to Japanese healthy subjects.</p> <p>Based on post-hoc AUC(0-<math>\infty</math>) estimates, Japanese healthy subjects had approximately 80% higher exposures than non-Japanese subjects and East Asian ITP patients had approximately 70% higher exposures than non-East Asian patients.</p>
	Hepatic & Renal Impairment	<p><b>Hepatic Impairment (HI):</b></p> <p>Mild HI: 41% higher AUC(0-<math>\infty</math>), 14% lower C<sub>max</sub></p> <p>Moderate HI: 93% higher AUC(0-<math>\infty</math>), 29% lower C<sub>max</sub></p> <p>Severe HI: 80% higher AUC(0-<math>\infty</math>), 49% lower C<sub>max</sub></p> <p><b>Renal Impairment (RI):</b></p> <p>Mild RI: 38% lower AUC(0-<math>\infty</math>), 38% lower C<sub>max</sub></p> <p>Moderate RI: 44% lower AUC(0-<math>\infty</math>), 28% lower C<sub>max</sub></p> <p>Severe RI: 73% lower AUC(0-<math>\infty</math>),</p>

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		69% lower C <sub>max</sub>
Extrinsic Factors	Drug interactions	<p><b>Antacid (1524mg aluminium hydroxide and 1425mg magnesium carbonate)</b></p> <p>Eltrombopag AUC(0-∞) decreased 70%, C<sub>max</sub> decreased 70%</p> <p><b>Rosuvastatin</b></p> <p>Rosuvastatin AUC(0-∞) increased 55%, C<sub>max</sub> increased 2.03-fold</p> <p><b>CYP probe cocktail including caffeine (CYP1A2), flurbiprofen (CYP2C9), omeprazole (CYP2C19, and midazolam (CYP3A4):</b></p> <p>No change in CYP probe substrates.</p>
	Food Effects	<p><b>Standard high-fat breakfast containing calcium:</b></p> <p>Eltrombopag AUC(0-∞) decreased 59%, C<sub>max</sub> decreased 65%</p> <p><b>Low-fat/low-calcium meal</b></p> <p>Eltrombopag AUC(0-∞) decreased 7%, C<sub>max</sub> decreased 13%</p> <p><b>High-fat/low calcium meal:</b></p> <p>No change in eltrombopag AUC(0-∞) or C<sub>max</sub></p> <p><b>High-fat/low calcium meal administered 1 hour after eltrombopag:</b></p> <p>Eltrombopag AUC(0-∞) decreased 13%, C<sub>max</sub> decreased 15%</p>
Expected High Clinical Exposure Scenario	<p>Populations that have exhibited impaired eltrombopag CL/F include subjects with hepatic impairment (HI) and patients infected with the Hepatitis C Virus (HCV). As described above for HI, patients with moderate to severe HI had 1.8 to 1.9-fold higher plasma eltrombopag AUC(0-∞) than healthy subjects. For HCV, plasma eltrombopag exposures at the 75mg QD dose were approximately 2.3-fold those observed in patients with HITP at the same dose.</p>	

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## 6.2 TABLE OF STUDY ASSESSMENTS

Appendix 2: Time and Events Table -- Part 2

Study Procedure	Screen1	Treatment										Follow-Up Visits	
		Periods 1, 2, 3, and 411										Day 14 (± 1 day)	Day 33 (± 3 days)
		Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 14			
Informed Consent	X												
Medical History/Medication History <sup>2</sup>	X												
Physical Examination <sup>3</sup>	X	X											
Physical Examination to Assess Evidence of Bruising				X	X	X	X	X	X			X	X
Ophthalmology examination <sup>18</sup>	X												
Blood Pressure and Heart Rate <sup>21</sup>	X	X		X	X	X	X	X	X			X	X
Safety 12-lead ECG	X <sup>4</sup>			X <sup>14</sup>			X <sup>4</sup>	X <sup>4</sup>					
Holter Monitoring			X <sup>15</sup>						X <sup>15</sup>				
Telemetry <sup>16</sup>				X	X	X	X	X	X	X			
Height and Weight	X												
Clinical Chemistry <sup>5</sup>	X	X		X	X			X				X	X
Hematology <sup>5</sup>	X	X		X	X			X		X <sup>23</sup>		X	X
Coagulation Tests <sup>22</sup>	X												
Lipid Panel <sup>8</sup>	X												
Urinalyses, 6	X	X		X	X			X				X	X
Urine drug screen (including alcohol and cotinine)	X	X <sup>19</sup>											
HBsAg, Hep C antibody and HIV Screening	X												
Pregnancy Test <sup>7</sup>	X	X											X
Serum FSH and serum estradiol <sup>20</sup>	X												
Study Drug Dosing <sup>12</sup>				X	X	X	X	X					
ELTROMBOPAG PK Samples <sup>9, 13</sup>								X	X				
Moxifloxacin PK Samples <sup>13, 17</sup>								X	X				
Pharmacogenetics Sample <sup>10</sup>		X											
Adverse Events										Continuous		X	X
Concomitant Medications										Continuous		X	X
Outpatient	X											X	X

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Study Procedure	Screen1	Treatment										Follow-Up Visits	
		Periods 1, 2, 3, and 411										Day 14 (± 1 day)	Day 33 (± 3 days)
		Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 14			
Admission to CRU													
Inpatient Check-out		X								X			

- Subjects should be fasting from all food and drink for 4 hours prior to screening assessments being performed.
- Medical history and medication history should include full history of drug, alcohol and nicotine-containing product use, complete history of all medications (including vitamin and herbal supplements) taken within 30 days prior to screening.
- Physical examination, performed at screening, Day -2 of each treatment period and at follow-up visits, will include vital signs (supine blood pressure and heart rate) and assessment of vascular bruits and spleen. Height, weight, and calculation of body mass index (BMI) will be performed at screening only.
- Three consecutive 12-lead ECGs will be taken at least 5 minutes apart.
- Hematology, clinical chemistry and urinalysis will be performed on Day -2, pre-dose on Day 2 (24 hr post-dose on Day 1) and pre-dose on Days 3 and 5. Any safety lab results outside the normal range will be repeated at the discretion of the investigator.
- Urinalysis should include a microscopic evaluation if dipstick urinalysis is positive for blood or protein.
- For female subjects of childbearing potential only: Serum β-hCG or urine pregnancy test is to be performed at screening, on Day -2 of each treatment period and at the Day 28 follow-up visit.
- Lipid panel includes total cholesterol, triglycerides, LDL and HDL.
- Serial blood samples (approximately 3 mL) for PK analysis will be collected pre-dose (within 30 minutes prior to the administration of study medication) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours post-dose of Day 5 of each ELTROMBOPAG treatment period (treatment regimen A, B and C).
- Pharmacogenetics sample (approximately 10 mL) may be taken at any time during the study but it is recommended that the sample be taken on Day -1.
- Each subject will participate in all 4 treatment periods in the order designated at randomization. Each treatment period will be separated by a 14-day wash-out period.
- Study medication will be administered by Unit personnel. Subjects must remain in a quiet room (no TV, no radio and minimal talking) in the supine position for 4 hours.
- No intravenous cannula may be inserted for approximately 24 hours for collection of PK samples.
- Single 12-Lead ECGs will be taken pre-dose (within 30 minutes prior to first dose of study medication) and 1, 2, 4 and 6 hours post-dose.
- On Day -1 and Day 5, subjects will be fitted with a H124 Holter recording device. ECGs will be extracted at the following timepoints within a five minute time window: Day -1 of each treatment period: 0.5, prior to planned dosing; 0.5, 1, 2, 3, 4, 6, 12 and 23.5 hours post planned dosing and Day 5 of each treatment period: pre-dose (30 minutes prior to administration of study medication) and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose. Subjects should be kept in a supine position at least 10-15 minutes prior to the collection timepoints. Whenever 12-lead ECGs are obtained at the same nominal time as blood draw or blood pressure/pulse rate measurement, the 12-lead ECG MUST be obtained first.
- On Day 1 of each treatment period, continuous dual-lead cardiac monitoring (telemetry) will be performed for at least 6 hours pre-dose and continue until at least 24 hours after the last dose of study medication for each treatment period.
- Serial blood samples (approximately 3 mL) for PK analysis will be collected pre-dose (within 30 minutes prior to administration of study medication) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours post dose of Day 5 of moxifloxacin treatment period (treatment regimen D).
- Refer to Appendix 9 for procedures to be followed for ophthalmology exam.

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19. On Day -2 of each treatment period, alcohol screening may be performed by a breath test.
20. For female subjects of non-childbearing potential only: Serum FSH and serum estradiol levels are to be measured at screening.
21. Supine blood pressure and heart rate will be measured at screening, on Day -2 and pre-dose on Days 1 - 5, post dose at hours 2, 3, 4, 6, and 24 of each treatment period and at the follow-up visits.
22. Coagulation tests will include PT/PTT, C-reactive protein (CRP), Factor V Leiden DNA, protein C, protein S and anti-thrombin III.
23. During the wash-out period, on Day 14 ( $\pm 1$  day after the first dose of each treatment period), a blood sample (approximately 5ml) will be obtained to assess platelet count only.

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