CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-291

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: **22-291**	Submission Date(s): **12/18/08, 1/14/08, 1/18/08, 2/27/08,3/3/08, 3/6/08, 3/14/08, 3/20/08, 4/1/08, 4/7/08, 4/7/08, 4/11/08, 4/14/08, 4/17/08, 4/18/08, 4/28/08, 5/10/08, 5/13/08, 5/20/08, 5/30/08, 6/4/08, 6/6/08, 6/13/08, 6/26/08, 7/21/08, 8/4/08, & 8/5/08**
Brand Name	**Promacta®**
Generic Name	**eltrombopag**
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OCP Division	**5**
OCP Briefing	**July 2, 2008**
ORM division	**OND/OODP/DMIHP**
Sponsor	**GlaxoSmithKline (GSK)**
Relevant IND(s)	**63,293**
Submission Type; Code	**NME, Priority Review, Orphan Status (5/5/08)**
Formulation; Strength(s)	**Oral Tablet; 25 mg and 50 mg**
Indication	**The treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.**

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1 Executive Summary

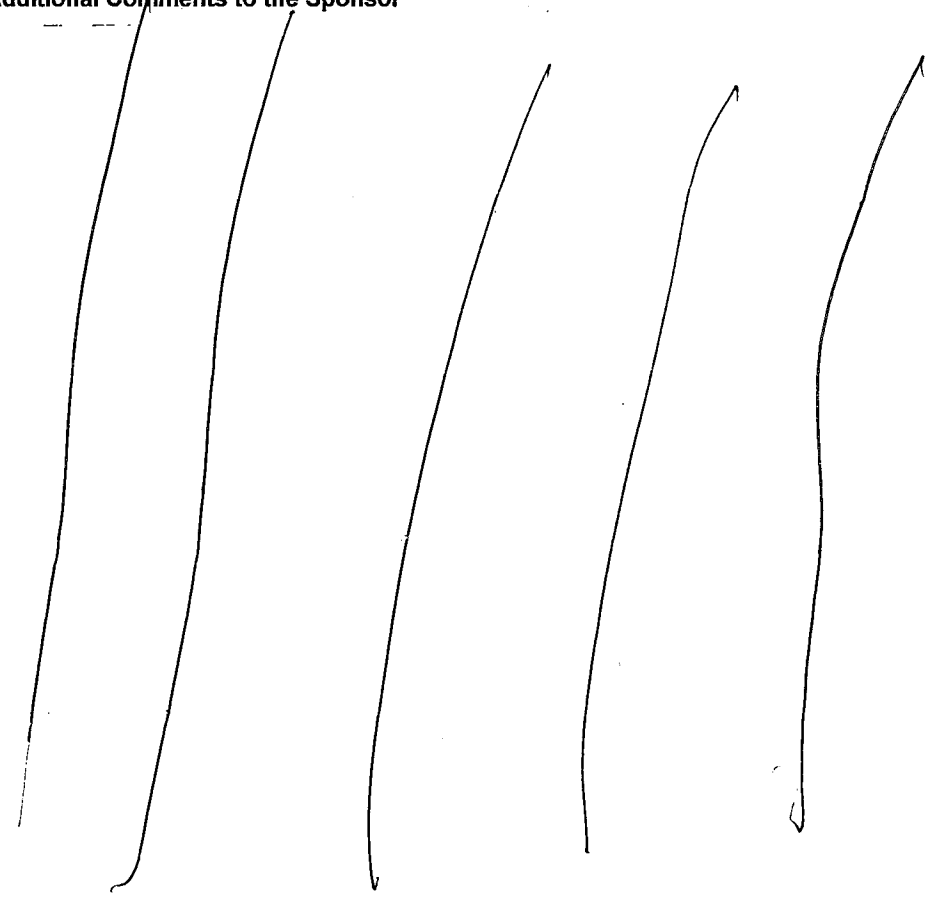
1.1 Recommendation

From a Clinical Pharmacology perspective, the application is ACCEPTABLE provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post Marketing Commitments

- None

1.3 Additional Comments to the Sponsor



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1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin receptor (TPO-R) agonist that interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag is being developed for the treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

A dose-dependent but highly variable increase in platelet count was observed following administration of eltrombopag for 5 to 10 days in all repeat-dose studies. The increase in platelet count reached a maximum two weeks after the initiation of dosing, and returned to baseline within approximately two weeks after the last dose of eltrombopag. The increase in platelet count in healthy subjects showed a trend toward greater increases in platelet count associated with higher AUC values; however, this was variable.

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

Similar to healthy subjects, the increase in platelet count for ITP patients peaked at approximately two weeks after the initiation of dosing and returned to baseline values within approximately two weeks after discontinuing eltrombopag. The increase in platelet count in the ITP population showed a trend toward greater increases in platelet count associated with higher AUC values; however, this was also highly variable. The magnitude of the platelet responses was markedly different in the two populations (healthy subjects 2-fold higher and the ITP population 5 to 50-fold higher) compared to the baseline count. The higher fold increase may, in part, reflect the lower baseline platelet counts in the ITP population.

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. No deaths were reported in any of the clinical pharmacology studies.

Pooled data from the two pivotal trials demonstrated that 16/164 (9.7%) of the subjects met FDA criteria for evaluation of hepatobiliary laboratory abnormalities (HBLA). Among eltrombopag-treated subjects (pivotal and supportive trials), a higher proportion of Asians (14/93 (15%)) experienced hepatobiliary laboratory abnormalities that met FDA criteria compared to Caucasian subjects (18/333 (5%)). Given the small sample size and the sparse pharmacokinetic sampling in these trails, a correlation between eltrombopag exposure and the incidence HBLA can not be determined. However, given the higher incidence of HBLA in the Asian population it can not be ruled out. Due to this issue and the increased exposure in seen some East Asian ITP patients discussed above, a reduced starting dose (e.g., 25 mg) should be considered.

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

Plasma eltrombopag AUC(0-∞) was 41% higher in subjects with mild hepatic impairment, and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy subjects. It is difficult to quantify the magnitude of this effect given the high variability in the data and the failure to report unbound eltrombopag (active) concentrations for this highly protein bound drug (liver disease can affect the protein binding of drugs). Given this increased exposure, a reduced starting dose (e.g., 25 mg) should be considered in subjects with moderate hepatic impairment and eltrombopag should be used with great caution in severe hepatic impairment.

There was a trend toward reduced plasma eltrombopag exposure in the interim analysis of data from subjects with varying degrees of renal impairment, but these data were inconclusive due to substantial variability as well as significant overlap in exposure between subjects with renal impairment and healthy subjects. In addition, the sponsor failed to report unbound eltrombopag (active) concentrations for this highly protein bound drug (renal disease can affect the protein binding of drugs). Close monitoring is recommended in patients with renal impairment.

Results of a thorough QTc study including model simulations suggest that eltrombopag will not have a clinically significant effect on QTc

A population-based pharmacokinetic model suggests that the pharmacokinetic profile for eltrombopag following oral administration is best described by a 2-compartment model with dual sequential first-order absorption and lag-time which highlights the complex absorption of this drug. Based on urinary excretion and biotransformation products eliminated in feces from healthy volunteers, the oral absorption of drug-related material following administration of a single 75mg oral solution dose was estimated to be at least 52%.

Following single-dose administration in healthy subjects, plasma eltrombopag concentrations were quantifiable within approximately 1 hour and peak concentrations occurred between 2 and 6 hours after oral administration of single and repeat doses of eltrombopag. Plasma eltrombopag exposure was significantly reduced by approximately 70% when coadministered with polyvalent cations (e.g., antacids, mineral supplements, and dairy products). A standard high-fat breakfast significantly decreased plasma eltrombopag AUC(0-∞) by approximately 59% and Cmax by 65% and delayed tmax by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure.

Plasma eltrombopag AUC(0-τ) increased in a dose proportional manner between 50 mg and 200 mg; Cmax increased in a dose proportional manner between 50 mg and 150 mg. A slightly greater than dose proportional increase was reported at lower eltrombopag doses. In healthy subjects, the plasma elimination half life of eltrombopag was approximately 21 to 32 hours. In healthy subjects receiving eltrombopag once daily (QD) for 10 days, the accumulation ratio (90% CI) was 1.44 (1.20, 1.63) for 50mg QD. Eltrombopag is highly (>99%) bound to human plasma proteins.

A mass balance study in healthy volunteers showed following a single 75mg dose (oral solution) of [14C]-eltrombopag, approximately 59% of the dose was recovered in feces (20% unchanged and 21% glutathione-related conjugates) and 31% was recovered in the urine (20% glucuronide of the phenypyrazole moiety). No unchanged eltrombopag was recovered in the urine. Samples from the circulation were comprised of the parent compound and metabolites (mono-oxygenation or glucuronidation). The concentration in blood cells was approximately 50-79% of plasma concentrations. *In vitro* studies suggest that CYP 1A2 and 2C8 are responsible for oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag. The glutathione conjugation pathway has yet to be fully characterized. Clinical studies evaluating the effect of strong inducers or inhibitors of these CYP and UGT enzymes responsible for the metabolism of eltrombopag have not been conducted.

Pre-clinical studies suggest eltrombopag is an inhibitor of CYP 2C8 & 2C9. However, a follow up clinical study using a "cocktail" approach in healthy volunteers showed eltrombopag did not inhibit or induce CYP 1A2, 2C19, 2C9, or 3A4. CYP 2C8 was not studied *in vivo*, but its *in vitro* potency for inhibition was similar to that for inhibition of CYP2C9. Both pre-clinical and clinical studies suggest eltrombopag also inhibits organic anion transporting polypeptide OATP1B1. In a clinical study of healthy volunteers, concurrent eltrombopag and rosuvastatin treatment resulted in a 2.03-fold increase in plasma rosuvastatin Cmax and 55% increase in AUC(0-∞). Pre-clinical studies using expressed human transporters suggest that eltrombopag is not a substrate for P-glycoprotein (Pgp) or OATP1B1.

In pre-clinical studies, eltrombopag was reported to be an inhibitor of UGT1A9, UGT1A3, UGT1A1, UGT2B15, UGT1A6, UGT2B7, and UGT1A4. Based on these *in vitro* data, eltrombopag inhibits UGT1A9 with the greatest potency. The effect of this inhibition was not studied clinically by the sponsor.

Eltrombopag tablets, 25 and 50 mg (each as the free acid) are film-coated immediate release debossed tablets proposed for commercialization. Early manufacturing experience of Eltrombopag tablets, 25 mg and 50 mg demonstrated that granulation is the critical manufacturing step that determines the physical properties of the granules and dissolution of the final product. An initial study of the relative bioequivalence of the 50 mg "phase 3" (commercial) tablet formulation compared to the "phase 2" tablet formulation showed a 15% reduction in exposure. A follow up study using a "Phase 2" tablet formulation made from a different substance batch demonstrated relative bioequivalence between the 50 mg tablets from the "phase 3" tablet formulation compared to the "phase 2" tablet formulation. Dose proportionality was not demonstrated between 25 mg and 50 mg commercial tablets. These differences are not likely to be clinically significant given the safety profile observed for the commercial product to date in Study TRA100773B and in the ongoing long-term studies

Signatures

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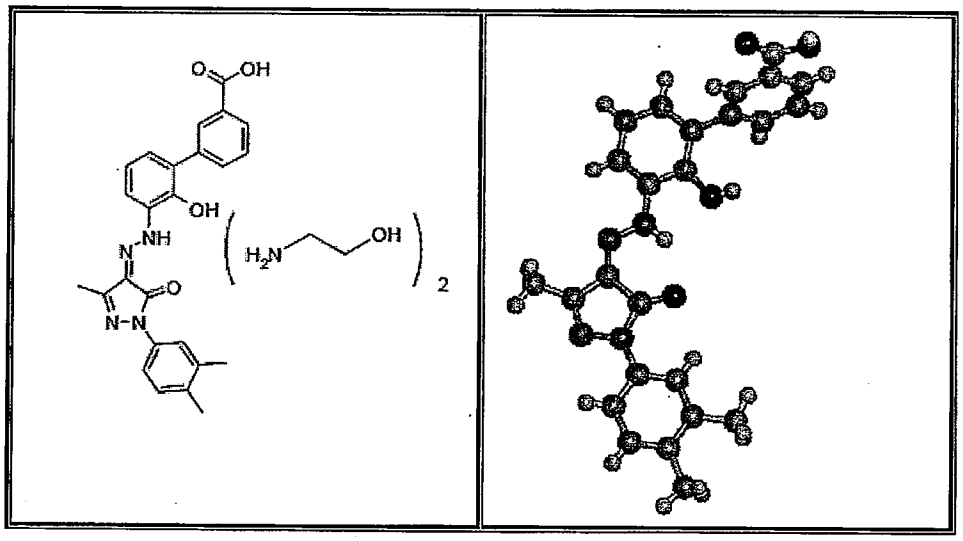
2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?



Established name: Eltrombopag olamine

Molecular Weight: 564.65

Molecular Formula: C_{25} H_{22} N_4 O_4. 2 (C_2 H_7 N O)

Chemical Name: 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2)

Description [redacted] b(4)

pKa: pKa1 = 4.06 (calculated), pKa2 = 9.57 (calculated), pKa3 = 11.88 (calculated)

Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

PROMACTA is supplied as 25 mg and 50 mg tablets. PROMACTA tablets contain eltrombopag olamine, the content of which is expressed as eltrombopag free acid. For additional information please see section 2.5

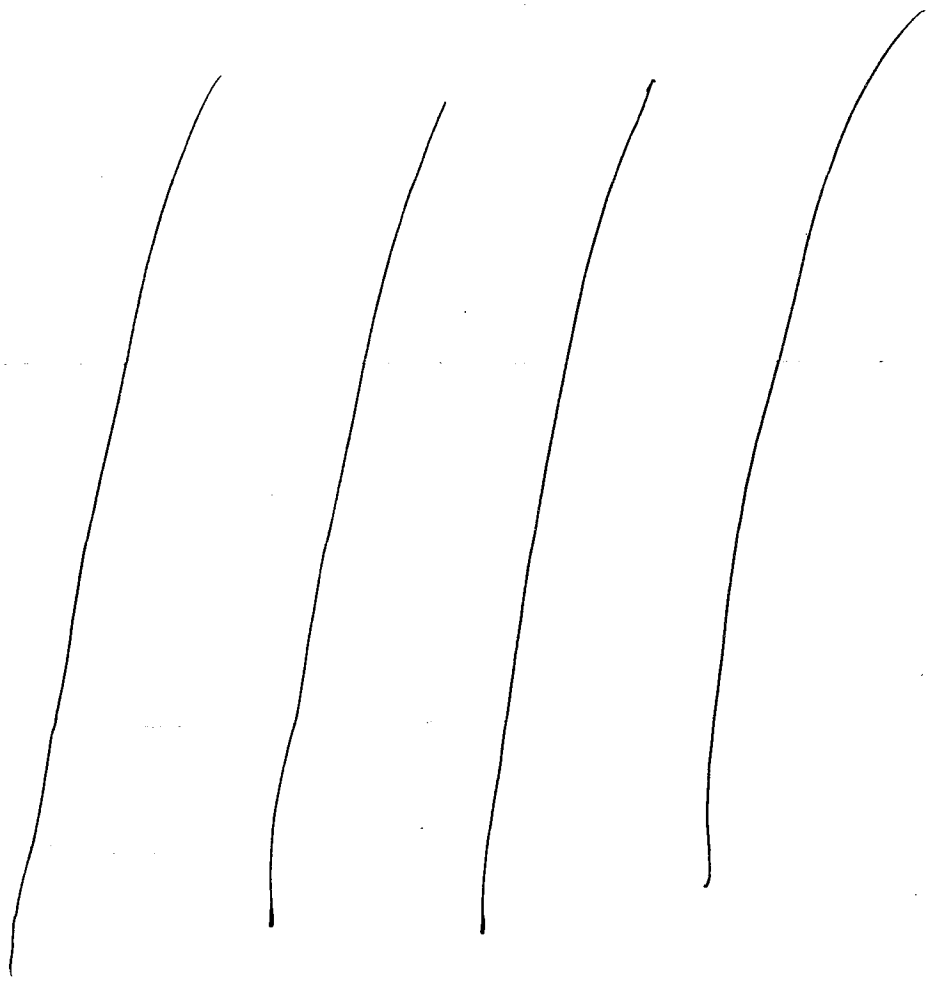
2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Thrombopoietin (TPO) is the main cytokine involved in the regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the thrombopoietin receptor (TPO-R). *In vitro* studies suggest that Eltrombopag is a thrombopoietin receptor agonist that interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades similar (but not identical) to that of endogenous TPO, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag is functionally different from TPO in that eltrombopag does not have the capacity to enhance ADP- or collagen-induced platelet

aggregation or activation. *In vitro*, human or chimpanzee platelets, but not platelets of other species such as mice or monkeys (cynomolgus), had STAT activation induced by eltrombopag.

The proposed therapeutic indication for PROMACTA 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.

2.1.3 What are the proposed dosage(s) and route(s) of administration?



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2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology and biopharmaceutics of eltrombopag is supported by sixteen clinical studies, three reports (ethnicity, pharmacogenomics, and population pharmacokinetic modeling) derived from these studies, and three supporting studies (i.e.,

safety) that do not support current indication. A description of the objectives and design each study is available in appendix 4.2.

Three studies evaluated the relative bioavailability and bioequivalence of eltrombopag capsule compared to tablet, R&D formulation versus commercial formulation, and dose proportionality between the 25 mg and 50 mg tablets. The effect of food was evaluated in two studies and the effect of antacids was evaluated in one study.

Four studies evaluated the single dose and two studies the repeat dose pharmacokinetics of eltrombopag in healthy volunteers. The pharmacokinetics of eltrombopag in healthy subjects was further investigated through the development of a population pharmacokinetic model. Three studies evaluated the pharmacodynamics of eltrombopag in healthy volunteers. One study included the effect of eltrombopag therapy on QTc. Mass balance and the characterization of major metabolites in healthy volunteers was evaluated in two studies.

The pharmacokinetics of eltrombopag in patients with ITP was evaluated through the development of a population pharmacokinetic model containing data from phase 2 and 3 studies in this population. The pharmacodynamics of eltrombopag was evaluated in the phase 2 and 3 studies.

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Intrinsic factors related to race and concurrent illnesses were evaluated in four studies and two reports. The effect of East Asian ethnicity on eltrombopag pharmacokinetics was evaluated in two studies (single dose and multiple dose) and two reports (ethnicity and pharmacogenomics). The effect of ethnicity was further investigated through the development of a population pharmacokinetic model. The effect of varying degrees of hepatic and renal (ongoing) disease was evaluated in two studies.

Extrinsic factors related to eltrombopag's inhibition potential for CYP 450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, or CYP3A4 (CYP2C8 not evaluated)) and human organic anion transporting polypeptide (OATP1B1) were evaluated in two clinical studies. Eltrombopag's inhibition of UGT1A9, UGT1A3, UGT1A1, UGT2B15, UGT1A6, UGT2B7, and UGT1A4 was not evaluated *in vitro,* but not *in vivo*. The effect of major inducers or inhibitors of CYP isoenzymes (CYP1A2 and CYP2C8) and UGT's (UGT1A1 and UGT1A3) responsible for the metabolism of eltrombopag in preclinical studies were not evaluated in clinical studies. Pre-clinical studies also report that eltrombopag is a weak activator of human PXR, is not a substrate of OATP1B1, and is not an inhibitor of substrate of human P-glycoprotein (Pgp). These were not further evaluated in clinical studies.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a chronically low peripheral blood platelet count (<150Gi/L). Persistently low platelet counts of <30Gi/L are associated with an increased incidence of spontaneous and induced bleeding, such as bruising, mucosal bleeding and intra-cranial hemorrhage.

Treatment guidelines suggest that treatment should be instituted for patients whose platelet counts are <30Gi/L. Short-term treatment may be necessary to raise platelet counts to a safe range (e.g., 50-400Gi/L) in patients with chronic ITP to manage a hemostatic challenge (e.g., a transient decrease in platelet count or normal disease fluctuation), or a bleeding episode that does not require emergency treatment. Additional scenarios where short-term treatment may be necessary are to raise platelets above a threshold required for a medical intervention or preventative procedure where bleeding is predictable (e.g., colonoscopy, surgical or dental procedures). The goal of short-term

treatment of chronic ITP is to elevate the platelet count for the duration of the hemostatic challenge (typically 2-3 weeks).

The primary efficacy endpoint for both pivotal studies was the proportion of subjects with a platelet count of ≥50Gi/L after up to 42 days of dosing (compared to a baseline count of <30Gi/L). This was considered a surrogate endpoint for bleeding risk in the ITP population.

The primary pharmacodynamic endpoint evaluated in clinical pharmacology studies was platelet count. Parameters evaluated based on platelet count include: maximum platelet count (p-Cmax), area under platelet count-time curve (p-AUC), observed time of maximum platelet count (p-Tmax), maximum change from baseline in platelet count (Δp-Cmax), maximum percent change from baseline in platelet count (%change p-Cmax), change from baseline in p-AUC (Δp-AUC), and percent change from baseline in p-AUC (%change p-AUC). Additional endpoints included reticulated platelet count, peripheral blood smear, platelet aggregation serum TPO levels, and surface biomarkers for platelet activation (P-Selectin and PAC-1).

These parameters were derived from blood sampling. Platelet counts were measured with an automatic cell counter (Direct current detection method). TPO was assayed by ELISA. Platelet activation was evaluated by flow cytometry for P-selectin and PAC-1 binding. Reticulated platelet count was determined by flow cytometry. Platelet aggregation was determined by using "currently approved analytical methods." Technical information regarding the development, validation, and reliability of these methods was not provided by the sponsor.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

For the most part active moieties in the plasma were appropriately identified using assays validated in a manner consistent with the guidance "Bioanalytical Method Validation" (see section 2.6). Several concerns were identified:

- Recovery was not reported as part of any assay method validation.
- Studies TRA104603 and TRA105580 (conducted in Japan) reported a significant number of concentrations above the upper limit of quantification for the assay used and may have been a source of systematic error which resulted in the significant variability noted in these studies (see study reviews in appendix section 4.3).
- Insufficient information was provided by the sponsor to evaluate the validity and reliability of radio-HPLC, LSC, LC/MS, LC/MS/MS, LC/NMR assays used in the mass balance (TRA 102861) and metaboloite characterization (05DMM155) studies (see study reviews in appendix section 4.3).

Where insufficient information is provided by the sponsor, the results were still included in this review is based on the sponsor's assurance regarding the appropriateness of these methods.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

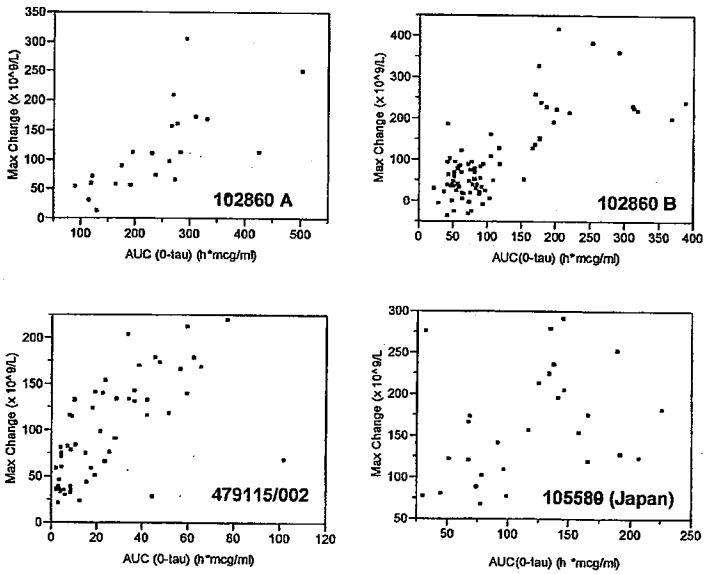
Following single dose oral administration of eltrombopag in healthy volunteers, platelet count did not increase (Study 497115/001, Study 497115/002, Study TRA105580 Study TRA104603). A variable dose/exposure-dependent increase in platelet counts were observed in three clinical pharmacology studies following repeat dose administration of

eltrombopag in healthy volunteers for five or ten days. Dosing for ten days had a greater impact on platelet response than dosing for five days (Table 1 & Figure 1). The increase in platelet count peaked approximately two weeks after the initiation of dosing, and returned to baseline within approximately another two weeks after dosing ceased. This is reasonably consistent with the timeframe for increased proliferation of normal marrow progenitor cells and differentiation of those progenitors into megakaryocytes.

Table 1: Summary of Maximum Change from Baseline in Platelet Count ($x10^9$/L) Following Repeat Dose Administration to Healthy Subjects

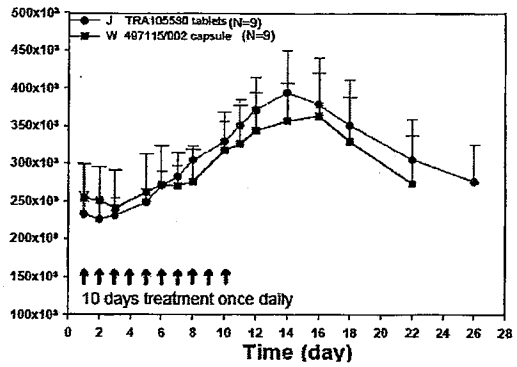
Eltrombopag Dose	Mean (SD)	Median (Range)
Study 497115/002 (10-days)		
Placebo (n=17)	47.9 (28.8)	44.0 (7, 117)
5mg (n=9)	44.7 (17.9)	37.0 (20, 80)
10mg (n=9)	65.2 (34.1)	70.0 (29, 115)
20mg (n=9)	60.7 (31.7)	57.0 (23, 122)
30mg (n=9)	104 (36.4)	98.0 (50, 152)
50mg (n=10)	143 (51.6)	140 (27, 211)
75mg (n=9)	152 (43.7)	168 (67, 219)
Study TRA105580 (10-days; in Japanese Subjects)		
Placebo (n=12)	27.8 (22.5)	27.5 (0, 78)
25mg (n=10)	126 (63.4)	111 (67, 275)
50mg (n=9)	165 (54.6)	174 (76, 225)
75mg (n=10)	184 (72.7)	168 (74, 290)
Study TRA102860—Part 1 (5-days)		
Placebo (n=6)	14.2 (22.5)	19.5 (- 25, 43)
100mg (n=10)	67.4 (26.2)	57.5 (29, 111)
150mg (n=9)	107 (51.8)	111 (12, 168)
200mg (n=8)	149 (99.3)	141 (36, 304)
Study TRA102860—Part 2 (5-days)		
Placebo (n=62)	16.3 (32.7)	8.0 (- 58, 96)
50mg (n=52)	47.5 (44.2)	46.0 (- 39, 182)
150mg (n=59)	110 (79.9)	116 (- 69, 256)

Figure 1: Maximum Change from Baseline in Platelet Count ($x10^9$/L) vs. AUC(0-tau). Following Repeat Dose Administration to Healthy Subjects



The PD response to eltrombopag was qualitatively similar in healthy East Asian (ancestry is of the countries of East Asia or Southeast Asia, such as Japan, China, Taiwan, and Korea) and Western subjects, with both the shape of the platelet count profile and the duration of response being comparable. However, at the same dose of eltrombopag, the absolute PD response was greater in healthy East Asian/Japanese subjects than healthy Western subjects (Figure 2). It is important to note that study 479115/002 used a capsule formulation that was not bioequivalent to the commercial formulation used in study 105580 (approximately 15-18% greater exposure with the capsule formulation). In addition, the exposure/response relationship (Figure 1) from study 105580 showed greater variability than study 479115/002 which may reflect systematic error related to the assay as discussed above. Despite this caveats, the magnitude of the difference in maximum change in platelet count from baseline was proportionally lower than the reported difference in systemic drug exposure based on race. The difference appears to be driven by systemic exposure to eltrombopag and not an inter-ethnic difference in the intrinsic response to a thrombopoeitin receptor agonist.

Figure 2: **Mean ± SD Platelet Counts Over Time Following Repeat Once Daily Dosing of 50mg Eltrombopag for 10 Days in Healthy Japanese (J) [TRA105580, Tablet] and Western (W) Subjects [497115/002, Capsule]**



Similar to healthy subjects, the increase in platelet count in the ITP population peaked at approximately two weeks after the initiation of dosing and returned to baseline values within approximately two weeks after discontinuing eltrombopag. The relationship between plasma eltrombopag AUC(0-τ) (based on exploratory population based pharmacokinetic (pop-pk) model predicted values) and platelet count at Week 2 is presented in subjects with ITP in Figure 3. As observed in healthy subjects, an exposure dependant, but variable, increase in platelet count was observed in ITP subjects. In addition, the magnitude of the responses were markedly different in the two populations. Healthy subjects showed a maximal increase in platelet count up to 2-fold higher than baseline while many of the ITP population showed maximal changes in platelet count 5 to 50-fold higher than the baseline count. As the maximal absolute platelet counts were no higher in the ITP population than in the healthy subjects, the higher fold increase may, in part, reflect the lower baseline platelet counts in the ITP population.

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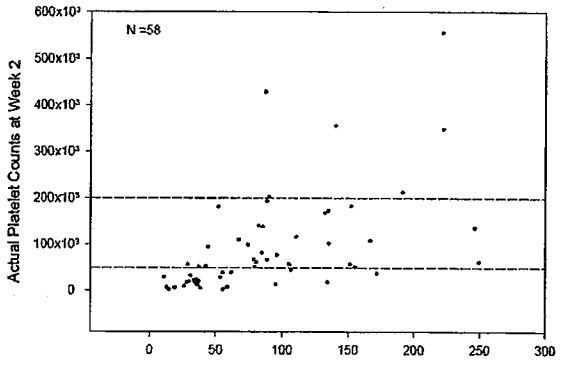
Figure 3: **Eltrombopag AUC(0-τ) vs Actual Platelet Count in ITP Subjects at Week 2 in Studies TRA100773A and TRA100773B. ***



After up to 6 weeks of treatment in pivotal trial TRA100773A, a dose-dependent increase in the proportion of ITP subjects meeting the primary response criteria was observed: placebo (11%), eltrombopag 30mg (28%), eltrombopag 50mg (70%) and eltrombopag 75mg (81%) was observed. In addition, pivotal trial TRA100773B reported that the percentage of responders after up to 6 weeks of dosing was significantly greater with eltrombopag as compared to placebo (59% versus 16%; $p<0.001$). During the course of the study, 46% of the patients increased their initial dose of eltrombopag from 50 mg QD to 75mg QD. An exploratory analysis of the primary efficacy response in East Asian versus Caucasian ITP patients does not suggest a substantive difference in response at the recommended starting dose of 50 mg daily (Table 2).

Table 2: Responders by Race at the Day 43 Visit (Efficacy Population) in Pivotal Trials

Race Category	TRA100773A Treatment Group				TRA100773B Treatment Group	
	PBO N=27	75mg N=26	30mg N=29	50mg N=27	PBO N=38	Eltrombopag 50 /75 mg N=74
East Asian						
n	2	2	1	7	1	0
Responders, n (%)	0	2 (100)	1 (100)	3 (42.9)	0	0
Dose increase n (%)					1 (100%)	0 (0%)
South-East Asian						
n	0	1	3	4	3	7
Responders, n (%)	0	1 (100)	2 (66.7)	3 (75)	1 (33.3)	3 (42.9)
Dose increase n (%)					3 (100%)	2 (29%)
White/Caucasian/European						
n	19	18	23	13	22	51
Responders, n (%)	2 (10.5)	14 (77.8)	5 (21.7)	10 (76.9)	3 (13.6)	32 (62.8)
Dose increase n (%)					16 (73%)	25 (49%)

An exploratory analysis of the primary efficacy response in males versus female ITP patients does not suggest a substantive difference in response despite the lower clearance in females predicted by the pop-pk model. In addition, an exploratory analysis of the primary efficacy response in ITP patients greater than 65 years of age does not suggest a substantive difference in response.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

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 (Table 3). No deaths were reported in any of the clinical pharmacology studies.

Table 3: Overall Summary of Subjects with Adverse Events During the Entire Study in TRA100773A

	TRA100773A			
	Placebo N=29	30mgN=30	50mgN=30	75mgN=28
Any AE, n (%),	18 (62)	20 (67)	17 (57)	19 (68)
Any SAE, n (%)	4 (14)	1 (3)	6 (20)	2 (7)
Any drug-related AE, n (%)	11 (38)	10 (33)	8 (27)	10 (36)
Any AE leading to withdrawal, n (%)	3 (10)	0	2 (7)	1 (4)
Any SAE leading to withdrawal, n (%)	2 (7)	0	1 (3)	0

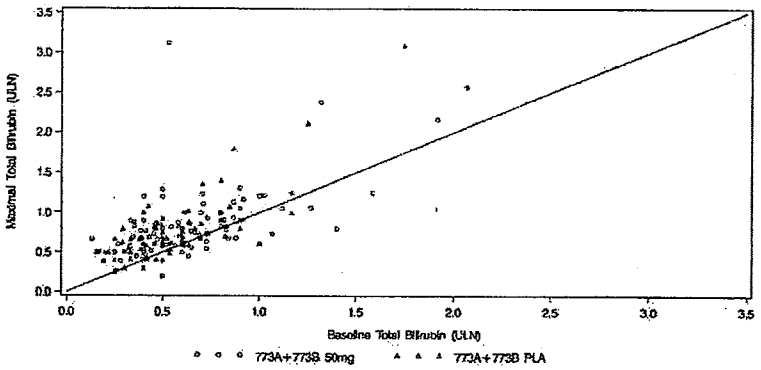
The most common adverse events (AEs) from the two pivotal trials are listed in Table 4. This is consistent with the incidence and type of common AEs in eltrombopag-treated subjects in the clinical pharmacology studies (e.g., headache, dizziness, somnolence, fatigue, nasopharyngitis, abdominal pain, and nausea). Serious AE's reported in the pivotal trials include bleeding, hepatobiliary events, pulmonary embolism, renal impairment, anemia, cataract, and reticulin bone marrow. There were no racial differences in the overall incidence of AEs, drug-related AEs, SAEs or AEs leading to withdrawal between the Caucasian and East Asian populations. There was no apparent racial difference in the maximum toxicity of AEs reported. The incidence of adverse reactions was slightly higher in patients 65 to 74 years of age (77%) who were treated with eltrombopag than in 18 to 49 year (61%) and in 50 to 64 year (67%) age groups.

Table 4: Summary of Subjects with Adverse Events Greater than or Equal to 5% Total Incidence in Either Treatment Group During the Entire Study in Both Pivotal Studies (Pooled Data)

Preferred Term	773A + 773B	
	Placebo N=67	50mg 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)
Diarrhea	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)

Most hepatobiliary assessments in the pivotal trials were Grades 0 to 1 during treatment. In the 50mg treatment group, a higher percentage of Grade 1 values (14%) for bilirubin was observed compared to placebo (8%) (Figure 4) which may reflect, in part, eltrombopag's inhibition of UGT1A1 which is responsible for the conjugation of bilirubin in the body.

Figure 4: Maximum Bilirubin vs. Baseline Value by Subject in Both Pivotal Trials



A different pattern regarding ALT elevations, AST elevations and hyperbilirubinemia occurring was noted in the Asian population with an incidence of 12%, 10% and 6%, respectively. In contrast, these AEs occurred in <5% of the Caucasian subjects. Pooled data from the two pivotal trials demonstrated that 16/164 (9.7%) of the subjects met FDA criteria for assessment of hepatobiliary laboratory abnormalities (HBLA). Among eltrombopag-treated subjects (pivotal and supportive trials), a higher proportion of Asians experienced hepatobiliary laboratory abnormalities that met FDA criteria compared to Caucasian subjects (Table 5). Given the small sample size and the sparse pharmacokinetic sampling in these trails, a correlation between eltrombopag exposure and the incidence HBLA can not be determined. Further, it is not clear whether this increased incidence of HBLA is the result of increased exposure or another, possibly genetic, predisposition in this ethnic group. However, given the higher incidence (Table 5) of HBLA in the Asian population it can not be ruled out. Given this issue and the increased exposure in seen some East Asian ITP patients, a reduced starting dose (e.g., 25 mg) should be considered.

Table 5: Proportion of Subjects with Hepatobiliary Abnormalities that Met the FDA Criteria by Ethnicity.

Studies	Race	# Subjects (eltrombopag treated)	No. (%) of subjects with hepatobiliary abnormalities
TRA100773A	Asian	19	3 (15.8%)
	White	59	6 (10.2%)
TRA100773B	Asian	12	2 (16.7%)
	White	53	4 (7.5%)
EXTEND	Asian	24	5 (20.8%)
	White	67	3 (4.5%)
REPEAT	Asian	10	0
	White	47	0
RAISE	Asian	28	4 (14.3%)
	White	107	5 (4.7%)

A dose dependent increase in the number and percentage of ITP subjects in each treatment group of pivotal trial 100773A who were at risk for thrombocytosis (i.e., a platelet count >200Gi/L) was observed. This relationship was not as apparent for subjects who achieved a platelet count >400Gi/L, but the sample size was smaller. The East Asian population showed a greater proportion of ITP subjects at risk for thrombocytosis compared to Caucasians and all subjects in pivotal study 100773A (Table 6)).

Table 6: Subjects at Risk for Thrombocytosis in Study 100773A (ITT Population)

	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
Subjects with platelets >200Gi/L	1 (3.4%)	6 (20%)	12 (40%)	14 (50%)
Asian (n=21)	0	0	6/12 (50%)	3/3 (100%)
Caucasian (n=79)	1/20 (5%)	6/24 (25%)	4/15 (26.7%)	8/20 (40%)
Subjects with platelets >400Gi/L	1 (3.4%)	1 (3%)	6 (20%)	5 (17.9%)
Asian (n=21)	0	0	3/12 (25%)	0
Caucasian (n=79)	1/20 (5%)	1/24 (4.1%)	2/15 (16.3%)	3/20 (15%)

2.2.4.3 Does this drug prolong the QT or QTc interval?

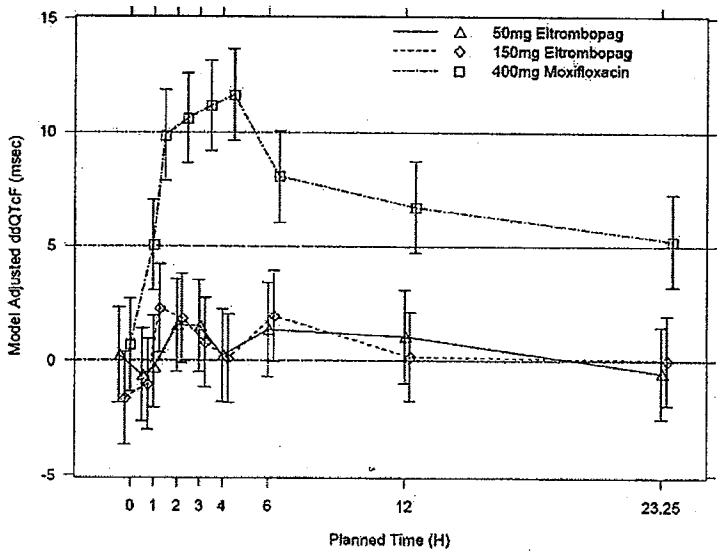
The following is the primary reviewer's assessment:

A thorough QTc study (TRA102860) investigated the potential for eltrombopag to increase the QTc interval. A total of 87 healthy subjects were enrolled in the QT study and 62 subjects were included in the analysis of QTc. Plasma eltrombopag concentrations included in the analysis ranged from 0.224 - 12.2 µg/mL for the 50mg dose and from 0.841 - 31.4 µg/mL for the 150 mg dose. Although this design is acceptable, it is important to note that the supratherapeutic dose might not fully cover the range of exposures that can be achieved with a 75 mg QD dose given the effect of intrinsic factors such as hepatic impairment and race on exposure.

Eltrombopag was shown to have a minimal effect on cardiac repolarization. The upper limits of the 90% CI for the mean ddQTcF were below 10 msec at all time points for both 50mg and 150mg doses. Assay sensitivity was established as moxifloxacin prolonged the QT interval by 10 to 11 msec at 2 to 4 hours, in comparison to placebo, and the lower limits of the 90% CI were greater than 5 msec for at least one time point. Similar results were observed for QTcB and QTci.

Mean model-adjusted ddQTcF (ANCOVA) over time showed slight fluctuations in QTcF after treatment with eltrombopag, and a clear time-dependent increase and decrease after treatment with moxifloxacin (Figure 6).

Figure 6: Model Adjusted ddQTcF (msec) Over Time From Study TRA102860



A population based plasma drug concentration (Cp)-ddQTcF modeling approach was applied using the non-linear mixed effects modeling. The final model was a linear model with no delay in the effect of concentration on ddQTcF; fixed effects for pre-dose ddQTcF on Day 5 (intercept, $\Theta 1$) and the slope relating plasma eltrombopag concentration to ddQTcF ($\Theta 2$) were included, along with inter-individual variability and inter-occasion variability (TRT1=50mg and TRT2=150mg) for both fixed effects, and additive random residual variability, as defined by the following equation:
$ddQTcF=\Theta 1+\eta 1+TRT1*\eta 3+TRT2*\eta 4 + (\Theta 2+\eta 2 +TRT1*\eta 5+TRT2*\eta 6)*Cp + \varepsilon 1$ (see individual study review in Appendix section 4.3). The stability of the model parameter estimates for ddQTcF versus plasma eltrombopag concentration was examined using the bootstrap techniques. The covariates BMI and sex were added into the final model.

The slope of eltrombopag effect on ddQTc was slight, with a model predicted value of 0.120 msec/µg/mL. The 90% CI obtained from the bootstrap analysis for the slope estimate (-0.014 to 0.244 msec/µg/mL) contained zero.

Based on the final Cp-ddQTcF model, simulations were performed to predict ddQTcF at Cmax for therapeutic and supratherapeutic plasma eltrombopag concentrations (at Cmax). Simulations were performed to predict the mean (90% CI) ddQTc 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 ddQTcF at concentrations predicted for a dose of 300 mg QD.

The reviewer's assessment was consistent with the Interdisciplinary Review Team consult (see Section 4.4) received on 5/15/08.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dosing regimen selected by the sponsor is consistent with the known relationship between dose-concentration-response as described below. The only unresolved dosing issue relates to the appropriate dose for patients with moderate or severe hepatic impairment which is described in detail in section 2.3.1.

Phase 1 dose ranging studies in healthy volunteers report that following repeat dose administration, plasma eltrombopag AUC(0-τ) and Cmax increased with increasing dose over the range of 50 mg to 150 mg QD. A slightly greater than dose proportional increase was reported at lower eltrombopag doses. As stated above, a dose/exposure-dependent but variable increase in platelet counts were observed in three clinical pharmacology studies following repeat dose administration of eltrombopag in healthy volunteers for five or ten days (see section 2.2.4.1).

In healthy subjects, the plasma elimination half life of eltrombopag was approximately 21 to 32 hours. Given the proposed daily dosing some accumulation is expected. In healthy subjects receiving eltrombopag once daily (QD) for 10 days, the accumulation ratio (90% CI) was 1.44 (1.20, 1.63) for 50mg QD.

Given the pharmacokinetic/pharmacodynamic response reported in the repeat dosing healthy volunteer studies, a randomized, double-blind, placebo-controlled, dose-ranging (eltrombopag 30mg, 50mg and 75mg) Phase 2 study (TRA100773A) was performed in 118 adults with chronic ITP and platelets <30Gi/L. A dose dependent increase in the proportion of responders, as defined in section 2.2.2, was observed: placebo (PBO) (11%), 30mg (28%), 50mg (70%) and 75mg (81%). The odds-ratio of treatment response to PBO was statistically significant in the 50mg and 75mg arms ($p<0.001$). While a dose dependent increase is AEs was not noted, platelet counts rose to ≥200Gi/L while on study medication in 4%, 14%, 37% and 50% of subjects who received placebo, eltrombopag 30mg, 50mg and 75mg, respectively.

Based on this phase 2 study, a phase 3 study (TRA100773B) was designed to assess the efficacy, safety, tolerability and pharmacokinetics of once daily oral administration of eltrombopag 50mg (with dose increase permitted to 75mg) or matching placebo in subjects with chronic idiopathic thrombocytopenic purpura (ITP) who had either failed or relapsed after at least one prior ITP therapy and had baseline platelet counts <30 Gi/L. Analysis of the primary endpoint confirmed that eltrombopag increases platelet counts in subjects with relapsed or refractory chronic ITP: 16.2% (6/37) of subjects on PBO and 58.9% (43/73) of subjects on eltrombopag achieved a platelet count of ≥50Gi/L on Day 43. More subjects (69%) in the PBO treatment group required a dose increase at the Day 22 visit compared to the eltrombopag treatment group (39%). Conversely, more subjects in the eltrombopag treatment group (11/35 (31%)) responded after having their dose increased, compared to the PBO treatment group (3/28 (11%)).

The appropriateness of the sponsor's proposal

nas not been thoroughly investigated.

b(4)

Given the concerns regarding a possible higher incidence of hepatobiliary abnormalities in the East Asian population and a projected ~70% increase in eltrombopag exposure in some East Asian ITP subjects, based on pop-pk model estimates, the recommended dose reduction to 25 mg QD with the option to titrate up to 50 mg in ?— weeks is reasonable until more is known about the etiology of this anomaly.

b(4)

b(5)

2.2.5 PK characteristics of the drug and its major metabolite

2.2.5.1 What are the single dose and multiple dose PK parameters?

Following single dose administration, plasma eltrombopag concentrations were quantifiable within approximately 1 hour; peak concentrations occurred between 2 and 6 hours after oral administration of single and repeat doses of eltrombopag. Following single dose administration of low doses ranging from 3 mg to 9 mg, plasma eltrombopag AUC(0-∞) and Cmax increased in a greater than dose proportional manner. Following single dose administration, plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner over the dose range of 5 mg to 75 mg and between 25 mg and 50 mg.

Plasma eltrombopag AUC and Cmax increased with increasing dose and the evaluation of proportionality was dose dependent. Following single dose administration of low doses ranging from 3mg to 9mg, plasma eltrombopag AUC(0-∞) and Cmax increased in a greater than dose proportional manner. Following single dose administration, plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner over the dose range of 5 mg to 75 mg and between 25 mg and 50 mg. Following repeat dosing using therapeutic and supra-therapeutic doses, plasma eltrombopag AUC(0-τ) and Cmax increased in a dose proportional manner between 50mg and 150mg

QD; proportional increases in plasma eltrombopag AUC(0-τ) were observed at 200mg QD, but Cmax values did not increase beyond 150mg QD.

In healthy subjects receiving eltrombopag QD for 10 days, the accumulation ratio (90% CI) was 1.41 (1.20, 1.63) for 50mg QD and 1.56 (1.23, 1.97) for 75mg QD. Eltrombopag demonstrated time-invariant PK over the dose range of 5mg to 75mg administered QD for 10 days.

Plasma eltrombopag t1/2 values were dependent on the duration of PK sampling; longer t1/2 estimates were obtained with longer sampling duration. Based on studies that sampled for at least 120 hours after single dose administration, the plasma elimination half-life of eltrombopag in healthy subjects was approximately 21 to 32 hours.

Between-subject variability (%CVb) in AUC and Cmax was generally between 30 and 40% in single and repeat dose healthy volunteer studies.

Study 497115/001 evaluated plasma eltrombopag PK following administration of single escalating doses of 3 mg, 6 mg, and 9 mg to healthy adult male subjects. Plasma PK samples were collected over 72 hours after single dose administration. This study used eltrombopag granules that were put into capsules at the clinical study site pharmacy. A total of 18 subjects received eltrombopag (six subjects at each dose) and six subjects received placebo.

Plasma eltrombopag concentrations were quantifiable within 1 to 1.5 hours across the doses and remained quantifiable in all subjects through 24 hours for the 3mg dose, 32 hours for the 6mg dose, and 72 hours for the 9mg dose (Table 7). Plasma eltrombopag AUC(0-∞) and Cmax increased in a greater than dose proportional manner where the slope estimate (90% CI) was 1.51 (1.14, 1.88) for AUC(0-∞) and 1.68 (1.39, 1.97) for Cmax over a range of 3mg to 9mg.

Table 7: Selected PK parameters from Study 497115/001

Plasma PK Parameter	3 mg (n=6)	6 mg (n=6)	9 mg (n=6)
AUC(0-∞)(ng.hr/mL) geometric mean (min, max) [Cvb%]	2424 (1646, 3934) [33.3]	6272 (3539, 10188) [44.5]	13033 (8926, 18000) [26.3]
AUC(0-t) (ng.h/mL) geometric mean (min, max) [Cvb%]	2148 (1482, 3638) [34]	5913 (3290, 9692) [46.3]	12538 (8686, 16876) [25.1]
Cmax (ng/mL) geometric mean (min, max) [Cvb%]	167 (134, 299) [30.7]	484 (332, 708) [27.3]	1083 (849, 1459) [22.4]
Tmax (hours) median (min, max)	3.5 (2.0, 6.0)	3.0 (1.5, 4.0)	3.0 (2.0, 4.0)
t1/2 (hours) Mean (SD) median (min, max)	13.3 (4.81) 14.1 (6.4, 18.7)	14.9 (3.65) 14.5 (9.7, 19.4)	17.3 (2.95) 15.9 (15.3, 22.9)

Study 497115/002 evaluated plasma eltrombopag PK following administration of both single and repeat escalating doses of 5 mg, 10 mg, 20 mg, 30 mg, 50 mg, and 75 mg to healthy adult subjects. Plasma PK samples were collected over 48 hours after single dose administration and over the 24-hour dosing interval at steady-state. This study used eltrombopag capsules of 5 mg and 25 mg strengths. Seventy-three subjects were enrolled in the dose escalation phase of the study. All subjects were male and predominantly Caucasian (92%).

Following single dose administration, plasma eltrombopag concentrations were quantifiable within 1 hour and remained quantifiable through the 48-hour sampling period (Table 8). Plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.13 (1.04, 1.22) for AUC(0-∞) and 1.15 (1.07, 1.24) for Cmax over a range of 5 mg to 75mg.

Following repeat dose administration, plasma eltrombopag AUC(0-τ) and Cmax increased in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.19 (1.11, 1.26) for AUC(0-τ) and 1.20 (1.12, 1.27) for Cmax over a range

of 5mg to 75mg QD. However, when doses greater than 20 mg were evaluated there was a trend toward dose proportionality (see section 2.2.5.8). A similar tend was noted for the evaluation of steady state.

Following QD dosing, geometric least squares (GLS) mean ratio (90% CI) estimates of Day 10 to Day 1 AUC(0-τ) were; 5mg: 1.15 (0.91, 1.45), 10mg: 1.26 (0.987, 1.61), 20mg: 1.38 (1.17, 1.62), 30mg: 1.37 (1.20, 1.56), 50mg: 1.41 (1.20, 1.64), and 75mg: 1.56 (1.23, 1.97). Accumulation was noted for the 20, 30, 50, and 75 mg cohorts. GLS mean ratios of Day 10 to Day 1 Cmax indicated no significant accumulation across all doses except for, the 20 mg dose cohort . Cmax point estimates ranged from 1.05 to 1.21.

Ratios of Day 10 AUC(0-τ) to Day 1 AUC(0-∞), presented as GLS mean ratio (90% CI), indicate that plasma eltrombopag PK was time invariant for 5mg: 0.941 (0.755, 1.17), 10mg: 0.880 (0.719, 1.08), 20mg: 1.03 (0.862, 1.23), 30mg: 0.996 (0.874, 1.14), 50mg: 0.994 (0.826, 1.20), and 75mg: 1.10 (0.854, 1.42).

Table 8: Selected PK parameters from Study 497115/002

Dose (mg)	Day	tmax (h) [c]	Cmax (µg /mL) [b]	t1/2 (h) [b]	AUC(0-τ) (µg.h/ mL) [b]	AUC(0-∞) (µg.h/ mL) [b]
5	1	2.50 (2–4)	0.318 (25)	10.13 (36)	2.98 (30)	3.65 (35)
	10	4.00 (2–6)	0.333 (24)	8.63 (17)	3.44 (30)	
10	1	3.00 (2–6)	0.625 (32)	16.14 (27)	6.08 (30)	8.72 (35)
	10	3.00 (2–6)	0.700 (32)	12.48 (48)	7.67 (34)	
20	1	3.00 (2–6)	1.27 (28)	14.70 (21)	12.17 (31)	16.31 (41)
	10	4.00 (2–6)	1.53 (36)	12.65 (26)	16.80 (37)	
30	1	2.50 (1.5–4)	2.64 (31)	15.69 (11)	21.21 (27)	29.10 (28)
	10	3.00 (2–4)	2.97 (25)	12.30 (15)	28.99 (28)	
50	1	3.00 (2–4)	4.90 (34)	17.96 (17)	40.84 (32)	57.77 (34)
	10	4.00 (2–6)	5.76 (29)	12.90 (12)	57.43 (28)	
75	1	4.00 (2.1–6)	6.03 (30)	16.05 (35)	50.72 (28)	71.84 (37)
	10	5.00 (2–10)	7.27 (15)	14.40 (49)	79.03 (23)	

a. median (range), n=9 (except n=8 for the 30 mg and 75 mg doses on Days 1 and 10).
b. geometric mean (CV%), n=9 (except n=8 for the 30 mg and 75 mg doses on Days 1 and 10).

This study was limited by the following issues: 1) Greater than 50% of the subjects studied had AUCext > 10%, 2) A pre-dose (time 0) sample was not collected prior to beginning session two so the potential for carryover from session one could not be assessed, 3) Sample size was based on the pharmacodynamic outcome so it can not be assumed that the analysis of accumulation and invariance were adequately powered, and 4) 16% of the plasma concentration samples were above the HLQ for the assay.

Study TRA105122 was a pivotal, Phase I, open-label, randomized, two-period, incomplete crossover study designed to demonstrate bioequivalence between eltrombopag oral film-coated tablets administered in the pivotal Phase II study TRA100773A and pivotal Phase III study TRA100773B. In addition, comparisons were made between 25 mg and 50 mg tablet strengths to assess dose proportionality. Consistent with the results of Study 497115/002, which assessed dose proportionality over the dose range of 5 mg to 75 mg, plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner between 25 mg and 50 mg in Study TRA105122. See section 2.5.2.2 for a more detailed description of this study.

As presented earlier, study TRA102860 investigated the potential for eltrombopag to increase the QTc interval. In addition PK was evaluated. Part 1 of this study was a double-blind, placebo-controlled, randomized, parallel, repeat dose escalation study designed to determine maximum eltrombopag doses that could be safely administered to healthy adult subjects. Eltrombopag doses of 100 mg, 150 mg, and 200 mg were administered QD for 5 days; plasma PK samples were collected over 24 hours after single dose administration on Day 1 and after repeat dose administration on Day 5. Part 2 of the study was a double-blind, placebo and active (moxifloxacin) controlled, randomized, balanced crossover study designed to evaluate the impact of standard and high doses of eltrombopag on the QTc interval. Eltrombopag doses of 50 mg and 150 mg were administered QD for 5 days; plasma PK samples were collected over 24 hours following repeat dose administration on Day 5. There was a washout of at least 14 days between each treatment period. Both part 1 and part 2 of this study used eltrombopag 50mg tablets. Thirty-three subjects were enrolled in part 1 and 87 in part 2 of the study.

Plasma eltrombopag PK parameters following single and repeat dose administration in Part 1 & Part 2 are summarized in Table 9. Between doses of 100 mg and 200 mg in part 1 of the study, AUC(0-τ) increased with increasing dose; whereas, there did not appear to be a further increase in Cmax beyond 150 mg. The dose proportionality slope estimate (90% CI) was 0.92 (0.45, 1.39) for AUC(0-τ) and 0.76 (0.29, 1.22) for Cmax over a range of 100 mg to 200 mg QD. Statistically significant accumulation in AUC(0-τ) was observed for all three doses in part 1 between Day 1 and Day 5; GLS mean ratio (90% CI) estimates were for 100 mg: 1.66 (1.35, 2.04), 150 mg: 1.69 (1.39, 2.05), and 200 mg: 1.81 (1.30, 2.52). GLS mean ratio (90% CI) estimates for Cmax were for 100mg: 1.45 (1.15, 1.83), 150mg: 1.32 (0.984, 1.77), and 200mg: 1.35 (0.975, 1.88).

Following repeat dosing in Part 2 of the study, plasma eltrombopag AUC(0-τ) and Cmax increased in a dose proportional manner between 50mg and 150mg, where the slope estimate (90% CI) was 1.04 (0.987, 1.09) for AUC(0-τ) and 1.01 (0.942, 1.08) for Cmax.

Table 9: Summary of Plasma Eltrombopag PK Parameters

Day	Dose (mg)	N	AUC (0-τ) (µg hr/mL)	Cmax (µg/mL)	tmax (h)
Part 1					
1	100	8	97 (79, 119) [25.0]	10.3 (8.3, 12.8) [26.2]	3.50 (2.00, 6.00)
	150	8	142 (104, 193) [38.6]	17.3 (12.4, 24.1) [41.5]	2.28 (1.50, 6.00)
	200	7	167 (121, 231) [36.2]	18.3 (11.6, 28.8) [52.3]	4.00 (2.50, 4.00)
5	100	8	161 (116, 222) [40.0]	14.9 (10.9, 20.4) [38.7]	3.01 (2.50, 4.00)
	150	8	239 (187, 304) [29.6]	22.8 (18.2, 28.5) [27.3]	2.75 (1.50, 4.00)
	200	7	302 (198, 463) [48.5]	24.8 (16.2, 37.7) [48.1]	2.50 (2.50, 3.00)
Part 2					
5	50	60	65.4 (59.7, 71.6) [36.4]	6.40 (5.87, 6.97) [34.2]	3.19 (2.17, 6.22)
	150	73	204 (186, 223) [39.3]	19.0 (17.4, 20.6) [37.5]	2.67 (1.67, 6.20)

Data presented as geometric mean (95% CI) [%CVb], except tmax presented as median (minimum-maximum)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK of eltrombopag was studied in subjects with ITP in Studies TRA100773A and TRA100773B. Study TRA100773A was a randomized, double-blind, placebo controlled, dose ranging study to investigate the safety, efficacy, and PK of eltrombopag administered as 30mg, 50mg, and 75mg QD for up to six weeks in adult subjects with ITP. One-hundred-seventeen subjects received study drug (eltrombopag [N=88] or placebo [N=29]). Seventy-three subjects (62%) were female and 44 (38%) were male, 79 (68%) were White of European descent, 14 (12%) were White of Arabic/North African descent, 13 (11%) were East Asian, 8 (7%) were Southeast Asian, 2 (2%) were Black, and 1 (<1%) was mixed race. Median (range) age was 50 years (18 to 85 years). Overall,

38 subjects (32%) were receiving other ITP medication at randomization, 55 (47%) had prior splenectomy, and 56 (48%) had baseline platelet counts of <15,000/μL.

Plasma eltrombopag PK profiles consisting of six samples collected at 1, 2, 4, 6, 8, and 24 hours after a single dose (Day 1) and seven samples collected at 0, 1, 2, 4, 6, 8, and 24 hours after repeat doses were collected in five subjects: one subject receiving 30mg, two subjects receiving 50mg, and two subjects receiving 75mg. In addition, 1 to 6 plasma PK samples were collected from each of an additional 77 subjects. A total of 404 samples from TRA100773A were available for population PK analysis.

Study TRA100773B was a randomized, double-blind, placebo-controlled, study to investigate the safety and efficacy of eltrombopag 50mg QD administered for up to six weeks in adult subjects with ITP. Subjects were permitted to increase the dose to 75mg QD after three weeks of dosing if platelet counts had not reached ≥50,000/μL. One hundred- fourteen subjects received study drug (eltrombopag [N=76] and placebo [N=38]). Seventy subjects (61%) were female and 44 (39%) were male, 76 (67%) were White of European descent, 8 (7%) were White of Arabic/North African descent, 10 (9%) were Southeast Asian, 9 (8%) were Central/South Asian, 1 (<1%) was East Asian, 1 (<1%) was Black, 6 (5%) were American Indian/Alaskan Native, and 3 (3%) were mixed race. Median (range) age was 48 years (19 to 84 years). Overall, 49 subjects (43%) were receiving other ITP medication at randomization, 45 (39%) had a prior splenectomy, and 55 (48%) had baseline platelet counts of <15,000/μL.

Plasma eltrombopag PK profiles consisting of six samples collected at 1, 2, 4, 6, 8, and 24 hours after a single dose (Day 1) and seven samples collected at 0, 1, 2, 4, 6, 8, and 24 hours after repeat doses were collected in five subjects receiving 50mg. A total of 62 samples from TRA100773B were available for population PK analysis.

The plasma eltrombopag concentration-time data collected in subjects with ITP in TRA100773A and TRA100773B were combined with data from healthy adult subjects in a pop-PK analysis. The pop-PK model was developed using eltrombopag concentration-time data, dosing regimens/records, demographics and covariate data that were combined from three Phase 1 and two Phase 2 eltrombopag clinical studies. The population PK model was built using a non-linear mixed-effect modeling approach. The first order conditional estimation method with interaction (FOCEI) was used in the development of the pop-PK model. The population PK analysis consisted of two steps: base model development and building of a covariate model. The base model was a 2-compartment model with a dual sequential first-order absorption including a lag-time. Covariates of interest were age, sex, race, weight, BMI, disease status (healthy or ITP), formulation (capsule or tablet), creatinine clearance, ALT, AST, bilirubin, albumin, corticosteroid use, and other concomitant medications such as CYP inducers or inhibitors and mineral supplements.

Once the final pop-PK model was developed, the ability of the final population model to describe the observed data was investigated using a predictive check procedure. The final model parameter estimates are listed in Table 10. The following were identified as significant covariates in the final model: 1) body weight (both CL/F and Vc/F), 2) male sex (CL/F), formulation (i.e., Study SB-497115/002 (capsule)), Japanese race (CL/F (Healthy subjects)), and corticosteroid use (CL/F (ITP patients)).

Table 10: Summary Output of Pop-PK Parameter Estimates (Final Model)

Parameter [Units]	Typical Value (%RSE*)	Inter-individual %CV (%RSE*)	Inter-occasion %CV (%RSE*)
Final Model Parameter Estimates: Structural Model and Inter-individual Variance Parameters			
CL/F Healthy Non-Japanese [L/hr]	0.794 (8.26)		
CL/F Healthy Japanese [L/hr]	0.490 (12.2)		
CL/F ITP w/o CORT [L/hr]	0.607 (7.35)	44.3 (7.67)	
CL/F ITP with CORT [L/hr]	0.458 (7.55)		
CL/F ~ WT	0.75 Fixed		

CL/F ~ SEX	1.27 (6.13)		
Vc/F [L]	11.0 (5.42)	41.8 (11.4)	
Vc/F ~ WT	0.821 (16.6)		
Ka1 [hr-1]	0.272 (15.9)	69.4 (83.6)	191 (15.0)
Ka2 [hr-1]	1.40 (8.71)		
MTIME [hr]	1.40 (1.44)		
Q/F [L/hr]	0.395 (4.20)		
Vp/F [L]	12.1 (6.60)	38.2 (36.2)	
ALAG [hr]	0.460 (0.452)		
F1 ~ FORM	1.21 (4.35)		
Corr η_{CL}, η_{Vc}		0.729 (12.1)	
Intra-individual, Residual Error			
Parameter	**Estimate (%RSE*)**		
σ^2 prop	25.0 (4.97)	25.5 (11.4)	
σ^2 add	26.1 (521)		

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
Abbreviations: CL/F = apparent clearance, Vc/F = volume of central compartment, Ka1 = absorption rate constant prior to MTIME, Ka2 = absorption rate constant after MTIME, Q/F = inter-compartmental exchange flow rate, Vp/F = volume of peripheral compartment, F1 = relative bioavailability of tablet formulation, with respect to capsule formulation ALAG1 = lag-time, σ2 prop = proportional component of the residual error model, σ2 add = additive component of the residual error model., FOMU = formulation, WT = weight, CORT = corticosteroids.

Post-hoc plasma eltrombopag AUC(0-τ) and Cmax estimates for patients with ITP are presented for each dose studied in Table 11. Based on post-hoc AUC(0-τ) estimates, plasma eltrombopag exposure was approximately 38% higher in patients with ITP taking concurrent corticosteroids (see section 2.4.2.8 for additional information). Based on these estimates, ITP patients are expected to have an approximately 30-70% lower total clearance compared to non-East Asian/Japanese healthy subjects as reflected in the differences in systemic exposure between these populations in repeat dose studies. For additional information regarding the pop-PK model please see the pharmacometrics consult in Section 4.4.

Table 11: Estimated Plasma Eltrombopag AUC(0-τ) and Cmax for Subjects with ITP in Studies TRA100773A and TRA100773B

Population	Eltrombopag Dose (QD)	N	AUC(0-τ) (µg.h/mL)	Cmax (µg/mL)
All ITP Patients	30 mg	28	39.2 (31.3, 49.1)	3.17 (2.45, 4.10)
	50 mg	34	91.9 (73.6, 115)	7.95 (6.46, 9.79)
	75 mg	26	146 (122, 176)	11.4 (9.39, 13.9)

2.2.5.3 What are the characteristics of drug absorption?

Eltrombopag olamine is considered a poorly soluble compound as it has a low solubility over the physiological pH range (pH 1 to 7.4). Early manufacturing experience of Eltrombopag Tablets, 25 mg and 50 mg demonstrated that granulation is the critical manufacturing step that determines the physical properties of the granules and dissolution of the final product.

The relative bioavailability of eltrombopag was determined from the mass balance study. Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single radiolabeled 75mg oral solution eltrombopag dose was estimated to be at least 52%. Estimating the oral absorption of eltrombopag is complicated by the potential for gut biotransformation and direct secretion of drug related material into the gut. This phenomenon as was observed pre-clinically in the dog, but was not explored further by the sponsor in humans.

Following single dose administration in healthy subjects, plasma eltrombopag concentrations were quantifiable within approximately 1 hour; peak concentrations occurred between 2 and 6 hours after oral administration of single and repeat doses of eltrombopag.

Administration of eltrombopag with a standard high-fat breakfast significantly decreased plasma eltrombopag exposure in Study 497115/005 (for a detailed summary see section 2.5.3). Plasma eltrombopag AUC(0-∞) by 59% and Cmax by 65% and delayed tmax by 1 hour. The 90 percent CI for the ratio of population geometric means between fed and fasted treatments failed to meet met the criteria as outlined in the guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies" for absence of a food effect. These results were considered to be clinically significant.

It is possible that the dairy content of the standard high-fat breakfast is responsible for a portion of the reduced eltrombopag exposure seen in Study 497115/005. A subsequent study, TRA104631, reported that low-calcium meals (<50 mg calcium), regardless of fat content, had a lower impact on plasma eltrombopag exposure (for a detailed summary see section 2.5.3). However, the 90 percent CI for the ratio of population geometric means between fed and fasted treatments of the "low calcium" treatment arms failed to meet the criteria for the absence of a food effect (intent to treat population).

In addition, the significant reduction in plasma eltrombopag exposure observed when eltrombopag was co-administered with an antacid. Study TRA104631 was conducted to determine the impact of co-administering eltrombopag 75mg with a polyvalent cation-containing antacid (1524mg aluminum hydroxide, 1425mg magnesium carbonate, and sodium alginate) on plasma eltrombopag PK. This was an open-label, randomized, five-period, balanced crossover study (only treatment "C" was antacid). There was a washout of at least 5 days between periods. PK samples were collected for 48 hours following single dose administration in each period. Twenty-six subjects were enrolled; 24 subjects were included in the PK summary for eltrombopag 75mg administered alone and 25 subjects were included in the PK summary for eltrombopag 75mg co-administered with antacid.

Co-administration of eltrombopag with a polyvalent cation-containing antacid decreased plasma eltrombopag AUC(0-∞) and Cmax by 70% (Table 12).

Table 12 Summary of Plasma Eltrombopag PK Parameters and Antacid Drug Interaction Results in Study TRA104631

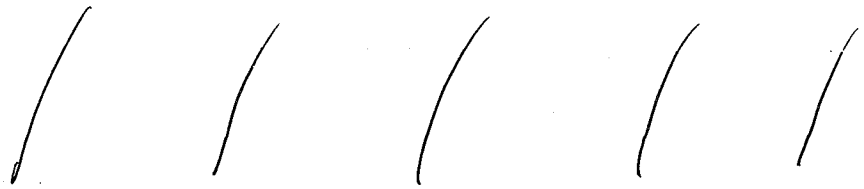
Plasma Eltrombopag PK Parameter	Eltrombopag (Treatment A) (N=24)	Eltrombopag +Antacid (Treatment C) (N=25)	Eltrombopag+Antacid vs Eltrombopag
AUC(0-∞) (µg·hr/mL)	76.9 (63.3, 93.4) [49]	23.1 (16.6, 32.1) [95]	0.295 (0.243, 0.358)
Cmax (µg/mL)	6.20 (5.19, 7.40) [44]	1.88 (1.32, 2.66) [103]	0.302 (0.241, 0.377)

Data presented as geometric mean (95% CI) [%CVb] for PK summary and GLS mean (90% CI) for treatment comparisons
Treatment A = eltrombopag 75mg single dose administered fasted
Treatment C = eltrombopag 75mg single dose administered with antacid (1524mg aluminium hydroxide ,1425mg magnesium carbonate, and sodium alginate) fasted

While these results are clinically significant, the use of [redacted] as the antacid in this study is concerning. Unlike other formulations, [redacted] contains sodium alginate. GSK's public advertising claims regarding this ingredient imply that on ingestion [redacted] reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents effectively impeding gastro-oesophageal reflux. The effect of this raft on the BA of eltrombopag was not assessed in this study and could be a confounding factor when extrapolating these results to other antacid products. b(4)

The proposed approved product labeling reads [redacted] b(4)

b(4)



Given the requirement of this population, the gastric emptying time of antacids and the Tmax of eltrombopag, the reviewer recommends amending the sponsor's product labeling to read "PROMACTA should be given at least 4 hours apart from any products such as antacids..."

2.2.5.4 What are the characteristics of drug distribution?

The estimated steady state volume of distribution for eltrombopag is approximately 23 Liters. Whole body autoradiography studies in rats demonstrated wide distribution into peripheral tissues, but very low radioactivity concentrations in the brain and spinal cord.

In vitro data show that eltrombopag is highly bound (>99%) to human plasma proteins; binding to specific proteins such as albumin and α1-acid glycoprotein has not been tested. A mass balance study in healthy volunteers showed the concentration in blood cells was approximately 50-79% of plasma concentrations.

In vitro studies using expressed human transporters demonstrated that eltrombopag is not a substrate or inhibitor of Pgp (see section 2.4.2.4 for an in depth review).

Eltrombopag is not a substrate of OATP1B1 (see section 2.4.2.5 for an in depth review). *In vitro* studies using Chinese hamster ovary (CHO) cells stably transfected with human OATP1B1 (CHO-OATP1B1) and wildtype CHO cells (CHO-WT) report that Eltrombopag is not a substrate for OATP1B1. This was further studied *in vitro* by measuring the uptake of [14C]eltrombopag in CHO-OATP1B1 and CHO-WT cells at high concentrations in the absence and presence of rifamycin or cyclosporine with the same conclusion. Eltrombopag does inhibit OATP1B1 (see section 2.4.2.5 for an in depth review) both *in vitro* and *in vivo*.

Eltrombopag has not been tested as a substrate or inhibitor of other transport proteins.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance study suggests that the hepatic route is the major route of elimination of eltrombopag.

Study TRA102861 evaluated [14C]-eltrombopag administered as a single 75mg dose (100 µCi) of oral solution to six healthy male subjects. Plasma, urine, and feces were collected over 168 hours post dose. Eltrombopag accounted for approximately 64% of plasma radiocarbon AUC(0-∞). Metabolites, each accounting for <10% of the plasma radioactivity, arising from glucuronidation and oxidation were also detected.

[1] Monés J, Carrió I, Roca M, Estorch M, Calabuig R, Sainz S, et. al. Gastric emptying of two radiolabelled antacids. *Gut* 1991;32;147-50.
[2] Monés J, Carrió I, Sainz S, Berna L, Clave P, Liszkay M, et al. Gastric emptying of two radiolabelled antacids with simultaneous monitoring of gastric pH. *Eur J Nucl Med.* 1995;22(10):1123-8.

Most of the eltrombopag dose was recovered in urine and feces by 144 hours post dose. Overall, 90% of the dose was recovered in the excreta; 59% of the dose was recovered in feces and 31% was recovered in urine (Table 13). Absorbed eltrombopag was extensively metabolized. On average, 59% of the dose was recovered in feces; 20% of the recovered dose was unchanged eltrombopag and 21% was three coeluting glutathione-related conjugates. On average, 31% of the dose was recovered in urine; none of the recovered dose was unchanged eltrombopag, and 20% was a glucuronide of the phenylpyrazole moiety resulting from hydrazine cleavage of eltrombopag. The remaining unaccounted dose in the excreta was comprised of multiple metabolites that could not be individually quantified.

Preclinical studies in the canine suggest the potential for gut biotransformation and direct secretion of drug related material into the gut. This was not fully explored in humans.

Table 13: Summary of Cumulative Recovery of Eltrombopag Radiocarbon in Urine and Feces

	Percent (%) of Administered Dose						
	Subject Number						
Collection Interval (h)	001	002	003	004	005	006	Individual Mean (SD)
Urine							
0 – 12							4.12 (2.30)
0 – 24							11.9 (5.45)
0 – 48							22.6 (7.48)
0 – 72							26.5 (7.72)
0 – 96							28.5 (7.99)
0 – 120							29.6 (8.13)
0 – 144							30.2 (8.24)
0 – 168							30.7 (8.32)
Feces							
0 – 12							0
0 – 24							0.02 (0.03)
0 – 48							9.50 (13.9)
0 – 72							24.4 (5.99)
0 – 96							36.0 (13.5)
0 – 120							48.7 (14.5)
0 – 144							58.0 (9.02)
0 – 168							58.9 (9.74)
Toilet Tissue							
0 – 24							0
0 – 48							0.01 (0.02)
0 – 72							0.02 (0.02)
0 – 96							0.02 (0.03)
0 – 120							0.03 (0.03)
0 – 144							0.03 (0.03)
0 – 168							0.03 (0.03)
Total Recovery (Urine + Feces)	83.8	86.3	92.4	90.4	93.2	91.5	89.6 (3.73)

b(4)

2.2.5.6 What are the characteristics of drug metabolism?

The proposed metabolic pathways characterized for SB-497115 in healthy adult male subjects are depicted in Figure 7.

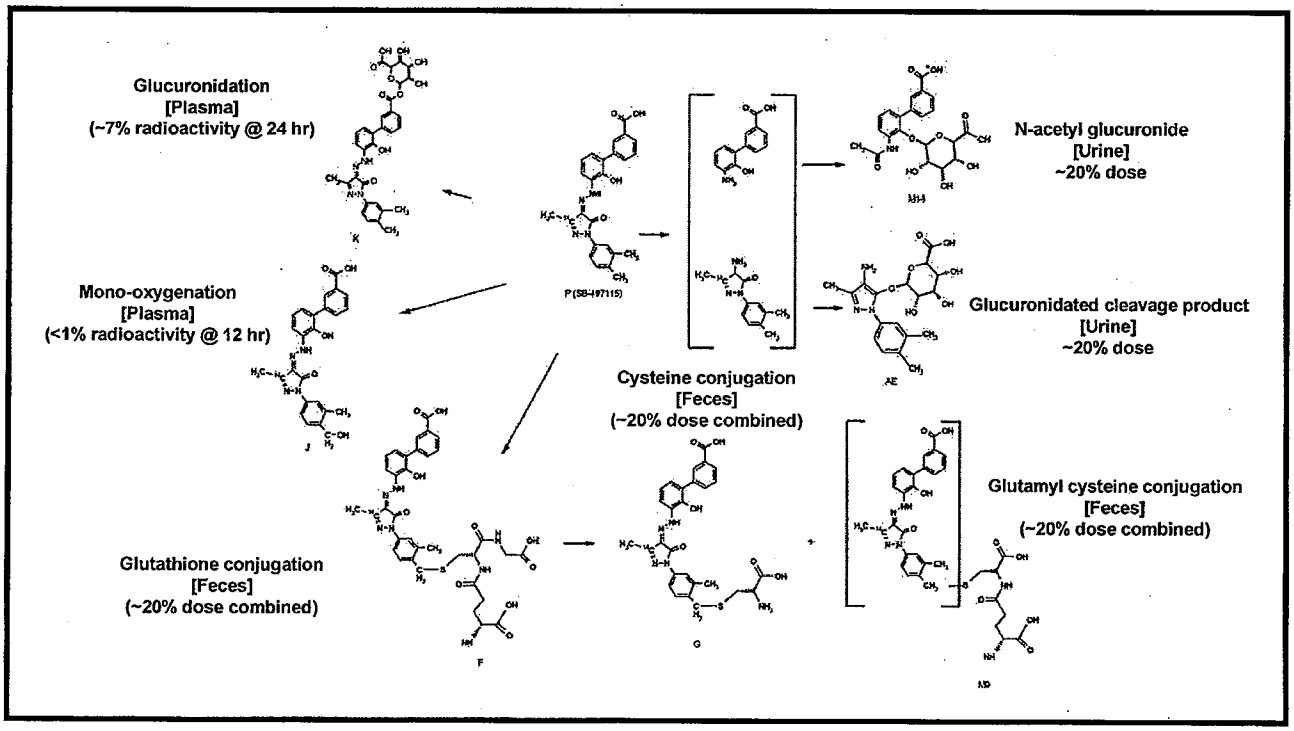
Following a single oral administration of [14C]SB-497115-GR (75 mg, 100 µCi) to six healthy male subjects (Study TRA102861), maximum mean concentrations of radioactivity were observed in blood and plasma at 4 h post-dose. Quantifiable levels of radioactivity were detected in blood and plasma for all subjects at 168 h post-dose. SB-497115 was the predominant component in plasma. Metabolites, products of glucuronidation or oxidation and each accounting for approximately 10% or less of the plasma radioactivity, were also detected.

The predominant radiometabolite present in the human urine (accounting for about 20% of the dose) was a glucuronide of the phenylpyrazole moiety (lower) portion of the molecule after the cleavage of the hydrazine linkage. NMR analysis confirmed that the biphenyl moiety (top) portion of SB-497115 was converted to a glucuronide after the cleavage. There was no evidence of the cleavage products in the circulation. The parent molecule was not detected in the human urine.

In feces, unchanged SB-497115 and three co-eluting glutathione-related conjugates were the predominant radio-components. The co-eluting metabolites, a glutathione, a glutamyl-cysteine, and a cysteine adduct of SB-497115, altogether accounted for approximately 21% of the dose. Though the exact mechanism of formation remains unknown, the glutathione conjugate was speculated to be derived from an oxidation intermediate followed by the addition of glutathione. The glutamyl-cysteine and cysteine adducts are likely further metabolic products of the glutathione conjugate of SB-497115. Thus, the oxidative pathways appear to account for the clearance of approximately 21% of the absorbed dose in humans. The unchanged SB-497115 accounted for approximately 20% of the administered dose.

Approximately 61% of the 90% dose recovered following a single oral administration of [14C]SB-497115-GR were assigned structures, while approximately 11% of the recovered dose has not been characterized (mostly nonextractable material from the fecal extraction pellet). The remaining radioactivity was comprised of radio-metabolites that were not identified and those close to or below the analytical backgrounds, and losses incurred during sample preparation. In addition, excreta samples containing insufficient radioactivity to warrant pooling (typically less than 2% of the administered dose), were not analyzed.

Figure 7: Proposed Metabolic Pathway of SB-497115 Following a Single Oral Administration of [14C]SB-497115-GR to Healthy Male Human Subjects at a Target Dose of 75 mg



Based on this metabolic profile, it is estimated that at least approximately 21% of a dose, represented by the three co-eluting glutathione-related conjugates, could be metabolized through the CYP system.

An *in vitro* study using human liver microsomes and ——— microsomes prepared from a heterologous expression system containing individual CYP enzymes) was conducted to provide information on human CYP enzymes involved in oxidative metabolism of eltrombopag. Pooled human liver microsomes and ——— were incubated with [14C]eltrombopag (5 or 50 µM) at 37°C for up to 60 minutes. Incubations with human liver microsomes were conducted in the presence and absence of a NADPH regenerating system and contained 1 mg/mL of microsomal protein. ——— incubations contained 300 pmoles/mL of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Incubations with pooled human liver microsomes (containing 1 mg/mL of microsomal protein) were also conducted with and without the probe substrate inhibitors ketoconazole (1 µM), sulphaphenazole (10 µM), quinidine (1 µM), quercetin (10 µM), ticlopidine (10 µM) or furafylline (10 µM) (inhibitors of CYP3A4, CYP2C9, CYP2D6, CYP2C8, CYP2C19 and CYP1A2, respectively). All samples were analyzed by both radio-HPLC and HPLC-MS. Insufficient information was provided by the sponsor to evaluate the validity and reliability of these assays. b(4)

Incubations of [14C]eltrombopag (5 or 50 µM) with human liver microsomes resulted in the formation of one metabolite, J (a mono-oxygenation product of eltrombopag), which was shown to depend on oxidative co-factor. Incubations of [14C]eltrombopag (5 or 50 µM) with CYP1A2 and CYP2C8 ——— resulted in the formation of metabolites J and M6 (co-eluting mono-oxygenation products of eltrombopag). An additional potential metabolite, AZ, was formed in incubations with only CYP1A2, but was not characterized by LC/MS. Scaling of metabolite formation by ——— to their relative content in human liver microsomes suggested that CYP1A2 and CYP2C8 were the primary enzymes involved in the *in vitro* oxidative metabolism of eltrombopag. These results were further stengthened by the use of specific CYP inhibitors in human liver microsome incubations. b(4)

An additional *in vitro* study was conducted to investigate the human UGT enzymes involved in the glucuronidation of eltrombopag in vitro. Pooled human liver microsomes (1 mg/mL) and ——— overexpressing individual UGT enzymes were incubated with [14C]eltrombopag (10 µM) at 37°C for up to 60 minutes. ——— incubations contained 0.25 mg/mL of UGT1A1, UGT1A3, UGT1A4, UGT1A7, UGT1A8, UGT2B4, UGT2B7 or UGT2B15; 0.15 mg/mL of UGT1A6 or UGT1A9; or 0.70 mg/mL of UGT1A10 or UGT2B17. Each ——— was tested for glucuronidation activity using the probe substrate trifluoperazine dihydrochloride (TFP) for UGT1A4, eugenol for UGT2B17 and 7-hydroxy 4-(trifluoromethyl)coumarin (HFC) for all other UGT enzymes tested. All samples were analyzed by both radio-HPLC and HPLC-MS. Insufficient information was provided by the sponsor to evaluate the validity and reliability of these assays. b(4)

During a 60 minute incubation with human liver microsomes, turnover of [14C]eltrombopag attributable to glucuronidation was 3%. One metabolite, K (glucuronide of eltrombopag), was observed. When incubated with individually expressed UGT enzymes, only UGT1A1 and UGT1A3 metabolized eltrombopag to form metabolite K. Thus, under these in vitro conditions, UGT1A1 and UGT1A3 were the enzymes responsible for the glucuronidation of eltrombopag.

2.2.5.7 What are the characteristics of drug excretion?

Fecal excretion is the major route of elimination of eltrombopag. Over the 168 hour collection period, 59% (20% unchanged) of the dose was recovered in feces and 31% (0% unchanged) was recovered in urine. Preclinical studies in the canine also suggest

biliary excretion and direct secretion of drug related material into the gut. This was not fully explored in humans.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Overall plasma eltrombopag AUC and Cmax increased with increasing dose. The evaluation of proportionality was dependent on the dose studied and suggested a slightly greater than dose dependent relationship at lower doses.

Following single dose administration (Study 497115/001)of low doses ranging from 3mg to 9mg, plasma eltrombopag AUC(0-∞) and Cmax increased in a greater than dose proportional manner (Table 14)

Table 14: Summary of Dose Proportionality Assessment in Study SB-497115/001

Plasma PK Parameter	Effect	Slope Estimate	Lower 95% CI	Upper 95% CI
AUC(0-∞) (ng.h/mL)	Log(dose)	1.51	1.14	1.88
AUC(0-t) (ng.h/mL)	Log(dose)	1.59	1.21	1.97
Cmax (ng/mL)	Log(dose)	1.68	1.39	1.97

Following single dose and repeat administration (Study SB-497115/002), plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner over the dose range of 5mg to 75mg (Table 15). When doses greater than 20 mg were only considered, a trend toward dose proportionality was noted.

Table 15: Summary of the Analysis of Dose Proportionality in Study SB-497115/002

	Parameter	90% CI		
		Slope	Lower	Upper
All Regimens				
Single Dose	Log(AUC) Log(Cmax)	1.130 1.151	1.038 1.066	1.222 1.236
Repeat Dose	Log(AUC) Log(Cmax)	1.187 1.196	1.111 1.118	1.264 1.273
Single and Repeat Dose	Log(AUC) Log(Cmax)	1.159 1.173	1.083 1.104	1.234 1.242
Regimens > 20 mg				
Single Dose	Log(AUC) Log(Cmax)	1.002 0.916	0.651 0.589	1.353 1.243
Repeat Dose	Log(AUC) Log(Cmax)	1.106 0.990	0.850 0.757	1.361 1.223
Single and Repeat Dose	Log(AUC) Log(Cmax)	1.054 0.953	0.780 0.702	1.328 1.204

Following five days of repeat dosing (study TRA102860), plasma eltrombopag Cmax and AUC(0-τ) 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-τ) and 1.01 (0.942, 1.08) for Cmax over a range of 50 mg QD to 150 mg QD.

Based on these results it would be reasonable to expect a dose proportional (linear) relationship within the recommended dosing range.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

In Study 497115/002 plasma eltrombopag PK following administration of both

single and repeat escalating doses of 5 mg (A), 10mg (B), 20mg (C), 30mg (D), 50mg (E), and 75mg (F) to healthy adult subjects was evaluated. Accumulation was assessed by comparing AUC(0-τ) and Cmax on Day 10, with comparable measures on Day 1, at each dose level. Ratios of Day 10 to Day 1 plasma SB-497115 AUC(0-τ) (geometric mean, 90% CI) showed accumulation for the 20, 30, 50, and 75 mg cohorts (Table 16).

Time dependence in plasma SB-497115 pharmacokinetics was also assessed in this study by comparing AUC(0-τ) on Day 10 with AUC(0-∞) on Day 1, at each dose level. Ratios of Day 10 AUC(0-τ) to Day 1 AUC(0-∞) (geometric mean, 90% CI) indicate no statistically significant time dependence across the doses. The geometric least-squares mean (90% CI) for time invariance ratio for each dose is also summarized in Table 16.

Table 16: Summary of Accumulation and Time Invariance in Study 497115/002

	Treatment	Repeat Dose Geometric LS Mean	Single Dose Geometric LS Mean	Ratio	90% CI
Ro [1]	A	3437.602	2982.672	1.153	(0.913, 1.454)
	B	7671.466	6081.692	1.261	(0.987, 1.612)
	C	16802.026	12172.976	1.380	(1.174, 1.623)
	D	28994.776	21209.897	1.367	(1.195, 1.564)
	E	57434.461	40843.174	1.406	(1.204, 1.643)
	F	79032.491	50716.877	1.558	(1.233, 1.969)
RCmax [2]	A	332.510	318.146	1.045	(0.814, 1.342)
	B	700.174	625.039	1.120	(0.829, 1.514)
	C	1532.927	1268.386	1.209	(1.009, 1.447)
	D	2973.423	2641.380	1.126	(0.933, 1.358)
	E	5764.693	4902.252	1.176	(0.984, 1.405)
	F	7266.714	6034.540	1.204	(0.982, 1.476)
Rs [3]	A	3437.602	3653.697	0.941	(0.755, 1.173)
	B	7671.466	8715.471	0.880	(0.719, 1.077)
	C	16802.026	16314.188	1.030	(0.862, 1.231)
	D	28994.776	29104.585	0.996	(0.874, 1.135)
	E	57434.461	57767.647	0.994	(0.826, 1.196)
	F	79032.491	71842.209	1.100	(0.854, 1.418)

[1] Observed Accumulation Ratio (Ro) = Day 10 AUCtau / Day 1 AUCtau.
[2] Cmax Accumulation Ratio (RCmax) = Day 10 Cmax / Day 1 Cmax.
[3] Time Invariance (Rs) = Day 10 AUCtau / Day 1 AUCinf.

In study TRA102860 accumulation was assessed for Eltrombopag doses of 100mg, 150mg, and 200mg were administered QD for 5 days. Plasma PK samples were collected over 24 hours after single dose administration on Day 1 and after repeat dose administration on Day 5. Significant accumulation of eltrombopag AUC(0-τ) was observed following administration of eltrombopag 100 mg, 150 mg, and 200 mg QD for five days (Table 17).

Table 17: Summary of Results of Analysis of Dose Accumulation Ratio in Study TRA102860

Parameter	Treatment	Ratio	90% CI (Lower, Upper)
Observed Accumulation Ratio (Ro)	Eltrombopag 100mg	1.6626	(1.3533, 2.0427)
	Eltrombopag 150mg	1.6858	(1.3854, 2.0513)
	Eltrombopag 200mg	1.8125	(1.3048, 2.5177)
Cmax Ratio (R[Cmax])	Eltrombopag 100mg	1.4501	(1.1520, 1.8253)
	Eltrombopag 150mg	1.3184	(0.9843, 1.7658)
	Eltrombopag 200mg	1.3535	(0.9749, 1.8792)

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Between-subject variability (%CVb) in AUC and Cmax was generally between 30 and 40%. Possible sources of reduced reliability may include practice variability across the large number of clinical sites, including the use of a broader range of concomitant medications; increased variability in dosing and sampling times; and increased variability in subjects' underlying disease status, and in the status of metabolizing organs. Pop-PK model identified many of the major causes of variability. The following were identified as significant covariates in the final population PK model: 1) body weight (both CL/F and Vc/F), 2) male sex (CL/F), formulation (Study SB-497115/002 (capsule)), Japanese race (CL/F (Healthy subjects)), and corticosteroid use (CL/F (ITP patients)).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

During the development of a pop-PK model intrinsic covariates of interest were age, sex, race, weight, BMI, disease status (healthy or ITP), creatinine clearance, ALT, AST, bilirubin, albumin, The following were identified as significant intrinsic covariates in the final model: 1) body weight (both CL/F and Vc/F), 2) male sex (CL/F), Japanese race (CL/F (Healthy subjects)), and corticosteroid use (CL/F (ITP patients)). These differences are outlined in Table 10 above.

Despite these estimated differences post hoc results from the two pivotal trials failed to show a trend toward a difference in efficacy or safety related to age or sex. The effect of weight on efficacy and safety was not evaluated in the pivotal trials. As discussed below, body weight appears to be partially responsible for some of the race differences noted between East Asian and Caucasian healthy subjects from clinical pharmacology studies conducted in Japan. A reviewer generated analysis of the effect of body weight based on pop-PK estimated parameters and the known pharmacodynamic response of eltrombopag (Table 18) suggests that it is unlikely that a weight based dosing approach would change the safety and efficacy profile of this drug appreciably.

Table 18: Reviewer generated table evaluating the effect of weight on exposure (AUC0-τ (mcg*h/ml))

Dose (mg)	Kg	lbs	Healthy Non-Japanese [L/hr]		Healthy Japanese [L/hr]		ITP w/o CORT [L/hr]		ITP with CORT [L/hr]	
			0.794		0.49		0.607		0.458	
			female	male	female	male	female	male	female	male
25	40	88	49.5	39.0	80.2	63.2	64.8	51.0	85.8	67.6
25	60	132	36.5	28.8	59.2	46.6	47.8	37.6	63.3	49.9
25	80	176	29.4	23.2	47.7	37.6	38.5	30.3	51.0	40.2
25	100	220	24.9	19.6	40.4	31.8	32.6	25.7	43.2	34.0
25	120	264	21.7	17.1	35.2	27.7	28.4	22.4	37.7	29.7
50	40	88	99.0	78.0	160.5	126.4	129.5	102.0	171.7	135.2
50	60	132	73.1	57.5	118.4	93.2	95.6	75.3	126.7	99.7
50	80	176	58.9	46.4	95.4	75.1	77.0	60.6	102.1	80.4
50	100	220	49.8	39.2	80.7	63.6	65.2	51.3	86.4	68.0
50	120	264	43.4	34.2	70.4	55.4	56.8	44.7	75.3	59.3

75	40	88	148.5	117.0	240.7	189.5	194.3	153.0	257.5	202.8
75	60	132	109.6	86.3	177.6	139.8	143.4	112.9	190.0	149.6
75	80	176	88.3	69.5	143.1	112.7	115.5	91.0	153.1	120.6
75	100	220	74.7	58.8	121.1	95.3	97.7	77.0	129.5	102.0
75	120	264	65.2	51.3	105.6	83.1	85.2	67.1	113.0	89.0

Plasma eltrombopag AUC(0-τ) was approximately 35% lower in healthy subjects as compared to patients with ITP. Based on post-hoc AUC(0-τ) pop-PK estimates, plasma eltrombopag exposure was approximately 38% higher in patients with ITP taking concurrent corticosteroids. The reason for this difference is unclear (see section 2.4.2.8).

The majority of subjects included in the eltrombopag clinical development program are of European ancestry. However, a considerable number of subjects of East Asian ancestry have also been studied. In healthy subjects, the information in subjects of East Asian ancestry was obtained predominantly in Japanese subjects resident in Japan, although a small number of East Asian subjects resident in the West were also studied. The Western subjects in the Phase 1 program have resided principally in North America and Europe and are predominantly of European ancestry; however, a small numbers of subjects from other ethnic groups, such as African Americans, were included. The eltrombopag ITP studies have also been predominantly performed in subjects of European ancestry but did include subjects of Asian ancestry, resident in East Asia and Central/South Asia. African American ITP patients were poorly represented.

The sponsor defines "East Asian" is as a person whose ancestry is of the countries of East Asia or Southeast Asia, such as Japan, China, Taiwan, and Korea. These East Asian populations are thought to be both genetically and environmentally distinct from the populations resident in Central and South Asia, some of whom have a greater genetic similarity to the peoples of Europe.

In healthy adult subjects and ITP patients receiving repeat doses of eltrombopag, plasma eltrombopag AUC(0-τ) was approximately 70 to 80% higher in East Asian subjects compared to non-Asian patients who were predominantly White Caucasian. This is based a two studies conducted in Japan and estimates from the pop-PK analysis.

Study TRA104603 was a single-center, placebo-controlled, double-blind, randomized, 4-period incomplete crossover, single dose escalation study conducted in Japanese healthy male subjects living in Japan. Subjects were randomized to one of the four treatment sequences and received placebo and three of the four eltrombopag doses, of 30 mg, 50 mg, 75 mg, or 100 mg. Plasma and urine PK samples were collected over 72 hours after single dose administration. This study used eltrombopag tablets of 5 mg and 25mg strengths of the Phase 2 formulation.

Sixteen subjects were enrolled in the study. All subjects were male and Japanese; mean (range) age was 26 years (20 to 33 years) across the doses and weight was approximately 61kg (55.5 to 69.6kg). Following single dose administration, plasma eltrombopag AUC(0-∞) increased in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.11 (1.03, 1.20) and Cmax increased in a dose proportional manner where the slope estimate (90% CI) was 1.02 (0.931, 1.11) over a range of 30mg to 100mg (Table 19).

Table 19: Selected PK parameters for study 104603

	30mg (n=12)	50mg (n=12)	75mg (n=12)	100mg (n=11)
Cmax (µg/mL)	4.00±0.86 (2.83-5.44)	7.26±1.49 (5.32-10.2)	10.1±2.15 (7.86-14.5)	13.1±3.46 (8.51-20.7)
Tmax	3.0	3.5	3.5	4.0

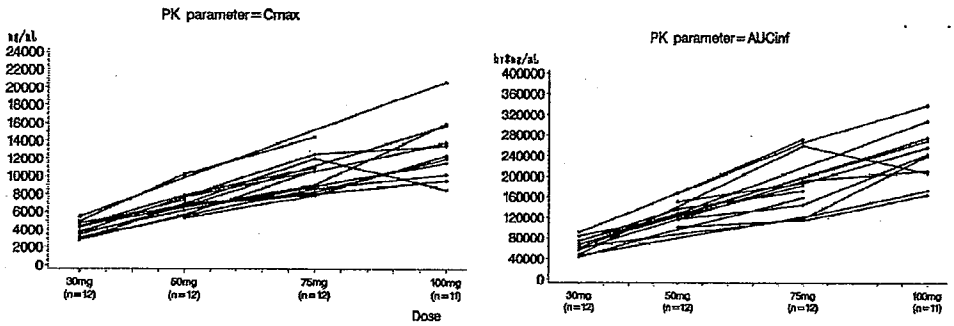
(hr)	(2.0-5.0)	(2.0-5.0)	(1.5-4.0)	(2.0-5.0)
t1/2 (hr)	23.1±2.8 (20.1-28.4)	27.5±5.8 (18.7-36.8)	27.9±4.4 (21.2-34.8)	28.1±6.5 (17.8-41.6)
AUCinf (µg·hr/mL)	64.5 ±14.6 (43.1-90.8)	130.8±22.3 (97.0-168.0)	182.7± 56.8 (114.9-272.4)	244.2± 53.6 (164.5-338.8)
AUC0-24 (µg·hr/mL)	40.3±8.6 (27.5-55.9)	74.1±11.7 (56.6-96.5)	102.0±23.3 (73.4-147.4)	134.8±24.2 (105.5-182.1)

PK parameters other than Tmax: arithmetic mean±SD (range), Tmax: median (range)

It appears the usefulness of these data may be limited by systematic error. While summary statistics of exposure show a trend toward increased exposure with increasing dose, careful inspection of the raw data shows that several patients show decreasing AUC with increasing dose going from 50 mg to 75 mg and 75 to 100 mg. Interestingly, this occurred in different subjects from 50 mg to 75 mg and 75 to 100 mg (Figure 8). Further, subjects contained in the upper 25th percentile for AUCinf were not consistent between the cohorts. 5/9 subjects were in the upper 25th percentile for AUCinf in two cohorts but none were in the upper 25th percentile for AUCinf for all three dosing cohorts.

Possible causes for this could be 1) Assay (49 concentrations above the upper limit of quantification for the plasma eltrombopag assay), 2) Formulation (the Phase 2 formulation was shown produce a ~15% higher exposure and NOT be bioequivalent or dose proportional to the commercial Phase 3 formulation), 3) Carryover (Twelve subjects had quantifiable concentrations (10.5-56.1 ng/L) following the 12 day washout which shows minor carryover), and 4) Administration/packaging error (incorrect doses given).

Figure: 8: Scattergrams of PK parameters (Cmax, AUCinf) plotted against dose (linear scale) for Study 104603



Study TRA105580 was a single-center, placebo-controlled, single-blind, randomized, parallel, single and repeat dose escalation study in Japanese healthy male subjects living in Japan. Three dose levels, including 25 mg, 50 mg, and 75 mg, were administered as single doses, followed by a 5-day wash-out, then as repeat doses for 10 days. At each dose level, ten subjects received eltrombopag and four subjects received placebo. Plasma PK samples were collected over 120 hours after single and repeat dose administration.

This study used eltrombopag 25mg Phase 3 formulation tablets. Forty-two subjects were enrolled in the study. All subjects were male and Japanese; mean age was 26 years (20 to 34 years) and weight was 63.6kg (55.8 to 82.0kg). Following single dose administration, plasma eltrombopag AUC(0-∞) and Cmax increased with increasing dose over the range of 25 mg to 75 mg (Table 20). Dose proportionality was not statistically tested; however, based on geometric mean values for the 50mg and 75mg doses,

AUC(0-∞) and Cmax increased approximately 30% for a 50% increase in dose, suggesting less than dose proportional increases in exposure.

Table 20: Selected PK parameters Study 105580

Dose (mg)	Single /Multiple	n	Cmax (µg/mL)	AUC0-24 (µg.hr/mL)	AUCinf (µg.hr/mL)	Tmax (hr)	t1/2 (hr)
25	Single	10	3.56±1.13 (1.77-5.85) [31.7]	33.2±10.1 (16.3-55.2) [30.3]	55.4±23.2 (21.6-104.3) [41.8]	3.0 (2.0-5.0)	29.6±5.0 (21.0-37.5) [16.9]
	Repeated (Day 10)	10	4.83±1.17 (2.81-6.44) [24.3]	58.9±18.4 (29.7-78.0) [31.2]	135.0±56.5 (50.7- 210.8) [41.9]	3.0 (1.5-5.0)	39.7±3.2 (36.0-44.5) [8.1]
50	Single	10	6.44±2.14 (2.64-8.88) [33.2]	63.9±17.6 (28.0-81.9) [27.6]	106.6±32.4 (47.1-145.9) [30.4]	3.0 (1.5-5.0)	31.0±5.9 (21.7-38.6) [19.1]
	Repeated (Day 10)	9	10.6±2.38 (7.06-14.77) [22.4]	133.8±33.6 (91.9-192.2) [25.1]	359.8±140.1 (218.5-655.0) [39.0]	4.0 (2.0-5.0)	51.3±12.2 (38.0-81.0) [23.8]
75	Single	10	8.39± 2.84 (4.52-12.23) [33.8]	80.7±20.7 (44.3-102.5) [25.7]	134.9±37.4 (70.4-196.5) [27.7]	3.0 (2.0-6.0)	32.4±7.6 (19.8-43.0) [23.3]
	Repeated (Day 10)	10	12.78± 2.84 (7.44-16.34) [22.2]	164.2±35.5 (117.3-225.4) [21.6]	460.6±159.8 (257.8-655.0) [34.7]	4.0 (2.0-5.0)	47.8±11.5 (30.9-63.7) [24.1]

mean±SD (range), Tmax : Median (range) [%CVb]

Following repeat dose administration, plasma eltrombopag AUC(0-τ) and Cmax increased with increasing dose over the range of 30 mg to 75 mg QD. Dose proportionality was not formally tested; however, based on geometric mean values for the 50 mg and 75 mg doses, AUC(0-∞) and Cmax increased approximately 20 to 25% for a 50% increase in dose, suggesting less than dose proportional increases in exposure.

Statistically significant accumulation in AUC(0-τ) and Cmax was observed for all three doses between Day 1 and Day 10; GLS mean ratio (90% CIs) estimates were for 25 mg: 1.75 (1.50, 2.05), 50 mg: 1.95 (1.64, 2.32), and 75 mg: 2.06 (1.74, 2.44). GLS mean ratio (90% CI) estimates for Cmax were for 25 mg: 1.38 (1.14, 1.65), 50 mg: 1.57 (1.28, 1.93), and 75 mg: 1.58 (1.28, 1.94).

Ratios of Day 10 AUC(0-τ) to Day 1 AUC(0-∞), presented as GLS mean ratio (90% CI), indicate that plasma eltrombopag PK was time invariant at 25 mg: 1.09 (0.932, 1.28) and 50 mg: 1.18 (0.998, 1.39), but time-dependent at 75 mg: 1.24 (1.06, 1.45).

While the sponsor allowed smokers in this study it failed to report information regarding the effect of this factor on PK in the study report. A reviewer analysis showed a minor trend toward lower exposure in the smoking population (see Appendix section 4.3). Given smoking can induce CYP 2A6 and UGT1A1 this may be significant in identifying metabolic pathways responsible for these ethnic differences. b(5)

Given this study used the same assay as 104603 and 60 concentrations were above the upper limit of quantification for the plasma eltrombopag assay, it may have suffered from the same systematic error. In addition, on Day 10 of multiple dosing, %AUCex exceeded 20% in one subject in the 50mg group and 3 subjects in the 75mg group. This may be responsible, in part, for the increased %CVb noted for AUCinf and the overall wide ranges for Cmax, AUC0-24, & AUCinf.

The single dose eltrombopag pharmacokinetic parameters in Japanese subjects over the dose range 25mg to 100mg and in Western subjects over the dose range 25mg to 200mg are given show the interindividual variation in eltrombopag Cmax and AUC(0-∞) in the Japanese and Western subjects (see representative example for 50 mg Table 21 and Figure 9). Some variation between studies conducted in the West or Japan was reported.

With single dosing, all of the eltrombopag Cmax values and the majority of the AUC(0-∞) in the Japanese subjects were within the range of values observed at the respective doses in the Western subjects. Although the geometric mean Cmax values tend to be slightly higher in the Japanese than Western subjects, considerable overlap is observed between the ethnic groups. Geometric mean AUC(0-∞) values are approximately 60% higher in the Japanese than Western subjects at all four doses.

In contrast, as seen in the representative example for 50 mg (Figure 9), the Cmax and AUC(0-∞) of eltrombopag in the East Asian and South East Asian subjects included in the Western studies are well within the range of values observed in the other Western subjects (red open circles). This discrepancy was not adequately explained by the sponsor

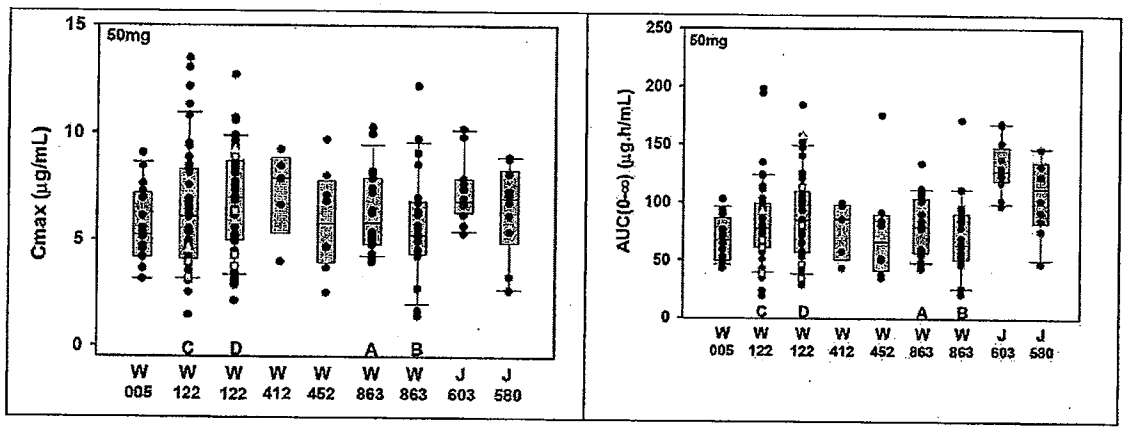
b(5)

Table 21: Eltrombopag pharmacokinetic parameters (geometric mean (95% CI)) following single 50 mg oral doses in healthy Japanese and Western subjects.

Study	Population[3]	n	Cmax (µg/mL)	Tmax[3] (h)	AUC(0-∞) (µg•h/mL)	t1/2(h)
TRA104603[2]	Japanese	12	7.13 (6.29, 8.07)	3.50 (2.00-5.00)	129 (116, 144)	26.96 (23.5, 30.8)
TRA105580[1]	Japanese	10	6.03 (4.50, 8.10)	3.00 (1.50-5.00)	101 (78.7, 130)	30.57 (26.4, 35.2)
497115/005[2]	Western	16	5.27 (4.41, 6.30)	3.50 (1.50-5.00)	65.2 (56.2, 75.6)	16.05 (15.0, 17.1)
TRA105122 C[2]	Western	46	5.73 (4.99, 6.58)	3.03 (2.00-6.00)	75.6 (65.9, 86.7)	19.26 (17.9, 20.7)
TRA105122 D[1]	Western	46	6.36 (5.64, 7.17)	4.00 (2.00-6.00)	79.5 (69.2, 91.4)	18.66 (17.3, 20.1)
TRA102863 A[2]	Western	22	6.11 (5.39, 6.93)	3.00 (1.48-4.15)	74.5 (64.1, 86.5)	18.95 (17.4, 20.6)
TRA102863 B[1]	Western	22	5.09 (4.07, 6.38)	3.00 (1.50-6.00)	63.2 (50.4, 79.2)	18.35 (16.5, 20.4)
TRA103452[1]	Western	8	5.43 (3.74, 7.88)	3.00 (2.50-6.02)	66.0 (42.1, 104)	21.37 (15.5, 29.4)
TRA104412[1]	Western	5	6.94 (4.58, 10.5)	2.55 (2.50-3.00)	72.7 (46.2, 115)	26.97 (21.4, 33.8)

1. Tablet manufactured at the Commercial site
2. Tablet manufactured at the R&D site
3. Median (range)

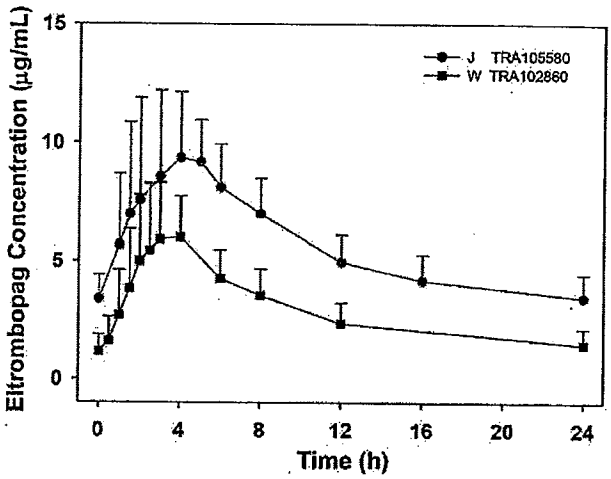
Figure 9: Eltrombopag Cmax in healthy Japanese (J) and Western (W) subjects following single 50 mg oral dose. Individual data are shown (symbols) as well as boxes representing the 25-75th percentiles (with median) and bars representing the 10-90th percentiles.



The half-life of eltrombopag, estimated in the single dose studies, was not always based on plasma concentrations collected over a consistent time interval. As the estimated eltrombopag terminal half-life depends on the interval over which it was calculated, the most reliable inter-ethnic comparisons are based on studies using the same collection intervals (72h or 120h). Considering values calculated from concentration time data for 72h after dosing, geometric mean eltrombopag half-life in Japanese subjects is 22.9 to 27.5h compared to 13.3 to 19.2h in Western subjects. Considering values calculated from concentration-time data for 120h after dosing, the geometric mean eltrombopag half-life in Japanese subjects is 29.2 to 31.6h compared to 21.3 to 26.9h in Western subjects. Although the geometric mean half-life values are longer in the Japanese than Western subjects there is overlap in the individual half-lives observed in the two groups.

The repeat dose pharmacokinetics of eltrombopag were studied in healthy Japanese subjects administered 25 to 75 mg doses of the phase 3 formulation once daily for 10 days (TRA105580). In healthy Western subjects, the repeat dose pharmacokinetics of eltrombopag were studied following administration of 50 to 200mg doses of the phase 3 formulation tablet formulation once daily for 5 days (TRA102860). The mean eltrombopag plasma concentration-time profiles in the Japanese and Western subjects over the dosage interval following administration of repeat once daily doses of 50 mg eltrombopag are shown in Figure 10.

Figure 10: **Eltrombopag dosage interval plasma concentration-time profiles (arithmetic mean plus SD) in healthy Japanese (J) (Day 10) and Western (W) (Day 5) subjects following repeat once daily administration of the 50 mg commercial tablet.**



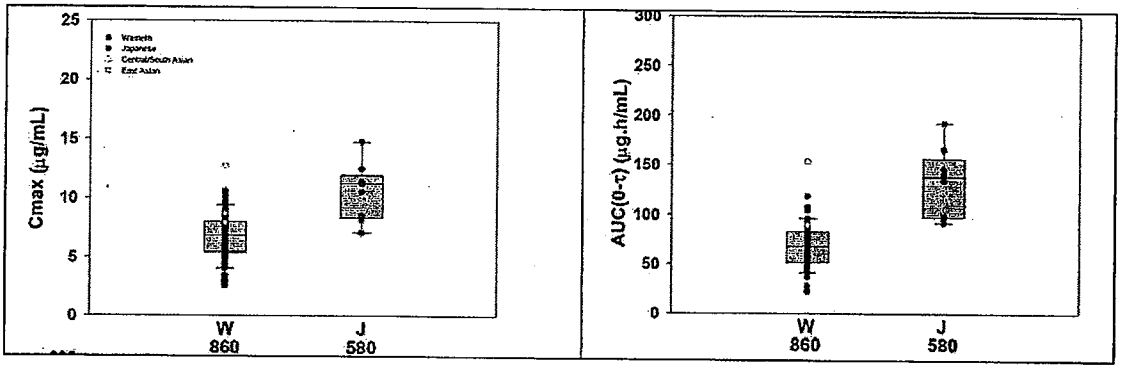
The mean plasma concentrations of eltrombopag reported following repeat once daily 50 mg doses are higher in the Japanese compared to the Western subjects. Both groups showed increased variability about Cmax with TRA105580 (Japan) having greater variability between subjects. The eltrombopag pharmacokinetic parameters reported in the Japanese (TRA105580) and Western (TRA102860) subjects following repeat 50 mg dose administration are given in Table 22. The eltrombopag repeat dose Cmax and AUC(0-τ) in the individual Japanese and Western subjects included in these studies at the once daily dose of 50mg are shown in Figure 11.

Table 22: **Eltrombopag pharmacokinetic parameters (geometric mean (95%CI)) following 50 mg once daily administration for 10 days in healthy Japanese subjects and for 5 days in healthy Western subjects. τ = 24h.**

Study	n	Dose (mg)	Cmax (µg/mL)	Tmax[1] (h)	AUC(0-τ) (µg•h/mL)
Japanese Day 10					
TRA105580	9	50	10.4 (8.68, 12.4)	4.00 (2.00-5.00)	130 (107, 158)
Western Day 5					
TRA102860 PII	60	50	6.40 (5.87, 6.97)	3.19 (2.17-6.22)	65.4 (59.7, 71.6)

1. Median (range)

Figure 11: **Eltrombopag Cmax and AUC(0-τ) in healthy Japanese (J) (Day 10) and Western (W) subjects (Day 5) following repeat doses of 50mg once daily. Individual data are shown (symbols) as well as boxes representing the 25-75th percentiles (with median) and bars representing the 10-90th percentiles.**



The results of study TRA105580 in healthy Japanese subjects and study TRA102860 in healthy Western subjects can be compared directly because the same tablet formulation was administered in both studies and a comparable separation of dose and food intake was applied in both protocols. The repeat dose pharmacokinetics in the Western subjects was determined on Day 5 and in the Japanese subjects on Day 10. Considering the half-life of eltrombopag in Western subjects, the Day 5 repeat dose pharmacokinetics have been determined following approximately 4-6 eltrombopag half-lives and should be close to steady-state (approximately 90-97% of steady-state). Since the mean eltrombopag half-life is longer in the Japanese than Western subjects, steady-state should be attained by Day 7 of once daily dosing.

Based on these studies, the repeat dose eltrombopag Cmax and AUC(0-τ) are 1.6-fold and 2-fold higher, respectively, in the Japanese compared to the Western subjects. Overlap in repeat dose parameter values is observed between the Japanese and Western subjects. In contrast, as seen in the single dose comparisons, the Cmax and AUC(0-τ) of eltrombopag in the East Asian subjects included in the Western repeat dose studies (Figure 11) are again within the range of values observed in the other Western subjects (red open circles). This discrepancy was not adequately explained by the sponsor

b(5)

A pop-PK analysis using information from five eltrombopag studies: one Phase I study in Japanese subjects using the tablet formulation (TRA105580), one Phase I study in Western subjects using the tablet formulation (TRA102860 Part 1), one Phase I study in Western subjects using the capsule formulation (497115/002) and the Phase II and Phase III global studies in ITP subjects using the two tablet formulations (TRA100773A and TRA100773B). This analysis did not include all the datasets available using the tablet formulation. The pharmacokinetic and pharmacodynamic analysis used a nonlinear mixed-effect population model approach (see section 2.2.5.2).

Based on the post-hoc AUC(0-τ) estimates of the population pharmacokinetic analysis, healthy Japanese subjects had an approximately 80% higher mean dose normalized plasma eltrombopag exposure (e.g., AUC(0-τ) values (1.89 (95%CI 1.69-2.09µg.h/mL))) compared to healthy non-Japanese subjects (e.g., (1.05 (95%CI 0.960-1.14µg.h/mL))). Estimated typical values of CL/F (for a weight of 73kg) were 0.490L/h for healthy Japanese subjects and 0.794L/h for healthy non-Japanese subjects, representing a 38% lower typical value of CL/F in healthy Japanese subjects than in healthy non-Japanese subjects. Since weight was also a significant covariate, the predicted CL/F in healthy male subjects (body weights from 43kg to 122kg) ranged from 0.418 L/h to 0.915L/h in Japanese subjects and 0.678L/h to 1.48L/h in non-Japanese subjects. While the trend is consistent with increased exposure in the East Asian population compared to non- East Asian, the potential for systematic error in studies TRA104603 and TRA105580 described above may have limited the ability to identify the true magnitude of this race difference. In addition, the lack of congruence in Western studies versus Japan

regarding the difference in exposure between East Asian and non-East Asian population was not addressed. Diet habits (e.g., beef consumption) may have played a role as discussed later in this section.

The pharmacokinetics of eltrombopag was investigated in subjects with ITP (studies TRA100773A and study TRA100773B). Subjects with ITP were administered placebo, 30, 50 or 75 mg eltrombopag once daily for up to six weeks (TRA100773A) or placebo and eltrombopag from a starting dose of 50 mg once daily for 6 weeks (TRA100773B). Plasma eltrombopag pharmacokinetic profiles in a small number of ITP subjects (consisting of six samples collected over 24 hour periods) or a limited number of samples (1 to 6) in a larger number of ITP subjects were collected. Plasma eltrombopag AUC(0-τ) estimates, based on the pop-PK model for the ITP subjects are presented in Table 23.

Table 23: Plasma eltrombopag AUC(0-τ) and observed Cmax Pop-PK estimates (geometric mean (95% CI)) for subjects with ITP.

Population	Eltrombopag Dose (once daily)	N	AUC(0-τ) (µg•h/mL)	Cmax (µg/mL)
All ITP Subjects	30mg	28	39.2 (31.3, 49.1)	3.17 (2.45, 4.10)
	50mg	34	91.9 (73.6, 115)	7.95 (6.46, 9.79)
	75mg	26	146 (122, 176)	11.4 (9.39, 13.9)
Non-Asian ITP Subjects	30mg	24	35.1 (28.0-44.2)	2.81 (2.15, 3.67)
	50mg	23	77.3 (59.6-100)	7.22 (5.82, 8.95)
	75mg	23	143 (118, 174)	11.3 (9.14, 14.1)
Asian ITP Subjects	30mg	4	75.8 (42.9, 134)	6.51 (4.05, 10.5)
	50mg	11	132 (89.9, 194)	9.74 (5.90, 16.1)
	75mg	3	175 (40.6, 757)	12.1 (4.23, 34.4)

At the dose of 50 mg once daily, the eltrombopag AUC(0-τ) and Cmax were higher (71% and 35%, respectively) in the Asian than the non- Asian ITP populations. In addition, the estimated eltrombopag exposure in Asian ITP subjects was greater than the exposure estimated at the same dose in the healthy Japanese subjects (TRA104603 and TRA105580) included in the pop-PK analysis. Given the concerns regarding the potential for systematic error in the Japan studies, these estimates were reevaluated by the pharmacometrics reviewer excluding the 104603 and 105580 studies and the approximately 70% increase in eltrombopag exposure for the Asian ITP population was still evident.

The underlying mechanism for this difference in exposure between the East Asian and Non-East Asian populations was not fully explored by the sponsor. While interethnic differences in some transporters have been identified, *in vitro* evaluations of these pathways have not been reported to affect eltrombopag. As stated earlier, human liver microsome studies identified CYP1A2 and CYP2C8 as the isozymes most likely responsible for the oxidative metabolism of eltrombopag. Differences in the activity of CYP2C8 between populations of East Asian and European ancestry have not been identified.[3]

Conversely, CYP1A2 activity is reported to be approximately 1.5-fold higher in European than East Asian subjects and does not appear to reflect known interethnic differences in the frequencies of CYP1A2 genotypes or haplotypes.[4] The as yet unidentified genetic variation that influences CYP1A2 gene regulation may contribute to the inter-ethnic difference in CYP1A2 activity. If CYP1A2 does metabolize eltrombopag in humans in vivo, the lower hepatic CYP1A2 activity in East Asian populations may contribute to the lower average eltrombopag CL/F. Therefore lower CYP1A2 activity may contribute to a

[3] Kim K, Johnson JA and Derendorf H. Differences in Drug Pharmacokinetics Between East Asians and Caucasians and the Role of Genetic Polymorphisms. *J Clin Pharmacol.* 2004; 44; 1083-1105.

[4] Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotypephenotype relationship in Swedes and Koreans. *Eur J Clin Pharm.* 2007; 63: 537-46.

lower rate of elimination and higher bioavailability as a consequence of a diminished first pass metabolism.

Inter-ethnic dietary habits may also play a role in this issue. A preclinical study in the rat reports that a low protein (6% vs 24% casein) diet decreases CYP1A2 expression 73% and decreases methoxyresorufin O-demethylase (MROD) activity 6-fold.[5] In addition, two studies report an increase in the CYP1A2 metabolic rate with increased protein dietary intake. One study reports a ~40% decrease in antipyrine (CYP1A2 substrate) t1/2 & ~12% increase in Vd in native Sudanese vs Sudanese following western migration and changing from vegetarian to meat diet.[6] Another study compared a British population eating a normal western diet to an Asian population residing in London but eating a more Asian diet. This study reported a 20-60% increase in Clomipramine (CYP1A2 substrate) AUCinf and 50-60% higher Cmax in the Asian population.[7] The authors cited diet as a likely cause. Further, charcoal-broiled beef is also known to induce CYP1A2 enzymes. This may, in part, explain the differences in exposure noted in East Asian subjects in the Western and Japan studies.

Human liver microsome studies identified uridine diphosphate glucuronosyltransferase UGT1A1 and UGT1A3 as the enzymes most likely responsible for the glucuronidation of eltrombopag. An inter-ethnic difference has been reported in the activity of UGT1A1 *in vivo*.[8] In addition, global studies of polymorphisms in UGT1A have shown alleles and genotypes to be unequally distributed among different ethnic human populations across the world resulting in significant pharmacokinetic variability and toxicity (e.g., irinotecan). It is very possible that any UGT1A1 mediated metabolism of eltrombopag may display an inter-ethnic difference between subjects of East Asian and European ancestry. Lower UGT1A1 activity will contribute to a lower rate of elimination and higher exposure as a consequence of a diminished Phase 2 metabolism.

Although inter-ethnic differences in the frequency of UGT1A3 alleles of functional consequence have been reported, the *in vivo* consequences of this variation are not known.[9] Therefore the role of UGT1A3 can not be ruled out.

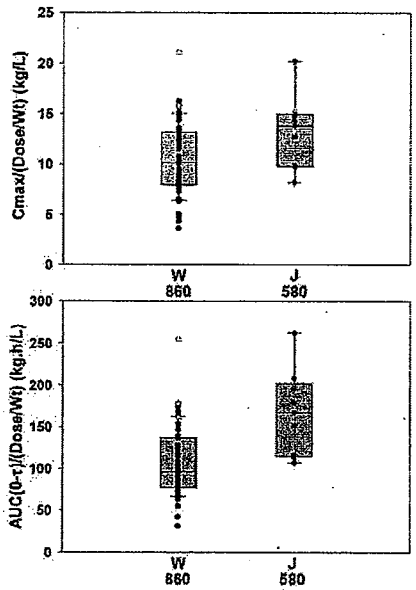
As stated earlier, body weight is a significant covariate for eltrombopag CL/F and Vc/F that was identified in the pop-PK analysis. One of the major factors contributing to inter-ethnic differences in pharmacokinetics between the East Asian and Caucasian populations is the well recognized difference in average body weight. The average body weight of the healthy Japanese subjects included in the eltrombopag studies (TRA104603 and TRA105580) was approximately 10kg lower than the average body weight of the healthy Western subjects studied.

The relationship between body weight and eltrombopag Cmax and AUC(0-∞) was considered in these two populations. Greater overlap was noted in the weight adjusted single dose eltrombopag parameters in both populations and the contribution of bodyweight was considered inconclusive. However, a similar adjustment in the repeat dose studies at the 50 mg dose suggests body weight contributes, somewhat, but does not totally account for the higher eltrombopag exposure between the two populations (Figure 12).

Figure 12: Eltrombopag Dose/Body Weight adjusted Cmax and AUC(0-τ) in healthy Japanese (J) (Day 10) and Western (W) subjects (Day 5)

[5] Cancino-Badías L, Reyes RE, Nosti R, Pérez I, Dorado V, Caballero S, et al. Modulation of rat liver cytochrome P450 by protein restriction assessed by biochemical and bacterial mutagenicity methods. *Mutagenesis*. 2003;18(1):95-100
[6] Branch RA, Salih SY, Homeida M. Racial differences in drug metabolizing ability: a study with antipyrine in the Sudan. *Clin Pharmacol Ther*. 1978;24(3): 283-6.
[7] Allen JJ, Rack PH, Vaddadi KS. Differences in the effects of clomipramine on English and Asian volunteers. Preliminary report on a pilot study. *Postgrad Med J*. 1977;53 Suppl 4:79-86.
[8] Chowbay B, Zhou S, Lee EJD. An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. *Drug Metab Rev*. 2005; 37: 327-78.
[9] Chen Y, Chen S, Li X, Wang X, Zeng S. Genetic variants of human UGT1A3: Functional characterization and frequency distribution in a Chinese Han population. *Drug Metab Disp*. 2006; 34: 1462-7.

following repeat doses of 50mg once daily. Individual data are shown (symbols) as well as boxes representing the 25-75th percentiles (with median) and bars representing the 10-90th percentiles.



To gain further insight into the mechanisms contributing to the higher eltrombopag exposure observed in Japanese than Western subjects, an exploratory pharmacogenetic investigation was performed (see Appendix 4.3). None of the genetic markers tested were associated with the difference in eltrombopag exposure observed between the East Asian and non-East Asian populations. Genetic markers within the CYP3A5 and SLCO5A1 gene regions were associated with variability in eltrombopag exposure in the Caucasian subjects. None of the tested genetic markers were reproducibly associated with the exposure variability in East Asians. Therefore the genetic association analysis did not provide any new insight into the potential determinants of the higher eltrombopag exposure observed between the East Asian and non- East Asian populations. Several limitations exist in the strength of this pharmacogenetic investigation to identify polymorphisms capable of predicting differences in eltrombopag PK and PD variability. These are discussed in detail below.

b(5)

Overall the percent of African American healthy subjects in the clinical trials of eltrombopag was very small. Increased exposure in African American subjects was noted in some but not all clinical pharmacology studies of eltrombopag. The mass balance study (1029861) enrolled 2 African American subjects and reported an approximately 15% increase in AUC(0-∞) and a 58% increase in half-life between African American subjects and non- African American subjects. The single dose study TRA105122 reported African American healthy subjects (N=12) had an approximately 40% higher plasma eltrombopag exposure compared to Caucasian healthy subjects (N=67). Repeat dose Study 497115/002 suggests a 12-15% higher plasma eltrombopag exposures in African American healthy subjects (n=3) than White Caucasian healthy subjects (N=89). Repeat dose study TRA 102860 showed a increase exposure (median) between African American (N=8) and Caucasian subjects (N=55) in some cohorts (i.e., 75 mg (29% increase AUC(0-∞) and 70% increase Cmax). Repeat dose study TRA 102863 showed a increase exposure (median) between African American (N=9) and

Caucasian subjects (N=22) in some cohorts (i.e., 100 mg (17% increase AUC0-τ) and 44% increase Cmax) and 200 mg (9% increase AUC0-τ and 14% increase Cmax)).

Additional information on the repeat dose pharmacokinetics of eltrombopag in healthy African American subjects is available from study TRA105120. In this study the influence of eltrombopag 75mg once daily on the pharmacokinetics of a single 10mg dose of rosuvastatin was studied in healthy subjects, including East Asian subjects (N=18), African American (N=11) subjects and Caucasian (N=3). The Cmax and AUC(0-τ) in East Asian and African American subjects was similar and approximately twice that of the Caucasian subjects. Given the apparent clearance of eltrombopag was noticeably higher in both Caucasian and Asian subjects in this study as compared to other studies (See section 4.3.11), the clinical significance of this study finding relative to African American ethnicity is unclear. b(5)

Based on these results it appears that there is a trend toward increased exposure in some African American subjects that may be approximately 40%. This can not be accurately quantified given the limited representation of this population in clinical studies. The rationale for these differences in exposure is likely due to differences in the metabolic pathways similar to that suggested for the East Asian population above.

An inter-ethnic difference has been reported in the activity of UGT1A1. The frequency of promoters with decreased activity was found to be highest in the African population.[10] Further, the mass balance study reported that the subject with the highest exposure was an African American who, interestingly, also had the highest screening bilirubin (a marker of UGT1A1 activity). This subject showed a lower fraction of fecal glutathione conjugates and higher urinary (oxidative) metabolite recovery compared to Caucasian subjects (see Appendix 4.3). Therefore, there is a potential for any UGT1A1 mediated metabolism of eltrombopag to display an inter-ethnic difference between the African American and Caucasian populations.

Dose adjustment is not appropriate at this time given the limited information on exposure in the African American population. b(5)

Study TRA103452 investigated the pharmacokinetics of eltrombopag in subjects with mild, moderate, and severe hepatic impairment compared to healthy subjects following administration of a single 50 mg dose of eltrombopag. Healthy subjects were matched to the moderate hepatic impairment group for age, body mass index (BMI), and sex. Plasma PK samples were collected over 120 hours after single dose administration.

Thirty-three subjects were enrolled in the study, including eight subjects with mild (Child-Pugh score of 5 to 6), eight subjects with moderate (Child-Pugh score of 7 to 9), nine subjects with severe hepatic impairment (Child-Pugh score of 10 to 15), and eight healthy control subjects; PK data were available for all except one subject with severe hepatic impairment.

Significant between-subject variability (%CVb) was observed in the plasma eltrombopag PK parameters. Variability in AUC(0-∞) and Cmax increased, and tmax was delayed with increasing severity of hepatic impairment. On average, plasma eltrombopag AUC(0-∞) values were 41% higher in subjects with mild hepatic impairment and 80 to 93% higher in subjects with moderate to severe hepatic impairment; t1/2 values were 71% higher in subjects with mild hepatic impairment and 2.08 to 2.14-fold higher in subjects with moderate to severe hepatic impairment compared to the healthy subjects (table 24). However, there was significant overlap in the data, particularly for AUC(0-∞), between the groups. In contrast, Cmax values appeared to decrease with increasing severity of hepatic impairment.

[10] Beutler E., Gelbart T., Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc. Natl. Acad. Sci. USA*, 95: 8170-4, 1998.

Table 24: Selected PK Parameters for Study TRA103452

Parameter	Healthy (N=8)	Hepatic-Impaired Mild (N=8)	Hepatic-Impaired Moderate (N=8)	Hepatic-Impaired Severe (N=8)
AUC(0-t)[a] (ng h/mL)	61,377 (59.2)	82,661 (41.6)	107,835 (54.3)	99,331 (83.3)
AUC(0-∞)[a] (ng h/mL)	66,026 (57.9)	92,814 (42.9)	127,211 (60.9)	118,752 (83.0)
Cmaxa (ng/mL)	5,427 (47.0)	4,677 (49.5)	3,843 (63.3)	2,754 (86.9)
t1/2a (h)	21.3 (39.9)	36.4 (56.7)	44.4 (34.4)	45.6 (12.3)
Tmax[b] (h)	3.0 (2.5, 6.0)	3.5 (2.5, 4.0)	4.9 (2.0, 7.0)	4.0 (3.0, 8.0)

a. Geometric mean (CVb%)
b. Presented as median and (minimum, maximum).

Plasma eltrombopag PK parameters did not correlate with Child-Pugh score. Plasma eltrombopag AUC(0-∞) and t1/2 were positively correlated with bilirubin. Cmax was positively correlated and t1/2 was negatively correlated with albumin and platelet count.

Attempts were made to determine plasma unbound eltrombopag concentrations in a portion of the plasma samples from subjects enrolled, using a 96 well plate equilibrium dialysis method. However, the results were deemed highly unreliable due to the large within- and between-run variability observed in the quality control plasma samples. Therefore, plasma unbound eltrombopag data are not available in subjects with hepatic impairment.

A reviewer generated analysis of albumin and total protein in the TRA103452 study population showed a trend toward lower albumin and total protein with worsening hepatic function (Table 25).

Given this increased exposure and the risk of a higher free eltrombopag, a reduced starting dose (e.g., 25 mg) should be considered in subjects with moderate hepatic impairment and eltrombopag should be used with great caution in severe hepatic impairment.

Table 25: Reviewer Generated Analysis of Albumin and Total Protein by Liver Function

Parameter	*Healthy*	*Hepatic Impairment*		
		Mild	*Mod*	*Severe*
Albumin (g/dL)	*3.9 (3.3--4.2)*	*3.7 (3-4.6)*	*3.1 (2.6-3.7)*	*3.1 (2-4.9)*
Total Protein (g/d/L)	*6.9 (5.6-7.3)*	*6.8 (6-7.1)*	*6.45 (6-7.1)*	*6.3 (5.4 -7.6)*

Study TRA104412 is an ongoing study investigating the pharmacokinetics of eltrombopag in subjects with mild, moderate, and severe renal impairment compared to healthy subjects following administration of a single 50 mg dose of eltrombopag. Healthy subjects were matched to the moderate renal impairment group for age, BMI, and sex. Plasma PK samples were collected over 120 hours after single dose administration.

At the time of the interim analysis, safety data were available for 25 subjects, including eight subjects with mild renal impairment (creatinine clearance (CrCL) 80 to 50mL/min), eight subjects with moderate renal impairment (CrCL 49 to 30mL/min), three subjects with severe renal impairment (CrCL <30mL/min), and six healthy control subjects. PK data were available for all except one healthy subject. Subjects with renal impairment were taking many chronic medications; however, drugs expected to significantly alter plasma eltrombopag exposure, such as antacids, were not co-administered with eltrombopag.

Following a single, oral 50 mg dose of eltrombopag, moderate to high between-subject variability (CVb%) was observed in PK parameters and variability increased with increasing severity of renal impairment. Plasma eltrombopag Cmax and CL/F were significantly correlated with serum creatinine (SCr). Cmax decreased and CL/F increased with increasing level of renal impairment. There were also trends for AUC(0-∞) and t1/2 to decrease with increasing level of renal impairment. Pearson's correlation coefficient for Cmax: -0.407 (p=0.05), CL/F: 0.406 (p=0.05), AUC(0-∞): -0.369 (p=0.08), and t1/2: -0.381 (p=0.07).

Although there appears to be a trend toward reduced plasma eltrombopag exposure in subjects with renal impairment, there was substantial variability, (particularly in the severe renal impairment group) and significant overlap in exposures between subjects with renal impairment and healthy subjects as reflected in the wide 90% CIs for the group comparisons of plasma eltrombopag AUC(0-∞), Cmax, and t1/2 (Table 26).

Table 26: Selected PK Parameters for Study TRA104412

Parameter	Healthy Subjects	Renal Impaired		
		Mild	Moderate	Severe
AUC(0-t) (ng.h/mL) [CVb%][a]	68.0 (42.1, 110) [40.2]	40.0 (24.8, 64.7) [62.6]	37.5 (22.1, 63.5) [69.9]	16.9 (0.162, 1763) [567]
AUC(0-∞) (ng.h/mL) [CVb%][a]	72.7 (46.2, 115) [37.9]	44.9 (28.5, 70.7) [58.6]	41.0 (24.9, 67.5) [65.4]	19.7 (0.245, 1588) [465]
Cmax (ng/mL) [CVb%][a]	6.94 (4.58, 10.5) [34.4]	4.29 (3.00, 6.11) [44.5]	5.01 (3.03, 8.29) [66.1]	2.12 (0.042, 107) [333]
CL/F (L/h) [CVb%][a]	0.69 (0.44, 1.08) [37.9]	1.11 (0.71, 1.75) [58.6]	1.22 (0.74, 2.01) [65.4]	2.53 (0.03, 204) [465]
t1/2 (h) [CVb%][a]	26.9 (21.4, 33.8) [18.5]	19.6 (14.0, 27.4) [42]	15.5 (10.4, 22.9) [49.8]	11.3 (0.70, 180) [158]
tmax[b] (h)	2.55 (2.50, 3.00)	3.00 (2.50, 4.00)	2.74 (1.00, 4.00)	3.00 (2.50, 6.00)

a. Geometric mean (95% CI [Coefficient of variation as a percentage, CVb%])
b. Presented as median and (minimum, maximum).

Plasma unbound eltrombopag data are not available in subjects with renal impairment for the same reason as reported above for hepatic impairment. This is significant given the high protein binding of eltrombopag and the potential effects of renal impairment on protein binding. A reviewer generated analysis of albumin and total protein (TP) concentrations was not possible because these data were not provided by the sponsor.

The lack of information regarding the protein binding of eltrombopag in the setting of renal impairment combined with the extreme variability noted above make this study inconclusive. Given that the mass balance study failed to identify parent compound in the urine, the problem of protein binding in the setting of renal impairment out ways concerns regarding accumulation. Close monitoring is recommended in patients with renal impairment.

The sponsor conducted an exploratory investigation of the impact of polymorphisms in genes regions key to the metabolism of eltrombopag on the pharmacokinetic (PK) and pharmacodynamic (PD) responses associated with eltrombopag (see Appendix 4.3). This investigation utilized data from ten clinical studies: TRA104603, TRA105580, 497115/002, 497115/005, TRA104631, TRA105122, TRA102863, TRA102860 Part 1, TRA100773A and TRA100773B. The analyses focused on Asian and Caucasian populations and included healthy volunteers and patients with ITP.

The primary objective of the study was to identify any genetic basis for the variability in PK following administration of eltrombopag, being the primary PK endpoint AUC. The secondary objective of the study was to evaluate the impact of genetic variants on eltrombopag PD variability, being the secondary endpoint the change in maximum platelet count from baseline.

The sponsor reported that 1) no polymorphisms were associated with differences in eltrombopag exposure between Asian and White subjects, 2) three polymorphisms in CYP3A5 were associated with variability in eltrombopag AUC in both Caucasian Healthy and ITP subjects. However, all these markers were in complete linkage disequilibrium with each other and more than a dozen known genes, making it difficult to define causative associations, and 3) One polymorphism in SLCO5A1, encoding the organic anion transporter, OATPJ (OATPRPM) was associated with variability in AUC in both Caucasian Healthy and ITP subjects.

Several limitations exist in the strength of this study to identify polymorphisms capable of predicting differences in eltrombopag PK and PD variability. First, this is a retrospective study that was not powered to identify those differences. Second, the samples were drawn from a highly heterogeneous population of multiple studies and with unequal distributions of Asian and White subjects. Finally, the selection of the studied genes and polymorphism was not based on their role on eltrombopag PK or PD and did not take into account the frequency of such genetic variants in the studied population.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

No geriatric clinical pharmacology studies were submitted with this application. Of the total of 106 patients in 2 randomized clinical studies of eltrombopag 50 mg dose, 22% were 65 years of age and older, and 9% were 75 years of age and older. No overall differences in effectiveness were observed between these patients and younger adult patients. The incidence of adverse reactions was slightly higher in patients 65 to 74 years of age (77%) who were treated with eltrombopag than in 18 to 49 year (61%) and in 50 to 64 year (67%) age groups. A dose adjustment in the geriatric population does not appear necessary.

2.3.2.2 Pediatric patients

GlaxoSmithKline is [redacted] for NDA 22-291. No pediatric data, therefore, have been included in this application. b(4)

2.3.2.3 Gender

As shown in Table 10 above, a pop-PK model predicts that males have a total body clearance of eltrombopag that is approximately 25% higher than females. Despite these estimated differences, post hoc results from the two pivotal trials failed to show a trend toward a difference in efficacy or safety related to sex (see sections 2.2.4.1 and 2.2.4.2). Dose adjustments based on sex do not appear necessary.

2.3.2.4 Race

Based on estimates from a pop-PK model, plasma eltrombopag exposure was estimated to be approximately 70% higher in some East Asian subjects with ITP as compared to non-East Asian subjects who were predominantly Caucasian. In addition,

the pharmacodynamic response to Eltrombopag was qualitatively similar, but the absolute response was somewhat greater in East Asian subjects (see section 2.2.4.1). The risk of heptobiliary toxicity may be higher in the East Asian population (see section 2.2.4.2).

Based on this, the initiation of eltrombopag at a reduced dose of 25 mg once daily should be considered for patients of East Asian ancestry such as Chinese, Japanese, Taiwanese, or Korean. If after 2 ⟶ weeks, the platelet count remains below 50,000/µL, a dose escalation to 50 mg once daily should be considered. b(5)

A trend suggesting approximately 40% higher systemic eltrombopag exposure in some healthy African-American subjects was noted in several clinical pharmacology studies. The effect of this difference on the safety and efficacy of Eltrombopag has not been established so a dosing recommendation can not be made at this time; b(5)

2.3.2.5 Renal impairment

The disposition of eltrombopag was studied in patients with varying degrees of renal impairment. Elimination of the drug was reported to be inversely correlated with the creatinine clearance. The total body clearance of eltrombopag was reported to increase in patients with impaired renal function by 60% in mild (CLcr = 80-50 mL/min), 77 % in moderate (CLcr = 49- 30 mL/min) and 3 fold in severe renal impairment (CLcr = < 30mL/min). Hemodialysis was not studied. Due to substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers the effect of varying degrees of renal function reported in this clinical study was deemed inconclusive. Protein binding of eltrombopag is likely affected by impaired renal function, but this was not evaluated in the clinical study.

Given the concern regarding the protein binding effects associated with renal impairment, patients with impaired renal function should use eltrombopag with caution and close monitoring. There is insufficient data to recommend a dose adjustment at this time.

2.3.2.6 Hepatic impairment

The disposition of eltrombopag was compared in patients with hepatic impairment and subjects with normal hepatic function. Total body clearance of eltrombopag was reduced by approximately 50% in patients with moderate (as indicated by the Child-Pugh method) hepatic impairment. The half-life of eltrombopag is prolonged 2 fold in patients with moderate hepatic impairment. Protein binding of eltrombopag is likely affected by impaired hepatic function, but this was not evaluated in the clinical study. These results were also limited by a high degree of variability in the moderate and severe populations.

Initiation of eltrombopag at a reduced dose of 25 mg once daily should be considered for patients with moderate hepatic impairment. b(5)

Eltrombopag should be used with great caution in severe hepatic impairment.

2.3.2.7 What pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies in pregnant women. Eltrombopag should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. No data regarding the excretion of eltrombopag or its metabolites in the milk of humans or animals was provided. Because many drugs are excreted in human milk, caution should be exercised when eltrombopag is administered to a nursing woman.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No specific studies or analyses were designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of eltrombopag. Antacids have been shown to reduce the biolavailability of eltrombopag by 70% (see section 2.2.5.3).

A reviewer generated exploratory analysis of smokers in Study TRA105580 (healthy Japanese subjects) showed a small trend toward lower accumulation at 50 mg & 75 mg with smokers (See Appendix 4.3). While not clinically significant, this may indicate residual enzyme induction since eltrombopag is a substrate of both CYP1A2 and UGT1A.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, eltrombopag is a substrate of CYP 1A2 and 2C8 see section 2.2.5.6. It is likely that the metabolism of eltrombopag is affected by genetics; however, the sponsor's pharmacogenomic analysis was exploratory and underpowered so this issue has not been fully explored (see section 2.3.1).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro, eltrombopag was not an inhibitor of CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5, and was an inhibitor of CYP2C8 and CYP2C9.

A preliminary study was performed using expressed enzyme systems to screen the potential of eltrombopag to inhibit human CYP enzymes. The ability of eltrombopag to inhibit the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 was determined by measuring the metabolism of various probe substrates in the presence and absence of eltrombopag (0.1 to 100 µM) over a 10 minute period using a fluorescence plate reader. To assess time-dependent inhibition, the rate of change in the metabolism of the probe substrate was determined every 5 minutes over a 30 minute period. The probe substrates and activities measured were 7-ethoxyresorufin O-dealkylation (EROD; CYP1A2), 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid O-dealkylation (FCA; CYP2C9), 3-butyryl-7-methoxycoumarin O-dealkylation or 7-ethoxy-4-trifluoromethyl-coumarin O-dealkylation (BMC or EFC; CYP2C19), 4-methylaminomethyl-7-methoxycoumarin O-dealkylation (MMC; CYP2D6), diethoxyfluorescein O-dealkylation (DEF; CYP3A4) and 7-{3-(4-phenylpiperazin-1-ylmethyl)benzyl}-resorufin O-dealkylation (PPR; CYP3A4).

Eltrombopag was an inhibitor of CYP1A2 and CYP2C9 activities in the expressed enzyme systems with IC50 values of 3.5 and 9.3 µM, respectively. Inhibition against CYP2D6 and CYP3A4 (substrate DEF) was observed, with IC50 values of 27 and 19 µM, respectively. Eltrombopag was also an inhibitor of CYP2C19 and CYP3A4 (substrate PPR) activities (IC50 values of 32 and 68 µM, respectively). Eltrombopag showed no evidence for time-dependent inhibition of CYP1A2, CYP2C9, CYP2C19 or CYP2D6; however, inhibition of CYP3A4 (substrates DEF and PPR) increased 50% to 70% over 30 minutes.

A definitive study was conducted using human liver microsomes to evaluate the potential of eltrombopag to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19,

CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11 enzymes in the microsomes. Pooled human liver microsomes were incubated at 37°C with eltrombopag (0.1 to 100 µM) in the presence of a NADPH regenerating system and CYP probe substrates. The probe substrates and activities measured were phenacetin O-deethylation (CYP1A2), coumarin 7-hydroxylation (CYP2A6), paclitaxel 6α-hydroxylation (CYP2C8), diclofenac 4'-hydroxylation (CYP2C9), S-mephenytoin 4'-hydroxylation (CYP2C19), bufuralol 1'-hydroxylation (CYP2D6), chlorzoxazone 6-hydroxylation (CYP2E1), lovastatin 6β-hydroxylation (CYP3A4/5), midazolam 1'-hydroxylation (CYP3A4/5), nifedipine oxidation (CYP3A4/5), testosterone 6β-hydroxylation (CYP3A4/5) and lauric acid 12-hydroxylation (CYP4A9/11).

Eltrombopag at concentrations up to 100 µM showed no *in vitro* inhibition of CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11. Eltrombopag was an inhibitor of CYP2C8 and CYP2C9 as measured using the probe substrates paclitaxel and diclofenac, with IC50 values of 24.8 µM and 20.2 µM, respectively. Eltrombopag was not found to be a metabolism-dependent inhibitor of the evaluated enzyme activities.

In addition, eltrombopag did show potential for CYP induction based on weak activation of human PXR and no increase in the mRNA level or catalytic activity of CYP1A2, CYP2B6 or CYP3A4 in a human hepatocyte study.

Study 497115/002 was conducted to evaluate the potential impact of co-administering eltrombopag 75mg QD for seven days on plasma PK of a "cocktail" of CYP substrates, including caffeine (CYP1A2), flurbiprofen (CYP2C9), omeprazole (CYP2C19), and midazolam (CYP3A4), administered as single doses. This study also evaluated plasma eltrombopag PK following single and repeat dose escalation. For the CYP interaction phase of the study, midazolam 5mg was administered (intravenous formulation administered by mouth) on Days 1 and 8, caffeine 100mg, flurbiprofen 50mg, and omeprazole 20mg were administered orally on Days 2 and 9, and eltrombopag 75mg QD was administered orally on Days 3 to 9.

Eltrombopag, administered as 75mg QD for 7 days, did not inhibit or induce CYP1A2, CYP2C9, CYP2C19, or CYP3A4 as evidenced by no change in probe substrate PK (Tables 27 and 28). The sponsor states that CYP 2C8 was not studied *in vivo*, but its *in vitro* potency for inhibition was similar to that for inhibition of CYP2C9 (IC50 values of 24.8 µM (CYP 2C8) and 20.2 µM (CYP 2C9)) and therefore "eltrombopag is not expected to interact with CYP2C8 substrates *in vivo*." While theoretically possible the reviewer believes the effect of eltrombopag on CYP2C8 substrates is unknown at this time.

Table 27: Summary of Metabolic Indices

CYP	Probe	Geometric LS mean before treatment	Geometric LS mean after treatment	Ratio (90% CI)
CYP1A2	paraxanthine/caffeine	0.80	0.78	0.97 (0.91–1.03)
CYP2C9	4-hydroxyflurbiprofen	0.67	0.65	0.96 (0.94–0.98)
	free 4-hydroxyflurbiprofen	0.67	0.63	0.93 (0.89–0.98)
CYP2C19	omeprazole/5- hydroxomeprazole (2 h post-dose)	0.74	0.74	1.00 (0.93–1.08)
	plasma omeprazole/5-hydroxomeprazole (3 h post-dose)	0.50	0.51	1.02 (0.88–1.18)

Table 28: Midazolam (CYP 3A4 probe) Pharmacokinetic Parameter Estimates

Parameters	Geometric LS mean before treatment	Geometric LS mean after treatment	Ratio (90% CI) b
AUC(0-∞) (ng.h/mL)	83.51	86.84	1.04 (0.96–1.13)
Cmax (ng/mL)	34.98	34.43	0.98 (0.89–1.09)
CL/F (mL/h)	59,875	57,574	0.96 (0.88–1.05)

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No, *in vitro* studies using expressed human transporters demonstrated that eltrombopag is not a substrate or inhibitor of Pgp.

The role of human Pgp in the transport of eltrombopag was investigated *in vitro* using confluent monolayers of Madin-Darby canine kidney type II cells (MDCKII-MDR1) overexpressing human Pgp. Directional transport was determined by measurement of apical to basolateral (A→B) and basolateral to apical (B→A) rates of transport using [14C]eltrombopag at a nominal concentration of 3 µM. In addition, transport rates in MDCKII-MDR1 cells were measured in the presence of 2 µM GF120918A (a potent inhibitor of Pgp) to evaluate whether eltrombopag is a substrate of Pgp and to determine the passive membrane permeability of [14C]eltrombopag. The efflux ratio of [14C]eltrombopag (B→A transport/A→B transport) in the absence and presence of GF120918A was 1.0 and 1.7, respectively (Table 29) suggesting that [14C]eltrombopag is not a human Pgp substrate. In addition, the passive membrane permeability of [14C]eltrombopag in the presence of GF120918A was moderate (65.0 nm/sec).

Table 29: Results of P-glycoprotein-mediated Transport Studies for SB-497115 in MDCKII-MDR1 Cell Monolayers

Compound	Rate A→B (nmoles/h/cm2)	Rate B→A (nmoles/h/cm2)	Apical Efflux Ratio	A→B Mass Balance (%)	B→A Mass Balance (%)	$P_{7.4}$ (nm/s)	Pgp Substrate	Passive Permeability Class
3 µM [14C]eltrombopag	0.04 ± 0.012	0.039 ± 0.008	1.0 1.7	41.0 ± 1.5	55.0 ± 2.3	-65.0 ± 15.0	N	-
3 µM [14C]eltrombopag + 2 µM GF120918A	0.029 ± 0.006	0.05 ± 0.009		50.0 ± 1.5	62.0 ± 2.5		-	Moderate
3 µM [3H]amprenavir	0.024 ± 0.005	0.664 ± 0.011	28.0 1.3	85.0 ± 2.2	87.0 ± 2.4	-371 ± 51.0	Y	-
3 µM [3H]amprenavir + 2 µM GF120918A	0.281 ± 0.011	0.354 ± 0.015		87.0 ± 3.3	87.0 ± 1.9			High

Data is the mean ± standard deviation from three monolayers, except for P7.4 (where n=6). All donor compartments contained Lucifer yellow to determine monolayer integrity (pass criterion P7.4 ≤50 nm/s) and wells designated for P-glycoprotein (P-gp) inhibition contained ca. 2 µM GF120918A in both donor and receiver compartments. [3H]Amprenavir was used as positive control (pass criterion apical efflux ratio ≥15).

A study was conducted to determine whether eltrombopag is an inhibitor of transport of a human Pgp probe substrate in MDCKII-MDR1 cells in vitro. The effect of eltrombopag on the Pgp-mediated transport of digoxin was assessed in MDCKII-MDR1 cells by determining the B→A transport of [3H]-digoxin in the absence or presence of eltrombopag (0.1, 1, 3, 10, 30, 50, 75 and 100 µM). GF120918A (2 µM) was used as a positive control. A tabulated summary of this study is provided in Table 30.

Table 30: The effect of eltrombopag on the Pgp-mediated transport of digoxin (30 nM)

Compound	Concentration (µM)	Digoxin transport rate (pmole/cm2/h)	Digoxin transport rate (% control)
Digoxin only	-	1.29 ± 0.175	100
Eltrombopag	0.1	1.11 ± 0.257	86.4 ± 19.9
	1	1.38 ± 0.058	107 ± 4.51
	3	1.56 ± 0.128	121 ± 9.91
	10	1.38a	106a
	30	1.74 ± 0.176	135 ± 13.6
	50	1.74 ± 0.304	135 ± 23.5
	75	1.47 ± 0.155	114 ± 11.9

	100	1.51 ± 0.20	116 ± 15.3
GF120918	2	0.25 ± 0.04	19.5 ± 3.02

Eltrombopag produced no marked inhibition of digoxin at any concentration. Therefore, the data suggest that eltrombopag is not an inhibitor of digoxin transport via Pgp at concentrations up to 100 µM.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Eltrombopag is not a substrate for OATP1B1, OATP1B1, but is an inhibitor of this transporter. Eltrombopag has not been tested as a substrate or inhibitor of other transport proteins.

The transport of [14C]eltrombopag by human OATP1B1 was investigated in Chinese hamster ovary (CHO) cells stably transfected with human OATP1B1 (CHO-OATP1B1) and wildtype CHO cells (CHO-WT) *in vitro*. Uptake of [14C]eltrombopag (0.6 µM) in both cells lines was measured in the absence and presence of 10 µM rifamycin (a potent OATP1B1 inhibitor) to confirm the role of OATP1B1 in the transport. The functional activity of OATP1B1 was demonstrated with the positive control, [3H]estradiol 17β-D-glucuronide (0.025 µM). Since eltrombopag exhibits >99% binding to plasma proteins, uptake experiments were also performed in the presence of 0.5% bovine serum albumin (BSA). [14C]Eltrombopag (0.6 µM) was not a substrate of human OATP1B1 under any of the assay conditions used (Table 31).

Table 31: A tabulated summary of the uptake of [14C]eltrombopag in the absence and presence of rifamycin

Compound	Uptake rate (pmoles/min/mg protein)			
	Absence of 0.5% Bovine Serum Albumin		Presence of 0.5% Bovine Serum Albumin	
	CHO-OATP1B1 cells	CHO-WT cells	CHO-OATP1B1 cells	CHO-WT cells
[14C]eltrombopag (0.6 µM)	14.2 ± 1.15	10.7 ± 1.04	0.641 ± 0.078	0.536 ± 0.080
[14C]eltrombopag (0.6 µM) + rifamycin (10 µM)	17.4 ± 1.70	16.6 ± 1.64	0.568 ± 0.078	0.483 ± 0.056
[3H]EG (0.025 µM)	0.407 ± 0.016	0.013 ± 0.003	0.256 ± 0.012	0.009 ± 0.001
[3H]EG (0.025 µM) + rifamycin (10 µM)	0.022 ± 0.002	0.013 ± 0.001	0.012 ± 0.002	0.008 ± 0.000

Key: Data are the mean ± standard deviation from 3 wells.
OATP1B1 = Organic anion transporting polypeptide 1B1.
CHO= Chinese hamster ovary.
WT = Wild type.
[3H]EG = [3H]Estradiol 17β-D-glucuronide.

The transport of [14C]eltrombopag by OATP1B1 was further investigated in CHO-OATP1B1 and CHO-WT cells *in vitro* at high concentrations using alternate labeled [14C]eltrombopag [Report CD2006/00841/00, m4.2.2.3]. Uptake of alternate labeled [14C]eltrombopag (3, 30 or 100 µM) in both cells lines was measured in the absence and presence of 10 µM rifamycin and 3 µM cyclosporine A (potent OATP1B1 inhibitors) to confirm the role of OATP1B1 in the transport. The functional activity of OATP1B1 was demonstrated with the positive control, [3H]estradiol 17β-D-glucuronide (0.025 µM). A tabulated summary of this study is provided in Table 32. [14C]Eltrombopag was not a substrate of human OATP1B1 at the concentrations studies (3 to 100 µM) under the assay conditions used.

Table 32: A tabulated summary of the uptake of [14C]eltrombopag in the absence and presence of rifamycin or cyclosporine A

	Uptake rate (pmoles/min/mg protein)							
	Absence of Rifamycin (10 µM)				Presence of Rifamycin (10 µM)			
	CHO-OATP1B1 cells		CHO-WT cells		CHO-OATP1B1 cells		CHO-WT cells	
Test Compound	37°C 0°C		37°C 0°C		37°C 0°C		37°C 0°C	
[3H]Estradiol 17β-D-glucuronide	0.783	0.19	0.0164	0.0093	0.0232	0.021	0.0118	0.0081
Alternate labeled [14C]eltrombopag (3 µM)	430	217	282	168	456	247	298	201

Alternate labeled [14C]eltrombopag (30 µM)	2569	887	1789	705	2692	910	1751	675
Alternate labeled [14C]eltrombopag (100 µM)	4848	1760	3411	1228	4660	1614	3223	1319

	Absence of Cyclosporine A (3 µM)				Presence of Cyclosporine A (3 µM)			
	CHO-OATP1B1 cells		CHO-WT cells		CHO-OATP1B1 cells		CHO-WT cells	
Test Compound	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
[3H]Estradiol 17β-D-glucuronide	0.664	0.929	0.0227	0.0174	0.0189	0.0408	0.0192	0.054
Alternate labeled [14C]eltrombopag (3 µM)	511	459	406	259	578	534	529	327
Alternate labeled [14C]eltrombopag (30 µM)	3064	2480	2691	1650	1609	1743	1552	1148
Alternate labeled [14C]eltrombopag (100 µM)	6698	5009	5378	3262	5437	4300	4336	2962

Key: Data are the mean ± standard deviation from 3 wells.
OATP1B1 = Organic anion transporting polypeptide 1B1.
CHO= Chinese hamster ovary.
WT = Wild type.

An *in vitro* study was undertaken to determine if eltrombopag was an inhibitor of OATP1B1. CHO-OATP1B1 monolayers were pre-incubated with eltrombopag (0.1, 1, 3, 10, 30 or 100 µM) or rifamycin (10 µM). Following removal of the pre-incubation solution, [3H]estradiol 17β-D-glucuronide (0.025 µM) was added to the wells and its uptake rates were then measured. A tabulated summary of this study is provided in Table 33.

Table 33: Inhibition of uptake of the probe substrate [3H]estradiol 17β-D-glucuronide by eltrombopag

Test Compound	Uptake rate of [3H]EG (fmoles/cm2/min)	Uptake rate of [3H]EG (% control)
[3H]EG only	3.6 ± 0.6	100 ± 18.1
[3H]EG + eltrombopag (0.1 µM)	3.7 ± 0.3	104 ± 7.4
[3H]EG + eltrombopag (1 µM)	3.0 ± 0.3	83.8 ± 7.5
[3H]EG + eltrombopag (3 µM)	1.7 ± 0.2	48.4 ± 4.8
[3H]EG + eltrombopag (10 µM)	0.2 ± 0.04	6.7 ± 1.1
[3H]EG + eltrombopag (30 µM)	0.1 ± 0.1	3.7 ± 3.6
[3H]EG + eltrombopag (100 µM)	0.04 ± 0.04	1.1 ± 1.2
[3H]EG + rifamycin (10 µM)	0.18 ± 0.08	4.9 ± 2.2a

The probe inhibitor rifamycin (10 µM) was used as a positive control.

Eltrombopag inhibited OATP1B1-mediated uptake of [3H]estradiol 17β-D-glucuronide with an IC50 value of 2.71 µM.

Study TRA105120 was conducted to determine the impact of coadministering eltrombopag on the PK of rosuvastatin, an HMG-CoA reductase inhibitor used to reduce total cholesterol and triglycerides, and an OATP1B1 substrate. This was an open-label, three-period, single sequence study. Subjects received a single dose of rosuvastatin 10mg in Period 1 followed by a 5-day washout, repeat doses of eltrombopag 75mg QD for four days in Period 2, and co-administration of rosuvastatin 10mg and eltrombopag 75mg for one day in Period 3. There was no washout between Period 2 and Period 3. PK samples were collected for 96 hours following single dose administration of rosuvastatin in each period.

Forty-two subjects were enrolled and 39 subjects were included in the statistical analysis of the PK data. Thirty-three (79%) of the subjects were male and nine (21%) were female. Twenty-two (52%) of the subjects were Asian (19 East Asian, 2 Central/South Asian, 1 Southeast Asian), 12 (29%) Black, four (10%) White, and four (10%) American Indian/Alaskan Native. Mean (range) age was 34 years (21 to 56 years), weight was 76kg (54 to 98kg), and BMI was 26kg/m^2 (18 to 35kg/m^2).

There are known racial differences in plasma rosuvastatin PK, with exposures in Asian subjects being approximately 2-fold those observed in non-Asian subjects. Therefore, rosuvastatin PK was evaluated for the overall population as well as for Asian and non-Asian subjects separately (see Appendix 4.3).

Co-administration of eltrombopag with rosuvastatin increased plasma rosuvastatin Cmax by 2.03-fold and AUC(0-∞) by 55% overall (Table 34). In the sub-population of

Asian subjects, plasma rosuvastatin AUC(0-∞) increased 32% and Cmax increased 61%; whereas, in the sub-population of non-Asian subjects, plasma rosuvastatin AUC(0-∞) increased 88% and Cmax increased 2.65-fold.

Table 34: Summary of Eltrombopag-Rosuvastatin Drug Interaction Results

Plasma Rosuvastatin PK parameter	Rosuvastatin+Eltrombopag (Treatment C)	Rosuvastatin (Treatment A)	Rosuvastatin+Eltrombopag vs. Rosuvastatin
AUC(0-∞) (ng·hr/mL)	96.0 (50)	61.9 (72)	1.55 (1.42, 1.69)
Cmax (ng/mL)	12.1 (53)	5.97 (81)	2.03 (1.82, 2.26)

Concomitant administration of eltrombopag and other OATP1B1 substrates should be used with caution. When substrates of OATP1B1 must be coadministered with eltrombopag, a reduced dose of the substrate should be considered and the patient should be carefully monitored for toxicity. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for coadministration with eltrombopag which appears reasonable.

A study was conducted to investigate the human UGT enzymes involved in the glucuronidation of eltrombopag *in vitro*. Pooled human liver microsomes (1 mg/mL) and ——— overexpressing individual UGT enzymes were incubated with [14C]eltrombopag (10 µM) at 37°C for up to 60 minutes. ——— incubations contained 0.25 mg/mL of UGT1A1, UGT1A3, UGT1A4, UGT1A7, UGT1A8, UGT2B4, UGT2B7 or UGT2B15; 0.15 mg/mL of UGT1A6 or UGT1A9; or 0.70 mg/mL of UGT1A10 or UGT2B17. Each ——— was tested for glucuronidation activity using the probe substrate trifluoperazine dihydrochloride (TFP) for UGT1A4, eugenol for UGT2B17 and 7-hydroxy 4-(trifluoromethyl)coumarin (HFC) for all other UGT enzymes tested. All samples were analyzed by both radio-HPLC and HPLC-MS. Insufficient information was provided by the sponsor to evaluate the validity and reliability of these assays. b(4)

During a 60 minute incubation with human liver microsomes, turnover of [14C]eltrombopag attributable to glucuronidation was 3%. One metabolite, K (glucuronide of eltrombopag), was observed. When incubated with individually expressed UGT enzymes, only UGT1A1 and UGT1A3 metabolized eltrombopag to form metabolite K. Thus, under these in vitro conditions, UGT1A1 and UGT1A3 were the enzymes responsible for the glucuronidation of eltrombopag. The drug interaction potential of this pathway not evaluated further *in vivo* because the sponsor states it is considered a minor pathway. ——— b(5)

The activities of human UGT enzymes UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 were investigated in vitro in the presence and absence of eltrombopag. Eltrombopag (0.25 to 250 µM) was incubated with ——— expressing individual UGT enzymes) and an appropriate probe substrate (TFP for UGT1A4 and HFC for all other enzymes tested) for 10 minutes at 37°C. A tabulated summary of this study is provided in Table 35. b(4)

Table 35: Inhibition of UGT

UGT Enzyme	Substrate	Eltrombopag IC50 (µM)	Positive Control	Positive Control IC50 (µM)
1A1	HFC	13	Curcumin	3.1
1A3	HFC	11	Curcumin	2.0
1A4	TFP	33	Curcumin	ND
1A6	HFC	21	Curcumin	6.0
1A9	HFC	3.0	Curcumin	0.83
2B7	HFC	21	Curcumin	9.7
2B15	HFC	20	Curcumin	7.7

Key:
UGT = Uridine diphosphate glucuronosyl transferase.
UGPGA = Uridine 5'-diphosphoglucuronic acid.

HFC = 7-hydroxy 4-(trifluoromethyl)coumarin.
TFP = Trifluoperazine dihydrochloride.
ND = Not determined.

Eltrombopag was a direct inhibitor *in vitro* of UGT1A9, UGT1A3, UGT1A1, UGT2B15, UGT1A6, UGT2B7 and UGT1A4 with IC50 values of 3.0, 11, 13, 20, 21, 21 and 33 µM, respectively. This was not explored further *in vivo* by the sponsor.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The drugs currently approved for use in the US for the short-term treatment of ITP are the intravenous immunoglobulins (anti-D and IVIg). After treatment with immunoglobulins, patients are generally retreated with either IVIg, or other drugs such as corticosteroids.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Corticosteroid use was identified as a significant covariate in the pop-PK model. Based on post-hoc AUC(0-τ) estimates, plasma eltrombopag exposure was approximately 38% higher in patients with ITP taking concurrent corticosteroids. There is no obvious clinical or metabolic rational for this increased exposure.

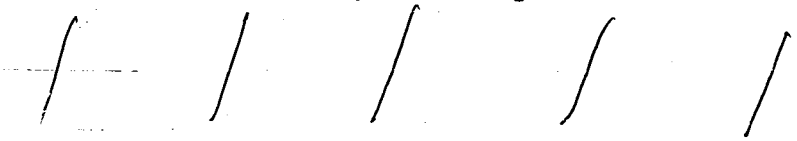
Corticosteroids are commonly involved in inducing the metabolism (e.g., UGT1A1) of many drugs including eltrombopag. This may suggest that the higher exposure observed in ITP patients receiving eltrombopag concurrently with corticosteroids may be due to factors other than a PK drug interaction. For example, the differences may be due in part to factors other than corticosteroid use, such as sex (a higher proportion of subjects taking corticosteroids were female), or perhaps corticosteroid use is a marker of more severe disease status.

A dose reduction in patient's that are concurrently taking corticosteroids with eltrombopag is not warranted at this time.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No pharmacodynamic drug-drug interactions were reported by the sponsor.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?



b(5)

Since the effect of UGT's inhibited by eltrombopag have not been explored in vivo patients concurrently taking these drugs (e.g., UGT1A1 [carvedilol, morphine, acetaminophen, etoposide, ironotecan], UGT1A3 [amitriptyline, clofibrate, ibuprofen, morphine, imipramine], UGT1A4[amitriptyline, imipramine, olanzapine], UGT1A6 [acetaminophen, morphine, valproic acid], UGT1A9[acetaminophen, morphine,

propofol, valproic acid], UGT2B7 [carbamazepine, codeine, , morphine , cyclosporine A, ketoprofen, zidovidine] and UGT2B15 [tolcapone, (s)-oxazepam]) with eltrombopag should be closely monitored.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None that have not been addressed in other sections (e.g., dosing in hepatic impairment, dosing in African American patients).

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Eltrombopag free acid is poorly soluble in water and exhibits a propensity to form both organic solvates and hydrates. It is a di-acid containing both a phenol and a carboxylic acid moiety with three calculated pKa's, pKa1 at 4.06, pKa2 at 9.57 and pKa3 at 11.88. Eltrombopag can, therefore, form both mono and bis-salts.

The bis-monoethanolamine salt of eltrombopag

b(4)

The aqueous solubility of eltrombopag is greatly affected by pH. It is insoluble up to pH 3 and has a solubility of approximately — mcg/mL at pH 7.4. Its solubility increases significantly beyond pH 7.4, reaching about — mcg/mL at pH 10. These data are presented in Table 36.

b(4)

Table 36: Solubility of Eltrombopag as a Function of pH at 25 degrees C in Aqueous Buffered Media

Buffer Media	Solubility (mcg/mL)
Up to pH 3	
pH 5	
pH 6	
pH 7.4	
pH 8	
pH 9	
pH 10	

b(4)

The passive apparent permeability of eltrombopag was determined using an MDCK cell line and was categorized as moderate (Table 37). No significant evidence of the involvement of p-glycoprotein in absorption was found.

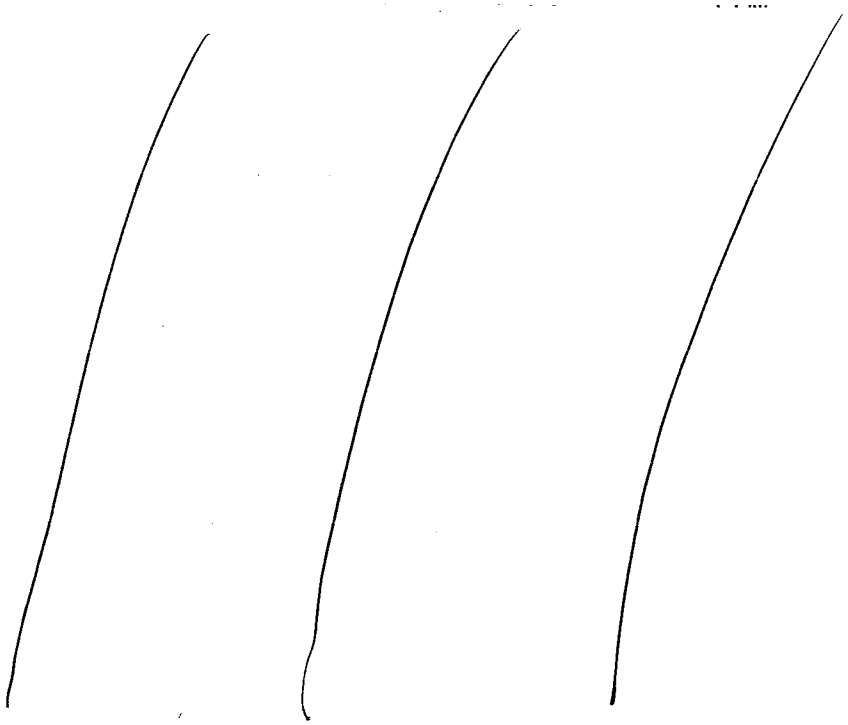
Table 37: Permeability of Eltrombopag Olamine in MDCK cell line

Compound	Passive Apparent Permeability (nm/sec)	Permeability Classification
Eltrombopag olamine		Moderate
Amprenavir (reference)		High
Propranolol (reference)		High

Based on solubility and permeability determinations, eltrombopag is classified as a Biopharmaceutics Classification System (BCS) Class 2/4 compound. For a BCS Class

2/4 compound, the particle size effects the dissolution behavior, and hence, the bioavailability. No *in-vitro in-vivo* correlation has been developed for eltrombopag.

The solubility of eltrombopag olamine presented some challenges to the development of a suitable dissolution method.



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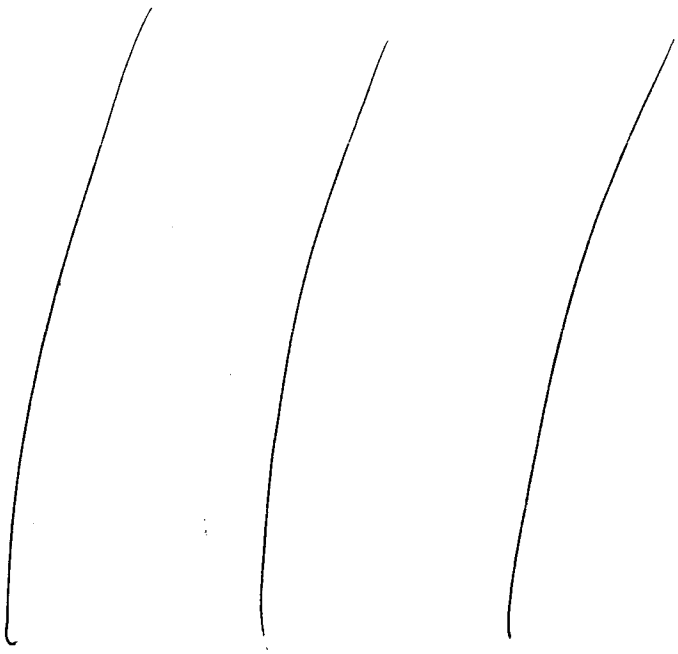

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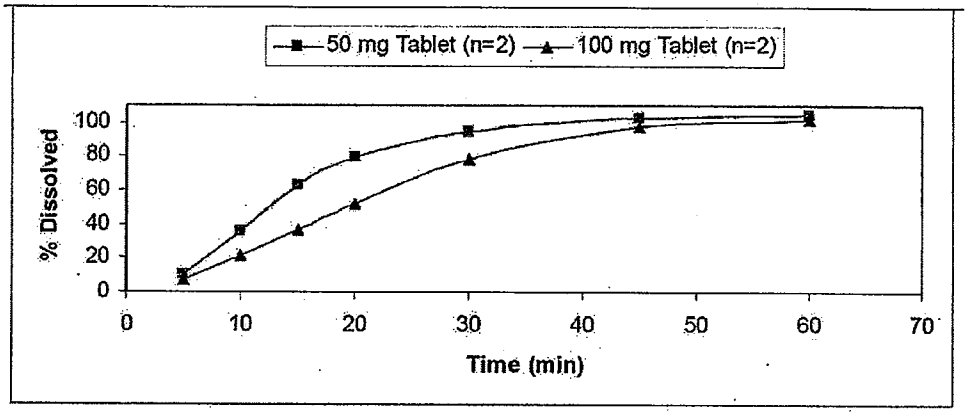
Based on these data, a discerning dissolution method was developed for release and stability testing. The dissolution medium is phosphate buffer pH 6.8 with 0.5% polysorbate 80 at 50 rpm. The proposed acceptance criterion has been set at Q = — at 45 minutes for 25 mg, 50 mg and 75 mg tablets and Q= —, at 60 minutes for 100 mg tablets. Dissolution profiles for 50 mg and 100 mg tablets by use of the validated method are provided in Figure 13.

Figure 13 Eltrombopag Tablets, pH 6.8 Buffer with 0.5% Polysorbate 80 and Apparatus 2 at 50 rpm



2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The sponsor reports that the absolute bioavailability of eltrombopag has not been determined because

b(4)

Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single 75 mg oral solution dose was estimated to be at least 52%.

Study 497115/005 was a Phase I, open-label, randomized, three-period, balanced crossover study designed to assess the relative bioavailability of the eltrombopag 25 mg oral capsule and film-coated tablet formulations (tablets manufactured at the R&D site) following administration of single 50mg doses (as two 25mg capsules or two 25mg tablets) in healthy adult subjects. The study also assessed the effect of food on the bioavailability of the tablet formulation. Plasma PK samples were collected over 48 hours after single dose administration in each period. There was a minimum 5- day washout

between each period. Eighteen subjects were enrolled and 16 subjects completed the study. All subjects were male and predominantly Caucasian (94%).

Following single dose administration in the fasted state, the eltrombopag 25mg oral film-coated tablet formulation delivered a 15% lower plasma eltrombopag AUC(0-∞) and 18% lower Cmax, on average, than the eltrombopag 25mg oral capsule formulation; there was no change in tmax (Table 41). The 90% CIs for the bioavailability comparison of the tablet versus the capsule fell outside of the 0.80 to 1.25 CI required to be considered equivalent, however these differences are not considered clinically significant and subsequent clinical studies, including all pivotal clinical safety and efficacy studies, used the tablet formulation.

Table 41: Summary of Plasma Eltrombopag PK Parameters and Treatment Comparisons to Assess Relative Bioavailability in Study 497115/005

Parameter	Capsule (Treatment A) N=16	Tablet (Treatment B) N=16	Tablet/Capsule (Treatment B/Treatment A) N=16
AUC(0-∞) (µg.h/mL)	76.2 (67.7, 85.7)	65.2 (56.2, 75.6)	0.85 (0.75, 0.97)
Cmax (µg/mL)	6.39 (5.59, 7.31)	5.27 (4.41, 6.30)	0.82 (0.70, 0.96)
tmax (h)	4.00 (2.00, 6.00)	3.50 (1.50, 5.00)	0.00 (-0.70, 0.50)

geometric mean (95% CI) for PK summary and GLS mean ratio (90% CI) for treatment comparisons, except tmax presented as median (range) for PK summary and median difference (90% CI) for treatment comparisons
Treatment A: Two eltrombopag 25mg oral capsules administered fasted
Treatment B: Two eltrombopag 25mg oral film-coated tablets administered fasted

Study TRA102863 was a Phase I, open-label, randomized, three-group, two-period, incomplete crossover study designed to assess the relative bioavailability of eltrombopag tablets. Plasma PK samples were collected over 48 hours after single dose administration in each period. There was a minimum 5-day washout between each period. Comparisons were made for eltrombopag doses of 50 mg. [redacted] b(4)
The Phase 2 doses were comprised of eltrombopag 25 mg and 50 mg tablets manufactured at the R&D site and Phase 3 doses were comprised of eltrombopag 50 mg, [redacted] mg tablets manufactured at the commercial site.

Sixty-six subjects were enrolled and 63 subjects completed the study. Subjects were primarily female (70%) and Caucasian (83%) with a mean (range) age of 43 years (19 to 64 years).

Following single dose administration in the fasted state:

- The Phase III eltrombopag 50mg tablet delivered 15% lower plasma eltrombopag AUC(0-∞) (GLS mean ratio [90% CI]: 0.848 [0.742, 0.970]) and 17% lower Cmax (0.834 [0.707, 0.983]) compared to the Phase II 50mg tablet (n=22).

[redacted] b(4)

The 90% CIs for the bioavailability comparison of Phase III vs Phase II 50mg tablets fell outside of the 0.80 to 1.25 CI required to be considered equivalent. This reduced exposure is not considered clinically significant and subsequent clinical studies, including all pivotal clinical safety and efficacy studies, used the Phase III tablet formulation. The higher proportion of females, which were shown to have a slower clearance compared to males in the pop-PK analysis, may be a source of variability in this study.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Not applicable to this application.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Study TRA105122 was a pivotal, Phase I, open-label, randomized, two-period, incomplete crossover study to assess the bioequivalence of pivotal Phase II and pivotal Phase III eltrombopag tablets. Eltrombopag 25 mg and 50 mg tablets manufactured at the R&D site were administered in the pivotal clinical safety and efficacy Phase 2 study TRA100773A. Eltrombopag 25mg and 50mg tablets manufactured at the commercial site of manufacture Ware, UK were administered in the pivotal clinical safety and efficacy Phase 3 study TRA100773B. In both Studies TRA100773A and TRA100773B, the 25mg tablet was only used in combination with the 50mg tablet to make a 75mg dose. The eltrombopag 25mg and 50mg tablets manufactured at the commercial site represent the intended commercial product.

Plasma PK samples were collected over 72 hours after single dose administration in each period. There was a minimum 5-day washout between each period. The primary bioequivalence assessment was between eltrombopag tablets of the same strength manufactured at the R&D and commercial sites. In addition, comparisons were made between 25 mg and 50 mg tablet strengths to assess dose proportionality. One-hundred subjects were enrolled and 94 subjects completed the study. Subjects were primarily male (68%) Caucasians (74%) with a mean (range) age of 27 years (18 to 50 years).

Following single dose oral administration, plasma eltrombopag concentrations were quantifiable within 1 to 2 hours and generally remained quantifiable through the 72-hour sampling period for the 50 mg tablet dose, but only through 24 to 48 hours for the 25 mg tablet dose. For both the 25 mg and 50 mg doses, peak plasma eltrombopag concentrations occurred 2 to 6 hours after oral administration, with median tmax values of 3 to 4 hours.

Following single dose administration in the fasted state, the eltrombopag 50mg tablets used in pivotal Phase II and Phase III studies were found to be bioequivalent (Table 42 and 43). It is important to note that the phase 2 formulation came from a different substance batch than study TRA102863.

Table 42: Selected PK parameters by treatment for Study TRA105122

Plasma Eltrombopag PK Parameter	Eltrombopag 25 mg (N=48)		Eltrombopag 50 mg (N=46)	
	Phase II Tablet Regimen A	Phase III Tablet Regimen B	Phase II Tablet Regimen C	Phase III Tablet Regimen D
AUC(0-∞) (µg.h/mL)	31.0 (26.9, 35.7) [52]	33.9 (29.8, 38.5) [47]	75.6 (65.9, 86.7) [49]	79.5 (69.2, 91.4) [50]
Cmax (µg/mL)	2.47 (2.13, 2.86) [54]	2.85 (2.51, 3.23) [46]	5.73 (4.99, 6.58) [49]	6.36 (5.64, 7.17) [42]
AUC_{LAST} (µg.h/mL)	27.4 (23.5,32.0) [57]	30.5 (26.6,34.9) [49]	69.8 (60.7,80.2) [49]	73.5 (63.9,84.5) [50]
T1/2 (hr)	13.3 (12,14.8) [37.5]	13.9 (12.4,15.6) [41]	19.2 (17.9,20.7) [25]	18.6 (17.3,20.1) [26]
TMAX (hr)	3.7 (3.3,4.1) [39]	3.3 (3.0,3.7) [34]	3.3 (3.0,3.6) [30]	3.4 (3.1,3.7)0 [26]

Treatment A: One eltrombopag 25mg oral film-coated tablet manufactured at the R&D site administered fasted
Treatment B: One eltrombopag 25mg oral film-coated tablet manufactured at the commercial site administered fasted

Treatment C: One 50mg eltrombopag oral film-coated tablet manufactured at the R&D site administered fasted
Treatment D: One 50mg eltrombopag oral film-coated tablet manufactured at the commercial site administered fasted

Table 43: Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest in Study TRA105122

Plasma Eltrombopag PK Parameter	Phase III vs. Phase II Regimen B/ Regimen A	Phase III vs. Phase II Regimen D/ Regimen C
AUC(0-∞) (µg.h/mL)	1.10 (0.992, 1.22)	1.05 (0.943, 1.17)
Cmax (µg/mL)	1.16 (1.04, 1.30)	1.11 (0.989, 1.24)

Following single dose administration in the fasted state, the Phase III eltrombopag 25 mg tablet delivered an equivalent plasma eltrombopag AUC(0-∞), but a 16% higher Cmax, on average, compared to the Phase II 25 mg tablet (Table 43). Bioequivalence was not established for the eltrombopag 25 mg oral film-coated tablet; however, the 16% higher Cmax for the 25 mg Phase III (commercial site) tablet is not likely to be clinically significant given the safety profile observed for the commercial product to date in Study TRA100773B and in the ongoing long-term studies.

The 25mg tablet delivered lower plasma eltrombopag dose-normalized AUC(0-∞) and Cmax values compared to the 50 mg tablet, regardless of site of manufacture (i.e. R&D or commercial), with the exception of Cmax for the 25 mg commercial tablet vs. 50 mg R&D tablet comparison which met equivalence criteria (Table 44). The approximately 11-15% difference between the commercial tablets is not likely to be clinically significant given the safety profile observed for the commercial product to date.

Table 44: Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest in Study TRA105122

Parameter	25 mg vs. 50 mg Phase III	25 mg Phase III vs. 50 mg Phase II	25 mg Phase II vs. 50 mg Phase III	25 mg vs. 50 mg Phase II
DN-AUC(0-t) (µg.h/mL)	0.830 (0.703, .979)	0.876 (0.742, 1.03)	0.745 (0.631, 0.879)	0.787 (0.667, 0.928)
DN-AUC(0-∞) (µg.h/mL)	0.851 (0.726, .998)	0.897 (0.765, 1.05)	0.777 (0.663, 0.911)	0.819 (0.698, 0960)
DN-Cmax (µg/mL)	0.896 (0.767, 1.05)	0.998 (0.854, 1.17)	0.773 (0.662, 0.903)	0.861 (0.737, 1.01)

Based on a power model, plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner between 25mg and 50mg (Table 45). This result is consistent with the results of Study 497115/002 where dose proportionality was assessed over the dose range of 5mg to 75mg.

Table 45: Slope estimate (90% Confidence Intervals) for Eltrombopag Comparisons of Interest in Study TRA105122

Parameter	25 mg vs. 50 mg Phase III	25 mg Phase III vs. 50 mg Phase II	25 mg Phase II vs. 50 mg Phase III	25 mg vs. 50 mg Phase II
AUC(0-∞) (µg.h/mL)	1.23 (1.01, 1.46)	1.16 (0.936, 1.38)	1.36 (1.12, 1.60)	1.29 (1.05, 1.52)
Cmax (µg/mL)	1.16 (0.949, 1.37)	1.01 (0.784, 1.23)	1.37 (1.14, 1.59)	1.22 (0.975, 1.46)

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

In formulations where bioequivalence was not established the difference in exposure is not deemed likely to be clinically significant given the safety profile observed for the commercial product to date in Study TRA100773B and in the ongoing long-term studies.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study 497115/005 was a Phase I, open-label, randomized, three-period, balanced crossover study designed to assess the effect of food on the bioavailability of the tablet formulation. The study also assessed the relative bioavailability of the eltrombopag 25 mg oral capsule and film-coated tablet formulations following administration of single 50 mg doses in healthy adult subjects. Eltrombopag was administered fasted and with a standard high-fat breakfast consisting of 2 eggs cooked in butter (1 teaspoon), 2 strips of bacon, 2 slices of toast, 2 teaspoons of butter, hash brown potatoes (125g), and whole milk (240mL). PK samples were collected for 48 hours following single dose administration in each period. There was a minimum 5-day washout between each period. Eighteen subjects were enrolled and 16 subjects completed the study. All subjects were male and predominantly Caucasian (94%).

Administration of the eltrombopag 25mg oral film-coated tablet formulation with a standard high-fat breakfast significantly decreased plasma eltrombopag AUC(0-∞) by 59% and Cmax by 65% and delayed tmax by 1 hour (Table 46). These results were considered to be clinically significant.

Table 46: Summary of Plasma Eltrombopag PK Parameters and Treatment Comparisons to Assess Food Effect in Study 497115/005

Parameter	Tablet Fasted (Treatment B) N=16	Tablet Fed (Treatment C) N=16	Fed/Fasted (Treatment C/Treatment B) N=16
AUC(0-∞) (µg.h/mL)	65.2 (56.2, 75.6)	26.5 23.0, 30.5)	0.41 (0.36, 0.46)
Cmax (µg/mL)	5.27 (4.41, 6.30)	1.86 (1.61, 2.16)	0.35 (0.30, 0.41)
tmax (h)	3.50 (1.50, 5.00)	4.00 (2.00, 12.0)	1.00 (-0.50, 2.25)

geometric mean (95% CI) for PK summary and GLS mean ratio (90% CI) for treatment comparisons
tmax presented as median (range) for PK summary and median difference (90% CI) for treatment comparisons
Treatment B: Two eltrombopag 25mg oral film-coated tablets administered fasted
Treatment C: Two eltrombopag 25mg oral film-coated tablets administered with a high-fat breakfast

Study TRA104631 evaluated the impact of various meals on plasma eltrombopag PK following administration of a 75mg dose. The study also evaluated the impact of coadministering eltrombopag 75mg with a polyvalent cation-containing antacid on plasma eltrombopag PK. This was an open-label, randomized, five-period, balanced crossover study. PK samples were collected for 48 hours following single dose administration in each period. There was a washout of at least 5 days between periods. Eltrombopag was administered fasted and with different meal types, including 1) a lowfat (5%), low-calcium meal (40 to 50mg of calcium), of approximately 500 calories, 2) a high-fat (50%), low-calcium meal (40 to 50mg of calcium), of approximately 800 to 1000 calories, 3) high-fat, low-calcium meal (as defined in number 2) administered one hour after eltrombopag.

Twenty-six subjects were enrolled. Subjects were primarily male (54%) Caucasian (65%) of with a mean (range) age was 36 years (19 to 56 years).

Administration of eltrombopag (simultaneous with or one hour prior to) either a high-fat or low-fat meal that was also low in calcium had an impact, albeit lower, on plasma eltrombopag exposure (Table 47).

Table 47: Summary of Plasma Eltrombopag PK Parameters and Treatment Comparisons to Assess Food Effect in Study TRA104631

Plasma EltrombopagPK Parameter	Fasted (Treatment A) N=24	Low-fat, Low-calcium (Treatment B) N=24	High-fat,Low-calcium (Treatment D) N=25	High-fat,Low-calcium, 1-hour after eltrombopag (Treatment E)N=25	Low-fat, Low-calcium vs Fasted (B/A)	High-fat,Low-calcium vs Fasted (D/A)	High-fat,Low-calcium, 1-hour after eltrombopag vs Fasted (E/A)
AUC(0-∞) (µg.h/mL)	76.9 (63.3, 93.4) [49]	70.9 (59.3, 84.7) [44]	79.8 (66.8, 95.3) [44]	68.4 (57.5, 81.3) [44]	0.928 (0.763, 1.13)	1.03 (0.843, 1.25)	0.874 (0.720, 1.06)
Cmax (µg/mL)	6.20 (5.19, 7.40) [44]	5.36 (4.49, 6.40) [44]	6.22 (5.18, 7.46) [46]	5.31 (4.45, 6.32) [44]	0.874 (0.699, 1.09)	1.01 (0.808, 1.26)	0.854 (0.684, 1.07)

geometric mean (95% CI) [%CVb] for PK summary and GLS mean ratio (90% CI) for treatment comparisons, except tmax presented as median (range) for PK summary and median difference (90% CI) for treatment comparisons
Treatment A: One eltrombopag 75mg oral film-coated tablet administered fasted
Treatment B: One eltrombopag 75mg oral film-coated tablet administered with a low-fat, low-calcium meal
Treatment D: One eltrombopag 75mg oral film-coated tablet administered with a high-fat, low-calcium meal
Treatment E: One eltrombopag 75mg oral film-coated tablet administered 1 hour prior to a high-fat, low-calcium meal

None of the study treatments (intent to treat) met the criteria as outlined in the guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies" that an absence of food effect on BA is not established if the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80-125 percent for either AUC0-inf (AUC0-t when appropriate) or Cmax.

The reviewer recommends the approved product labeling include the statement "PROMACTA should be taken only on an empty stomach (1 hour before or 2 hours after a meal." Since 1) as stated above none of the treatment arms met the criteria for the absence of a food effect, 2) The sponsor failed to prove that calcium alone was the reason for the food effected noted in SB-497115/005 given other potential confounding factors may exist, and 3) the reviewer recommends deleting from the approved product labeling.

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2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable since these studies were conducted.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Not applicable. This will be addressed in CMC review per MOU between our two divisions.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Bioequivalence was not established for the commercial 25 and 50 mg tablets as described in section 2.5.2.2. The difference in exposure of approximately 9% is not deemed likely to be clinically significant given the safety profile observed for the commercial product to date in Study TRA100773B and in the ongoing long-term studies.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Active moieties are quantified in plasma using HPLC-MS/MS methods that were validated in a manner consistent with the guidance "Bioanalytical Method Validation." Recovery not reported for any assay method.

A radio-high performance liquid chromatography (HPLC) method used for radiopurity analysis of the dose administered in the mass balance study. Insufficient information was provided by the sponsor to assess whether this radio-HPLC method was validated in a manner consistent with the guidance "Bioanalytical Method Validation."

Liquid Scintillation Counting was used to determine radiocarbon concentration in the mass balance study. Insufficient information was provided by the sponsor to assess whether this LSC method was adequately validated (e.g., calibration, reproducibility, etc.)

Metabolites were qualified using from plasma, urine and fecal extracts were analyzed by LC/MS, LC/MS/MS, and LC/NMR in order to provide structural identification information. Insufficient information was provided by the sponsor to assess whether the LC/MS, LC/MS/MS, and LC/NMR methods were appropriately validated.

As stated earlier, where insufficient information is provided by the sponsor, the results were still included in this review is based on the sponsor's assurance regarding the appropriateness of these methods.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolites were not selected for analysis. Based on the mass balance study the major component recovered from plasma was parent compound and circulating metabolites that accounted for approximately 12% of the recovered components from plasma at 48 hours (Table 48).

Table 48: Major components recovered from plasma

Time	Parent	J	K
4 hours	94%	<1%	<1%
12 hours	80%	<1%	2%
24 hours	62%	<LLQ	7%
48 hours	44%	<LLQ	12%

LLQ= Low Limit of Quantification

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Given the high protein binding of this drug the measurement of both free and bound drug would have been ideal; however, this was not done by the sponsor. The sponsor's rationale for not measuring both free and bound concentrations was not communicated to FDA in this application.

The sponsor attempted to measure free concentration in the studies of hepatic and renal impairment but failed due to problems with the analytical method. Given the issue with protein binding in these diseases it would be important to evaluate free concentrations in these populations at a minimum.

2.6.4 What bioanalytical methods are used to assess concentrations?

See Table 49 below.

Table 49: Summary of Bioanalytical Methods

Assay	Clinical Studies Supported	Method Description and Performance	
FD2002/00179/00	497115/001 497115/002	Eltrombopag is extracted from 50uL human plasma by protein precipitation using [redacted] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0ng/mL
		Validated Range	10.0 to 2500ng/mL
		Within-run Precision (%CV)	≤6.5%
		Between-run Precision (%CV)	≤2.2%
		Accuracy (%Bias)	-0.3% ≤ bias ≤9.9%
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 24 hours at ambient temperature
CD2004/01045/00	497115/005 TRA100773 TRA102861 TRA102863 TRA104631	Eltrombopag is extracted from 50uL human plasma by protein precipitation using [redacted] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0ng/mL
		Validated Range	10.0 to 2500ng/mL
		Within-run Precision (%CV)	≤9.5%
		Between-run Precision (%CV)	≤5.6%
		Accuracy (%Bias)	-6.2% ≤ bias ≤ 10.9%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 24 hours at ambient temperature
CD2006/00175/00	TRA102860 TRA103452 TRA104412 TRA105120 TRA105122	Eltrombopag is extracted from 50uL human plasma by protein precipitation using [redacted] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	100ng/mL
		Validated Range	100 to 50,000ng/mL
		Within-run Precision (%CV)	≤7.7%
		Between-run Precision (%CV)	≤8.1%

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		Accuracy (%Bias)	-9.3% ≤ bias ≤ 13.6%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 3 days at ambient temperature
JBA/SB-497115/02/01	TRA105580 TRA104603	Eltrombopag is extracted from 50µL human plasma by protein precipitation using [redacted] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	b(4)
		LLQ	10.0ng/mL
		Validated Range	10.0 to 10,000ng/mL
		Within-run Precision (%CV)	≤6.5%
		Between-run Precision (%CV)	≤8.5%
		Accuracy (%Bias)	-10.0% ≤ bias ≤ 5.3%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
		Processed Extract Stability	at least 54 hours at ambient temperature
JBA/SB-497115/04/01	TRA104603	Human urine samples containing eltrombopag are diluted with [redacted] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	b(4)
		LLQ	10ng/mL
		Validated Range	10 to 2500ng/mL
		Within-run Precision (%CV)	≤3.9%
		Between-run Precision (%CV)	≤1.1%
		Accuracy (%Bias)	-1.7% ≤ bias ≤ 2.3%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -80°C at least 25 hours at ambient temperature
		Processed Extract Stability	at least 3 days at ambient temperature

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Table 49 above. Correlation coefficients obtained using 1/x (JBA/SB-497115/04/01 and FD2002/00179/00) or $1/x^2$ weighted linear regression.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Table 49 above.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

See Table 49 above.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See Table 49 above.

2.6.4.5 What is the QC sample plan?

Quality Control (QC) samples were analyzed with each batch of study samples against separately prepared calibration standards. Spiked duplicate standard curve and QC samples were extracted daily to permit the determination of the concentration of eltrombopag, and to monitor the day-to-day performance of the method, respectively.

For the analysis to be acceptable, no more than one-third of the QC sample results could deviate from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration should be within 15% of nominal. All applicable analytical runs for the clinical studies met these predefined run acceptance criteria. The between run accuracy and precision of QC samples from each of the studies are summarized in Table 50.

Table 50 Between-run Accuracy and Precision of Quality Control (QC) Samples

Protocol No.	Total number of QC samples	Average overall precision (≤ %CV)	Accuracy (%bias range)
497115/001	42	4.46	-4.4 to -4.2
497115/002	249	10.53	-1.0 to -4.3
497115/005	108	5.2	-0.7 to 0.5
TRA100773	246	6.8	-2.6 to -1.0
TRA102860	246	6.9	-6.3 to 0.8
TRA102861	24	4.7	2.4 to 8.8
TRA102863	336	5.8	1.1 to 6.0
TRA103452	102	6.0	-7.2 to 2.3
TRA104412	66	8.8	-3.3 to 1.6
TRA104603 (plasma)	84	2.3	-0.1 to 0.4
TRA104603 (urine)	18	1.3	-3.3 to 0.8
TRA104631	212	6.2	-1.4 to 9.0
TRA105120	24	3.0	-7.4 to 4.0
TRA105122	204	6.9	-2.1 to -0.3
TRA105580	108	3.5	0.9 to 4.0

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4 Appendices

4.1 Proposed labeling

4.1.1 Product Labeling

16 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2 Overview of Study Designs

4.2.1 Biopharmaceutics Studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
497115/005 Complete	Relative bioavailability of eltrombopag oral 25mg capsule and oral 25mg film-coated tablet formulations Effect of food on bioavailability of the eltrombopag 25mg oral film-coated tablet formulation	Phase I, open-label, randomized, three period, balanced crossover	18 subjects M/F 18/0 23y (18-28y) Healthy Subjects	**Treatment A:** eltrombopag/50mg/ Capsule (25mg)/R&D/oral/single dose/fasting **Treatment B:**eltrombopag/50mg/Tablet/ (25mg)/R&D/ oral/single dose/fasting **Treatment C** : eltrombopag/50mg/Tablet (25mg)/R&D/ oral/single dose/fed
TRA102863 Complete	Relative bioavailability of eltrombopag oral film-coated tablet formulations manufactured at the R&D and commercial sites	Phase I, open-label, randomized, three group, two period, incomplete crossover	66 subjects M/F 20/46 43y (19-64y) Healthy Subjects	**Treatment A** :eltrombopag/50mg/Tablet/ (50mg)/R&D/ oral/single dose/fasting **Treatment B** :eltrombopag/50mg/Tablet /(50mg)/commercial/oral/single dose/fasting **Treatment C**:eltrombopag/75mg/Tablet/ (25mg & 50mg)/R&D/oral/single dose/fasting **Treatment D** [redacted] **Treatment E:** [redacted] **Treatment F:** [redacted]
TRA105122 Complete	Bioequivalence of eltrombopag oral film-coated tablet formulations manufactured at the R&D and commercial sites	Pivotal, Phase I, open-label, randomized, two group, two period, incomplete crossover	100 subjects M/F 68/32 27y (18-50y) Healthy Subjects	**Treatment A**: eltrombopag/25mg/Tablet/ (25mg)/R&D/ oral/single dose/fasting **Treatment B** :eltrombopag/25mg/ Tablet/(25mg)/commercial/oral/single dose/fasting **Treatment C** :eltrombopag/ 50mg/Tablet/(50mg)/R&D/oral/single dose/fasting **Treatment D**:eltrombopag/ 50mg/Tablet/(50mg)/commercial/oral/single dose/fasting
TRA104631 Complete	Effects of high- and low-fat meals with low calcium content on the bioavailability of the eltrombopag 75mg oral film-coated tablet formulation Effect of cation-containing antacid on eltrombopag PK	Phase I, open-label, randomized, five period, balanced cross-over	26 subjects M/F 14/12 36y (19-56y) Healthy Subjects	**Treatment A** :eltrombopag/75mg/ Tablet/(75mg)/ [redacted] oral/single dose/fasting **Treatment B:** eltrombopag/ 75mg/Tablet/(75mg) [redacted] /oral/single dose/low-fat, low-calcium meal **Treatment C:** eltrombopag/75mg/Tablet/(75mg)/ [redacted] /oral/single dose/fasting + 30mL [redacted] = aluminum hydroxide (1524mg) and magnesium carbonate (1425mg)/ suspension/oral/single dose/fasting **Treatment D:** eltrombopag/75mg/Tablet/ (75mg) [redacted] oral/single dose/high-fat, low-calcium meal **Treatment E:** eltrombopag/ 75mg/Tablet/(75mg)/ [redacted] /oral/single dose/one hour prior to high-fat, low-calcium meal

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4.2.2 Healthy Volunteer Studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
497115/001 Complete	1) Safety and tolerability of single oral doses of eltrombopag & 2) Pharmacokinetics of single dose eltrombopag Pharmacodynamics of single dose eltrombopag	Phase I, single blind, single oral dose, dose-rising, placebo controlled, randomized (with respect to placebo)	24 subjects 24M 32y (22-42y) Healthy subjects	**Treatment A:** eltrombopag/3mg/granules filled into capsules/ (26,160, 660mg/gm)/ R&D/oral/single dose/fasting, **Treatment F:** eltrombopag/6mg/granules filled into capsules/(26,160, 660mg/ gm)/ R&D/oral/single dose/fasting, **Treatment G:** eltrombopag/ 9mg/granules filled into capsules/(26,160, 660mg/gm)/ R&D/ oral/single dose/fasting, & **Treatment P:** Matched placebo
497115/002 Complete	1)Safety and tolerability of a single oral dose and after 10 days of repeat dosing, 2)Pharmacokinetics of a single oral dose and after 10 days of repeat dosing, 3) Potential to inhibit or induce cytochrome P450 enzymes after 7 days of repeat dosing, & 4) Effect on platelet biomarkers of a single oral dose and after 10 days of repeat dosing	Single and Repeat Dose Escalation Phase I, single-blind, placebo-controlled, randomized (with respect to placebo), parallel, single and repeat dose escalation CYP Probe Phase I, open-label, single sequence, two period, incomplete crossover	97 subjects (73 dose escalation, 24 CYP probe) 97M 25.3y (18-45y) Healthy subjects	**Treatment A:**eltrombopag/5mg/ Capsule/(5mg)/R&D/oral/single and 10 day repeat dose/fasting, **Treatment B:**eltrombopag/ 10mg/ Capsule/(5mg)/R&D/oral/single and 10 day repeat dose/fasting, **Treatment C:**eltrombopag/20mg/ Capsule/ (1mg,5mg)/R&D/oral/single and 10 day repeat dose/fasting, **Treatment D:**eltrombopag/30mg/ Capsule/(30mg)/R&D/oral/ single and 10 day repeat dose/fasting, **Treatment E:** eltrombopag/50mg/ Capsule/(25mg)/R&D/oral/single and 10 day repeat dose/fasting, **Treatment F:**eltrombopag/75mg/ Capsule/ (25mg)/R&D/oral/single and 10 day repeat dose/fasting, **Treatment G:**eltrombopag/75mg/ Capsule/(25mg)/R&D/oral/7 day repeat dose (Days 3-9)/ midazolam 5mg, caffeine 100mg, omeprazole 20mg, flurbiprofen 50mg (Day 1-2, Day 8-9) /fasting, & **Treatment P:** matched placebo
TRA102861 Complete	1) Determine total recovery and relative excretion of radiocarbon in urine and feces after a single, oral dose of [14C] eltrombopag 75mg (100 µCi), 2) Compare total radiocarbon (drugrelated material) in blood and plasma relative to parent plasma concentration, 3) Determine plasma eltrombopag PK parameters following single-dose oral administration of [14C] eltrombopag 75mg (100 µCi), & 4) Evaluate the safety and tolerability of eltrombopag 75mg.	Phase I, open-label, single dose mass balance study	6 subjects 6M 35.8y (30-49y) Healthy subjects	eltrombopag/75mg containing approximately 100µCi (0.70 mSv) of radiocarbon/ solution/R&D/oral/single dose/fasting
OSDMM 1 55 Complete	Quantify and characterize the major metabolites of SB-497115 in plasma, urine and feces following a single oral administration (75 mg/100 µCi) of [14C]SB-497115-GR to healthy adult male subjects.	See TRA102861	See TRA102861	See TRA102861

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
TRA104603 Complete	1) Safety and tolerability of eltrombopag following single oral doses in healthy Japanese adult male subjects, 2) Pharmacokinetics of eltrombopag following single oral doses in healthy Japanese adult male subjects, & 3) Pharmacodynamics of eltrombopag following single oral doses in healthy Japanese adult male subjects.	Phase I, placebo-controlled, double-blind, randomized, dose-escalation, 4-period crossover, single oral dose	16 subjects 16M 25.9 y (20-33y) Healthy subjects	**Treatment A:** eltrombopag/30mg/ Tablet/(5mg, 25mg)/R&D/oral/ single dose/fasting, **Treatment B:** eltrombopag/50mg/ Tablet/ (25mg)/R&D/oral/single dose/fasting, **Treatment C:** eltrombopag/ 75mg/ Tablet/(25mg)/R&D/oral/single dose/fasting, **Treatment D:** eltrombopag/100mg/ Tablet/(25mg)/R&D/oral/single dose/fasting, & **Treatment P:** matched placebo
TRA105580 Complete	Safety and tolerability of eltrombopag following single and repeat oral doses in healthy Japanese adult male subjects. Pharmacokinetics of eltrombopag following single and repeat oral doses in healthy Japanese adult male subjects. Pharmacodynamics of eltrombopag following single and repeat oral doses in healthy Japanese adult male subjects.	Phase I, placebo-controlled, single-blind, randomized, dose-escalation, three doses, parallel group, single and multiple oral dose	42 subjects 42M 25.6 y (20-34 y) Healthy subjects	**Treatment A:** eltrombopag/25mg/ Tablet/(25mg)/R&D/oral/single dose/ single and 10-day repeat dose/fasting, **Treatment B:** eltrombopag/50mg/ Tablet/(25mg)/R&D/oral/single dose/ single and 10-day repeat dose/fasting, **Treatment C:** eltrombopag/ 75mg/ Tablet/(25mg)/R&D/oral/single dose/ single and 10-day repeat dose/fasting, & **Treatment P:** matched placebo
TRA102860 Complete	Part 1: Safety, pharmacokinetics, and platelet response after single and 5 day repeat dosing with eltrombopag 100mg to 200mg QD. Part 2: Demonstrate lack of effect of eltrombopag 50mg and 150mg QD on QTcF Characterize the effect of eltrombopag on QT, QTci, QTcB, and heart rate relative to placebo and moxifloxacin Pharmacokinetics of eltrombopag and moxifloxacin Safety of eltrombopag Platelet response of eltrombopag and moxifloxacin	Part 1: Phase I, double-blind, placebo-controlled, randomized, parallel group, single and repeat dose escalation Part 2: Phase I, double-blind, placebo and active controlled, randomized, balanced crossover	Part 1: 33 subjects 18M/15F 29.5y (18-49y) Healthy subjects Part 2: 87 subjects 62M/25F 29.9y (18-49y) Healthy subjects	**Part 1: Treatment A:** eltrombopag/100mg/ tablet (50mg)/ commercial/oral/single and 5 day repeat dose/fasting, **Treatment B:** eltrombopag/150mg/ tablet (50mg)/commercial/oral/single and 5 day repeat dose/fasting, & **Treatment C:** eltrombopag/200mg/ tablet (50mg)/commercial/oral/single and 5 day repeat dose/ fasting **Part 2: Treatment A:** eltrombopag/50mg/ tablet (50mg)/ commercial/oral/ 5 day repeat dose/fasting, **Treatment B:** eltrombopag/150mg/ tablet (50mg)/commercial/oral/5 day repeat dose/fasting, **Treatment C:** placebo, & **Treatment D:** moxi-floxacin/400mg/ tablet (400mg)/commercial/oral/single dose/ fasting (preceded by 4 days of placebo)

4.2.3 Intrinsic factor studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
TRA104412 Ongoing	1) Pharmacokinetics of a single dose of eltrombopag (50mg) in subjects with renal impairment compared to healthy subjects, 2) Safety of a single dose of eltrombopag (50mg) in healthy subjects and those with renal impairment, & 3) Effect of renal impairment on the plasma protein binding of eltrombopag	Phase I, open-label, single dose	25 subjects 11M/14F 64.0y (39-74y) 19 patients, 8 with mild, 8 with moderate, 3 with severe renal impairment 6 healthy subjects	eltrombopag/50mg/Tablet (50mg)/commercial/oral/single dose/fasting

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
TRA103452 Complete	1) Pharmacokinetics of a single dose of eltrombopag (50mg) in subjects with hepatic impairment compared to healthy subjects, 2) Tolerability of a single dose of eltrombopag (50mg) in healthy subjects and those with hepatic impairment, & 3) Effect of hepatic impairment on the plasma protein binding of eltrombopag	Phase I, open-label, single dose	33 subjects 30M/3F 51y (38-64y) 25 patients, 8 with mild, 8 with moderate, 9 with severe hepatic impairment 8 healthy subjects	eltrombopag/50mg/Tablet (50mg)/commercial/oral/single dose/fasting

4.2.4 Extrinsic factor studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
TRA105120 Complete	1) To compare the pharmacokinetics (PK) of rosuvastatin when administered alone and with eltrombopag, 2) To examine the pharmacokinetics of rosuvastatin metabolites when rosuvastatin is coadministered with eltrombopag compared to single-dose administration of rosuvastatin alone, & 3) To assess the safety and tolerability of eltrombopag when coadministered with rosuvastatin	Phase I, open-label, three period, single sequence	42 subjects 33M/9F 33.6y (21-56y) Healthy subjects	**Treatment A:** Day 1 rosuvastatin/10mg/Tablet(10mg)/ commercial/oral/single dose/fasting, **Treatment B:** Day 6 to Day 9 eltrombopag/75mg/Tablet/(25mg and 50mg)/commercial/oral/ 4 day repeat dose/fasting, & **Treatment C:** Day 10 rosuvastatin/ 10mg/Tablet(10mg)/ commercial/oral/single dose PLUS eltrombopag/75mg/Tablet/(25mg and 50mg)/commercial/ oral/single dose/fasting

4.2.5 Pivitol studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
TRA100773A completed	1) To determine the efficacy of eltrombopag, 2) To assess the safety and tolerability of eltrombopag, 3) To characterize the population pharmacokinetic profile of oral eltrombopag using a combined sparse and serial pharmacokinetic sampling strategy, 4) To determine the pharmacodynamic effect of eltrombopag on markers of thrombopoiesis, 5) To assess the impact of eltrombopag on the incidence and severity of symptoms	Multi-center, double-blind, randomized, placebo-controlled Phase 2 study that used an adaptive sequential design to allow for two separate and independent studies	118 (117 safety) previously treated adult subjects with chronic ITP 73F/44M 50 (18 – 85)	**Treatment A1:** eltrombopag 30 mg/tablet (10 mg)/ R&D/oral/repeat dose up to 6 weeks/fasting, **Treatment A2:** eltrombopag 50 mg/tablet (50 mg)/ R&D/ oral/repeat dose up to 6 weeks/fasting, **Treatment A3:** eltrombopag 75 mg/tablet (25 mg, 50 mg)/ R&D/oral/repeat dose up to 6 weeks/fasting, & **Treatment A4:** matching placebo.

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
	of thrombocytopenia , & 6) To assess the impact of eltrombopag on the health-related quality.			
TRA100773B completed	1) To determine the efficacy of eltrombopag, 2) To assess the safety and tolerability of eltrombopag, 3) To characterize the population pharmacokinetic profile of oral eltrombopag using a combined sparse and serial pharmacokinetic sampling strategy, 4) To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia , & 5) To assess the impact of eltrombopag on the health-related quality.	Multi-center, double-blind, randomized, placebo-controlled Phase 3 study that used an adaptive sequential design to allow for two separate and independent studies	114 previously treated adult subjects with chronic ITP 70F/44M 48 (19 – 84)	**Treatment B1:** eltrombopag 50 mg/tablet (50 mg)/ commercial/ oral/repeat dose up to 6 weeks/fasting, **Treatment B2:** eltrombopag 75 mg/tablet (25 mg, 50 mg)/ commercial/oral/ repeat dose up to 6 weeks/fasting, & **Treatment A3:** matching placebo. Dose escalation to 75mg after Day 21 allowed for nonresponders.

4.2.6 Additional Supporting studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
TRA108057 REPEAT ongoing	1) To evaluate the effect of eltrombopag on platelet counts when administered during 3 cycles of repeated, intermittent treatment, 2) To assess the number of subjects requiring rescue treatments over 3 cycles of therapy, 3) To assess the safety and tolerability of eltrombopag when administered over 3 cycles of therapy, 4) To assess anti-platelet antibody levels during the 3 cycles of eltrombopag treatment, & 5)To assess the impact of eltrombopag on the incidence and severity of bleeding symptoms over 3 cycles of therapy.	Multi-center, open-label, single-group, repeat-dose, phase 2, study.	66 previously treated adult subjects with chronic ITP Completed = 4 45F/21M 50.5 (20-79)	Eltrombopag 50 mg/tablet (50 mg)/ oral/repeat dose up to 6 weeks/fasting, off-therapy for up to 4 weeks for 3 cycles; Dose escalation to 75mg after Day 21 allowed for nonresponders.
TRA105325 EXTEND ongoing	1) To describe the long-term safety and tolerability of oral eltrombopag treatment of subjects with ITP with or without concomitant ITP medication, 2) To describe the clinical efficacy, pharmacodynamics, and durability of efficacy response to eltrombopag, 3) To describe the effect of re-treatment on platelet counts in subjects previously treated with eltrombopag 4) To gain information on the optimal dosing of	Multi-center, open-label, extension study to evaluate the safety and efficacy of eltrombopag as a treatment for This study allows each subject to achieve an individualized dose and schedule of eltrombopag based upon their platelet counts.	117 (109 safety) subjects with ITP previously enrolled eltrombopag trial (e.g., TRA100773, TRA102537, or TRA108057) Completed = 0 70F/39M 47 (19-82)	Starting oral daily dose of eltrombopag 50 mg/tablet (50 mg)/ oral/repeat dose > 6 weeks/fasting, with modification to 25mg or 75mg; Dose modification allowed based on individual platelet counts

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
	eltrombopag, 5) To describe the effect of eltrombopag on reduction and/or sparing of concomitant ITP therapies & 6)To assess the impact of eltrombopag on physical and mental health status, the symptoms of fatigue and bleeding and bruising, and the impact of such symptoms on health-related quality of life.			
TRA102537 RAISE ongoing	1) To determine the efficacy of oral eltrombopag, for 6 months duration, 2) To assess the ability of eltrombopag to prevent the use of rescue treatment, 3) To describe the pharmacodynamics and durability of eltrombopag response, 4) To determine the efficacy of oral eltrombopag, when administered once daily, for 6 weeks duration, 5) To assess the safety and tolerability of eltrombopag when administered for 6 months, 6) To describe the effect of eltrombopag on reduction of concomitant ITP medications from baseline, 7) To assess the impact of eltrombopag on the incidence and severity of bleeding symptoms of thrombocytopenia when administered once daily for 6 months, & To assess the impact of eltrombopag on the health-related quality of life and subject reported outcomes.	Multi-center, randomized, double-blind, placebo-controlled, Phase III study	156 previously treated adult subjects with chronic ITP 106F/50M 48.5 (18 - 85)	Eltrombopag 50 mg/tablet (50 mg)/ oral/repeat dose 6 months/fasting or matching PBO; Dose modification (to 25mg or 75mg) allowed based on individual platelet counts

4.2.7 Compiled Reports

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
Population PK and PK/PD Report completed	Characterize plasma eltrombopag PK in patients with ITP Identify variables that impact plasma eltrombopag PK such as demographics, clinical laboratory parameters, and concurrent medications Explore relationships between plasma eltrombopag PK and platelet response relationships between plasma eltrombopag PK and platelet response	Population PK analysis of data across studies TRA100773A, TRA100773B, 497115/002, TRA105580, & TRA102860	Healthy volunteers and ITP subjects	Subject data from other studies

Protocol Status	Study Objective(s)	Study Design	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Treatment Details
Pharmaco-genetic report completed	Pharmacogenetic investigation of associations with PK and PD outcomes	Pharmacogenetic investigation of data across studies TRA104603, TRA105580, 497115/002, 497115/005, TRA104631, TRA105122, TRA102863, TRA102860, & TRA100773.	Healthy volunteers and ITP subjects	Subject data from other studies
Influence of East Asian Ethnicity report completed	Influence of East Asian Ethnicity on Eltrombopag PK and PD	Investigation of data across studies TRA104603, TRA105580, 497115/005; TRA105122, TRA102863; TRA102860, TRA103452, TRA104631, TRA104412, TRA100773A, & TRA100773B	Healthy volunteers and ITP subjects	Subject data from other studies

4.3 Individual Study Reviews

4.3.1 Study TRA100773B: Phase 3 Safety and Efficacy Study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: A double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of SB-497115-GR, a thrombopoietin receptor agonist, administered at 30, 50 and 75 mg as oral tablets once-daily for 6 weeks to adult male and female subjects with refractory, chronic immune thrombocytopenic purpura

Study period: 06Feb2006 – 31Jan2007

Objectives:

Primary

- The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once-daily for 6 weeks to previously treated adult subjects with chronic idiopathic thrombocytopenia (ITP).

Secondary

- To assess the safety and tolerability of eltrombopag when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To characterize the population pharmacokinetic profile of oral eltrombopag using a combined sparse and serial pharmacokinetic sampling strategy when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To determine the pharmacodynamic effect of eltrombopag on markers of thrombopoiesis when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To assess the impact of eltrombopag on the health-related quality of life when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP.

Methodology:

Protocol TRA100773 was a double-blind, randomized, placebo-controlled study that used an adaptive sequential design to allow for two separate and independent studies (TRA100773A, (phase 2, dose finding) and TRA100773B (phase III)). Based upon the efficacy and safety results from Study TRA100773A, the dose chosen for Study TRA100773B was eltrombopag 50 mg (with increases to 75mg permitted). In Study TRA100773B, adults with chronic ITP were randomized in a 2:1 fashion to eltrombopag 50mg or placebo (PBO). This report focuses solely on theTRA100773B study.

Test Product, Dose and Mode of Administration, Batch Numbers:

Eltrombopag was supplied by GSK as ——— round film coated tablets containing eltrombopag olamine equivalent to 25mg and 50mg of eltrombopag free acid. Matching placebo tablets were also supplied (Table 1). b(4)

Table 1: Batch Numbers for Study Medication

Product	Formulation/ Formulation Code	Drug Substance Batch Number	Drug Product (Batch Number)
Placebo	Tablet/APV Tablet/APV	N/A	(051069222) (051074350)

	Tablet/APV		(061114790)
25 mg Tablet	Tablet/AS Tablet/AS ?	F081598 F081601 ?	(051109557) (051109558) (051109559)
50 mg Tablet	Tablet/AR ?	F081598 ?	(051109563) (051109564)

The treatment phase of the study involved once-daily dosing with eltrombopag for up to 6 weeks. Subjects with platelet counts <50Gi/L could have had their dose increased to eltrombopag 75mg (or matching PBO) on or after Day 22. Subjects who attained a platelet count >200Gi/L were required to discontinue treatment, but continued to attend follow-up visits. After the dosing period, subjects were assessed at 1, 2, 4 and 6 weeks to assess the durability of the platelet response.

Subjects were instructed to take their study medication in the morning upon awaking and before eating breakfast. If this was not possible, subjects were instructed to fast for 2h pre- and 2h post-dosing of study medication. Ingestion of water or coffee during the fasting period was acceptable.

Criteria for evaluation:

- Sample Size: The primary analysis was to compare the differences between eltrombopag 50 mg versus PBO in the proportion of responders 42 days after initiation of dosing (Day 43 measurement). Assuming 25% and 60% responses on PBO and eltrombopag 50mg, respectively, 87 evaluable subjects (58 on eltrombopag, 29 on PBO) were needed in order to provide 90% power at the 5% level of significance (two-sided). However, in order to provide additional safety data, 66 subjects were to be recruited to the eltrombopag treatment group and 33 subjects to the PBO treatment group.
- Efficacy: The primary assessment for efficacy was platelet count (collected as part of the complete blood count). The primary endpoint was the proportion of subjects with a platelet count of ≥50Gi/L after up to 42 days of dosing (compared to a baseline count of <30Gi/L). Other efficacy assessments included the odds of responding (a shift from a baseline platelet count <30Gi/L to a platelet count of ≥50Gi/L) to treatment at each assessment during Weeks 2-6 of the 6 week treatment period, the proportion of subjects with a platelet count ≥50Gi/L and at least 2x baseline after up to 42 days of dosing, the incidence and severity of bleeding associated with chronic ITP and Health-Related Quality of Life assessment using the SF-36v2 tool.
- Pharmacokinetics:
  - Serial PK assessments were performed in a subset of subjects from 3 to 5 selected sites. For each serial PK subject, 6 plasma samples were to be collected for analysis of eltrombopag olamine plasma concentrations on Day 1 (pre-dose and 1, 2, 4, 6, and 8h post-dose); on Day 2, a single trough (pre-dose) specimen was collected, 24 h after the first dose. Subsequently, 6 plasma samples were collected for analysis of eltrombopag olamine plasma concentrations on Day 8, and on Day 9; a single trough (pre-dose) specimen was collected, 24 h after the Day 8 dose.
  - Plasma specimens were assayed using a validated analytical method (Table 2).

Table 2: Assay Validation Information

Eltrombopag is extracted from 50uL human plasma by protein precipitation using [redacted] as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	10.0ng/mL
Validated Range	10.0 to 2500ng/mL
Within-run Precision (%CV)	≤9.5%
Between-run Precision (%CV)	≤5.6%

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Accuracy (%Bias)	-6.2% ≤ bias ≤ 10.9%
Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 24 hours at ambient temperature

Reviewer Comment: Appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation." Recovery not reported.

- Pharmacodynamics
  - Pharmacodynamic endpoint was platelet count which was Platelet count data was collected as part of the CBC to determine the proportion of subjects that responded to treatment.
- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety assessments included detection and documentation of adverse events (AEs), clinical laboratory evaluations, physical examination, 12-lead ECGs, spleen size by ultrasound examination, and detailed ocular examination. No formal statistical analyses of the safety data were performed.

Number of Subjects

A total of 114 subjects were enrolled in the study, with 76 randomized to the eltrombopag treatment group, and 38 randomized to PBO (Table 3).

Table 3: Subject disposition

Disposition Category	Number of Subjects, n (%)		
	PBO	Eltrombopag	Total
All randomized subjects	38	76	114
Safety Population	38 (100)	76 (100)	114 (100)
ITT Population	38 (100)	76 (100)	114 (100)
Completed	30 (79)	52 (68)	82 (72)
Discontinued prematurely from study medication	8 (21)	24 (32)	32 (28)

Thirty-two (28%) subjects withdrew from treatment prior to completion of the full 6-week treatment period. The most common reason for withdrawal from study medication in the eltrombopag treatment group was a platelet count >200Gi/L, which occurred in 17 (22%) subjects. AEs leading to withdrawal occurred in a total of 5 subjects; 2 subjects (5%) in the PBO treatment group and 3 subjects (4%) in the eltrombopag treatment group.

Population Demographics

The population demographics from this study are listed in Table 4 & 5 below

Table 4: Population Demographics

Demographic Characteristic	Treatment Group		
	PBO N=38	Eltrombopag N=76	Total N=114
Age, yrs Median Min – Max	51.0 21-79	47.0 19-84	48.0 19-84
Sex, n (%)			
Female	27 (71)	43 (57)	70 (61)
Male	11 (29)	33 (43)	44 (39)
Race, n (%)			
African American/African	0	1 (1)	1 (<1)
American Indian/Alaskan Native	2 (5)	4 (5)	6 (5)
Asian - East Asian	1 (3)	0	1 (<1)
Asian - South-East Asian	3 (8)	7 (9)	10 (9)
Asian – Central/South Asian	4 (11)	5 (7)	9 (8)

White - Arabic/North African	3 (8)	5 (7)	8 (7)
White - White/ Caucasian/European	23 (61)	53 (70)	76 (67)
Mixed Race	2 (5)	1 (1)	3 (3)
Ethnicity, n (%)			
Hispanic or Latino	6 (16)	10 (13)	16 (14)
Not Hispanic or Latino	32 (84)	66 (87)	98 (86)

Table 5: Current Medical Conditions Reported in 4% or more of Subjects

Preferred Term	Treatment Group, n (%)		Total
	PBO N=38	EltrombopagN=76	N=114
Any condition	24 (63)	52 (58)	76 (67)
Hypertension	5 (13)	22 (29)	27 (24)
Diabetes mellitus	3 (8)	5 (7)	8 (7)
Hypercholesterolemia	0	6 (8)	6 (5)
Hypothyroidism	0	4 (5)	4 (4)
Menorrhagia	1 (3)	3 (4)	4 (4)
Hepatic steatosis	0	3 (4)	3 (3)
Sarcoidosis	2 (5)	0	2 (2)

Results-Efficacy analysis:

Fifty-nine percent of subjects treated with eltrombopag had increased platelet counts to ≥50Gi/L after up to 6 weeks of dosing compared to 16% of subjects treated with PBO, confirming the elevation of platelet counts following treatment with eltrombopag 50mg after up to 6 weeks observed in the phase II dose-finding study. The odds of responding were statistically significantly greater ($p<0.001$) for subjects in the eltrombopag treatment group compared to subjects in the PBO treatment group (Table 6).

Table 6: Responders (Efficacy Population)

Responders at the Day 43 Visit (Efficacy Population)	Treatment Group	
	PBO N=38	Eltrombopag N=74
Evaluable	37	73
Responders, n (%)	6 (16.2)	43 (58.9)
Odds ratio for Active/PBO Treatments		9.61
95% CI		(3.31, 27.86)
p-value (two-sided)		<0.001

At any point during Weeks 2-6 of the treatment period, subjects in the eltrombopag treatment group had a greater odds of responding than subjects in the PBO treatment group (OR=8.79; CI=3.54, 21.86; $p<0.001$).

Seventy percent of subjects treated with eltrombopag had increased platelet counts to at least twice baseline after up to 6 weeks of dosing compared to 19% of subjects treated with PBO. The eltrombopag treatment group achieved a statistically significant treatment effect compared to PBO ($p<0.001$).

More subjects (18, 25%) in the eltrombopag treatment group achieve platelet counts >200Gi/L after up to 6 weeks of dosing compared to PBO (1, 3%). Also, discontinuation of study medication was successful in inhibiting platelets above 400Gi/L. Two subjects treated with eltrombopag achieved platelets >400Gi/L, however, this was their first count >200Gi/L. Platelet counts for subjects who achieved platelets >200Gi/L dropped within 2 weeks after stopping study medication.

Results-PK analysis:

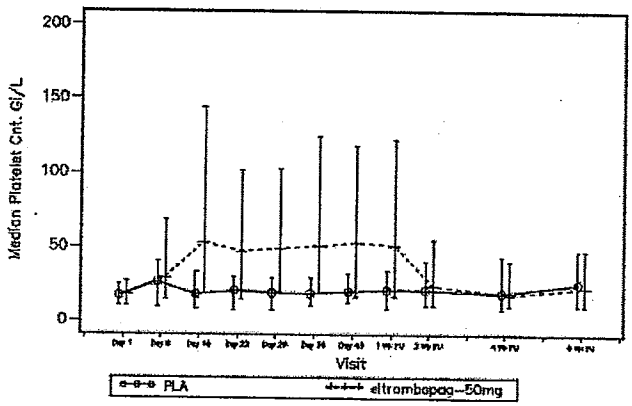
The planned characterization of plasma eltrombopag PK in adult subjects with ITP was not reported because it will be the subject of a separate report (pop-pk).

Results- Pharmacodynamic Analysis:

Baseline median platelet counts were similar in the 2 treatment groups. From the Day 8 to Day 43 Visits, the median platelet counts for the eltrombopag treatment group were higher than that in the PBO treatment group and the increase in the median platelet count was maintained throughout the on-therapy period of the study. For the PBO treatment group, the median platelet count at each on-therapy visit remained <26Gi/L. The median platelet count for the eltrombopag treatment group was >55Gi/L beginning on Day 15 and remained at this level or higher for the rest of the on-therapy visits (Figure 1).

Median platelet counts in the eltrombopag treatment group showed an elevation as early as Day 15 and remained elevated through Day 50. A slight decrease in the median platelet count was observed after Day 15 in the eltrombopag treatment group. As previously described, this decrease may be explained by the number of subjects withdrawn due to a platelet response >200Gi/L . However, the median platelet levels remained elevated (≥47Gi/L) throughout daily administration of eltrombopag between Days 15 and 43. One week following discontinuation of eltrombopag, median platelet counts remained elevated. Two weeks following discontinuation of eltrombopag, median platelet values returned to baseline levels. Median platelet counts in the PBO treatment group remained consistently lower than those in the eltrombopag treatment group through the first post-therapy visit (nominal Day 50).

Figure 1: Median Platelet Counts with 25th and 75th percentiles



Reviewer Comment: While a trend toward a platelet count increase greater than placebo was demonstrated it is important to note the significant variability in these results.

The change in platelet count from baseline using the primary dataset was analyzed with an ANCOVA model, including actual baseline platelet count, ITP medication use at randomization, splenectomy status and treatment as covariates (Table 7). There were greater increases in platelet counts from baseline in the eltrombopag treatment group compared to the PBO treatment group at the Day 43 Visit. The difference in the model-adjusted mean changes from baseline between eltrombopag and PBO treatment groups was statistically significant (p<0.001).

Table 7: Analysis of Change in Platelet Counts (Gi/L) From Baseline to the Day 43 Visit (Efficacy Population)

	Treatment Group

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

A greater percentage of subjects in the eltrombopag treatment group achieved a platelet count >200Gi/L, compared to PBO (Table 8). These subjects discontinued study medication, their last platelet count was carried forward and they were considered responders. Two subjects in the eltrombopag treatment group attained platelet counts exceeding 400Gi/L, compared to none in the PBO treatment group.

Table 8: Subjects With Platelet Counts >200Gi/L at the Day 43 Visit (Efficacy Population)

Day 43 Visit	Treatment Group	
	PBO N=38	Eltrombopag N=74
Platelets >200Gi/L n	37	73
Responders, n (%)	1 (2.7)a	18 (24.7)b
Platelets >400Gi/L		
n	37	73
Responders, n (%)	0	2 (2.7)

Results of a logistic regression analysis, adjusting for the covariates of use of concomitant medication at randomization, splenectomy, baseline platelet count (≤15Gi/L, >15Gi/L) and baseline WHO Bleeding Grade indicated a tend suggesting any bleeding in the eltrombopag arm was lower than that of PBO at the Day 43 Visit. An analysis of bleeding (WHO Grades 1-4) throughout weeks 2-6 indicated a tend suggesting a decrease in bleeding at any point during the treatment period of the trial for subjects treated with eltrombopag compared to PBO.

Results-Safety:

The incidence of on-therapy AEs, regardless of causality, was 37% in PBO group and 59% in the eltrombopag treatment arm. (Table 9). Headache was the most commonly reported AE in both treatment groups. Nausea, vomiting and diarrhea were reported more frequently in the eltrombopag group; however, all were mild or moderate. Similar rates of other AEs were noted when comparing the 2 treatment groups. On-therapy SAEs occurred in 2 subjects each in both treatment groups. AEs leading to withdrawal occurred in 2 subjects in the PBO treatment group, and in 3 subjects in the eltrombopag treatment group.

The majority of subjects in both treatment groups had AEs with a maximum CTCAE toxicity grade of Grade 1 or Grade 2 (Table 47). In general, more Grade 1 and Grade 2 AEs occurred in the eltrombopag treatment group compared to the PBO treatment group. Bleeding AEs were reported on-therapy for 5 PBO subjects who experienced 9 events and 7 eltrombopag subjects who experienced 9 events. All bleeding AEs occurred in subjects who had platelet counts <30Gi/L proximate to the AE.

Table 9: On-therapy Adverse Events Reported by 5% or More of Subjects in Any Treatment Group (Safety Population)

Preferred Term	Treatment Group, n (%)	
	PBO N=38	Eltrombopag N=76
Any AE	14 (37)	45 (59)
Headache	4 (11)	6 (8)
Nausea	0	6 (8)
Nasopharyngitis	3 (8)	5 (7)
Diarrhea	1 (3)	4 (5)
Vomiting	0	4 (5)
Gingival bleeding	3 (8)	0

Post-therapy AEs were defined as AEs with onset at least 1 day post-therapy. Nine subjects (24%) in the PBO treatment group and 26 subjects (34%) in the eltrombopag treatment group experienced at least 1 post-therapy AE. Headache was the most common post-therapy AE in both treatment groups.

A total of 4 subjects experienced on-therapy SAEs during the study: 2 subjects in the PBO treatment group and 2 subjects in the eltrombopag treatment group. No deaths occurred during the study. A total of 5 subjects experienced post-therapy SAEs.

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

There were no clinically significant abnormalities seen in vital signs for each treatment regimen and none were reported as AEs. There were no ECG values of potential clinical concern in the study.

In total, 13 of the 112 subjects who had 1 or more ocular examinations reported events that met the pre-defined criteria of report of cataract as specified for this study. While on-study or in follow-up, 4 subjects had reports of cataract that were not observed at baseline. Three subjects reported progression of a pre-existing cataract while on study or in follow-up. None of the 4 incident reports and none of the 3 reports of progression met the protocol defined criteria for an ocular event of clinical concern. The remaining 6 reports were of pre-existing cataracts that remained stable throughout treatment and the 6-month follow-up.

None of the examined subjects had abnormal spleens which were considered to be a clinically significant abnormality.

Conclusions (sponsor):

- The results from TRA100773B confirmed the efficacy and safety profile of eltrombopag in subjects with relapsed or refractory chronic ITP that was observed in the Phase II study, TRA100773A. This study provides the first randomized, controlled evidence of any ITP treatment decreasing the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP, thus clearly demonstrating the potential clinical benefit of eltrombopag in this patient population with a significant unmet medical need. Eltrombopag 50 mg (with increases up to 75 mg) once daily for up to 6 weeks of treatment was found to be a well tolerated and effective treatment option for ITP.
- All current treatment options for patients with chronic ITP focus on the platelet destruction aspect of the disease, rather than on impaired platelet production. As a thrombopoietic agent that stimulates platelet production, eltrombopag represents a novel, oral treatment option.

Reviewer Comment: Platelet response highly variable. PK/PD relationship in the ITP population could not be assessed in this study.

4.3.2 Study TRA100773A: Phase II Safety and Efficacy Study

Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: A double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of SB-497115-GR, a thrombopoietin receptor agonist, administered at 30, 50 and 75 mg as oral tablets once-daily for 6 weeks to adult male and female subjects with refractory, chronic immune thrombocytopenic purpura

Study period: 02Feb2005 – 26Aug2006

Objectives:

Primary

- The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once-daily for 6 weeks to previously treated adult subjects with chronic idiopathic thrombocytopenia (ITP).

Secondary

- To assess the safety and tolerability of eltrombopag when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To characterize the population pharmacokinetic profile of oral eltrombopag using a combined sparse and serial pharmacokinetic sampling strategy when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To determine the pharmacodynamic effect of eltrombopag on markers of thrombopoiesis when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP
- To assess the impact of eltrombopag on the health-related quality of life when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP.

Methodology:

Protocol TRA100773 was a double-blind, randomized, placebo-controlled study that used an adaptive sequential design to allow for two separate and independent studies (TRA100773A, (phase II, dose finding) and TRA100773B (phase III)). In the TRA100773A study, adult subjects with chronic ITP were randomized equally to one of four treatment groups to determine the optimal eltrombopag starting dose, based on efficacy, safety and pharmacokinetic data.

Test Product, Dose and Mode of Administration, Batch Numbers:

Eltrombopag was supplied by GSK as [redacted], round film coated tablets containing eltrombopag olamine equivalent to 10mg, 25mg and 50mg of eltrombopag free acid. Matching placebo tablets were also supplied (Table 10). b(4)

Table 10: Batch Numbers for Study Medication

Product	Formulation/ Formulation Code	Drug Substance Batch Number	Drug Product (Batch Number)
Placebo	Tablet/ALC Tablet/ALC Tablet/ALC Tablet/ALC	N/A	(041050619) (041032123) (041048098) (051069874)

10 mg Tablet	Tablet/AM	TPO-E-02C —	(041032127)
	Tablet/AM	TPO-E-02C —	(041048100)
	Tablet/AM	F074714	(051069875)
25 mg Tablet	Tablet/AL	TPO-E-02C —	(041032128)
	Tablet/AL	TPO-E-02C —	(041048101)
	Tablet/AL	F074714	(051069876)
50 mg Tablet	Tablet/AN	TPO-E-02C —	(041032129)
	Tablet/AN	TPO-E-02C —	(041048102)
	Tablet/AN	F074714	(051069877)

b(4)

The treatment phase of the study involved once-daily dosing with PBO or eltrombopag (30 mg, 50 mg, 75 mg) for up to 6 weeks. Subjects who attained a platelet count >200Gi/L discontinued treatment, but continued in the study with their follow-up visits. After the dosing period, subjects were assessed every 2 weeks for up to 6 weeks to assess the durability of the platelet response.

Subjects were instructed to take their study medication in the morning upon awaking and before eating breakfast. If this was not possible, subjects were instructed to fast for 2 hours pre- and 2 hours post-dosing of study medication. Ingestion of water or coffee during the fasting period was acceptable. On study visits where PK samples were taken, subjects were specifically instructed to fast for 2 hours pre- and for 2 hours post-dosing with study medication.

Criteria for evaluation:

- Sample Size: The primary analysis was to compare the relative differences in the odds of responding between each eltrombopag treatment group and the placebo treatment group after up to 42 days of dosing. Assuming 30% and 60% of subjects respond on placebo and eltrombopag, respectively, a maximum of 68 evaluable subjects per group were needed in order to provide 90% power at the 2.5% level of significance (one-sided). The maximum planned sample size defined in the protocol for TRA100773A was 272 evaluable subjects.
- Efficacy: The primary assessment for efficacy was platelet count (collected as part of the complete blood count). The primary endpoint was the proportion of subjects with a platelet count of ≥50Gi/L after up to 42 days of dosing (compared to a baseline count of <30Gi/L). Other efficacy assessments were incidence and severity of bleeding associated with chronic ITP and health-related quality of life (HR-QoL) assessment using the SF-36v2 tool.
- Pharmacokinetics:
  - PK sampling was performed for determination of plasma eltrombopag concentrations. A subset of subjects underwent serial PK sampling (seven 2.7mL samples) on both Day 1 and Day 8. Other subjects were asked to participate in sparse sampling, which consisted of three samples (pre-dose and 2 post-dose samples) on two occasions separated by at least 2 weeks. The PK results will be the subject of a separate (Population-PK) report.
  - Plasma specimens were assayed using a validated analytical method (Table 11).

Table 11: Assay Validation Information

Eltrombopag is extracted from 50µL human plasma by protein precipitation using — as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	10.0ng/mL
Validated Range	10.0 to 2500ng/mL
Within-run Precision (%CV)	≤9.5%
Between-run Precision (%CV)	≤5.6%
Accuracy (%Bias)	-6.2% ≤ bias ≤ 10.9%

b(4)

Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 24 hours at ambient temperature

Reviewer Comment: Appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation." Recovery not reported.

- Pharmacodynamics
  - Pharmacodynamic endpoints were platelet count, endogenous serum TPO levels, and optional assessment of platelet aggregation and of platelet activation during and after up to 6 weeks of therapy.
    - Samples were to be collected at Screening and/or Day 1, Days 22, 43 and follow-up Day 85. Platelet aggregation and platelet activation results were reported as normal or abnormal.
  - Serum TPO assays were performed by a central laboratory, while platelet aggregation assays (using ADP, epinephrine, arachidonic acid, collagen and/or ristocetin as agonists) and platelet activation assays were conducted by the local laboratories according to the local procedures, at sites where the assay was available.

  Reviewer Comment: Sponsor did not provide sufficient information to evaluate the validity and reliability of these methods.

- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety assessments included detection and documentation of adverse events (AEs), clinical laboratory evaluations, physical examination, 12-lead ECGs, spleen size by ultrasound examination, and detailed ocular examination. No formal statistical analyses of the safety data were performed.

Number of Subjects

From a maximum planned sample size of 272 evaluable subjects, 118 subjects were randomized in the study. Enrollment was stopped after the results of the first planned interim analysis met the pre-determined efficacy stopping criteria (Table 12).

Table 12: Subject disposition

Number of Subjects	PBO	Eltrombopag 30mg	Eltrombopag 50mg	Eltrombopag 75mg
Planned, N	68	68	68	68
Randomized, N	29	30	30	29
Completed, n (%)	22 (76)	23 (77)	17 (57)	12 (43)
Total Withdrawn, n (%)	7 (24)	7 (23)	13 (43)	16 (57)
Withdrawn due to AE, n (%)	3 (10)	0	2 (7)	1 (4)
Withdrawn due to Lack of Efficacy, n (%)	0	2 (7)	0	1 (4)
Withdrawn for other reasons, n (%)	4 (13)	5 (16)	11 (37)	14 (49)

The most common reason for discontinuation of study medication in all eltrombopag treatment groups was a platelet count >200Gi/L, which occurred in 28 subjects (24%). In contrast, the most common reason for withdrawal for PBO subjects was due to an AE. AEs leading to withdrawal occurred in 6 subjects; three subjects in the placebo group, two in the 50mg group and one in the 75mg group, respectively. Reasons for withdrawal categorized as 'Other' included: glaucoma surgery necessitating IVIg, subject's request for rescue medication and need to initiate treatment with a medication not allowed per protocol.