The majority of AEs were mild in intensity, except for one subject experiencing a moderate headache while receiving rosuvastatin 10 mg QD on Day 1; (resolved) and a subject diagnosed with moderate streptococcal pharyngitis while receiving rosuvastatin 10 mg QD + eltrombopag 75 mg QD (Day 10) (resolved). Overall there were no treatment-related trends were noted in the drug-related AEs reported; the events resolved prior to completion of the follow-up visit. No non-fatal or fatal SAEs were reported during the study.

At the follow-up visit, 16 subjects (38%) had platelet counts >400 Gi/L (min-max: 415- 684). The changes from baseline for these increased values ranged from 32% to 113%; three subjects (7%) had a change from baseline of >100%. The Investigators followed all subjects with elevated platelet counts and reported that the platelet counts subsequently returned to normal range values by day 117 at the latest.

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. Although abnormal findings (sinus bradycardia) were observed in some subjects after administration of the investigational products during the study, none of them were judged clinically significant abnormal findings. No abnormal findings were observed on ophthalmologic examination performed at follow up except for four subjects with changes in visual acuity, but no changes in ocular status due to cataracts.

Conclusions (sponsor):

- Administration of eltrombopag 75 mg QD for four days, immediately followed by co-administration of eltrombopag 75 mg and rosuvastatin 10 mg on Day 5 increased plasma rosuvastatin exposure. Geometric mean (90% CIs) increases in plasma rosuvastatin Cmax were 2.03-fold (82%, 126%) and AUC(0-∞) were 55% (42%, 69%) for the overall population.
- The impact of eltrombopag on plasma rosuvastatin exposure differed by race. Drug interaction results for Asian subjects demonstrated geometric mean (90% CI) increases of 32% (19%, 46%) for AUC(0-∞) and 61% (44%, 80%) for Cmax when eltrombopag was co-administered; results for non-Asian subjects demonstrated larger increases of 88% (68%, 110%) for AUC(0-∞) and 2.65-fold (135%, 200%) for Cmax.
- Plasma eltrombopag PK was similar between Asian and non-Asian subjects. At the follow-up visit, 16 subjects (38%) had platelet counts >400 GI/L (min-max: 415-684). The Investigators followed all subjects with elevated platelet counts and reported that the platelet counts subsequently returned to normal range values by Day 117 at the latest.
- There were no notable treatment-related changes in vital signs from pre-dose.
- There were no deaths, SAEs or treatment-related AEs leading to discontinuation.
- There were no clinically-significant ECG abnormalities related to treatment. No QTc prolongation was noted in this study.

Reviewer Comments:

- *Given these data and other in vitro data included in this submission, I agree that a drug interaction has been demonstrated and the eltrombopag's inhibition of OATP1B1 is the likely mechanism.*
- *I do not agree with the sponsors conclusions regarding ethnic differences. Given the imbalance and low number of Caucasians in this group I find the results regarding ethnicity inconclusive.*
- [redacted]

b(5)

4.3.12 Study TRA102861 Phase 1 Mass Balance Study

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

Title: An open-label mass balance study to investigate the metabolic disposition of a single oral dose of 14CSB-497115-GR in healthy male subjects

Study period: 15 September 2005 - 01 October 2005

Objectives:

Primary:

- To determine the total recovery and relative excretion of radiocarbon in urine and feces after a single, oral dose of [14C] eltrombopag 75 mg (100 µCi) in healthy male subjects.
- To generate samples (for a separate study) with which to characterize and quantify the metabolic profile of eltrombopag in plasma, urine, and feces following administration of [14C] eltrombopag olamine to healthy male subjects.
- To compare total radiocarbon (drug-related material) in blood and plasma relative to parent plasma concentration.

Secondary:

- To determine plasma eltrombopag PK parameters following single-dose oral administration of [14C] eltrombopag 75 mg (100 µCi).
- To evaluate the safety and tolerability of eltrombopag 75 mg following single-dose, oral administration in healthy male subjects.

Methodology:

This was an open-label, single dose, mass balance study. Six healthy adult males received a single 75 mg oral dose of [14C] eltrombopag (≤ 100 µCi). During the treatment period, blood samples were collected for a minimum of 48 h (hours), continuing until either the measured radiocarbon for two consecutive samples fell to less than or equal to twice the background, or until both the urine and feces collections had ceased, whichever occurred first.

Urine and feces were collected for a minimum of 4 days (96 h post-dose) and a maximum of 7 days (168 h post-dose). Collection could be discontinued if the 48-72 h and 72-96 h samples were collected and results of radiocarbon measurements indicated that the two consecutive samples (of urine and feces) contained ≤ 1 % of the administered dose of radioactivity.

Test Product, Dose And Mode Of Administration, Batch Numbers:

For each subject, the study pharmacist was provided with a bottle containing [redacted] of [14C]SB- 497115-GR (bis-monoethanolamine salt) which is equivalent to 80 mg (106.7µCi) of [14C]SB-497115, as free acid (Formulation powder "AT," substance batch number R14845/101 051102174, and batch number 051097294). The powder was reconstituted at the study site and aliquot stored for analysis. Each subject received a [redacted] oral dose of [14C]SB-497115-GR, equivalent to 75 mg (100 µCi) of study medication as free acid. Subjects were fasted from 10 pm the prior evening until 4 hours after dosing.

b(4)

Reviewer Comment: Site of manufacture for the substance batch and formulation batch was not provided by the sponsor.

Criteria for evaluation:

- Sample size: Convenience sample. No formal sample size calculation made.
- Pharmacokinetics:
    - Plasma SB-497115: Blood samples were collected to determine plasma concentrations of SB- 497115-GR, total radioactivity, and relevant metabolites at the following times: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48

hours post-dose. Collections continued every 12 hours until the stopping criteria is met. Additional samples were collected at pre-dose, 4, 12, 24 and 48 hours post dose for metabolite profiling. Urine and feces were collected during the following intervals: pre-dose, 0-12, 12-24, 24-48, 48-72, and 72- 96 hours post-dose. Collections continue every 24 hours until the stopping criteria is met.

Noncompartmental analysis of concentration-time data was performed using WinNonLin version 4.1 (Pharsight Corporation, Mountain View, CA, USA). In plasma, pharmacokinetic parameters (AUC0-∞, AUC0-t, Cmax, tmax, and t1/2), for total radioactivity, SB-497115-GR and any relevant metabolites were summarized (mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters). In urine and feces, percent recovery of GW572016, total radioactivity, and any relevant metabolites were listed and summarized.

- Plasma and Whole Blood Radiocarbon Concentration: The individual mean, and median plasma and whole blood radiocarbon concentration-time profiles were plotted. Pharmacokinetic parameters were calculated and summarized as above for SB-497115. The blood:plasma ratio of [14C]SB-497115 related material will was calculated at each time point and listed by subject and summarized.. Plasma concentration-time profiles for SB4-497115 were compared with those for total radiocarbon to estimate how much of the total measured radiocarbon is due to metabolite.
- Plasma specimens were assayed using a validated analytical method (Table 123).

Table 123: Assay validation information

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.	
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

b(4)

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

- The radio-high performance liquid chromatography (HPLC) method used for radiopurity analysis. The sponsor reports that due to the variability in results obtained during the radioactivity concentration analysis, the amount of radioactive dose administered to each subject was calculated based on the results of the concentration analysis of individual dose vials at the CRU, the solution weights administered to each subject (weights provided by the CRU) and the specific activity from the Certificate of Analysis.

  Reviewer Comment: 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." The reviewer can not rule out that the assay method itself did not contribute to the variability in the radioactivity concentration analysis noted above.

- All sample combustions were performed in a [redacted] Sample Oxidizer [redacted] The resulting 14CO2 was trapped in [redacted] scintillation cocktail was added and the radioactivity content was quantitated by LSC. All samples directly counted by LSC were analyzed using [redacted] scintillation cocktail. The samples were counted in a [redacted] liquid scintillation counter [redacted] for at least 5 min or 100,000 counts. All samples were analyzed in triplicate if sample size allowed. If results for sample replicates (calculated as dpm/g of sample) differed by more than 10% from the mean value, the sample was rehomogenized (where appropriate) and reanalyzed. This specification was met for all sample aliquots that had radioactivity greater than 500 dpm. b(4)

  Reviewer Comment: Insufficient information was provided by the sponsor to assess whether this LSC method was adequately validated (e.g., calibration, reproducibility, etc.)

- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. The safety analysis included extent of exposure, AEs, clinical laboratory evaluations, vital signs and ECGs. No formal statistical analyses of the safety data were performed.

Number of subjects: A total of 6 male subjects were enrolled in the study, all of which completed the study in accordance with the study protocol

Population Demographics:

The population demographics from this study are listed in Table 124 below.

Table 124: Population Demographics

Parameter	
Age in Years, Mean (SD) [range]	35.8 (6.85) [30-49]
Sex, n (%)	
Male:	6 (100)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	6 (100)
Race	
African American/African Heritage	2 (33)
White – White/Caucasian/European Heritage	4 (67)

Reviewer Comment: Weight, height, BMI was not provided by the sponsor.

Results-PK analysis:

Selected plasma PK parameters and selected blood and plasma radiocarbon PK parameters derived from this study are listed in Table 125 below. Mean plasma, radiocarbon plasma and radiocarbon blood eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figures 28, 29 and 30.

Table 125: Selected PK parameters

Matrix	N	AUC(0-∞) (ng.h/mL) GM(CVb%)	AUC(0-t) (ng.h/mL) GM(CVb%)	Cmax (ng/mL) GM(CVb%)	tmax (h) median [range]	t1/2(h) GM(CVb%)
HPLC/MS/MS						
Plasma	6	144739 (35.5)	142289 (34.7)	10851 (21.5)	2.50 (2.00-4.02)	32.3 (18.3)
Radiocarbon						
Plasma	6	240492 (38.1)	223577 (37.2)	10019 (25.5)	2.50 (1.50-4.00)	49.3 (28.7)
Blood	6	135178 (36.8)	123780 (36.5)	5290 (27.4)	2.50 (2.00-4.00)	51.9 (41.0)

Figure: 28: Mean plasma SB-497115 concentration

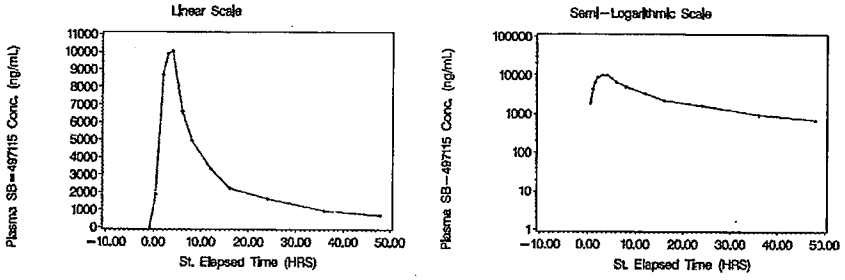


Figure: 29: Mean total blood radioactivity concentration

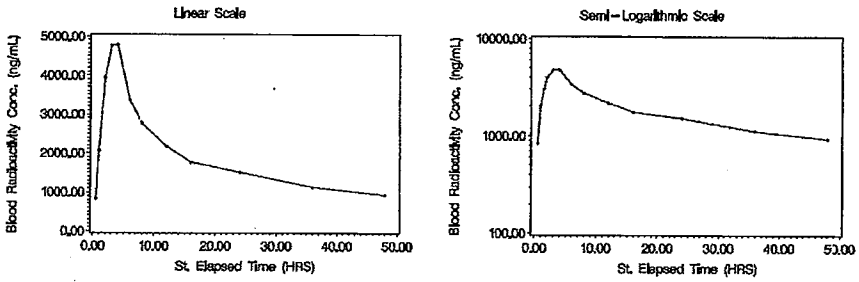
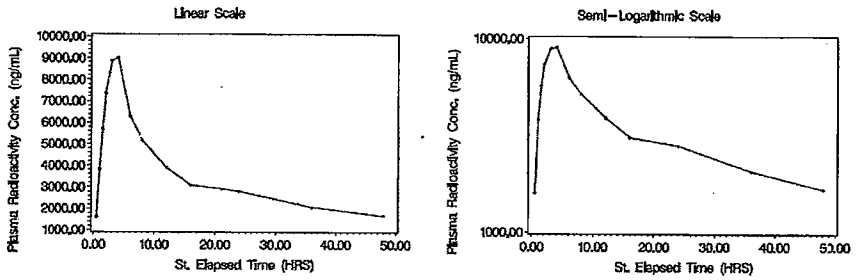


Figure: 30: Mean total plasma radioactivity concentration



Using the mean plasma AUC (0-∞) and AUC(0-t) ratios of unchanged eltrombopag to total radiocarbon, the percentage of total radiocarbon in the form of parent compound was approximately 64 %, suggesting the presence of metabolites.

Mean blood concentrations of total radiocarbon were roughly 50-79% of plasma radiocarbon concentrations.

Reviewer Comment: Blood/plasma ratio showed low intra individual variability (GM (CVb%) ~ 0.554 (5.9))

Summaries and individual listing of the cumulative excretion of total radiocarbon in urine and feces are summarized in Table 126. Eltrombopag, the parent compound, was not detected in urine.

Table 126: Summary of Cumulative Recovery of Eltrombopag Radiocarbon in Urine and Feces

	Percent (%) of Administered Dose						
	Subject Number						Individual Mean (SD)
Collection	001	002	003	004	005	006	

Interval (h)							
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						05	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)

b(4)

b(4)

Reviewer Comment: *It appears the two African American subjects (#2 and #3) had a higher renal elimination and lower fecal elimination (especially during the early time points) as compared to Caucasian subjects. This is especially apparent in subject #2 who also had the largest Tmax and AUCinf. Interestingly subject #2 also had the highest total bilirubin at screening:*

Level	Screening Total bilirubin
TRA102861.0000001	10.26
TRA102861.0000002	**17.1**
TRA102861.0000003	8.55
TRA102861.0000004	6.84
TRA102861.0000005	10.26
TRA102861.0000006	8.55

This may point to a UGT1A1 polymorphism issue. This is significant given sponsors assertion that the lack of a difference in PK parameters between Asians and non-Asians noted in *TRA105120* was related to the higher proportion of African Americans.

b(5)

Results-Safety:

In total, 2 of the 6 subjects reported at least one treatment emergent AE (33%). Subject # 1 reported stomach discomfort that resolved in one day; Subject # 3 reported urinary incontinence overnight that resolved in two days. Both AEs were mild in intensity and considered by the investigator to be related to eltrombopag olamine. No non-fatal or fatal SAEs occurred during the study and No subject prematurely discontinued from participation in the study due to an AE. No drug related changes were seen in vital signs or clinical laboratory value. No clinically significant ECG or ocular abnormalities occurred.

Conclusions (Sponsor):

- Eltrombopag accounted for approximately ~64% of plasma radiocarbon AUC(0-∞), suggesting the presence of metabolites.
- Mean total recovery of radiocarbon was 89.6% (range of 83.8% and 93.2%) as a percentage of radiocarbon administered, with urine accounting for a mean of 30.7% (range 23.4% to 45.4%) and feces accounting for a mean of 58.9% (range of 40.9 to 69.8%).
- Association of radiocarbon with red blood cells was minimal.
- Eltrombopag-GR appeared to be well tolerated in healthy male subjects.
- Two subjects reported mild drug-related AEs that resolved within two days.
- There were no deaths, SAEs or drug-related AEs leading to discontinuation.
- There were no drug-related changes in vital signs.
- There were no clinically significant ECG abnormalities.

Reviewer comment: [redacted] b(5)

4.3.13 Study 05DMM155: Human Metabolite Characterization

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

Title: Identification and Quantification of the Major Metabolites of SB-497115 Following a Single Oral Administration (75 mg 100 pCi) of [14c]s~-4917 1 5-GR to Healthy Adult Male Subjects

Study period: 27 September 2005 - 20 August 2007

Objectives: The objective of this study was to 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 (the bismonoethanolamine salt of SB-497115) to healthy adult male subjects.

Methodology:

The plasma samples (4, 12, 24 and 48 hours acidified and non-acidified), selected urine (0-12, 12-24, 24-48, 48-72 and 72-96 hours, acidified and non-acidified) and feces (0-12, 12-24, 24-48, 48-72 72-96, 96-120, 120-144 and 144-166), pre-dose and residual dose formulations from the six subjects from study TRA102861 were used in this study.

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

Single oral administration of [14C]SB-497115-GR at dose of 75 mg (See review for study TRA102861).

Criteria for evaluation:

- All samples were assayed for radioactivity by liquid scintillation counting (LSC) using [redacted] with counting efficiency determined by an external standard ratio procedure. b(4)

  Reviewer Comment: Insufficient information was provided by the sponsor to assess whether this LSC method was adequately validated (e.g., calibration, reproducibility, etc.)

- Radiometabolite profiles were determined by analysis of aliquots of plasma and fecal extracts, as well as urine samples using radio-HPLC.

  Reviewer Comment: 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."

- Selected samples of plasma extracts, urine and fecal extracts were analyzed by LC/MS, LC/MS/MS, and LC/NMR in order to provide structural identification information. In addition, pre-dose samples were also analyzed. During these analyses, radio- HPLC detection was used in parallel with the mass spectrometer to assist in the identification of radiolabeled metabolites and confirm peak assignments.

  Reviewer Comment: Insufficient information was provided by the sponsor to assess whether the LC/MS, LC/MS/MS, and LC/NMR methods were appropriately validated.

- All data were calculated using Microsoft Excel 2002. Calculations were performed within Excel using the "Precision as Displayed" option. Statistical analysis was limited to calculation of means, where appropriate. Rounding of calculated values has been performed for presentation purposes resulting in minor numerical differences in some total and mean values.

  Reviewer comment: Serious problems with statistical functionality in Excel have been well-known within the statistics profession for some time. Given only the mean was calculated it is probably okay here, but reporting statistical results based on an Excel analysis is inappropriate.

Number of subjects:

Six subjects from study TRA102861

Population Demographics: See review for study TRA102861

Results:

Plasma

- The total recoveries of radioactivity were 107%, 106% and 105% for the 12, 24 and 48 hour plasma samples, respectively.
- There were no notable qualitative differences in the radiometabolite profiles of plasma samples among the individual subjects.
- Unchanged SB-497115 (P) was the major component in plasma. Two minor radio-components (metabolites J (mono-oxygenated product) and K (acyl glucuronide)) were also detected.

Table 127: 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

Urine

- No parent compound detected
- Metabolite AE (glucuronide of the phenylpyrazole moiety) was the predominant radiolabeled component 73% detected in urine (~20% of the administered dose). A minor metabolite (AN) (unknown) was only detected in the urine of subject M003, and accounted for approximately 5% of administered dose. In addition, LC/MS analysis of the urine samples of subject M002 suggested that an acetyl glucuronide (metabolite AG) and an oxygenated glucuronide (metabolite AH) were present. Based on NMR analysis, metabolite M14, an N-acetyl glucuronide was present in approximately similar quantity as metabolite AE. The remaining 11% of the dose in the urine remained uncharacterized.

Fecal

- There were two prominent radio-peaks in the fecal extracts. One peak was characterized as the unchanged parent compound, accounting for a mean of approximately 35% of the fecal radioactivity (corresponding to a mean of ~20% of the administered dose). The other peak contained three co-eluting glutathione related conjugates of eltrombopag (metabolites F, G and M9), which together accounted for a mean of approximately 33% of the fecal radioactivity (corresponding to a mean of approximately 21% of the administered dose). Metabolite F was identified as a glutathione adduct of eltrombopag, while metabolites G and M9 are cysteine and glutamyl cysteine conjugates of eltrombopag respectively. There were a couple of minor uncharacterized components (metabolites AO and AP) quantifiable in the fecal extracts, however, neither of these metabolites accounted for more than 4% of the administered dose individually. The remaining 3% of the dose in the fecal extract was comprised of minor metabolites close to or below the background levels.

Reviewer Comment: In addition to a different urine profile above, the two African American subjects (#2 & 3) had lower fecal M9, F, G metabolites and possibly higher AO compared to Caucasians. This was most noticeable in subject # 2 who had a 1.5x higher AUCinf and the highest screening bilirubin in study TRA10286. Is this a possible UGT1A1 polymorphism?

Table 128: Major Components Recovered From Feces

Metabolite	Subjects						Mean
	M1	M2	M3	M4	M5	M6	
P	29.89 (17.89)	37.99 (15.54)	43.88 (25.87)	23.91 (15.39)	33.06 (23.06)	39.09 (22.99)	34.637 (20.123)
M9,F,G	43.60 (26.09)	10.64 (4.35)	20.54 (12.11)	57.05 (36.72)	45.80 (31.95)	21.09 (12.41)	33.120 (20.605)
AO	ND	16.07 (6.57)	10.35 (6.10)	ND (ND)	ND (ND)	14.99 (8.81)	6.902 (3.580)
AP	<LLQ	ND (ND)	ND (ND)	ND (ND)	4.45 (3.10)	ND (ND)	0.742 (0.517)
Total	73.490 (43.980)	64.700 (25.460)	74.770 (44.080)	80.960 (52.110)	83.310 (58.110)	75.170 (44.210)	75.400 (44.825)

LLQ= Low Limit of Quantification ND= Not Detected

b(4)

Conclusions (sponsor):

- Following a single oral administration of [14C]SB-497115-GR to healthy adult male subjects, majority of the radioactivity was extractable from the plasma, while the noneextractable material decreased over time and accounted for approximately 10-14 pmole/mg plasma protein at the time points studied.
- Eltrombopag was the predominant component circulating at all time points studied. Minor metabolites arising from mono-oxygenation or glucuronidation were also detected in circulation. There was no evidence for any cleavage products in plasma.
- A glucuronide of the phenylpyrazole moiety (lower portion containing the radiolabel) of eltrombopag after cleavage of the hydrazine linkage was the primary metabolite detected in human urine. A glucuronide of the unlabelled biphenyl moiety (top portion) after cleavage was detected by NMR analysis and it was estimated to be present at approximately the same concentration as the labeled portion. Unchanged SB-497115 was not detected in urine.
- SB-497115 and three glutathione related conjugates were the predominant drug-related components in the feces.

Reviewer comment: b(5)

4.3.14 Study 497115/005 Phase 1 relative bioavailability & Food effect

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

Title: An open label, randomized, three period, crossover study to assess the relative bioavailability of SB-497115-GR 25mg capsules and SB-497115-GR 25mg tablets and the effect of food on SB-497115-GR 25mg tablet pharmacokinetics in healthy, adult, volunteer subjects following a 50mg single dose of SB-497115-GR.

Study period: 26 July 2004 - 08 September 2004

Objectives:

Primary:

- To evaluate the relative bioavailability of 50 mg single oral doses of SB-497115-GR when administered as 25 mg capsules or as 25 mg tablets in healthy adult volunteers.

Secondary:

- To evaluate the effect of food on the pharmacokinetics of 50 mg single oral doses of SB-497115-GR as 25 mg tablets in healthy volunteers.
- To assess the safety and tolerability of 50 mg single oral doses of SB-497115-GR administered as 25 mg capsules or tablets.

Methodology:

The study was conducted as a single dose, open-label, randomized, three-period, crossover study. Each subject participated in three study sessions. Subjects were admitted to the clinical study unit on the evening prior to dosing (Day -1). Dosing occurred on the morning of Day 1, subjects received SB-497115-GR orally in each study session as follows:

- Regimen A: 50 mg single dose SB-497115-GR as two 25 mg capsules
- Regimen B: 50 mg single dose SB-497115-GR as two 25 mg tablets
- Regimen C: 50 mg single dose SB-497115-GR as two 25 mg tablets in the fed state.

Subjects were assigned to one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA). Subjects were screened prior to the study, remained in-house for three study periods, and attended a post-study follow-up visit 10 to 15 days following the last dose. A washout period of at least five days existed between study sessions. Subjects were admitted to the unit the evening prior to dosing (Day -1). They remained in the unit for a minimum of 48 hours following dosing. Blood samples for pharmacokinetic analysis of plasma SB-497115-GR concentrations were collected pre-dose and over a 48-hour period following dosing in each session.

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

During each study session, subjects received a single, 50 mg oral dose of SB-497115-GR as two 25 mg capsules (Formulation capsule "AF," batch number 041019400, and substance batch F033082 (Dartford)) or two 25 mg tablets (Formulation capsule "AL," substance batch number TPO-E-02C ___ and batch number 041027127 (Tonebridge)). Tablets were manufactured at the King of Prussia R& D site (USA). Study medication administered with 240 mL water by study personnel during each study session. b(4)

Reviewer Comment: The tablet formulations used in this and study and TRA104631 were derived from the same synthesis route but bear different formulation codes and drug substance batch numbers. Tablet Formulation code "AP" (Tonebridge) was used in this study and formulation code "AL" (Tonebridge) was used in study SB-497115/005. It is not clear if this difference contributes anything to the results of this study compared to that reported in TRA104631.

Test Diet: A "standard high-fat FDA breakfast" (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)) was provided prior to study medication administration in Regimen C.

Reviewer Comment: Specific calorie breakdown was not provided by the sponsor but it is safe to assume it is within limits outlines in the guidance "Food-Effect Bioavailability and Fed

Bioequivalence Studies" (i.e., approximately 800 to 1000 calories with 150, 250, and 500-600 calories derived from protein, carbohydrate, and fat, respectively).

Criteria for evaluation:

- Sample size: Sample size calculations were based on preliminary within-subject estimates of variability (CVw %) from study 497115/002 (data on file, GSK). These estimates were 25.2% for AUC and 44.2% for Cmax. Based on the largest within-subject variability estimate (44.2% for Cmax) a sample size of 16 subjects, the half-width of the 90% confidence interval about the ratios of interest should have been no more than 29% of the point estimate. This calculation was based on a two-tailed procedure with a type I error rate of 10%. A sensitivity analysis was conducted in the event that the variability was greater than estimated. Using the highest estimate of variability (44.2% for Cmax), an upper bound of the 90% confidence interval for the variability was determined (60.2% for Cmax). Based on this larger variability, it was estimated that the precision of the estimates was no more than 40% of the point estimate. No adjustment was made to the type I error rate for multiple comparisons.
- Pharmacokinetics: AUC(0-t), AUC(0-∞), Cmax, tmax, and t1/2 following a single oral dose administered as two 25 mg capsules or tablets that of SB-497115-GR (50 mg). were derived from plasma concentration versus time data.
    - Blood samples (approximately 2 ml) for SB-497115 pharmacokinetics analysis were collected over a 48 hour period at the following times: prior to dose administration of medication (pre dose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24 and 48 (out-patient) following SB-497115 administration on Day 1 (post dose). A total of 16 samples per subject were to be obtained. Blood samples were collected into tubes containing EDTA and promptly chilled. Plasma was separated by centrifugation within 1 hour of collection. Plasma was frozen and stored at approximately -20°C until shipment to the analytical laboratory.
    - Plasma specimens were assayed using a validated analytical method (Table 129)

Table 129: 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%
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

b(4)

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

- SB-497115 plasma concentration-time data were analyzed by non-compartmental methods using the computer program WinNonlin Professional, version 4.1. as follows: 1) Calculations were based on actual collection times recorded during the study, 2) The maximum observed plasma concentration (Cmax) was obtained directly from the SB-497115 concentration-time data, as was the time to Cmax (tmax), 3) Area under the plasma concentration-time curve was estimated from the time of dosing to t, where t is the time of the last

quantifiable concentration (AUC(0-t)), and from the time of dosing extrapolated to infinity (AUC(0-∞)) linear trapezoidal rule for all incremental trapezoids arising from increasing concentrations, and the log trapezoidal rule for those arising from decreasing concentrations. AUC(0-∞) was estimated as the sum of AUC(0-t) and Ct divided by the elimination rate constant, where Ct was the last observed concentration, and 4) The terminal elimination rate constant (λz) was derived from the log-linear disposition phase of the concentration-time curve using least-squares regression analysis with visual inspection of the data to determine the appropriate number of terminal data points for regression analysis. The elimination half-life (t1/2) was calculated as ln 2/λz.

- Following $\log_e$ transformation, AUC and Cmax of SB-497115 were analyzed separately by ANOVA fitting a mixed effects model with fixed effect terms for sequence, period, and regimen. Subject within sequence was fitted as a random effect. Point estimates and associated 90% confidence intervals for the differences (B-A) and (C-B) were constructed using the appropriate error term. The point and interval estimates on the $\log_e$ scale were then backtransformed to give point and interval estimates for the ratios B:A and C:B. The parameter tmax was analyzed non-parametrically.

  Distributional assumptions underlying the analyses were assessed by visual inspection of residual plots. Homogeneity of variance was assessed by plotting the residuals against the predicted values from the model, while normality was examined by normal probability plots. If the assumptions are seriously violated then appropriate statistical methods were considered.

- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety data, including adverse events, vital signs, clinical laboratory data, and ECG monitoring (continuous telemetry & 12-lead), were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of subjects: A total of 18 male subjects were randomized to the study, 16 of which completed the study in accordance with the study protocol. Two subjects withdrew prematurely, after the administration of regimen A in the first dosing session after experiencing adverse events. A total of 16 subjects completed the study: Safety (n=18), PK (n=16).

Population Demographics:

The population demographics from this study are listed in the Table 130 below.

Table 130: Population Demographics

Demographic Characteristic	Total N=18
Gender, n (%)	Male 18 (100%)
Age (years) Mean (SD) [Range]	23 (2.7) [18-28]
Race, n (%)	White 17 (94.4%) Persian 1 (5.6%)
Height (cm) Mean (SD) [Range]	177 (6.7) [167-193]
Weight (kg) Mean (SD) [Range]	70.3 (8.22) [56.5-92.8]
BMI (kg/m2) Mean (SD) [Range]	22.28 (1.56) [19.50-24.90]

Results-PK analysis:

Selected PK parameters derived from this study are listed in Table 131 below. Mean plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic

and linear scales by treatment in Figure 31. Individual parameters of interest are compared by treatment in Figures 32 & 33

Table 131: Selected PK parameters by treatment

Parameters	Treatment A N=16	Treatment B N=16	Treatment C N=16
AUC(0-∞) (µg.hr/ml)	76.2 (22)a	65.2 (28)	26.5 (27)
Cmax (µg/ml)	6.4 (26)a	5.3 (34)	1.9 (28)
tmax (hours)	4.00 (2, 6)b	3.50 (1.5, 5)	4.00 (2, 12)
t1/2 (hours)	16.6 (15)a	16.0 (13)	15.1 (15)

a. A:Geometric Means (95% CV)
b. B: Median (range) values

Figure: 31: Mean plasma SB-497115 by treatment

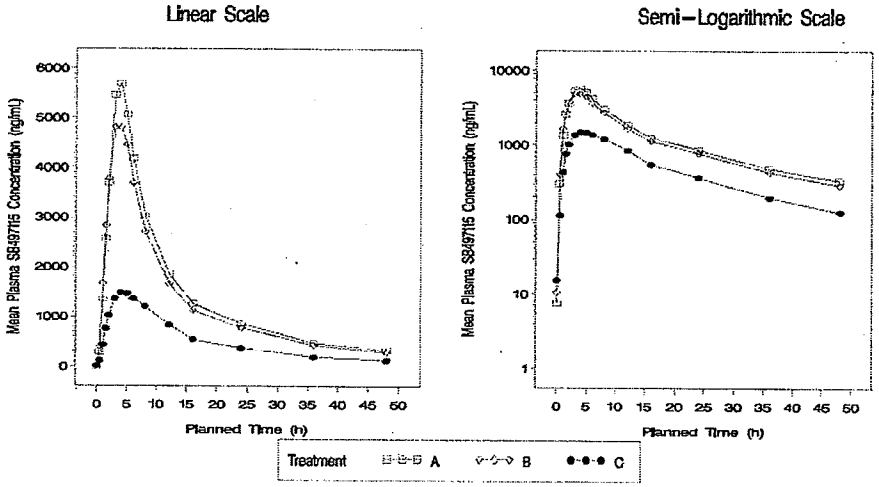


Figure 32: Individual $AUC_{0-\infty}$ (hr*ng/mL) by treatment

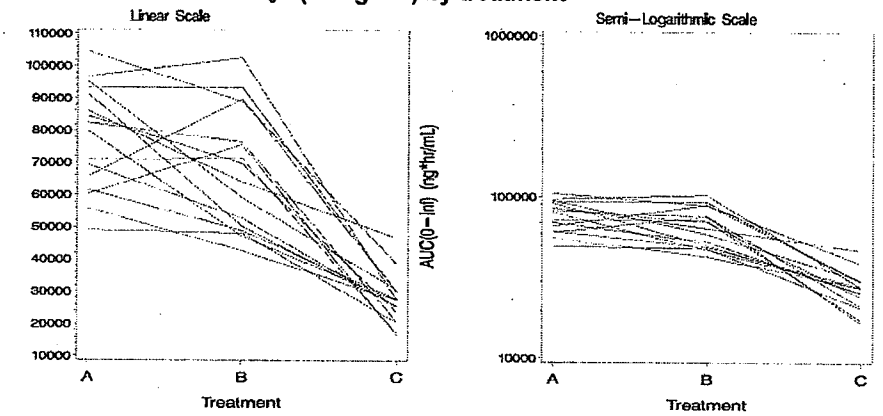
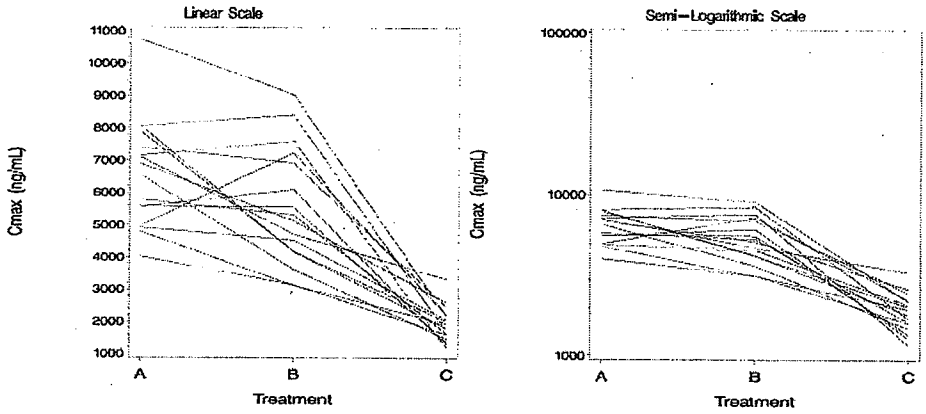


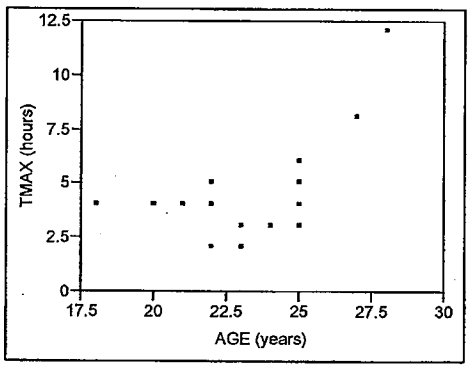
Figure 33: Individual Cmax (ng/mL) by treatment



Reviewer comment:

- *Although not reported by the sponsor, the reviewer analysis showed that 23 subjects had pre-dose concentrations that were quantifiable (Group A: 12.5 ng/mL (10.4-34.4) (median (range)), Group B: 29.2 ng/mL (25.2-47.4), & Group C: 16.35 ng/mL (10.3-74)) following the washout between treatment periods. These were <5% of Cmax.*
- *Significantly greater variability in Tmax for group "C" compared to others. It appears these data are skewed to the right with 25% of the data greater than 5 hours. Interestingly, there is a trend suggesting a relationship between a age and Tmax in group "C" that was not apparent in groups A or B (Figure 34). While anecdotal, it could suggest that age related GI/hepatic system changes may impact the magnitude of this food effect.*

Figure 34: ***Reviewer Generated Graph Showing the Effect of Age on Tmax in Group "C"***



The effect of food on AUC0-∞ and CMax is outlined in Table 132 below (Ratio (90% CI). Median Tmax was prolonged 30 minutes in the presence of food. Terminal t1/2 was not affected by the presence of food.

Table 132: **Summary of the Effects of Food on SB-497115-GR Pharmacokinetic Parameters**

Parameter	Treatment C: Treatment B
AUC(0-∞) (µg.hr/ml)	0.41 (0.36, 0.46)a
Cmax (µg/ml)	0.35 (0.30, 0.41)

Reviewer comment: This study treatments failed to meet 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 parameters related to the assessment of relative bioavailability are listed in Table 133 below. The estimated ratio of geometric least square means for AUC(0-∞) and Cmax indicates that the relative bioavailability of the tablet is 82-85% compared to the capsules.

Table 133: Summary of the Effects of Formulation on SB497715-GR Pharmacokinetic Parameters

Parameter	Treatment B: Treatment A
AUC(0-∞) (µg.hr/ml)	0.85 (0.75, 0.97)a
Cmax (µg/ml)	0.82 (0.70, 0.96)

Reviewer comment: Sponsor states in the Biopharmaceutics Summary (Module 2.7.1) that "The absolute bioavailability of eltrombopag has not been determined [redacted] " However, in the absence of an intravenous formulation, 21 CFR 320.25(d)(2) states that "The reference material in such a bioavailability study should be a solution or suspension containing the same quantity of the active drug ingredient or therapeutic moiety as the formulation proposed for marketing." The use of a capsule to establish relative bioavailability *is not consistent with this FDA regulation.* b(4)

Results-Safety:

In total, five of the 18 subjects reported at least one treatment emergent AE (27.8%). The five subjects reported a total of 11 AEs; three AEs were reported by two subjects (11.1%) after Regimen A, five AEs were reported by five subjects (31.3%) after Regimen B, and three AEs were reported by three subjects (18.8%) after Regimen C. One moderate headache was reported after the administration of Regimen C, the remaining AEs were all mild in intensity. No serious adverse events were reported in the study. The specific adverse events are listed in Table 134 below:

Table 134: Post dose adverse effects:

Treatment Regimen	A N= 18	B N = 16	C N = 16
Subjects (%) With at Least One AE	2 (11.1)	5 (31.3)	3 (18.8)
Gastrointestinal disorders			
Abdominal discomfort	1 (5.6)		
Abdominal pain – upper		1 (6.3)	1 (6.3)
General disorders and administration site conditions			
Feeling cold	1 (5.6)		
Injury, Poisoning and procedural complications			
Medical device site reaction		2 (12.5)	
Musculoskeletal and connective tissue disorders			
Muscle twitching			1 (6.3)
Nervous system disorders			
Dizziness		1 (6.3)	
Headache			1 (6.3)
Respiratory, thoracic and mediastinal disorders			

Pharyngolaryngeal pain	1 (5.6)		
Skin and subcutaneous tissue disorder			
Dry skin		1 (6.3)	

Laboratory values of potential clinical concern are presented in Table 135

Table 135: Laboratory values of potential clinical concern

Subject	Regimen	Relative Time to Dosing	Parameter type	Parameter	High or Low	Value	Threshold Range Low-High	Units
104	A	+24 hours	Haematology	Haemoglobin	High	18.8	12 – 18	g/dL
106	C	Pre-dose	Biochemistry	Total bilirubin	High	32	0 – 30	µmol/L
	-	Follow-up	Biochemistry	Total bilirubin	High	44	0 – 30	µmol/L
110	-	Screening	Biochemistry	Total bilirubin	High	36	0 – 33	µmol/L
	-	Follow-up	Biochemistry	Total bilirubin	High	36	0 – 33	µmol/L

Reviewer Comment: Increase total bilirubin not noted at all in study TRA104631. This formulation was made from substance batch TPO-E-02C → Study 104603 (JAPAN) also used this formulation and reported primarily hepatic laboratory abnormalities. b(4)

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.

Conclusions (sponsor):

- The relative bioavailability of the SB-497115-GR tablet was 82-85% compared to the capsule.
- Compared to the fasted state, Cmax and AUC(0-∞) for SB-497115 were reduced 60-65% in the presence of food, and tmax was slightly prolonged.
- Single oral doses of SB-497115-GR were well tolerated in this study. There was no apparent difference in the safety and tolerability between the capsule and tablet formulations of SB-497115-GR.
- There were no clinically significant laboratory abnormalities, changes in vital signs or ECG recordings during the study.

Reviewer comment:

- *The use of a capsule to establish relative* bioavailability *is not consistent with FDA regulation 21 CFR 320.25(d)(2) as stated above.*

b(5)

- *Criteria for relative bioequivalence as outlined in the FDA Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" was not met for the comparison of the capsule to the tablet formulation in this study.*

- *While the increase in bilirubin in two subjects was not clinically significant in this study. It adds to the safety concern regarding hepatotoxicity associated with this drug and noted in the approved product labeling.*

4.3.15 Study TRA 102863 - Phase 1 Relative Bioavailability

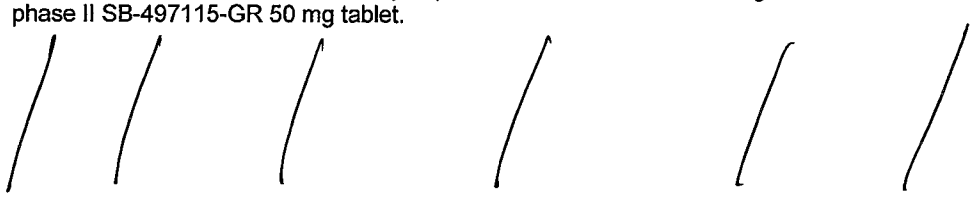
Study Reviewer: Joseph A. Grillo, Pharm.D.

Title: A randomized, open-label, two-period, period-balanced, crossover study with three parallel groups to evaluate the relative bioavailability of single oral doses of SB-497115-GR phase III tablets [50 mg, 75 mg, 100 mg] compared to SB-497115-GR phase II tablets [25 mg and 50 mg] in healthy volunteers.

Objectives:

Primary:

- To evaluate the relative bioavailability of phase III SB-497115-GR 50 mg tablet relative to phase II SB-497115-GR 50 mg tablet.



Secondary:

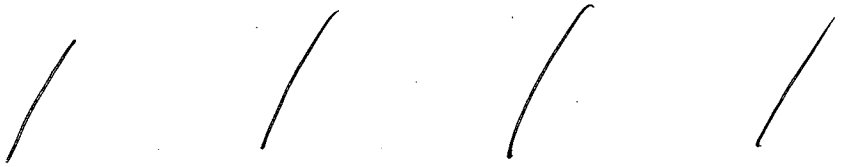
- To characterize additional pharmacokinetic parameters of single doses of SB-497115-GR in healthy volunteers.
- To assess the safety and tolerability of single oral doses of SB-497115-GR.

b(4)

Methodology:

This was an open-label, single-dose, randomized, two-period, period-balanced, crossover study conducted in healthy subjects. The study treatment groups are as follows:

- A= One Phase II 50 mg tablet while fasting
- B= One Phase III 50 mg tablet while fasting



b(4)

Subjects were assigned to a treatment sequence according to a randomization schedule prepared in advance of the study (i.e., B/A, D/C, & F/E). Each subject participated in two study periods, separated by a washout period of at least five days.

During each study period, subjects were admitted to the clinical study unit on the evening prior to dosing (Day -1). Study medication was administered on the morning of Day 1. Blood samples for pharmacokinetic analysis of SB-497115 were collected pre-dose and over a 48-hour period following dosing in each period. Subjects remained in-house for at least 48 hours after dosing. Subjects returned for a follow-up visit approximately 10-15 days following the last dose of study medication.

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

During each study period, subjects received one of the regimens listed above, according to the treatment sequence to which the subject was randomized. The study medication was

administered with 240 mL of water in a fasted state. Information regarding the formulations used in this study can be found in Table 136 below:

Table 136: Study Medications

Study Medication	Batch Number	Formulation Code	Substance batch (site)	Site of manufacture
Phase II 50 mg tablet	051069877	AN	F074714 (Tonebridge)	R&D site (USA)
Phase III 50 mg tablets	051074351	AR	F076633 (Tonebridge)	Commercial site (UK)

b(4)

Reviewer Comment: The tablet formulations used in this study were derived from the same synthesis route but bear different formulation codes and drug substance batch numbers.

Criteria for Evaluation:

- Sample size: From study SB-497115/005, the observed estimates of within-subject CV for the primary endpoints AUC(0-∞) and Cmax are 21.7% and 26.3%, respectively. The largest of these estimates (26.3%) translates to a standard deviation of 0.259 on the natural log scale. When the sample size is 20 subjects, the upper 90% confidence limit for the true ratio of phase III formulation to phase II formulation (A:B, C:D, and E:F) for the most variable PK parameter of primary interest will be no more than 16% greater than the observed ratio of means of the two formulations. A sensitivity analysis was conducted and based on all available historical information. An 80% upper confidence bound of the true within-subject standard deviation of the most variable primary pharmacokinetic endpoint to be analyzed was 0.360. If, under all other assumptions outlined above, the actual within subject standard deviation were 0.360 rather than 0.259, it is estimated that the upper 90% confidence limit for the true ratio of phase III formulation A to phase II formulation for that parameter will be no greater than 22% of the observed ratio of the two means.

  Reviewer Comment: No adjustment was made for multiple comparisons.

- Pharmacokinetics: AUC(0-t), AUC(0-∞), AUC%ex, Cmax, tmax, tlag, and t1/2 following a single oral dose administered as described above were derived from plasma concentration versus time data.
  - During each period, blood samples (2 mL) were collected for the determination of SB- 497115 concentrations in plasma prior to dosing and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing.

    Reviewer comment: Information regarding the handling of samples was not provided by the sponsor.
  - Plasma specimens were assayed using a validated analytical method (Table 137)

Table 137: Assay validation information

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.	
LLQ	10.0ng/mL
Validated Range	10.0 to 2500ng/mL
Within-run Precision (%CV)	≤9.5%

b(4)

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

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

- SB-497115 plasma concentration-time data were analyzed by non-compartmental methods using the computer program WinNonlin Professional, version 4.1 as follows: 1) Actual elapsed time from dosing was used to estimate all individual plasma PK parameters, 2) The maximum observed plasma concentration (Cmax) was obtained directly from the SB-497115 concentration-time data, as was the time to Cmax (tmax) and the time to the first quantifiable concentration (tlag), 3) Area under the plasma concentration-time curve was estimated from the time of dosing to the time of the last quantifiable concentration (AUC(0-t), and from the time of dosing extrapolated to infinity (AUC(0-∞). AUCs were calculated using the linear trapezoidal rule for all incremental trapezoids arising from increasing concentrations, and the log trapezoidal rule for those arising from decreasing concentrations. AUC(0-∞) was estimated as the sum of AUC(0-t) and Ct divided by the elimination rate constant (λz), where Ct was the last observed concentration. The percentage of AUC(0-∞) obtained by extrapolation (%AUCex) was calculated as [(AUC(0-∞)-AUC(0-t))/AUC(0-∞)] * 100, and 4) The λz was derived from the log-linear disposition phase of the concentration-time curve using least-squares regression analysis with visual inspection of the data to determine the appropriate number of terminal data points for regression analysis. The elimination half-life (t1/2) was calculated as ln2/λz.
- The analysis of derived pharmacokinetic parameters from plasma SB-497115-GR concentration-time data was performed using the SAS/STAT® module of the SAS® System, Version 8.2 or higher or a comparable statistical package. To estimate the relative bioavailability of SB-497115-GR Phase III tablets compared to SB-497115-GR Phase II tablets for each of the primary PK endpoints, AUC(0-∞), and Cmax, a mixed effects linear analysis of variance (ANOVA) model was fit to the natural logarithm of the PK parameter. Effects associated with treatment sequence, period, and treatment were assumed fixed; effects associated with subject within each treatment sequence were assumed random. Point and 90% confidence interval (CI) estimates of the difference in least-squares means of the test minus the reference treatment were calculated. These estimates were then exponentiated (back-Transformed) to express point and interval estimates on a ratio scale. The final estimates, therefore, represent the ratio of the geometric least square (GLS) mean of the test treatment to the GLS mean of the reference treatment. The comparison of D vs C and F vs E were analyzed separately in a similar manner. Assumptions underlying the analyses of primary endpoints were assessed. Period and treatment sequence effects from the crossover study design were assessed in the ANOVA model. Carryover effects were assessed by examination of the pre-dose concentration prior to the second period.

- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety data, including adverse events, vital signs, clinical laboratory data, ophthalmic assessments, and ECG monitoring (12-lead), were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects: A total of 66 subjects (n=11 per sequence) were enrolled in this study and received at least 1 dose of study medication. Three subjects withdrew prematurely, due to an

adverse event (E), protocol violation (E), or lost to follow up (F) respectively. A total of 63 subjects completed the study: Safety (n=66), PK period A, B, C, & D (n=22), and PK period E & F (n=20).

Population Demographics:

The population demographics from this study are listed in Table 138 below.

Table 138: Population Demographics

Demographic Characteristic	Total N=66
Age (yrs) (Mean (SD) [Range])	
Adults	42.9 (13.46) [19-64]
Sex n (%)	
Female:	46 (70%)
Male:	20 (30%)
Ethnicity n (%)	
Hispanic or Latino:	14 (21%)
Not Hispanic or Latino:	52 (79%)
Race n (%)	
African American/African Heritage:	8 (12%)
American Indian or Alaska Native	2 (3%)
White:	55 (83%)
Mixed Race	1 (2%)
Height (cm) **(Mean (SD) [Range])**	164.7 (8.33)[149-189]
Weight (kg) **(Mean (SD) [Range])**	70.0 (12.90) [50-101]
Body mass index (kg/m2) **(Mean (SD) [Range])**	25.6 (2.95) [20-31]

Reviewer Comment: Sponsor study report table 3 states range for age 18-64 years, however; source table 9.5 reports range to be 19-64 years.

Results-PK analysis:

Selected PK parameters derived from this study are listed in Table 139 below. Mean plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figure 35. Individual parameters of interest are compared by treatment in Figures 36 & 37

Table 139: Selected PK parameters by treatment[1]

Dosing Group	Treatment	N	AUC(0-t) (ng.hr/mL)	AUC(0-∞) (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)[2]	t1/2 (hr)
50 mg	A	22	64553 (32.3)	74458 (35.0)	6111 (29.0)	3.00 (1.48-4.15)	18.9 (19.6)
	B	22	55059 (51.5)	63160 (54.6)	5094 (54.3)	3.00 (1.50-6.00)	18.3 (24.8)
[redacted]							

b(4)

[	]

1. geometric mean (between-subject coefficient of variation [CVb%])
2. median (range)

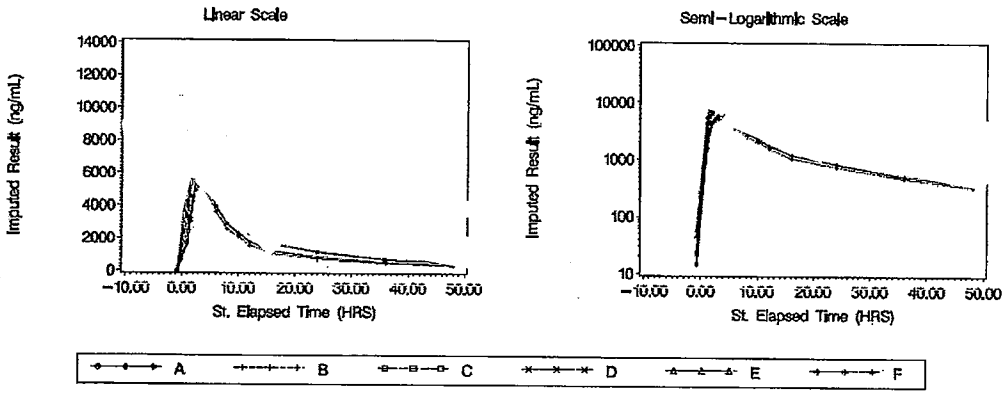
b(4)

Reviewer Comment: *Subject 321 Tmax 6-8 hrs (group E/F)*

In Period 2, quantifiable pre-dose plasma SB-497115 concentrations (carryover from Period 1) were observed in almost all subjects. The pre-dose concentrations were low, ranging from below the lower limit of quantification to — ng/mL, and therefore are not expected to significantly impact the overall study results.

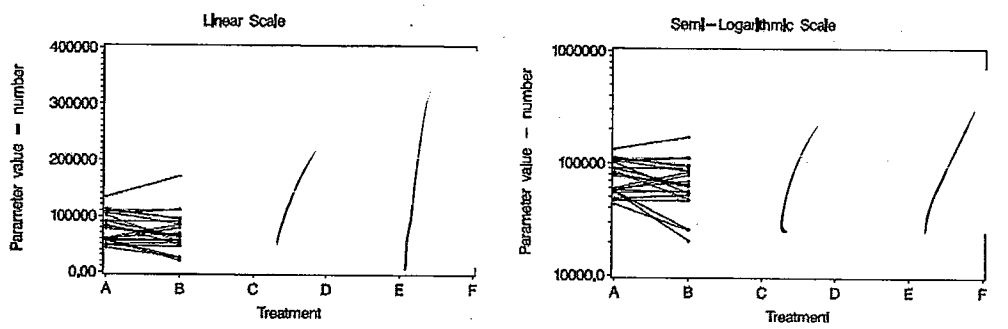
b(4)

Figure: 35: Mean plasma SB-497115 by treatment



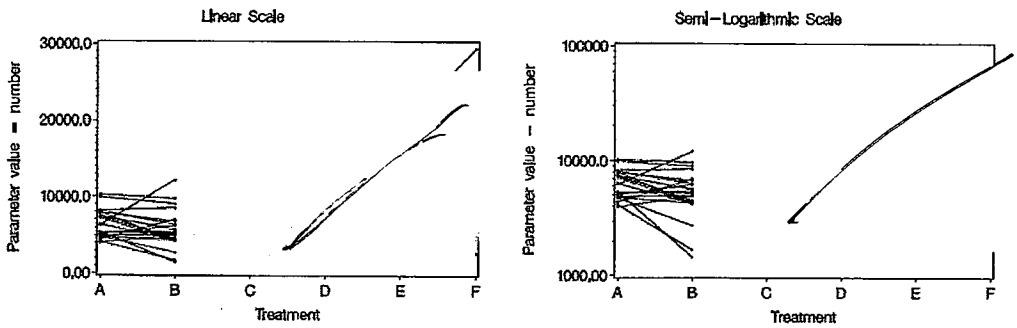
b(4)

Figure 36: Individual $AUC_{0-\infty}$ (hr*ng/mL) by treatment



b(4)

Figure 37: Individual Cmax (ng/mL) by treatment



b(4)

Reviewer Comment:

Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest is presented in Table 140.

Table 140: Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest

Parameter	Ratio of GLSMeans (90% CI) Relative Bioavailability
	B/A n=22
AUC(0-∞)	0.848 (0.742, 0.970)
Cmax	0.834 (0.707, 0.983)

b(4)

Reviewer Comment: Criteria for relative bioequivalence as outlined in the FDA Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" was not met for the comparisons B/A and F/E.

Results-Safety:

There were disproportionately fewer AEs reported for Regimens E and F. Except for one case of severe abdominal pain, which was considered a serious adverse event, all other Aes were mild to moderate in intensity. There were no deaths during this study. One subject was withdrawn due to an AE and one subject experienced a SAE but was not withdrawn. The specific adverse events are listed in Table 141 below:

Table 141: Post Dose Adverse Effects:

Adverse Event	Number of Subjects					
	Group 1		Group 2		Group 3	
	A	B	C	D	E	F
Headache	3	3	2	1	0	0
Abdominal pain	1	1	1	0	1	0
Nausea	1	0	1	1	1	0
Dizziness	1	1	0	0	1	0
Conjunctival hyperaemia	1	1	0	1	0	0
Somnolence	0	1	1	0	0	0
Syncope vasovagal	2	0	0	0	0	0

Diarrhea	0	0	0	1	1	0
Flatulence	0	1	1	0	0	0
Fatigue	0	0	0	1	0	1
Vessel puncture site hemorrhage	1	0	0	1	0	0
Muscle spasms	0	1	0	0	0	1
Number of Subjects Exposed	22	22	22	22	22	20
Number (%) of Subjects with AE	9 (41%)	7 (32%)	9 (41%)	5 (23%)	2 (9%)	3 (15%)
Number (%) of Subjects with any AE related to investigational product	6 (27%)	4 (18%)	5 (23%)	3 (14%)	2 (9%)	1 (5%)
The following AEs were reported once during the study: constipation, dry mouth, vomiting, feeling hot, musculoskeletal pain, myalgia, erythema, rash papular, ventricular extrasystoles, nasal congestion, flushing.						

There were no subjects with laboratory values of potential clinical concern. Occasional abnormal laboratory values and urinalysis (dipstick) results were observed. These observations were not considered clinically significant.

Vital sign data were similar across all regimens tested. A single subject had an abnormal ECG of clinical concern. Subject 301 was reported to have asymptomatic ventricular extrasystole on a predose ECG for Regimen F (period 2; ——— 100 mg——— This subject was withdrawn from the study due to this AE. This AE had not resolved at the time of withdrawal. b(4)

Ocular examinations were conducted at screening and at follow-up. At both time points tested, there were no abnormalities in visual acuity or with ophthalmoscopy that affected subject vision or required treatment.

Conclusions (Sponsor):

- The eltrombopag 50 mg oral film-coated Phase III 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 50 mg oral film-coated Phase II tablet.

b(4)

- Administration of SB-497115 was safe and well-tolerated with both Phase II and Phase II formulations at doses of 50 mg ___ , respectively.

Reviewer Comment: While the reviewer agrees disagrees that the differences in bioavailability of the 50 mg , Phase III and 50 mg Phase II tablets are not considered to be clinically significant, "the differences are relevant given that the Phase II 25 mg tablet was used in study TRA104603 (single dose Japanese), where a significantly higher Cmax & AUC was noted. It does add an additional confounding factor to the ethnicity issue.

4.3.16 Study TRA 105122 – Phase 1 Relative Bioavailability

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

Title: Phase I Bioequivalence Study for SB-497115-GR Phase II and Phase III Tablets

Study period: 20 March 2006 – 06 July 2006

Objectives:

Primary

- To demonstrate the bioequivalence of 25 mg eltrombopag tablets commercially manufactured for Phase III studies to the 25 mg tablets manufactured at the R & D site used for Phase II in fasted healthy subjects.
- To demonstrate the bioequivalence of 50 mg eltrombopag tablets commercially manufactured for Phase III studies to the 50 mg tablets manufactured at the R & D site used for Phase II in fasted healthy subjects.

Secondary

- To investigate the safety and tolerability of the 25 mg Phase II and Phase III formulations of eltrombopag in the fasted state.
- To investigate the safety and tolerability of the 50 mg Phase II and Phase III formulations of eltrombopag in the fasted state.

Methodology:

This was an open-label, single dose, randomized, two-period, period balanced, crossover study with two parallel groups conducted in healthy subjects. The treatment groups are as follows:

- A = One Phase II 25 mg tablet
- B = One Phase III 25 mg tablet
- C = One Phase II 50 mg tablet
- D = One Phase III 50 mg tablet

Subjects were assigned to a treatment sequence (e.g., AB or CD) according to a pre-defined randomization schedule. Each subject participated in two dosing periods (Period 1 and Period 2), separated by a washout of at least 10 days. During each dosing period, subjects received a single dose of eltrombopag.

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

During each study period, subjects received one of the regimens listed above, according to the treatment sequence to which the subject was randomized. Information regarding the formulations used in this study can be found in Table 142 below:

Table 142: Study Medications

Study Medication	Batch Number	Formulation Code	Substance batch (site)	Site of manufacture
Phase II 25 mg tablet	051069876	AL	F074714 (Tonebridge)	R&D site (USA)
Phase III 25 mg tablet	051109558	AS	F081601 (Tonebridge)	Commercial site (UK)
Phase II 50 mg tablets	051069877	AN	F074714 (Tonebridge)	R&D site (USA)
Phase III 50 mg tablet	051109563	AR	F081598 (Tonebridge)	Commercial site (UK)

Reviewer Comment: It is important to note that while the formulation codes for the 50 mg tablets used in this study are the same as those used in study TRA102863, the substance batch numbers are different for the Phase III 50 mg tablet and may explain the different conclusions seen in these two trials regarding BE.

Each dose of eltrombopag was administered with 240 mL of water after fasting for at least 8 hours; subjects continued to fast for 4 h following administration of study drug. Following each dose of study medication, serial blood samples were collected over 72 h for PK analysis.

Criteria for evaluation

- Sample Size: Based on information from TRA102863, the intra-subject standard deviation from single dose of 50mg eltrombopag for log (AUC(0-∞) is estimated as 0.258 and estimated as 0.317 for log (Cmax). Assuming an intra-subject standard deviation of 0.317, forty-six (46) evaluable subjects should provide at least 90% power of declaring bioequivalence, for either PK parameter, if the true ratio of the geometric means of the test and reference treatments is equal to one. A sensitivity analysis showed that If, under all other assumptions outlined above, the actual within-subject standard deviation were 0.380 rather than 0.317, then, for a particular test and reference formulation, power to conclude bioequivalence would be approximately 75%.

  Reviewer Comment: No adjustment was made for multiple comparisons.

- Pharmacokinetics: AUC(0-∞) and Cmax of eltrombopag were the primary pharmacokinetic endpoints and were derived from plasma concentration versus time data. Other pharmacokinetic endpoints included AUC(0-t), tmax, and t1/2 of eltrombopag.

  - Following single dose administration of study drug in each period, serial blood samples were collected for measurement of eltrombopag concentration in plasma as listed in Table 143.

Table 143: PK sampling times

Day	Analyte	Planned Time Relative to Dose (hours)
Day 1 through 4 (Period 1)	eltrombopag	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 h post-dose
Day 12 through 15 (Period 2)	eltrombopag	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 h post-dose

  - Plasma specimens were assayed using a validated analytical method (Table 144)

Table 144: Assay validation information

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.	
LLQ	100 ng/mL
Validated Range	100 to 50,000 ng/mL
Within-run Precision (%CV)	≤7.5%
Between-run Precision (%CV)	≤8.1%
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

b(4)

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

PK analysis of plasma eltrombopag concentration-time data was conducted using the noncompartmental Model 200 of WinNonlin Professional Edition version 4.1 as follows: 1) Actual elapsed time from dosing was used to estimate all individual plasma PK parameters, 2) The maximum observed plasma concentration (Cmax) and the first time to reach Cmax (tmax) were the actual observed values, 3) The terminal elimination rate constant (λz) was derived from the log-linear disposition phase of the concentration-time curve using least-squares regression analysis with visual inspection of the data to determine the

appropriate number of terminal data points for regression analysis. The elimination half-life (t½) was calculated as ln 2/λz, and 4) Area under the plasma concentration-time curve was calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC(0-t)) and from time zero to infinity (AUC(0-∞)) were determined. Values for AUC(0-∞) were estimated as the sum of AUC(0-t) and Ct divided by the elimination rate constant, where Ct was the last observed quantifiable concentration.

- Analysis of variance (ANOVA), using SAS (Version 8.2) Mixed Linear Models procedure, considering treatment sequence, period, and treatment as fixed effects and subject within sequence as a random effect was performed on log-transformed plasma eltrombopag PK parameters (except tmax) to assess, separately, the bioequivalence of eltrombopag 25 mg tablets and the bioequivalence of eltrombopag 50 mg tablets. For each primary PK endpoint, results from these analyses were exponentiated to obtain a point estimate and 90% CI estimate of the test-to-reference ratio of GLS means. Data from combined sequence AB and sequence BA were used to assess bioequivalence for the 25 mg tablets and data from combined sequence CD and sequence DC were used to assess bioequivalence for the 50 mg tablet.

  Distributional assumptions underlying the statistical analyses were assessed by visual inspection of the residual plots. Normality was examined by normal probability plots, while homogeneity of variance was assessed by plotting the residuals against the predicted values for the model. If the assumptions were seriously violated, then nonparametric methods were considered. Carryover effects were assessed by examination of the pre-dose concentration prior to Period 2.

  Dose proportionality was assessed by fitting the Power Model and ANOVA. The Power Model related log-transformed plasma eltrombopag single dose AUC(0-t), AUC(0-∞), and Cmax to log-transformed dose (log-transformed pharmacokinetic parameter = $\alpha + \beta$ * log-transformed dose), by Linear Regression. The slope was estimated and the associated 90% CI was constructed to examine linearity. The ANOVA approach compares the PK parameters of the 25 mg to the 50 mg tablet by dividing the PK parameters of 50 mg by two. The ratio was estimated and the associated 90% CI was constructed to examine linearity. Both approaches used SAS Version 8.2 Mixed procedure.

  Reviewer Comment: Power model is more useful to detect nonlinear response.

- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety data, including adverse events, vital signs, clinical laboratory data, ophthalmic assessments, and ECG monitoring (12-lead), were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects: A total of 100 subjects (n=25 per sequence) were enrolled in this study and received at least 1 dose of study medication. Six subjects withdrew prematurely, due to an adverse event (2 CD, 1 DC), protocol violation (1 CD), or subject decision (2 AB), respectively. A total of 94 subjects completed the study: Safety (n=100), PK period AB (n=23), BA (n=25), CD (n=22), & DC (n=24).

Population Demographics:

The population demographics from this study are listed in Table 145 below.

Table 145: Population Demographics

Parameter	Sequence				
	AB	BA	CD	DC	Total
Age (Years) *	27.3 (8.70) [18-49]	27.4 (7.84) [19-42]	25.7 (8.44) [18-50]	26.2 (7.41) [18-47]	26.7 (8.02) [18-50]
Male:	14 (56)	19 (76)	15 (60)	20 (80)	68 (68)
Ethnicity, n (%)					
Hispanic or Latino:	3 (12)	2 (8)	3 (12)	2 (8)	10 (10)
Race, n (%)					
African American/African Heritage:	2 (8)	4 (16)	5 (20)	2 (8)	13 (13)
American Indian or Alaskan Native	0	0	1 (4)	0	1 (1)
Asian	2 (8)	3 (12)	2 (8)	3 (12)	10 (10)
Central/South Asian Heritage	0	0	0	1(4%)	1(1%)
Japanese/East Asian Heritage	2(8%)	3(12%)	2(8%)	2(8%)	9(9%)
South East Asian Heritage	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (4)	0	2 (8)	1 (4)	4 (4)
White	20 (80)	19 (76)	16 (64)	19 (76)	74 (74)
Height (cm)*	170.1 (9.72) [154-189]	177.4 (9.80) [160-194]	172.6 (9.06) [155-189]	175.5 (10.11) 155-194]	173.9 (9.93) [154-194]
Weight (kg)*	70.5 (14.93) [48-99]	75.6 (14.24) [51-103]	73.5 (9.50) [51-91]	75.6 (11.08) [52-99]	73.8 (12.62) [48-103]
BMI (kg/m2)*	24.14 (3.34) [18.59-30.01]	23.89 (3.28) [18.62-30.70]	24.71 (2.98) [19.78-30.40]	24.52 (2.86) [19.97-30.44]	24.321 (3.09) [18.59-30.70]

*Mean (SD) [range]

Reviewer Comment: *Unclear why sponsor chose to consolidate Asians in its report given the PK issues with Japanese/East Asians.*

Results-PK analysis:

Selected PK parameters derived from this study are listed in Table 146 below. Mean plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figure 38. Median %AUCex values were 7 to 10% across the treatments. Four subjects had %AUCex >20%. Pre-dose concentrations were quantifiable in several subjects following a 7-14 day washout between treatment periods, but were generally <5% of Cmax. Individual parameters of interest are compared by treatment in Figures 39 & 40

Table 146: Selected PK Parameters by Treatment

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]

Figure: 38: Mean plasma SB-497115 by treatment

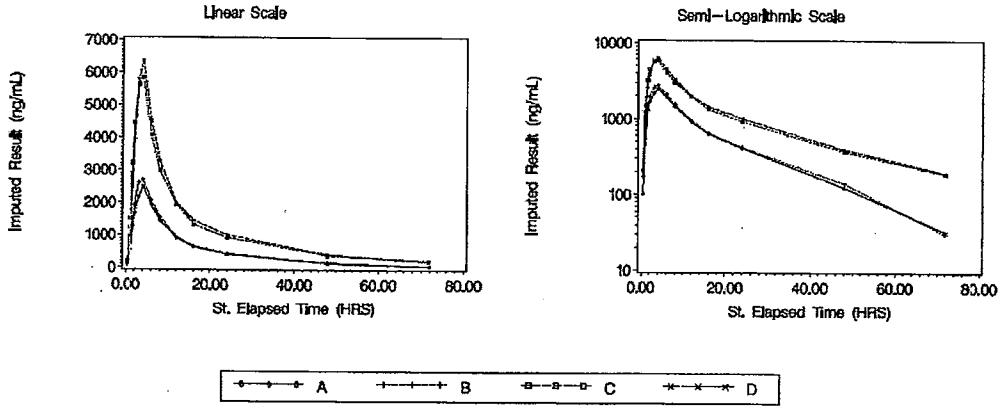


Figure 39: Individual $AUC_{0-\infty}$ (hr*ng/mL) by treatment

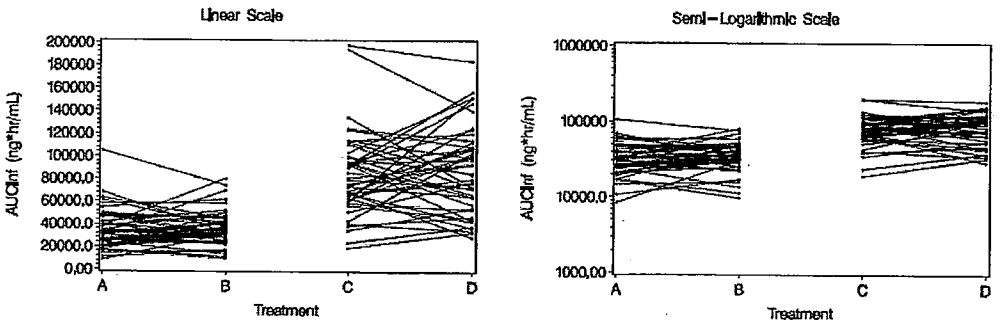
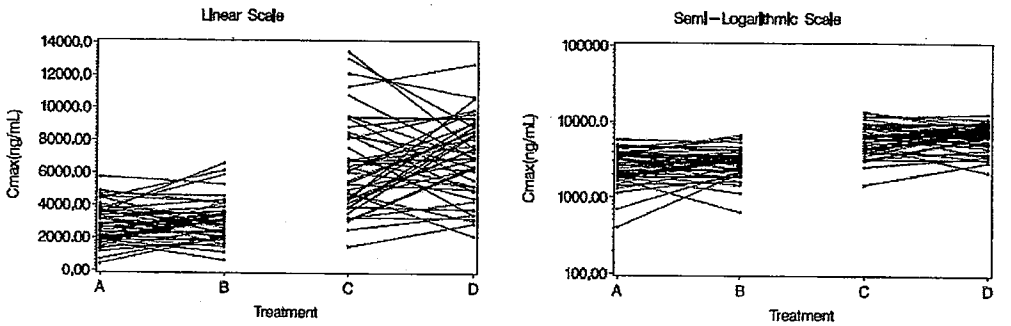


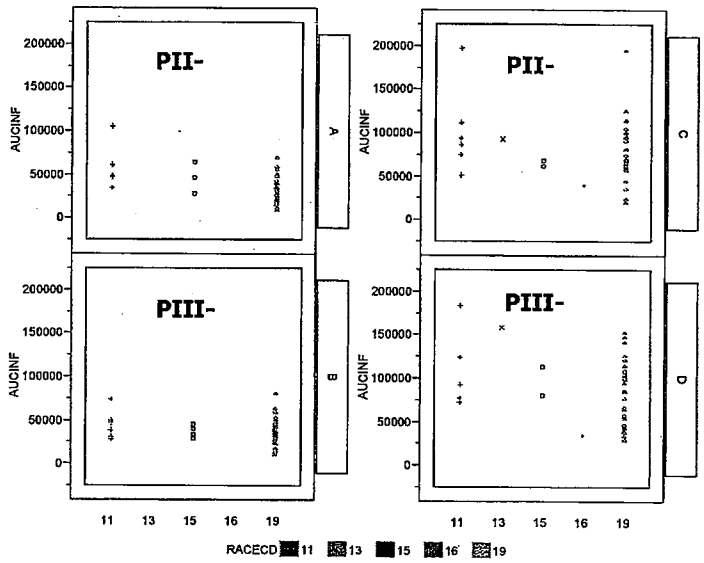
Figure 40: Individual Cmax (ng/mL) by treatment



Reviewer comment:

- *Greater variability in Tmax for group "A." Greater variability in Cmax & AUCinf for CD compared to AB.*
- *Reviewer analysis of the relatively small US Asian populations vs. Caucasian from this study* ***did not*** *show a difference in AUC and Cmax noted for Japanese/east Asians in the trials conducted in Japan and Hong Kong (See Figures 41 and 42 below). This discrepancy should be explored further as a phase IV commitment.*

Figure 41: **Reviewer generated analysis of AUCinf between Asian and Caucasian populations from this US study.**



Central/South Asian Heritage = 13	African-American = 11
Japanese/East Asian Heritage = 15	Caucasian = 19
South East Asian Heritage = 16	

Figure: 42: **Reviewer generated analysis of Cmax between Asian and Caucasian populations from this US study.**

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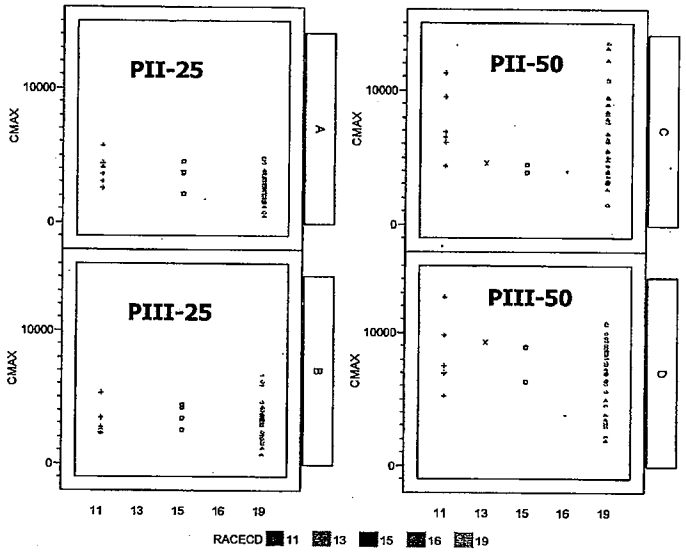


Central/South Asian Heritage = 13	African-American = 11
Japanese/East Asian Heritage = 15	Caucasian = 19
South East Asian Heritage = 16	

The comparison of Regimen B/A and D/C relative to AUC0-∞ and CMax is outlined in table 147 below (Ratio (90% CI).

Table 147: Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest

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)

Reviewer Comment: Criteria for relative bioequivalence as outlined in the FDA Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" was not met for the comparisons B/A. While the criteria was met for D/C it is important to note that the substance batch numbers are different for the Phase III 50 mg tablet used in study TRA102863 and this may explain the different conclusions seen in these two trials regarding BE.

The comparison of 25 mg to 50 mg formulations relative to AUC0-∞, AUC0-t and CMax using a dose normalized ANOVA approach to evaluate dose proportionality is outlined in Table 148 below (Ratio (90% CI).

Table 148: Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest

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, 0.979)	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, 0.998)	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)

*Reviewer Comment: Assuming dose proportionality criteria similar to that for relative bioequivalence, dose proportionality **was not** demonstrated for these comparisons.*

The comparison of 25 mg to 50 mg formulations relative to AUC0-∞ and CMax using a power model approach is outlined in Table 149 below (Ratio (90% CI).

Table 149: Slope estimate (90% Confidence Intervals) for Eltrombopag Comparisons of Interest

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)

Reviewer Comment: Assuming dose proportionality criteria similar to that for relative bioequivalence, dose proportionality was not demonstrated for these comparisons.

Results-Safety:

A total of 99 AEs occurred during the study (Table 150); of these, six AEs were reported pretreatment. The majority of AEs were mild (75 events) or moderate (22 events) in intensity. Two severe events were reported (a pre-treatment headache and benign breast lump). Three subjects (3%) were withdrawn from the study due to AEs. No deaths or SAEs were reported during the study

Table 150: Post Dose Adverse Events

	Treatment Regimen			
	A	B	C	D
Preferred Term	N=50 n (%)	N=48 n (%)	N=49 n (%)	N=47 n (%)
Number of Subjects with Any Event	11 (22)	16 (33)	16 (33)	12 (26)
Headache	6 (12)	8 (17)	10 (20)	2 (4)
Dizziness	2 (4)	0	2 (4)	1 (2)
Pharyngolaryngeal pain	0	2 (4)	1 (2)	2 (4)
Nasopharyngitis	1 (2)	2 (4)	1 (2)	0
Somnolence	2 (4)	0	1 (2)	1 (2)
Nausea	0	0	0	2 (4)

Changes in laboratory parameters that met the protocol-defined criteria for potential clinical concern were noted in this study. Elevated ALT, AST, and creatinine kinase were reported in two subjects and was deemed exercise induced rhabdomyolysis by the investigator.

There were no notable treatment-related changes in vital signs from pre-dose. One subject had ECG signs of myocardial ischemia of moderate intensity occurring eight days after administration

of the second dose of study medication (follow-up visit). No associated symptoms of myocardial ischemia were reported. Subject did not report for follow up ECG.

Ocular examinations (visual acuity, ophthalmoscopy [indirect] and slit lamp examinations) showed no notable treatment-related changes in ophthalmic assessments.

Conclusions (Sponsor):

- Bioequivalence was demonstrated between eltrombopag 50 mg Phase II and III tablets manufactured at the R&D and commercial sites, when each was administered as a single dose in the fasted state.
- The eltrombopag 25 mg Phase III tablet manufactured at the commercial site delivered an equivalent mean AUC(0-∞), but a 16% higher mean Cmax compared to the 25 mg Phase II tablet manufactured at the R&D site.
- Plasma eltrombopag AUC(0-∞) and Cmax increased in a slightly greater than dose proportional manner between 25 mg and 50 mg doses for both formulations.
- The AEs reported in this study are consistent with the known safety profile of eltrombopag.
- There were no clinically significant treatment-related changes in vital signs. No treatment-related increases in laboratory abnormalities were noted. There were no clinically-significant ECG abnormalities.
- No deaths or SAEs occurred during the study.

Reviewer Comment: As stated above, the criteria for relative bioequivalence as outlined in the FDA Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" was not met for the comparison B/A (25 mg). While the criteria was met for D/C it is important to note that the substance batch numbers are different for the Phase III 50 mg tablet used in this study and study TRA102863 and this may explain the different conclusions seen in these two trials regarding BE.

4.3.17 Study TRA104631 - Phase 1 Food effect/antacid effect

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

Title: An open-label, randomized, five-period, period-balanced, crossover study to assess the effect of food and antacid on the pharmacokinetics of a single dose of SB-497115-GR in healthy volunteers

Study period: 01 August 2005 – 23 October 2005

Objectives:

- To evaluate the effects of high- and low-fat meals consisting of foods with low calcium content (40-50 mg of calcium) and no dairy products on the pharmacokinetics of a single oral dose of 75 mg of eltrombopag in healthy volunteers.
- To evaluate the effect of cation-containing antacid on the pharmacokinetics of a single oral dose of 75 mg of eltrombopag in healthy volunteers.
- To evaluate the effect of timing of meal consumption in relation to study drug administration on the pharmacokinetics of eltrombopag.

Methodology:

This was a single dose, open-label, randomized, five-period, period balanced, crossover study in healthy male and female subjects between the ages of 18 to 64, with body weight ≥ 50 kg for males and ≥ 45 kg for females and body mass index in the range of 19 – 30 kg/m2. The study treatment groups are as follows:

- A = 75 mg eltrombopag while fasting
- B = 75 mg eltrombopag with low-fat meal (low calcium/no dairy)
- C = 75 mg eltrombopag while fasting with cation-containing antacid [redacted] b(4)
- D = 75 mg eltrombopag with high-fat meal (low calcium/no dairy)
- E = 75 mg eltrombopag administered one hour prior to consumption of high-fat meal (low calcium/no dairy)

Subjects were randomly assigned to 1 of 10 possible sequences (n=2 per sequence except "3" where n=3)). Subjects were admitted to the clinical study unit on the evening prior to dosing (Day -1) of each period. Dosing occurred on the morning of Day 1 of each study period. There was a washout period of 7-14 days between study periods. Blood samples for pharmacokinetic analysis were collected over a 48-hour period.

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

During each study period, subjects received one tablet of eltrombopag 75 mg (Formulation code "AP," substance batch number F076634 & batch number 051074355 (Tonebridge)), according to the treatment sequence to which the subject was randomized. Tablets were manufactured at the Ware commercial site (UK) site. Study personnel administered the study medication with 240 mL of water. In regimen C, 30 mL [redacted] Liquid Antacid (1524 mg aluminium hydroxide,1425 mg magnesium carbonate, and alginic acid) was administered concomitantly with eltrombopag 75 mg. b(4)

Reviewer Comment:

- *The use of [redacted] as the antacid in this study is concerning since, unlike other formulations, it contains sodium alginate. The sponsor's 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)
- *Formulations used in this and study and 497115/005 were derived from the same synthesis route but bear different formulation codes and substance batch numbers. Tablet Formulation code "AP" (Tonebridge) was used in this study and formulation code "AL" (Tonebridge) was used in study SB-497115/005. It is not clear if this difference contributes anything to the results of this study compared to that reported in 497115/005.*

Test Diet:

- High fat/low calcium: Non-Dairy Shake (3/4 cup soymilk (unfortified), 1/4 cup non-dairy creamer, 1 Tbsp. Canola Oil, 1/4 tsp. vanilla, 4 Large Frozen Strawberries, 1.5 oz 100% apple juice (not calcium fortified)), 7 oz. Roast Beef Hash, and 3 oz. Canned Peach Slices (in Light Syrup). This meal was 947 total calories (38.95 gm protein (152.63 calories from pro), 64.82 gm total carbs (254 calories from carb), 61.04 gm, & total fat (538.16 calories from fat)) and 46.95 mg calcium.
- Low fat/low calcium: 2 Slices Pineapple (in its own juice), 4 oz. Apple Juice, 3 oz. Lean Ham, 1 cup Regular Oatmeal (made with water), 1 Tbsp. Brown Sugar, 1 Tbsp. Raisins. This meal was 490 total calories (25 gm protein (100 calories from protein), 77 gm total carbohydrates (310 calories from carbs), 9.1 gm total fat (79.8 calories from fat)) and 42.5 mg calcium)

Reviewer Comment: The sponsor did not supply any information to support that these low calcium meals had comparable meal volume and viscosity to the "standard FDA high fat meal" used in study SB-497115/005 as outlined in the FDA guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies." Therefore, comparisons made by the sponsor implying that

calcium content alone is responsible for the differences in BA observed between these two studies are inconclusive unless this confounding factor can be resolved.

Criteria for evaluation:

- Sample size: From study SB-497115/005, the observed estimates of within-subject CV for the primary endpoints AUC(0-∞) and Cmax are 21.7% and 26.3%, respectively. The largest of these estimates (26.3%) translates to a standard deviation of 0.259 on the natural log scale. Based on the largest within-subject variability estimate (26.3% for Cmax) and a sample size of 20 subjects, the half-width of a 90% confidence interval about the ratios of interest should be no more than 16% of the point estimate. A sensitivity analysis was conducted in the event that the variability was greater than estimated. Based on this larger variability, it is estimated that the half-width of a 90% confidence estimate will be no more than 19% of the point estimate. **No adjustment was made for multiple comparisons.**
- Pharmacokinetics: AUC(0-∞) and Cmax of eltrombopag were the primary pharmacokinetic endpoints and were derived from plasma concentration versus time data. Other pharmacokinetic endpoints included AUC(0-t), tmax, and t1/2 of eltrombopag.
    - Blood samples (2 mL) were collected for the determination of eltrombopag concentrations in plasma at the following timepoints: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours post-dose.
    - Plasma specimens were assayed using a validated analytical method (Table 151)

Table 151: 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%
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

b(4)

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

- PK analyses of plasma eltrombopag concentration-time data were conducted using the noncompartmental Model 200 of WinNonlin Professional Edition version 4.1 [WinNonlin User's Guide, 2003] as follows: 1) The maximum observed plasma concentration (Cmax) and the time to reach Cmax (tmax) were the actual observed values; 2) When possible, the terminal elimination rate constant (λz) was derived from the loglinear disposition phase of the concentration-time curve using least-squares regression analysis with visual inspection of the data to determine the appropriate number of terminal data points for regression analysis (t1/2) was calculated as ln 2/λz), & 3) Area under the plasma concentration-time curve was calculated using the linear trapezoidal rule. Values for AUC(0-∞) were estimated as the sum of AUC(0-t) and Ct divided by the elimination rate constant, where Ct was the last observed quantifiable

concentration. The percentage of AUC(0-∞) obtained by extrapolation [%AUCex] was also calculated ([(AUC(0-∞)-AUC(0-t))/AUC(0-∞)] * 100).

- To assess the effect of food on the bioavailability of SB-497115 for each primary PK endpoint (AUC and Cmax), a mixed effects linear analysis of variance (ANOVA) model was fit to the natural logarithm of the derived endpoint. Effects associated with sequence, period, and treatment were assumed fixed; effects associated with subject were assumed random. The geometric least-squares mean ratios (B:A, C:A, D:A, E:A, E:D) and associated 90% confidence interval for each treatment comparison were estimated using the SAS mixed linear models procedure (SAS Proc Mixed). The parameter tmax was analyzed non-parametrically.

- Safety: All subjects who received at least one dose of study medication were included in the evaluation of clinical safety and tolerability. Safety data, including adverse events, vital signs, clinical laboratory data, ophthalmic assessments, and ECG monitoring (12-lead), were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of subjects: A total of 26 subjects were enrolled in this study and received at least 1 dose of study medication. Three subjects withdrew prematurely, due to subject choice, protocol deviation, or elevation in laboratory value respectively. A total of 23 subjects completed the study: Safety (n=26), PK period A & B (n=24), and PK period C, D, & E (n=25).

Population Demographics:

The population demographics from this study are listed in Table 152 below.

Table 152: Population Demographics

Age (Mean (SD) [Range])	35.6 (11.3) [19-56]
Sex, n (%)	Male: 14/26 (54%)
Ethnicity, n (%)	Hispanic or Latino: 1/26 (4%)
Race, n (%)	African American/African Heritage: 8/26 (31%) White – White/Caucasian/European Heritage: 17/26 (65%) Mixed Race 1/26 (4%)
Height (cm)	170.1 (10.28) [152-190]
Weight (kg) (Mean (SD) [Range])	76.0 (12.05) [51.0-93.9]
Body mass index (Mean (SD) [Range])	26.13 (2.55) [21.5-30.4]

Results-PK analysis:

Selected PK parameters derived from this study are listed in Table 153 below. Mean plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figure 43 Pre-dose concentrations were quantifiable in several subjects following a 7-14 day washout between treatment periods, but were generally <5% of Cmax.

Table 153: Selected PK parameters by treatment

Regimen	N	AUC(0-∞)(ng·hr/mL)1	Cmax (ng/mL)1	Tmax (hr)2	t1/2(hr)1
A	24	76876 (48.58)	6198 (44.00)	4.00 (2.00-6.00)	16.8 (15.8)
B	24	70871 (44.15)	5362 (43.97)	4.00 (2.07-6.00)	17.0 (15.1)

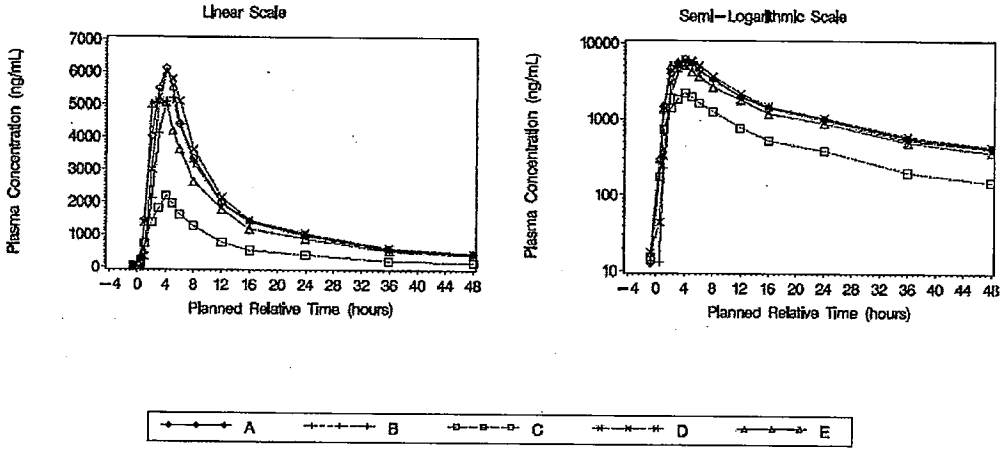
C	25	23057 (95.08)	1875 (102.99)	4.00 (1.00-8.00)	15.0 (20.8)
D	25	79829 (43.97)3	6218 (46.32)	4.00 (2.00-6.00)	17.1 (18.0)3
E	25	68414 (43.83)	5306 (44.35)	3.00 (2.00-5.00)	17.5 (17.4)

1. geometric mean (CVb%)
2. median (range)
3. For Regimen D, N=24 for AUC(0-∞) and t1/2

Reviewer Comment:

- *Variability is higher than the sensitivity analysis used in the calculation of sample size. Group "C" shows significant variability which calls into question if the assumptions of the mixed effects linear analysis of variance (ANOVA) model were actually met when the Geometric Mean Least-Squares Ratio was developed for the C:A comparison.*
- *The presentation of Tmax hides several concerns regarding in period "C", including increased variability, a potential outlier (Subject 110), and a trend toward a reduced Cmax (omitting the outlier). This was not addressed by the sponsor. The potential contribution of the sodium alginate component of [redacted] to this issue (see comment above) can not be ruled out..* b(4)

Figure 43: Mean Plasma SB-497115 by Treatment



Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest is presented in Table 154. Individual parameters by treatment are presented in Figures 44 and 45.

Table 154: Geometric Mean Least-Squares Ratio (90% Confidence Intervals) for Eltrombopag Comparisons of Interest

	Include Subjects with quantifiable Pre-dose concentrations		Exclude Subjects with quantifiable Pre-dose concentrations	
AUC$_{0-\tau}$ (hr*ng/mL)				
B vs. A	0.928	(0.763, 1.127)	0.925	(0.784, 1.091)
C vs. A	0.295	(0.243, 0.358)	0.335	(0.283, 0.397)
D vs. A	1.025	(0.843, 1.247)	1.019	(0.863, 1.203)
E vs. A	0.874	(0.720, 1.060)	0.868	(0.737, 1.023)
E vs. D	0.852	(0.703, 1.034)	0.852	(0.723, 1.003)
Cmax (ng/mL)				
B vs. A	0.874	(0.699, 1.094)	0.871	(0.721, 1.052)
C vs. A	0.302	(0.241, 0.377)	0.350	(0.289, 0.424)

D vs. A	1.010	(0.808, 1.262)	1.002	(0.831, 1.209)
E vs. A	0.854	(0.684, 1.067)	0.848	(0.703, 1.023)
E vs. D	0.846	(0.679, 1.053)	0.847	(0.704, 1.019)

Reviewer Comment:

- *Including or excluding Subjects with quantifiable Pre-dose concentrations does not appear to change the overall conclusions regarding these data.*

Figure 44: Individual $AUC_{0-\infty}$ (hr*ng/mL) by treatment

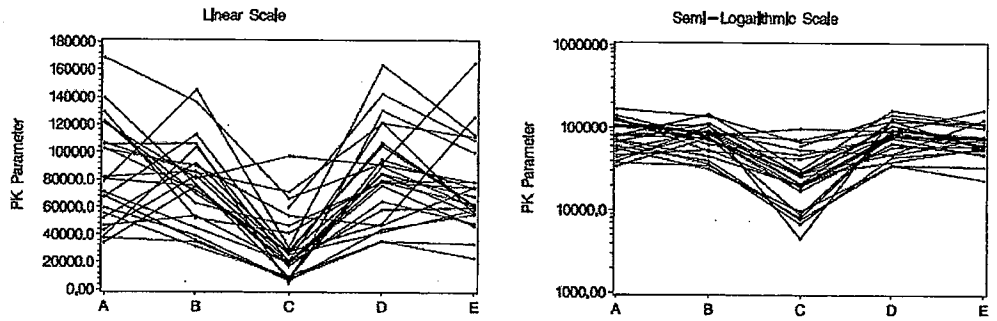
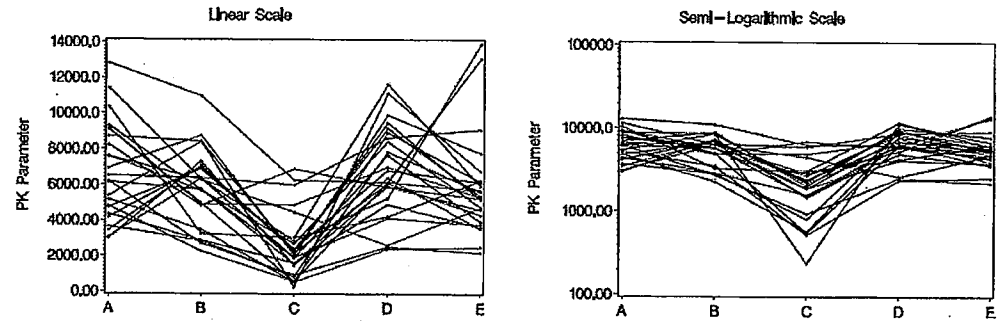


Figure 45: Individual Cmax (ng/mL) by treatment



Results-Safety:

Adverse events were reported by 24% to 38% of subjects per session (Table 155). The most common event was headache, followed by nausea and dizziness. All events were mild with the exception of vomiting, musculoskeletal chest pain, and four events of headache, which were considered moderate in intensity. No subjects died, experienced a SAE, or withdrew due to an AE in this study. Adverse events reported by only one subject during the study were arthropod bite, arthropod sting, joint sprain, tinea pedis, viral upper respiratory tract infection, increased upper airway secretion, nasal congestion, lacrimation increased, ocular hyperemia, hunger, blood creatine phosphokinase increased, musculoskeletal chest pain, insomnia, urethral discharge, hot flush, somnolence, syncope vasovagal, abdominal pain upper, erythema, petechiae, rash pruritic.

Table 155: Post Dose Adverse Events

Adverse	Number of Subject Sessions

Event	Eltrombopag 75 mg fasted N=24	Eltrombopag 75 mg with low fat meal N=24	Eltrombopag 75 mg with antacid N=25	Eltrombopag 75 mg with high fat meal N=25	Eltrombopag 75 mg 1 hour before high fat meal N=26
Any Event	9 (38%)	6 (25%)	8 (32%)	6 (24%)	8 (31%)
Headache	7 (29%)	3 (13%)	3 (12%)	3 (12%)	4 (15%)
Nausea	0	1 (4%)	2 (8%)	1 (4%)	0
Dizziness	0	0	2 (8%)	1 (4%)	0
Contusion	0	0	1 (4%)	1 (4%)	0
Excoriation	0	0	0	1 (4%)	1 (4%)
Skin laceration	0	0	1 (4%)	0	1 (4%)
Vomiting	1 (4%)	0	1 (4%)	0	0
Adverse events reported by only one subject during the study were arthropod bite, arthropod sting, joint sprain, tinea pedis, viral upper respiratory tract infection, increased upper airway secretion, nasal congestion, lacrimation increased, ocular hyperemia, hunger, blood creatine phosphokinase increased, musculoskeletal chest pain, insomnia, urethral discharge, hot flush, somnolence, syncope vasovagal, abdominal pain upper, erythema, petechiae, rash pruritic.					

Changes in laboratory parameters that met the protocol-defined criteria for potential clinical concern were principally changes in glucose (Table 156).

Table 156: Subjects with Post-Dose Laboratory Values of Potential Clinical Concern

Subject	Regimen	Parameter	Reference Range	Potential Concern Level	Time of Change1	Value of Concern
101	E B	Potassium Glucose	3.4-4.8 mmol/L 3.89-6.38 mmol/L	>5.3 mmol/L >7.0 mmol/L	S2D-1 S5D2	5.4 7.27
105	E	Hemoglobin Glucose	137-177 g/L 3.89-6.38 mmol/L	>180 g/dL >7.0 mmol/L	S1D3 F/U	182 7.83
112	B	Glucose	3.89-6.38 mmol/L	<3.33 mmol/L	S5D-1	3.22
117	D	Potassium	3.4-4.8 mmol/L	>5.3 mmol/L	S5D3	5.6
121		Glucose	3.89-6.38 mmol/L	<3.33 mmol/L	F/U	2.78
125	A	Glucose	3.89-6.38 mmol/L	>7.0 mmol/L	S2D-1	7.22

1. S = session number, D = day of session, and F/U = follow-up visit.

Subject 119 was withdrawn prematurely due to elevated creatine kinase (CK) values. The subject entered with a screening CK value of 61 IU/L (11Aug2005, normal range 0-175 IU/L). Predose in Session 4 (15Sep2005), her CK value was 882 IU/L. The next day CK was 837 IU/L. At follow-up visits on 30Sep2005, CK was 256 IU/L, and on 02Nov2005 CK was 81 IU/L. The subject reported lifting pumpkins on the farm the day before Session 4 began. Elevated CK values were reported as an adverse event for Subject 107. The subject completed dosing in all five sessions, with the last dose on 23Sep2005. The cause of the elevated CK for this subject is unknown.

Ophthalmoscopy and slit lamp examination were within normal limits predose in Session 1 as well as at follow-up at the end of the study for all subjects. Visual acuity for the majority of subjects was 20/15 or 20/20. AREDS evaluation of the lens were also unchanged from the beginning through the end of the study for all subjects.

Changes in vital signs at three hours following dosing were minor and similar across all dosing regimens during the study. No values that met the protocol defined criteria for potential clinical concern were reported.

No clinically significant ECG findings were reported. ECG intervals were all within the normal range with the exception of a two PR intervals. Subject 118, 3 hours after receiving eltrombopag

one hour before a high-fat meal in Session 2, had a PR interval of 117 msec, below the clinical concern threshold of 120 msec but this subject's PR interval was consistently low throughout the study with predose values of 120 and 124 for Session 2. Subject 112, had a PR interval of 231 msec, above the clinical concern threshold of 220 at predose of Session 5.

Conclusions (sponsor)

- Administration of a single 75mg dose of eltrombopag with either high-fat or low-fat meals that were also low in calcium had minor non-significant impacts on plasma eltrombopag exposure; mean AUC(0-∞) treatment ratios (90% CIs) were 0.928 (0.763, 1.127) for low-fat/low-calcium meal versus fasted, 1.025 (0.843, 1.247) for high-fat/low-calcium meal versus fasted, and 0.852 (0.703, 1.034) for high-fat/low calcium meal administered one hour after eltrombopag versus fasted.
- Administration of a single 75mg dose of eltrombopag with a cation-containing antacid (1524mg aluminum hydroxide and 1425mg magnesium carbonate) significantly decreased plasma eltrombopag AUC(0-∞) and Cmax by 70% compared to administration in the fasted state, Thus in order to avoid clinically significant reductions in plasma eltrombopag exposure, eltrombopag should not be given concurrently with antacids or other products containing polyvalent cations such as mineral supplements and dairy products.
- Eltrombopag 75 mg administered fasted, with a low-fat meal, high-fat meal, or with an antacid was well tolerated by healthy adults.

Reviewer Comments:

- *Despite the sponsors assertion, 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 "* b(4)
- *Given the increased and disproportionate variability in the antacid treatment arm and a lack of information regarding the impact of sodium alginate to BA, the reviewer recommends adding the following to section 7.3 of the approved product labeling."* b(5)
- *The proposed approved product labeling reads* b(4)

[11] 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.
[12] 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.

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

b(4)

4.3.18 Study TRA105325: Phase 3 Safety and Efficacy Extension Study

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

Title: EXTEND (Eltrombopag eXTENded Dosing Study): An extension study of eltrombopag olamine (SB-497115-GR) in adults, with idiopathic thrombocytopenic purpura (ITP), previously enrolled in an eltrombopag study.

Study period: 06Jul2006 – ongoing

Objectives:

Primary

- The primary objective of the study was to describe the long-term safety and tolerability of oral eltrombopag treatment of subjects with ITP with or without concomitant ITP medication.

Secondary

- To describe the clinical efficacy, pharmacodynamics, and durability of efficacy response to eltrombopag when administered to previously treated subjects with ITP as measured by platelet counts.
- To describe the effect of re-treatment on platelet counts in subjects previously treated with eltrombopag.
- To gain information on the optimal dosing of eltrombopag in individual subjects with ITP.
- To describe the effect of eltrombopag on reduction and/or sparing of concomitant ITP therapies, while maintaining a platelet count ≥ 50Gi/L.
- 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.

Methodology:

EXTEND is an open-label, extension study to evaluate the safety and efficacy of eltrombopag as a treatment for subjects with ITP who have previously been enrolled in a study of eltrombopag (e.g., TRA100773, TRA102537/RAISE, or TRA108057/REPEAT). This study allows each subject to achieve an individualized dose and schedule of eltrombopag based upon their platelet counts.

The study was designed to include four different stages, each defined by specific goals and /or specific dosing instructions (see Table 157).

Table 157: Treatment Stages

Stage	Goal of Stage
Stage 1: Eltrombopag Initial Dosing	To identify a dose of eltrombopag that increases platelet counts to a level high enough (≥ 100Gi/L) to support dose reduction of concomitant ITP medication.
Stage 2: Concomitant ITP Medication Minimization	To reduce or eliminate concomitant ITP medication, while maintaining platelet counts ≥ 50Gi/L.
Stage 3: Eltrombopag Dose Adjustment	To identify the minimal effective dose of eltrombopag necessary to maintain platelet counts ≥ 50Gi/L in conjunction with the minimal dose of concomitant ITP medication.
Stage 4: Eltrombopag Long-term Dosing	To monitor safety and efficacy of eltrombopag at the minimal effective dose that in conjunction with the minimal dose of concomitant ITP medications maintains platelet count ≥ 50Gi/L.

Consenting subjects began the study in Stage 1 and proceeded through stages as necessary based on platelet count.

Subjects were allowed to remain on eltrombopag for > 6 months provided that, in the opinion of the investigator, they continued to receive benefit and did not experience greater than moderate side effects associated with eltrombopag.

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

Eltrombopag was supplied by GSK as _____ film coated tablets containing eltrombopag olamine equivalent to 25mg and 50mg of eltrombopag free acid (Table 158). b(4)

Table 158: Batch Numbers for Study Medication

Product	Formulation/ Formulation Code	Drug Substance Batch Number	Drug Product (Batch Number)
25 mg Tablet	Tablet/AS Tablet/AS	F081601 F081598/F081601	(051109558) (061114791)
50 mg Tablet	Tablet/AR Tablet/AR Tablet/AR	F081598 F081598/F081601 F081604/F083255	(051109563) (061114792) (061125231)

Subjects are instructed to take 1 tablet from each bottle daily and are instructed on how to take their medication by the study personnel. Dose adjustment of study medication were allowed to maintain platelet counts ≥50Gi/L and <400Gi/L. All subjects start the study receiving 50mg eltrombopag once daily and follow the appropriate stages of eltrombopag treatment and dose adjustment as described in Table 159.

Table 159: Eltrombopag Dose Adjustment Guidelines

Eltrombopag Dose	Platelets <100,000/μL	Platelets ≥100,000/μL and <200,000/μL	Platelets ≥200,000/μL and <400,000/μL	Platelets ≥400,000/μL
75 mg once daily	If platelets are ≥50,000/μL consider change to Stage 2 If platelets are <50,000/μL, continue eltrombopag only if physician, subject, and GSK Medical Monitor agree due to perceived clinical benefit of eltrombopag.	Maintain dose or consider decrease to 50 mg	Decrease to 50 mg	Interrupt eltrombopag for at least 1 week and until platelet count is ≤150,000/μL, then decrease to 50 mg
50 mg once daily (Starting dose)	Increase to 75 mg	Maintain dose or consider decrease to 25 mg	Decrease to 25 mg	Interrupt eltrombopag for at least 1 week and until platelet count is ≤150,000/μL, then decrease to 25 mg
25 mg once daily	Increase to 50 mg	Maintain dose	Interrupt eltrombopag for at least 1 week and until platelets ≤150,000/μL, and contact Medical Monitor	Interrupt eltrombopag for at least 1 week and until platelets ≤150,000/μL and contact Medical Monitor

Criteria for evaluation:

- Sample Size: In total, approximately 440 subjects were expected to be enrolled in studies TRA100773A, TRA100773B, TRA102537/RAISE and TRA108057/REPEAT. It was estimated that of these subjects, approximately 200 would participate in EXTEND. No sample size re-estimation was planned for this study.
- Efficacy: The primary assessment for efficacy was platelet count which was collected throughout the study and used as part of the assessment of efficacy. Platelet count data were collected as part of the CBC, weekly during the first 4 weeks of administration of study drug, at any dose change (eltrombopag or concomitant ITP medication) or change of stage. If a subject continued on a stable dose during any stage of the study for greater than 4 weeks, a CBC (including platelet count) with differential was performed no less

frequently than every 4 weeks. Further information regarding reduction in use of concomitant ITP medications, use of rescue therapy, incidence and severity of symptoms associated with ITP was collected.

Additionally, bruising and bleeding assessments were performed at each visit using the WHO Bleeding Scale and ITP Bleeding Score. ITP bleeding score data were collected, and will be summarized later in a separate report and are not reported in detail in this aCSR. Hemostatic challenges and surgical procedures were collected at each visit.

- Pharmacokinetics:
    - A pharmacokinetic sample was to be collected as soon as possible (preferably within 12 hours of last dose) for any subject who withdrew from study medication due to an SAE, or whose platelet count was ≥400Gi/L. The time of the last dose of eltrombopag and the actual time and date of the collected sample was to be recorded.
    - Plasma samples were analyzed in house at GSK using what the sponsor refers to as a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for SB-497115 was 100 ng/mL, using a 50 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 50,000 ng/mL.

      Reviewer Comment: The sponsor failed to provide adequate information to allow the reviewer to evaluate the method of analysis of the plasma PK data. It is possible that the sponsor is using assay CD2006/00175/00 which appears to be validated in a manner consistent with the guidance "Bioanalytical Method Validation," however, this was not identified in its report.
- 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, and detailed ocular examination. No formal statistical analyses of the safety data were performed.

Number of Subjects

A total of 117 subjects were enrolled in the study and 109 subjects received at least one dose of study medication (Table 160).

Table 160: Subject disposition

	N
Entered, N	117a
Received eltrombopag, n	109b
TRA100773A n(%)	48(41)
TRA100773B	53(45)
TRA102537/RAISE	13(11)
TRA108057/REPEAT	3(3)
Completed study, n (%)	0
Withdrawn from the Study, n(%)	31(28)
Ongoing, n(%)	78(72)

To date, 31 (28%) subjects have withdrawn from the study (Table 3). The most common reason for withdrawal from the study was lack of efficacy (12 subjects, 11%) followed by AEs leading to withdrawal (7 subjects, 7%).

Population Demographics

The population demographics from this study are listed in Table 161 & 162 below

Table 161: Population Demographics

Characteristic	N=109
Age, yrs, n	109
Mean (SD)	48.2 (15.46)
Median (Min-Max)	47.0 (19-82)
Sex, n (%)	
Female	70(64)
Race, n(%)	
White - White/Caucasian/European	67(61)
Asian - East Asian	19(17)
White - Arabic/North African	12(11)
American Indian or Alaskan Native	5(5)
Asian - Central/South Asian	3(3)
Asian - South-East Asian	2(2)
African American/African	1(<1)
Baseline Platelet Count, n(%)	
<30Gi/L	76(70)
30-50Gi/L	18(17)
>50Gi/L	15(14)
Splenectomy, n(%)	
No	61(56)
Concomitant ITP Medication, n(%)	
No	69(63)

Table 162: Current Medical Conditions Reported in 3% or more of Subjects

Preferred Term	Number of Subjects, N=109
Any condition	**60(55)**
Splenectomy	10(9)
Hysterectomy	5(5)
Cholecystectomy	4(4)
Cholelithiasis	4(4)
Breast Cancer	4(4)
Cataract operation	3(3)
Gastric ulcer	3(3)
Menorrhagia	3(3)
Rash	3(3)

Results-Efficacy analysis:

A summary of subjects achieving a platelet count ≥50Gi/L at one or more visits during the study is presented in Table 163. At the time of analysis, 80% of subjects had achieved a platelet count ≥50Gi/L at least once during the study; whereas 15% of subjects entered the study with platelet counts ≥50Gi/L.

Table 163: Subjects Achieving Platelet Counts ≥50Gi/L, ≥50-≤400Gi/L and >400Gi/L (ITT Population)

	Total N=109 n(%)
Baseline, N	109
Counts >50Gi/L	16(15)a
At any On-therapy Visit, N	108b
Counts >50Gi/L	86(80)
Counts >50-<400Gi/L	67(62)
Counts >400Gi/L	19(18)

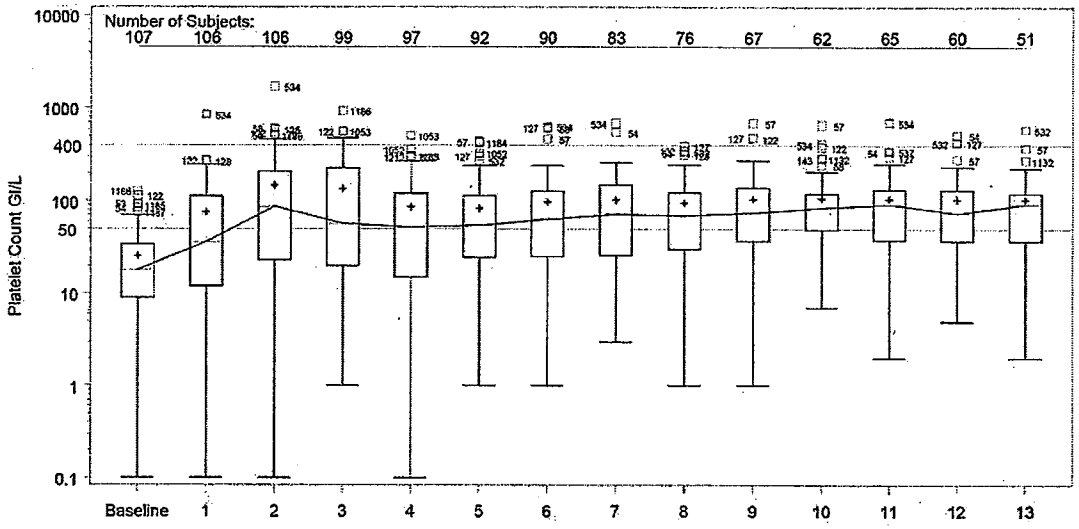
The proportion of subjects achieving platelet counts >50Gi/L at any point during the study was similar regardless of splenectomy status or use/non use of concurrent ITP medication at baseline. Approximately 70% of subjects with baseline platelet counts <30Gi/L achieved platelet counts ≥50Gi/L during eltrombopag treatment compared to >90% in subjects with higher baseline platelet counts (Table 164). Forty percent of subjects with baseline platelet counts >50Gi/L had an on study platelet count >400Gi/L, compared to <20% of subjects with baseline platelet counts <50Gi/L. A greater proportion of subjects with a prior splenectomy (25%) and subjects receiving concomitant ITP medications at baseline (23%), had platelet counts >400Gi/L on study compared to non-splenectomized subjects (12%) and subjects not receiving concomitant ITP medications at baseline (15%), respectively.

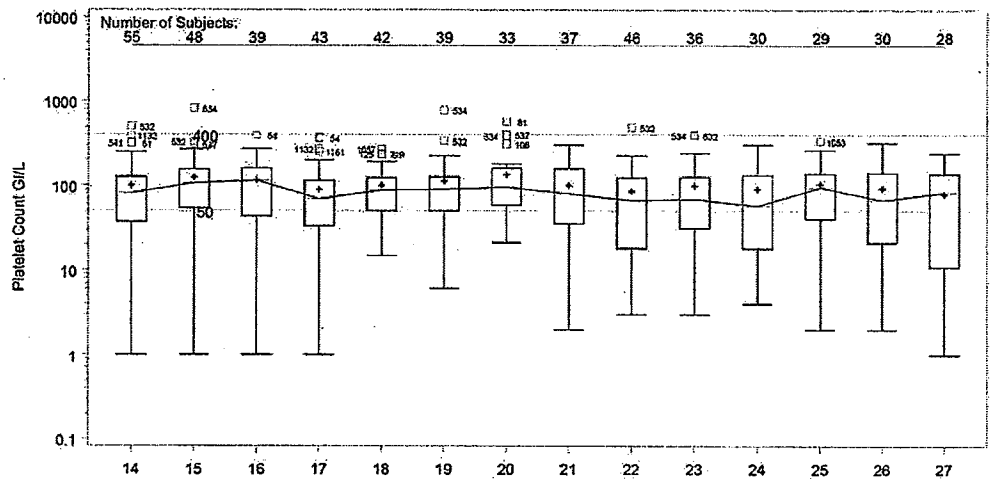
Table 164: Subjects Achieving Platelet Counts ≥50Gi/L, ≥50-≤400Gi/L and >400Gi/L (ITT Population)

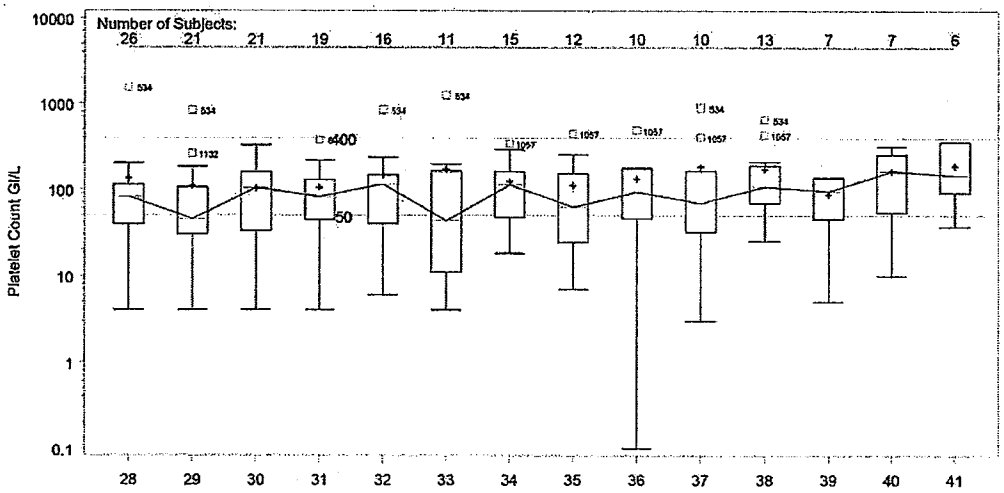
Platelet Counts	Baseline Platelet Counts (Gi/L)			Splenectomy		Use of ITP Medication	
	<30 N=76	30-50 N=18	>50 N=15	Yes N=48	No N=61	Yes N=40	No N=69
Evaluable, n	75	18	15	48	60	39	69
≥50Gi/L, n(%)	55(73)	17(94)	14(93)	39(81)	47(78)	29(74)	57(83)
≥50 -≤400Gi/L, n(%)	44(59)	15(83)	8(53)	27(56)	40(67)	20(51)	47(68)
>400Gi/L, n(%)	11(15)	2(11)	6(40)	12(25)	7(12)	9(23)	10(15)b

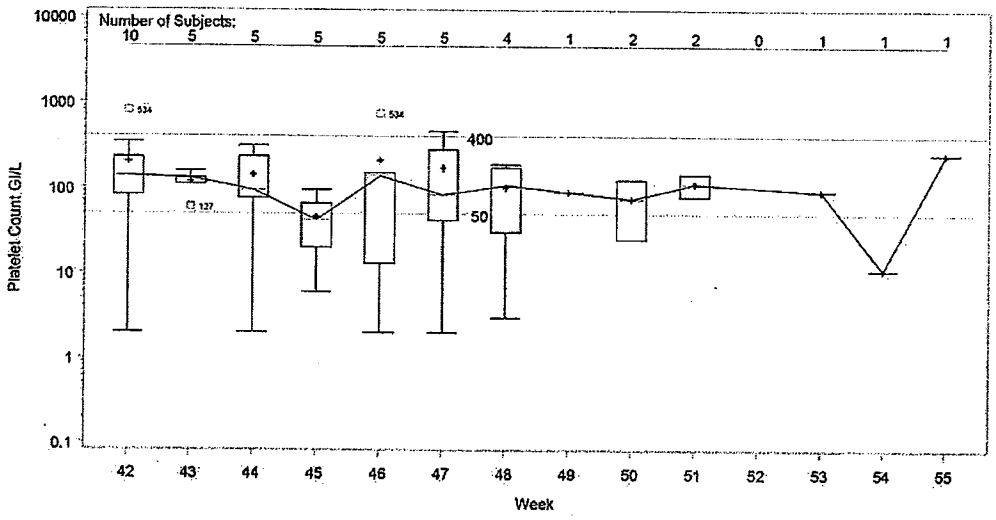
Box whisker plots were used to demonstrate the weekly median platelet counts over time of eltrombopag treatment, together with the 25th and 75th percentiles. A graphical representation of weekly median platelet counts on study is given in Figure 45. This figure shows the median platelet counts by week during the study and the number of subjects contributing data to each weekly assessment. The horizontal lines of the box represent the median and 25th and 75th percentiles, with the end of the whiskers representing the lowest/highest value within 1.5 times the inter-quartile range. Platelet counts were to be measured weekly during the initial weeks of the study, but visits could be changed to a monthly basis if eltrombopag dose and dose on concomitant ITP medication were both stable for 4 or more weeks. Therefore, the number of subjects contributing data to each weekly assessment differs throughout the study.

Figure 45: Median Platelet Counts (25th and 75th percentiles) by week









A graphical representation of all platelet data, for all available subjects is shown Figure 46. Each subject is listed in order of their time in the study on the y-axis and their platelet counts, <50Gi/L or ≥50Gi/L, are indicated at each weekly visit that a subject has attended on the x-axis. Periods of continuous platelet count elevation are indicated graphically by a continuous blue line; periods below 50Gi/L by a orange line. Subjects who have permanently discontinued treatment with study medication at the time of the data cut-off (31Aug2007) are indicated with a yellow line at the time of discontinuation.

Figure 46: Platelet Count by Subject (<50Gi/L or ≥50Gi/L) Over Time

Individual Subject's Platelet Count Response (< 50Gi/L or ≥ 50Gi/L) Over Time

b(4)

Reviewer Comment: *It is evident from these figures that some patients benefited minimally from eltrombopag. It may be worthwhile to explore any potential genetic basis for this resistance in the future.*

The maximum number of weeks of continuous platelet count elevations ≥50Gi/L was assessed for all subjects (Table). The majority of subjects (55%) experienced clinically significant (≥4 weeks) continuous elevation of platelets ≥50Gi/L while receiving eltrombopag. Additionally 54% of subjects had a continuous response of ≥10 weeks. At approximately 6 months (25 weeks), 24% of subjects who had been in the study for ≥25 weeks had continuous elevation
≥50Gi/L of 25 weeks or longer. Of the 4 subjects included in this analysis who were treated in the study for ≥52 weeks, one subject (Subject 125) had a continuous elevation of platelet counts ≥50Gi/L for all 53 weeks on study, with no counts below 50Gi/L.

Table 165: Maximum Continuous Weeks of Maintaining Platelet Counts >50 Gi/L

Number of Continuous Weeks (wks)	Total n/N(%)
Total	109
No continuous wks	33/109 (30)
≥1 wks response	76/107 (71)
>4 wks response	56/101 (55)
>7 wks response	49/89 (55)
>10 wks response	43/80 (54)
>13 wks response	32/74 (43)

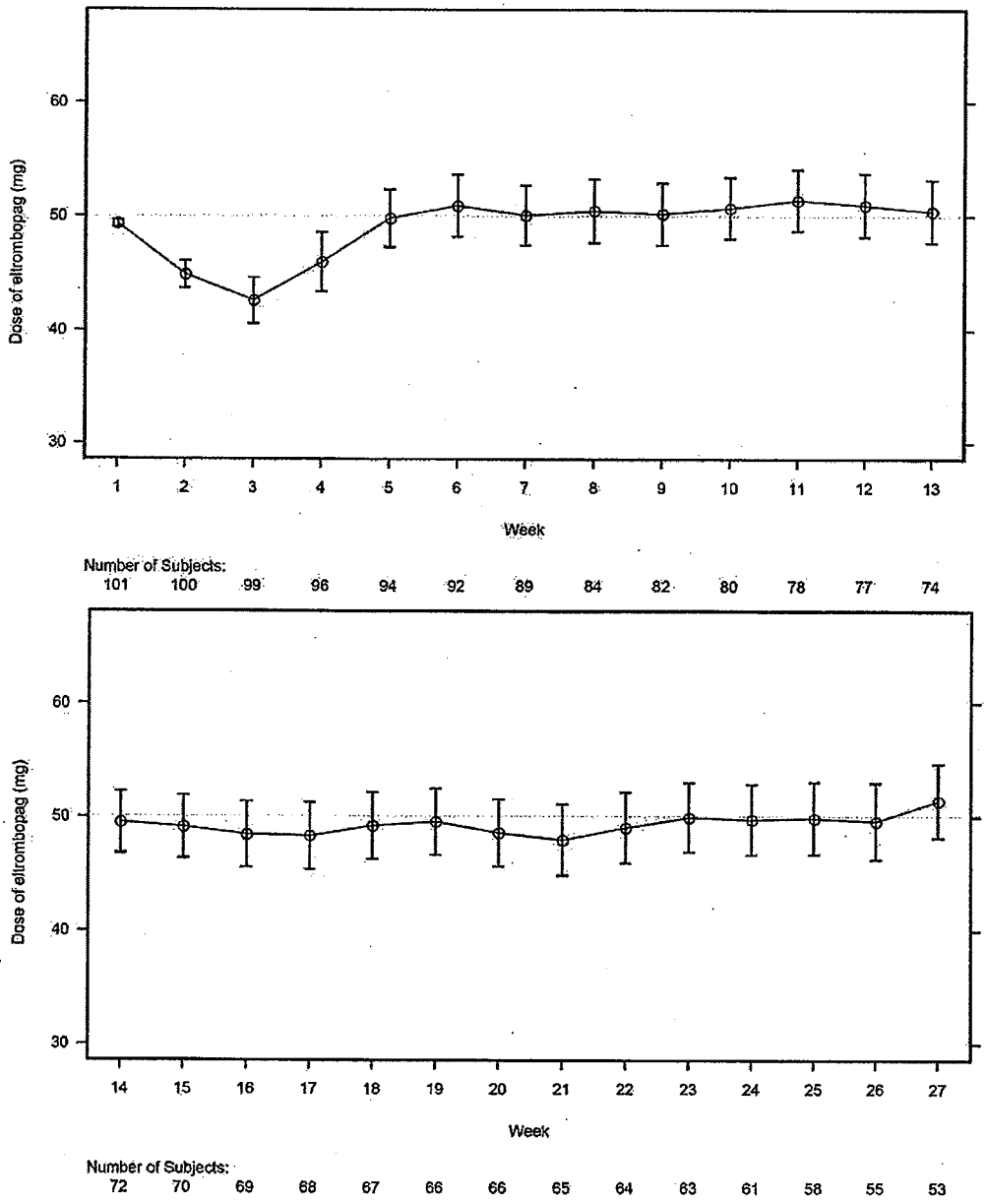
>16 wks response	31/70 (44)
>19 wks response	27/67 (40)
>22 wks response	21/66 (32)
>25 wks response	15/63 (24)
>28 wks response	14/56 (25)
>31 wks response	10/41 (24)
>34 wks response	6/31 (19)
>37 wks response	3/24 (13)
>43 wks response	2/17 (12))
>52 wks response	1/4 (25)

In 18 (45%) of the 40 subjects, the investigator discontinued and/or reduced the dose of baseline concomitant ITP medications. Fourteen subjects (35%) stopped at least one baseline ITP medication and did not require any subsequent rescue treatment as of the clinical cut-off date. Three of the 14 subjects discontinued two different concomitant medications (danazol and prednisolone). To date 14 subjects (13%) had treatment meeting the definition of rescue while on study. Two of the 14 subjects received treatment.

The proportion of subjects with any bleeding (Grade 1-4) and clinically significant bleeding (Grade 2-4) decreased from baseline, beginning at week 1 on study, and remained below baseline for all weeks through week 41. Data from the ITP Bleeding Score indicate that for all physical examinations (oral, ecchymosis and petechiae), the number of subjects with Grade 1 or Grade 2 ITP bleeding scores decreased from baseline at each weekly assessment throughout the study including follow-up. Grade 1 and 2 ITP Bleeding Scores for oral examinations were reduced from 12% and 3% respectively to 0% for the majority of on study assessments. Similarly, the percentage of subjects with ITP Bleeding Scores for ecchymosis (Grade 1, 41% and Grade 2, 14% at baseline) and petechiae (Grade 1, 30% and Grade 2, <1% at baseline) were also reduced at the majority of on study assessments. Thirteen subjects experienced at least one hemostatic challenge during the study, ranging greatly in terms of bleeding risk (e.g. tooth repair and bone marrow biopsies to colonoscopies, arthroscopy and uterine polypectomy). All subjects tolerated the procedures well without bleeding complications.

The mean weekly eltrombopag dose for all subjects available from baseline through week 55 is shown in Figure 47.

Figure 47: Mean Daily Dose (+/- Standard Error of the Mean) by Week



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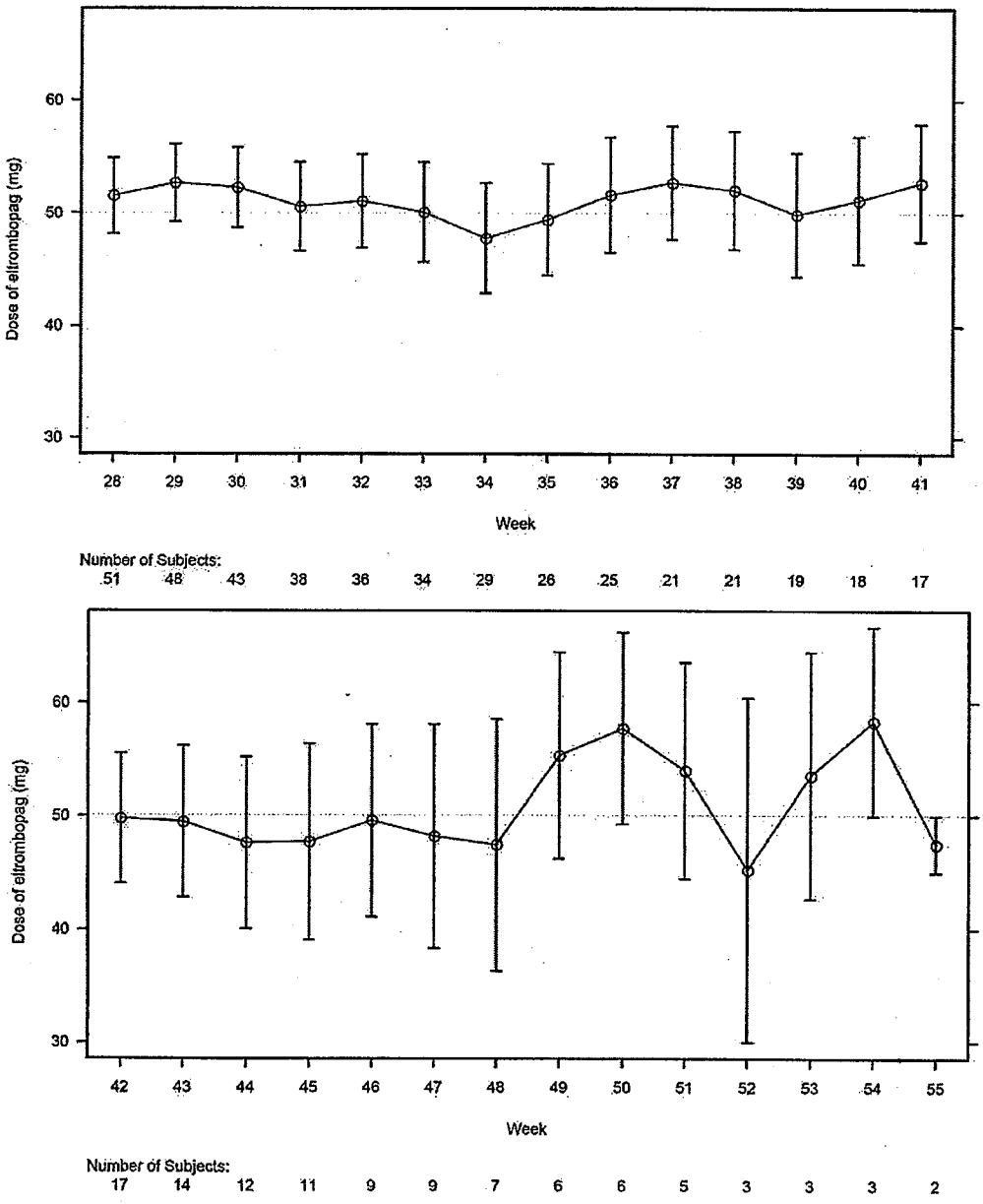


Reviewer Comment:

- *It is important to note the increase in variability at week 34-55. While this can partly be explained by the reduced sample size in the later weeks, the sample size was relatively stable from week 36 to 42 yet a difference in variability is obvious. In addition, sample size alone can not explain the "roller coaster" pattern seen following week 48.* b(5)
- *An exploratory reviewer initiated analysis of the effect of race on dose (Figure48-51 and Table 166) suggests that in this study Asian and Caucasian subjects had similar dose*

requirements. The single African American subject required a lower dose relative to Caucasian and Asian populations.

Figure 48: Reviewer Generated Exploratory Analysis of Mean Weekly Platelet Count Race

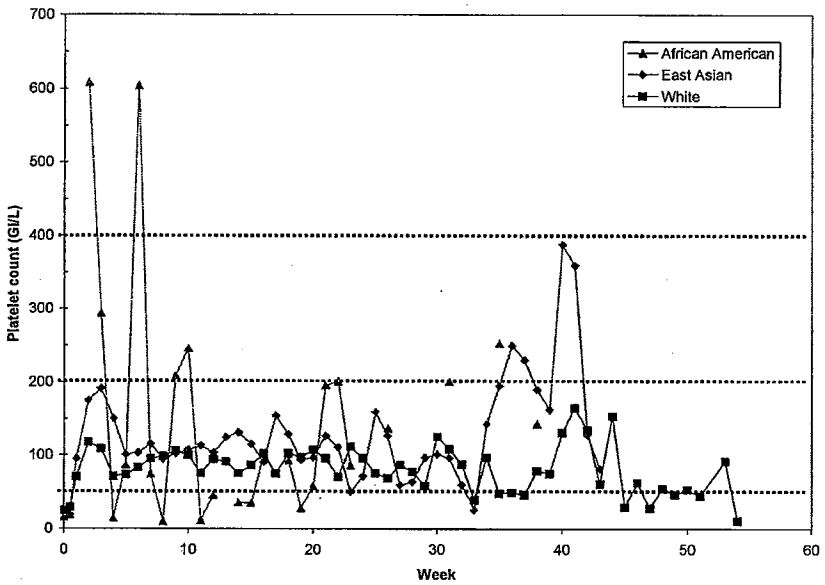


Figure 49: Reviewer Generated Exploratory Analysis of Mean Weekly Dose by Race

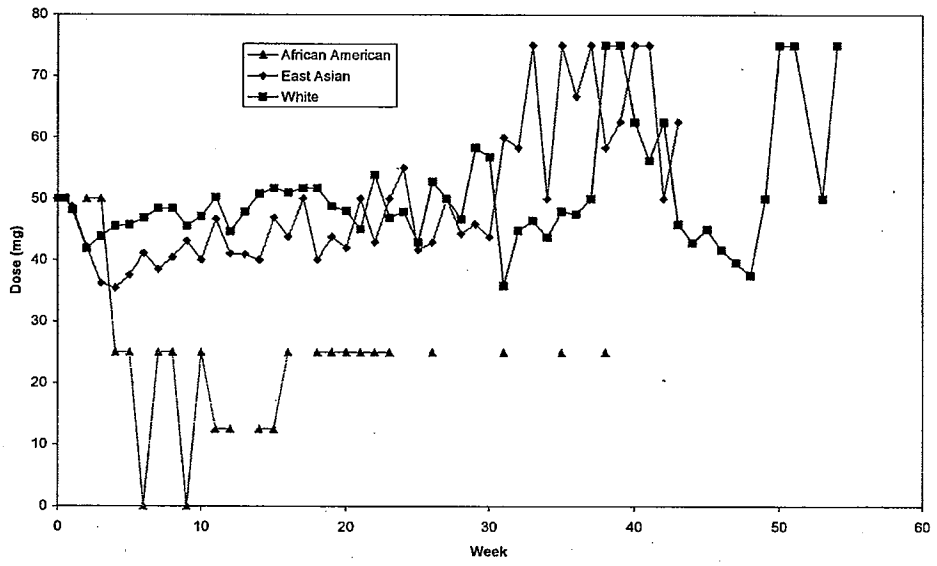


Figure 50: Reviewer Generated Exploratory Analysis of Median Weekly Platelet Count Race

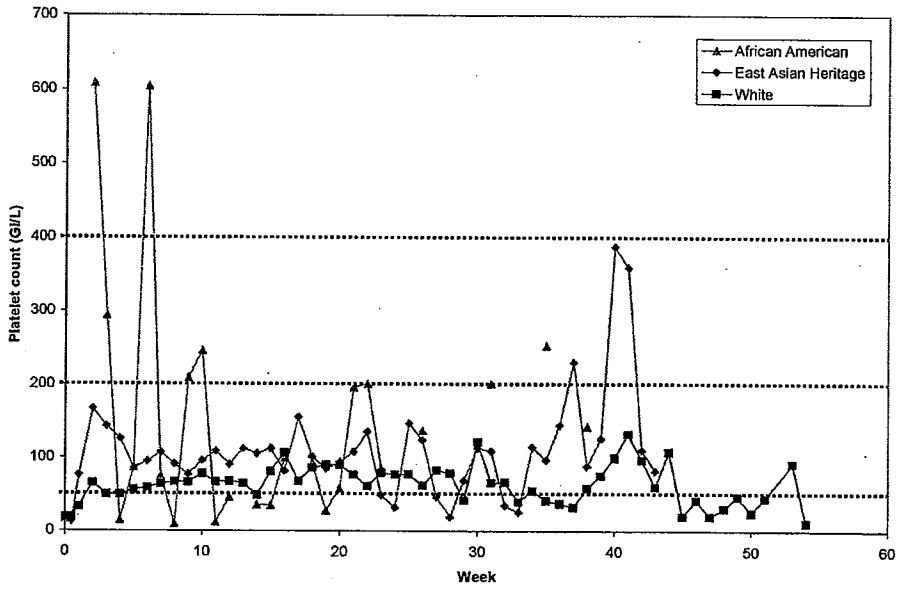


Figure 51: Reviewer Generated Exploratory Analysis of Median Weekly Dose by Race

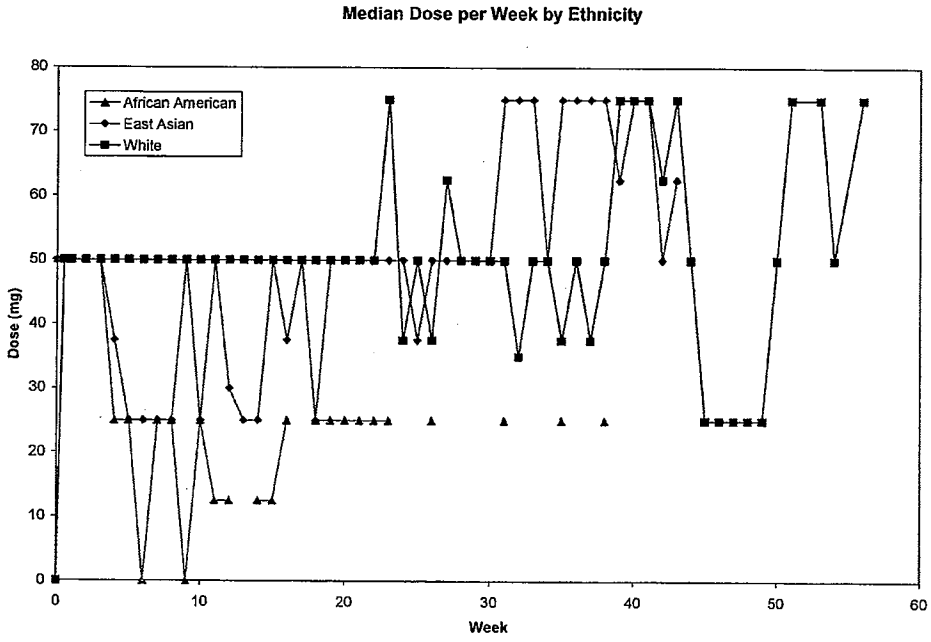


Table 166: Reviewer Generated Exploratory Analysis of Daily Dose by Race

RACE	Dose (mg)							
	N	Mean	Std Dev	Median	25th	75th	Min	Max
African American/African Heritage	1	15.1	13.7	25	0	25	0	50
American Indian or Alaskan Native	5	38	18.1	25	25	50	0	75
Asian - Central/South Asian Heritage	3	34.4	26.5	37.5	6.25	50	0	75
Asian - East Asian Heritage	19	40.2	19.9	50	25	50	0	75
Asian - South East Asian Heritage	2	68.8	11.6	75	56.25	75	50	75
White - Arabic/North African Heritage	12	38.6	17.7	50	25	50	0	75
White - White/Caucasian/European Heritage	67	41.7	25.3	50	25	75	0	75

Twenty-six subjects (24%) received a regimen other than once daily during the first 6 months of treatment in EXTEND (Table 167).

Table 167: EXTEND Alternate Daily Dosing Regimens

Subjects	N=109 n(%)	Patient Numbers
Total Alternate Daily Dosing Regimens	**26 (24)**	
<25mg once daily	**17 (16)**	
25mg (2 days on, 1 day off)	2 (2)	818, 58
25mg every other day	16 (15)	54, 58, 72, 81, 106, 127, 128, 534, 646, 719, 1061, 1131, 1132, 1133, 1161, 1184
<25mg every other day	4 (4)	54, 127, 534, 719
>25mg once daily + <50mg once daily	**9 (8)**	
50mg every other day	3 (2)	61, 819, 822
25/50mg every other day	6 (6)	81, 128, 536, 537, 1052, 1055
50/50/25mg (repeated every 3 days)	2 (2)	61, 81
>50mg once daily	**2 (2)**	
50/50/75mg (repeated every 3 days)	1 (1)	532
50/75mg every other day	1 (1)	57

Reviewer Comment:

- *The sponsor's 6/25/08 revised labeling recommends*

- *A reviewer generated exploratory analysis of the effect of ethnicity on the requirement for < 25 mg qd dosing (Table 168) suggests a higher incidence in Asian and Arabic/African subjects, however; the relevance of this find is uncertain given the limited sample size.*

Table 168: Effect of Ethnicity on the Requirement for < 25 mg qd Dosing

Race	N	25 mg QOD N(%)

White - White/Caucasian/European	67	8 (12)
Asian - East Asian	19	4 (21)
White - Arabic/North African	12	2 (17)
American Indian or Alaskan Native	5	1 (20)
Asian - Central/South Asian	3	1 (67)
Asian - South-East Asian	2	0 (0)
African American/African	1	1 (100)

Results-PK analysis:

Analyses of all samples collected have not been performed since this is an ongoing study. Individual samples in specific cases of interest were analyzed to help explain AEs and SAEs of special interest.

Reviewer Comment: While the sponsor provided these data, a usable electronic data set or pertinent information regarding the samples (e.g., dose, date, time after dose, etc.) were not provided. This significantly limited the usefulness of this information.

Results-Safety:

Exposure to study medication is summarized in by the average daily dose, the number of days on treatment, and by cumulative dose in Table 169. At the time of clinical data cut-off, the median daily dose was 50 mg, the median number of days on treatment was 194.0 days (6.5 months), and the median cumulative dose was 6725 mg. Eighty-two percent of subjects required either an increase or decrease in dose or frequency of eltrombopag, and 31% (34 subjects) required an interruption to eltrombopag dosing at some point in the study. Of the subjects requiring a dose interruption, 7 had a dose interruption lasting 1 to 7 days and 27 had a dose interruption lasting >7days. Forty-five percent of subjects who were interrupted as part of a dose adjustment were interrupted due to platelet counts between 200 and 400Gi/L (in deviation from the protocol specified dosing guidelines, which recommended a reduction in dose or schedule of eltrombopag when platelet counts were between 200-400Gi/L). Fifty-five percent of subjects who were interrupted as part of a dose adjustment were interrupted due to platelet counts >400Gi/L as specified in the protocol specified dosing guidelines (which recommended an interruption for at least 7 days and a reduction in dose or schedule of eltrombopag).

Table 169: Summary of Exposure to Study Medication and Change in Dose

	Eltrombopag N=109
Average Daily Dose (mg), N	102
Mean (SD)	50.2 (19.05)
Median (Min – Max)	50.0 (9 – 79)
Cumulative Dose (mg), N	102
Mean (SD)	8789.7 (6396.15)
Median (Min – Max)	6725.0 (100 – 27625)
Days on Study Drug, N	102
Mean (SD)	177.8 (102.67)
Median (Min – Max)	194.0 (2-387)
Eltrombopag Dosage Changes or Interruptions, N	
Any Increase or Decrease in Dose and/or Frequency, n(%)	89(82)
Increase in Dose and/or Frequency, n(%)	81(74)
Decrease in Dose and/or Frequency, n(%)	55(50)
Any Dose Interruption, n(%)	34(31)

Overall, 78% of subjects have reported at least one AE (on-therapy + 1 day) as of the clinical cut-off date of 31Aug2007 (Table 170). On-therapy SAEs occurred in 14 subjects (13%). There were 35 subjects (32%) who reported 115 events considered by the investigator as related to study medication. Six subjects experienced 11 AEs leading to withdrawal from study medication. All SAEs and AEs leading to withdrawal are detailed in individual subject narratives (Section 14, Subject Narratives).

Table 170: Overall Summary of Adverse Events Started On-therapy +1 Day

	Eltrombopag N=109	
	Subjects n(%)	Events n
Any AE	85(78)	551
Any SAE	14(13)	23
AEs related to study medication	35(32)	115
AEs leading to withdrawal	6(6)	11
SAEs leading to withdrawal	4(4)	7

Headache (17%) was the most commonly reported on-therapy AE, followed by upper respiratory tract infection (15%), diarrhea (12%), nasopharyngitis (12%), and arthralgia (10%) (Table 171). The following table depicts any AE reported in 5% or more of subjects.

Table 171: On-therapy (+ 1 Day) Adverse Events Reported by 5% or More of Subjects

Preferred Term	Eltrombopag N=109
	n(%)
Any AE	**85(78)**
Headache	19(17)
Upper respiratory tract infection	16(15)
Diarrhea	13(12)
Nasopharyngitis	13(12)
Arthralgia	11(10)
Fatigue	9(8)
Vomiting	9(8)
ALT increased	8(7)
Cough	8(7)
Epistaxis	8(7)
Hyperbilirubinemiab	8(7)
Nausea	8(7)
Anemia	7(6)
AST increased	7(6)
Pain in extremity	7(6)
Pharyngolaryngeal pain	7(6)
Back pain	6(6)
Contusion	5(5)
Ecchymosis	5(5)
Hypertension	5(5)
Edema peripheral	5(5)
Pruritus	5(5)
Respiratory tract infection viral	5(5)

Reviewer Comment: A reviewer initiated exploratory analysis of the incidence of any AE by Race (Table 172) does not show a trend toward a higher incidence in Asian vs. Caucasian subjects. It is interesting that a trend toward lower dose requirements and a higher incidence of AE's is seen in the American Indian or Alaskan Native subjects.

Table 172: Reviewer Generated exploratory analysis of AE/subject by Race

RACE	N	# AE 's	~AE/subject
African American/African Heritage	1	5	5
American Indian or Alaskan Native	5	72	14.4
Asian - Central/South Asian Heritage	3	11	3.7
Asian - East Asian Heritage	19	86	4.5
Asian - South East Asian Heritage	2	7	3.5
White - Arabic/North African Heritage	12	28	2.3
White - White/Caucasian/European Heritage	67	354	5.3

AEs were assigned a toxicity grade using the NCI CTCAE v3. The number of subjects experiencing AEs were summarized by the maximum toxicity grade of the events experienced. On-therapy, of the subjects experiencing an AE, the majority had events with a maximum CTCAE toxicity grade of Grade 1 or Grade 2 (Table 173). Fifteen subjects experienced at least one AE with a maximum toxicity grade of 3; 3 subjects experienced events with a maximum toxicity grade of 4. There were 2 fatal SAEs reported in the study to date: Subject 122 died while on-therapy secondary to a road traffic accident (passenger) and Subject 1051 died due to hypovolemic shock secondary to gastrointestinal hemorrhage (event occurred 55 days after the last dose of eltrombopag).

Table 173: Subjects with On-therapy (+1 Day) AEs by Maximum Toxicity Grade

Grade	Eltrombopag N=109
Grade 1	35(32)a
Grade 2	30(28)
Grade 3	15(14)
Grade 4	3(3)
Grade 5	1(<1)

Four subjects experienced 4 thromboembolic events (2 pulmonary embolisms, 1 transient ischemic attack, 1 deep vein thrombosis) during the study. The time to these events after the first dose was between 58-387 days and the platelet counts at the time of the events ranged from 27-407 Gi/L. All 4 subjects had risk factors for the development of thromboembolic events.

Reviewer Comment: A reviewer generated exploratory analysis of the incidence of at least one platelet count result > 400 Gi/L (Table 174) showed a trend toward a higher incidence in Asian and African patients compared to Caucasian subjects.

Table 174: Proportion of Subjects with at Least one Platelet Count >400 Gi/L by Ethnicity

Race	N	At least 1 Platelet count ≥400, n (%)

White - White/Caucasian/European	67	7 (10)
Asian - East Asian	19	4 (21)
White - Arabic/North African	12	5 (42)
American Indian or Alaskan Native	5	1 (20)
Asian - Central/South Asian	3	2 (67)
Asian - South-East Asian	2	0 (0)
African American/African	1	1 (100)

Eight subjects in this study were identified who met the criteria specified in the FDA guidance document about drug-induced liver injury. There were no deaths, no lasting clinical sequelae and no subject met Hy's rule criteria. However, the analysis shows that eltrombopag treatment can be associated with elevated hepatobiliary laboratory abnormalities.

Reviewer Comment: A separate sponsor analysis suggests a higher rate of subjects with Hepatobiliary Abnormalities that Met the FDA Criteria in Asian's compared to Caucasian subjects (Table 175). It is not clear from these data whether this is a result of higher exposure as reported in earlier studies or a yet undetermined genetic predisposition.

b(5)

Table 175: Proportion of Subjects with Hepatobiliary Abnormalities that Met the FDA Criteria, and Odds Ratios for Hepatobiliary Abnormalities by Ethnicity

Studies	Race	No. of Subjects on Study Medication	No. (%) of subjects with hepatobiliary abnormalities	Odds ratio (95% CI)Asian vs. White
EXTEND	Asian	24	5 (20.8%)	5.61 (1.23, 25.67)
	White	67	3 (4.5%)	

It is important to note that none of the subjects requiring < 25 mg qd dosing met this HBA criterion. Since exposure was not evaluated the significance of this finding is unkown.

Fifteen subjects with 19 possible on-therapy renal-related events were identified. The most frequent AEs were peripheral edema (5 events in 4 subjects) and pyelonephritis, hypertension, and UTI (2 events in 2 subjects each). Eleven of those 19 events were Grade 1 (in 9 subjects), 7 events were Grade 2 (in 7 subjects), and one event was Grade 3. Most subjects had serum creatinine values within normal ranges during the study. Of the 15 subjects with renal events, 12 had creatinine levels within normal limits (WNL) while on study medication.

Eighteen on-therapy cardiac-related events were reported in 11 subjects. The most frequent events were chest pain/discomfort and hypertension/blood pressure increased in 6 subjects each. The majority of cardiac-related AEs were Grade 1. Six of the 11 subjects had pre-existing cardiac conditions and 2 additional subjects had reported current risk factors for cardiac conditions.

A total of 10 on-therapy ocular-related AEs were observed in 8 subjects. In total, 13 of the 102 subjects who had one or more ocular examinations, reported events that met the criteria for a report of cataract as specified for this study.

Twenty subjects experienced 38 discreet episodes of a platelet count elevations ≥400Gi/L up to the clinical cut-off date of the study. Of the 20 subjects experiencing thrombocytosis during treatment, 11 had one period with an elevation of platelet counts ≥400Gi/L, 5 subjects had 2 periods (Subjects 57, 58, 122, 532, and 537), 2 subjects had 3 periods (Subjects 54 and 127), and one subject (Subject 534) had 10 separate periods with an elevation of platelets ≥400Gi/L, of which 3 assessments were over 1000Gi/L (counts =1700Gi/L, 1560Gi/L, and 1256Gi/L). The median duration of platelet count elevation ≥400Gi/L was 8.5 days (range 5 to 49 days). Potential clinical consequences of thrombocytosis were evaluated in these 20 subjects by looking for thromboembolic events during the episode of thrombocytosis. Subject 71 experienced a pulmonary embolism with a proximal platelet count of 407Gi/L.

Most subjects had clinical chemistry values within normal limits for all the post-baseline clinical chemistry assessments.

One hundred and three subjects completed an ECG assessment. There were no meaningful differences in ECG assessments during the study. The median QTc intervals were similar at baseline (400msec at screening, 414msec at day 1 pre-dose), and during the study at both post-dosing assessments (day 1 post dose, 406msec; and study medication withdrawal, 400msec). The median change from baseline at day 1 post-dose was 0msec and at the study medication withdrawal visit was -6.3msec. Of the 12 subjects with QTc values ≥450msec occurring after dosing, none had any clinical sequelae associated with these values.

Conclusions (sponsor):

- In this ongoing, open-label extension study to evaluate the safety and efficacy of eltrombopag, durable, clinically meaningful elevations of platelet counts were observed, as 55%, 54% and 24% of subjects had at least 4, 10 and 25 continuous weeks of platelet counts ≥50Gi/L, respectively. Approximately one third (35%) of subjects receiving concomitant ITP medications at baseline were able to reduce and/or eliminate them, and clinically significant bleeding as assessed by the WHO Bleeding Scale was reduced from baseline. Thirteen subjects who had a hemostatic challenge on study, tolerated the procedures well without bleeding complications.
- The safety profile was consistent with that observed in the studies with short-term exposure to eltrombopag. Thromboembolic and hepatobiliary events were noted.
- These findings from this ongoing study indicate that eltrombopag is an effective and well tolerated therapeutic option for long-term treatment in subjects with chronic ITP.

Reviewer Comments:

- *Platelet response and dosing requirements are highly variable—especially at the later time points.*
- [redacted] b(4)
- *The long term PK/PD relationship in the ITP population could not be adequately assessed in this study.*
- *The comparative weekly dosing requirements between East Asian and Caucasian populations were not as different as anticipated given the exposure differences noted in the earlier PK studies. This may be the result of the difference in exposure vs. PD between these populations. The potentially higher incidence of hepatobiliary abnormalities in the Asian population is of concern.*

4.4 Consult Review (including Pharmacometric Review)

4.4.1 Pharmacogenomics Review

GENOMICS REVIEW

NDA (Serial Number): 22-291
Sponsor: GSK
Drug: PROMACTA (eltrombopag)
Proposed Indication: idiopathic thrombocytopenic purpura (ITP) b(4)

Review Due Date: 4/15/2008
Requested Genomic Review: Joseph Grillo
Material Submitted: Pharmacogenetic study of associations with pharmacokinetic and pharmacodynamic outcomes in subjects exposed to eltrombopag (Promacta®).
Genomic Reviewer: Silvana Borges, M.D.

Background:

Eltrombopag is a thrombopoietin (TPO) receptor agonist for the . As a TPO b(4)
receptor agonist, eltrombopag functions through the thrombopoietin signaling pathway to induce proliferation and differentiation of megakaryocytes to enhance platelet production. Preliminary data suggests that the drug exposure in Japanese subjects is higher than that in non-Japanese subjects. The source of this PK variability is currently unexplained.

Pharmacogenetic study

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. 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 White populations and included healthy volunteers (HVT) and patients with idiopathic thrombocytopenic purpura (ITP).
The **primary objective** of this study was to identify any genetic basis for the variability in PK following administration of eltrombopag, being the primary PK endpoint the area under the plasma concentration curve (AUC).
The **secondary objective** of this 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.
Collection of DNA. There is no sufficient information about the conditions of blood collection, storage of the blood samples before DNA extraction and DNA extraction procedures.
Genetic variants or SNP selection. The sponsor selected genes that are known to play a role (CYP1A2, CYP2C8 and UGT1A1/1A3) or that are suspected to participate in eltrombopag ADME, i.e. NAT1/2, ABCG2 (BCRP), SLCO1B1 (OATP1B1), ABCB1 (MDR1), SLC10A1 (NTCP1), SLC10A2 (NTCP2), SLCO2B1 (OATP2B1) and SLCO1B3 (OATP1B3). In exploring the PGx-PD relationship, six genes involved in the TPO signaling pathway were evaluated, i.e. THPO (megakaryocyte stimulating factor), MPL (thrombopoietin receptor), JAK2 (tyrosine protein kinase jak2), STAT5A (signal transducer and activator of transcription 5A), STAT5B (signal transducer and activator of transcription 5B) and ITGA2B (platelet fibrinogen receptor, alpha subunit). This investigation included 4,991 SNPs in the ADME panel and 138 SNPs identified within the six PD candidate genes, bringing the total number of markers intended for evaluation to over 5,129. Many of the selected genes and SNPs are arguably not specific and have a low potential to play a substantial role, if any, in the PK or PD of eltrombopag. Another caveat is that it is not possible to calculate the power of the study without knowing the frequency of these variants in the studied population. However, the exploratory nature of this study, make this over inclusive approach acceptable.
Genotyping procedures. Genotyping assays were performed to evaluate the 5129 SNPs using standard Sanger-based sequencing techniques, a single base chain extension protocol (FAST), and methods. All assays were validated against the HapMap cohort of subjects. The genotyping procedures as b(4)

well as the quality control are adequate. However, assays were removed from analysis if less than 80% of subjects returned genotypes, if more than one duplicate error was detected, if assays had less than 99% concordance with published HapMap data (when available), or if they could not be uniquely mapped. The exclusion of the assays from the analysis due to low performance is questionable and a source of bias.

Genotyping results. Polymorphisms that appeared monomorphic in this study set were not included in the association analysis. Out of 5129, 2,828 unique SNPs were detected as polymorphic and used for analyses. Although it is reasonable to exclude monomorphic traits from the analysis, since they are not expected to explain the variability, the fact that a polymorphism appears monomorphic in the studied population, suggests a selection bias and raises questions on the validity of the study. Table 6 & 7 show the PGx, PK and PD data available for anaylisis in HVT and ITP, respectively.

Table 6 HVT Population Availability[1]

Racial Group	ITT	PGx Consent	Genotype Data[2]	PK AUC(0-∞)[3]	PK AUC(0-τ)[4]	PK/PD[5]	PD[6]
Asian	55	40	40	40	21	21	21
White	199	136	120	110	22	22	23
African American	36	17	13	9	5	5	5
All	290	193	173	159	48	48	49

1. Data from Asians, Whites, and African Americans is provided. Data from subjects of mixed race or other races including American Indian is not included.
2. Genotype Data : Samples were excluded if not collected, quality was poor, volume was insufficient, or QC results were inconsistent
3. PK AUC(0-∞): Number of samples with genotype data, AUC(0-∞) from Single Dose treatment, and all other independent variables for PK analysis.
4. PK AUC(0-τ): Number of samples with genotype data, AUC(0-τ) from Repeat Dose treatment, and all other independent variables for PK analysis.
5. PK/PD: Number of samples with genotype and PK AUC(0-τ) data, PD data, and all other independent variables for PD analysis
6. PD: Number of samples with genotype, PD data, and all other independent variables for PD analysis.

Table 7 ITP Population Availability[1]

Racial Group	ITT	PGx Consent	Genotype Data[2]	PK AUC(0-τ)[3]	PK/PD[4]	PD[5]
Asian	31	21	19	11	11	19
White	126	82	81	43	42	77
African American	2	0	0	0	0	0
All	159	103	100	54	53	96

1. Data from Asians, Whites, and African Americans is provided. Data from subjects of mixed race or other races including American Indian is not included.
2. Genotype Data : Samples were excluded if not collected, quality was poor, volume was insufficient, or QC results were inconsistent
3. PK AUC(0-τ): Number of samples with genotype data, AUC(0-τ) from Repeat Dose treatment, and all other independent variables for PK analysis.
4. PK/PD: Number of samples with genotype, AUC(0-τ), PD data, and all other independent variables for PD analysis.
5. PD: Number of samples with genotype, PD data, and all other independent variables for PD analysis.

Data Source: Table 7.2, Table 7.38.

The number of patients is in some cases very small (e.g. with PGx and PD data), thus limiting the ability to reach definite conclusions. As stated before, there is no information on the power to detect differences between genotype groups.

After the analysis of different SNP combinations and grouping of the studied subjects,

- No polymorphisms were associated with differences in eltrombopag exposure between Asian and White subjects.
- No polymorphisms in the six genes analyzed in the thrombopoietin signaling pathway were associated with variability in PD.

Interpretation of results. Several limitations exist in the strength of this study to identify polymorphisms capable of predicting differences in eltrombopag PK and PD variability. This is a retrospective study that has not been powered to identify those differences. The samples were drawn from a highly heterogeneous population of multiple studies and with unequal distributions of Asian and White subjects. 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.

Conclusions and Recommendations:

We agree with the Sponsor in the exploratory nature of this study and in considering that no definite conclusion on the genetic contribution to eltrombopag PK and PD variability can be derived from this study.

4.4.2 IRT Review

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

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

Summary

Overall Summary of Findings

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

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

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

Treatment	Time, h	ΔΔQTcF, ms	90% CI, ms
Eltrombopag 50 mg QD	6	1.58	(–2.98, 6.14)
Eltrombopag 150 mg QD	6	1.26	(–3.03, 5.56)
Moxifloxacin 400 mg*	3	10.62	(6.54, 14.70)

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

The supratherapeutic dose of 150 mg QD covers the 2-fold increase in the exposures that can be achieved with the highest therapeutic dose of 75 mg QD. However, the supratherapeutic dose might not fully cover the range

of exposures that can be achieved with a 75 mg QD dose in HCV patients who are reported to have 2.3 fold increases in exposures.

There was no relationship between eltrombopag concentrations and ΔΔQTcF.

Proposed Label

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

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

BACKGROUND

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

Market approval status

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

Preclinical Information

Source: Non-Clinical Summary

> "A study was conducted to measure the effect of eltrombopag on hERG currents recorded from HEK293 cells stably transfected with hERG-1 cDNA [Report FD2004/00272/00, m4.2.1.3]. The maximum soluble concentration of eltrombopag (21.7 µM, equivalent to 9.62 µg/ml) determined and the concentration-dependent effect of eltrombopag on hERG tail current was subsequently studied at 0.00652, 0.0217, 0.0652, 0.217, 0.652 and 2.17 µM (equivalent to 0.003, 0.010, 0.029, 0.096, 0.288 and 0.961 µg/ml, respectively). E-4031 (0.1 µM), a known inhibitor of the IKr current, was used as a reference substance.
>
> Eltrombopag was found to inhibit hERG channel tail current in a concentration-dependent manner. The nominal IC25, IC50 and IC75 values were estimated to be 0.09, 0.69 and 5.13 µM (equivalent to 0.04, 0.31 and 2.27 µg/ml), respectively.
>
> "The effects of eltrombopag (10 or 25 µM) on action potential duration at 30%, 60% and 90% repolarization (APD_{30}, APD_{60} and APD_{90}, respectively), maximum rate of depolarization (MRD), upstroke amplitude (UA) and resting membrane potential (RMP) were investigated in isolated dog Purkinje fibers paced at stimulation frequencies of 1 and 0.5 Hz [Report FD2002/00064/00, m4.2.1.3]. In fibers paced at 3 Hz (control and 25 µM), only MRD was measured.
>
> Eltrombopag had no effects on RMP or APD_{30}. In fibers stimulated at 0.5 or 1 Hz, exposure to 10 and 25 µM resulted in decreases in MRD (14% to 16% and 22% to 24%, respectively). In fibers stimulated at 1 Hz and exposed to 10 and 25 µM, significant decreases in UA (3 and 5 mV, respectively), APD_{60} (8% and 14%, respectively) and APD_{90} (6% and 11%, respectively) were noted. At a stimulation frequency of 0.5 Hz, exposure to 10 and 25 µM had no effect on UA whereas slightly larger decreases in APD_{60} (12% and 18%, respectively) and APD_{90} (10% and 16%, respectively) were found in comparison to stimulation at 1 Hz. When the stimulation frequency was increased from 1 to 3 Hz, MRD was reduced in both the control and 25 µM samples (9% and 6%, respectively), and comparisons to results obtained at 1 Hz indicated no significant differences between the treated and control fibers. However, the effects on MRD at 1 and 0.5 Hz suggested that eltrombopag may produce a tonic (i.e., not use-dependent) inhibition of cardiac sodium channels.
>
> "Conscious male beagle dogs (n=4) were administered eltrombopag at 3, 10 and 30 mg/kg orally in capsules on separate days in a crossover study design with 7 days between treatments [Report SB-497115/RSD-101TT9/1, m4.2.1.3]. The following parameters were measured continuously from ~2

hours prior to dosing to 48 hours post dose: mean arterial pressure, heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, ECG intervals (PR, QRS, QT, QTc) and ECG waveforms.

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

"Additionally, there was no evidence of ECG abnormalities (e.g., heart rate; PR, QRS, QT and RR intervals and QTc) when evaluated pre- and post dose in conscious dogs after repeated oral administration for 52 weeks at doses up to 30 mg/kg/day (C_{max} of 34.5 µg/ml and AUC_{0-t} of 418 µg.h/ml)."

Reviewer's Comment: IC_{50} for hERG current inhibition was estimated to be 0.69 µM. The effects in isolated canine Purkinje fibers suggested sodium channel inhibition. The in vivo studies showed no evidence of QT prolongation.

Previous Clinical Experience

Source: Summary of Clinical Safety- Dec 17, 2007

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

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

"One subject died of cardiopulmonary failure in Study TRA100773A (Subject 144, eltrombopag 50 mg). This subject had a medical history of pneumonectomy for right lung carcinoma with concomitant medications including prednisone due to asthma and emphysema and experienced SAEs of renal insufficiency and hepatitis which were considered by the investigator as related to study medication. On Day 25, Subject 144 suffered a fatal SAE cardiopulmonary failure which was assessed as not related to study treatment and the subject died 2 days later. Two additional fatal SAEs were reported: embolism and pulmonary embolism. These SAEs were considered drug-related and were identified upon autopsy.

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

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

Clinical Pharmacology

Appendix 0 summarizes the key features of eltrombopag's clinical pharmacology.

SPONSOR'S SUBMISSION

Overview

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

TQT Study

Title

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

Protocol Number

TRA 102860 (Part 1 & 2)

Study Dates

13 March 2006 - 02 August 2007

Objectives

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

Study Description

Design

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

Controls

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

Blinding

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

Treatment Regimen

Treatment Arms

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

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

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

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

Sponsor's Justification for Doses

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

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

Instructions with Regard to Meals

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

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

ECG and PK Assessments

Table 1: Sampling Schedule

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

-0.5, 0.5, 1, 2, 3, 4, 6, 12 and 23.25 hours post-dose
++++ pre-dose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12, 24 hours post-dose

Baseline

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

ECG Collection (Source Protocol)

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

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

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

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

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

Sponsor's Results

Study Subjects

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

Twenty-six subjects were withdrawn from the study due to elevated platelet counts greater than 400 x 109/L. Twenty-four of these subjects were withdrawn after the eltrombopag 150 mg treatment period, one subject after the 50 mg treatment and one subject after the placebo treatment.

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

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

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

Source Data: Table 9.203

Statistical Analyses

Primary Analysis

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

Table 3: The Sponsor's ΔQTcF analysis: Eltrombopag 50 mg versus Placebo (A vs. C)

Day	Time	Treatment Difference: ΔΔQTcF		
		Estimate	S.E.	90% CI
5	1	−0.03	1.22	(−2.04, 1.98)
	2	1.54	1.22	(−0.47, 3.55)
	3	1.52	1.22	(−0.48, 3.53)
	4	0.23	1.23	(−1.79, 2.25)
	6	1.36	1.25	(−0.69, 3.41)
	24	−0.53	1.23	(−2.55, 1.49)

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

Table 4: The Sponsor's ΔQTcF analysis: Eltrombopag 50 mg versus Placebo (B vs. C)

Day	Time	Treatment Difference: ΔΔQTcF		
		Estimate	S.E.	90% CI
	1	2.29	1.18	(0.341, 4.24)
	2	1.86	1.18	(−0.09, 3.81)

5	3	0.79	1.19	(–1.16, 2.75)
	4	0.10	1.18	(–1.83, 2.04)
	6	1.95	1.20	(–0.02, 3.93)
	24	0.03	1.19	(–1.92, 1.99)

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

Table 5: The Sponsor's ΔQTcF analysis: 400 mg Moxifloxacin versus Placebo (D vs. C)

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

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

Based on the sponsor's analysis:

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

Safety Analysis

There were no deaths or serious adverse events. Twenty-six subjects were withdrawn from the study due to elevated platelet counts greater than 400 x 109/L. There were 6 withdrawals due to other adverse events.

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

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

Source data: Table 10.209

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

Subject 5218 had completed Period 1 (50 mg eltrombopag). On Day 3 of Period 2 (400 mg moxifloxacin) prior to receiving the moxifloxacin, multiple unifocal (87) PVCs/ventricular extrasystoles were observed on telemetry over a 66 h period. The maximum intensity of these events was reported as mild. The subject was withdrawn from the study on Day 3 of Period 2. The events resolved, and were considered by the investigator to be related

to study drug. No abnormal findings were recorded on ECG for this subject on or around the time these events were observed on telemetry. (Table 10.214)

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

Other abnormal ECG findings reported are summarized below.

Table 7: Summary of Abnormal ECG Findings in Part 2

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

Source Data: Table 10.214

Clinical Pharmacology

Pharmacokinetic Analysis

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

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

Day	Dose (mg)	N	AUC(0-τ) (μg hr/mL)	Cmax (μg/mL)	Cτ (μg/mL)	tmax (h)
5	50	60	65.4 (59.7, 71.6) [36.4]	6.40 (5.87, 6.97) [34.2]	1.19 (1.05, 1.34) [51.2]	3.19 (2.17, 6.22)
	150	73	204 (186, 223) [39.3]	19.0 (17.4, 20.6) [37.5]	4.07 (3.64, 4.55) [50.3]	2.67 (1.67, 6.20)

Data presented as geometric mean (95% CI) [CVb%], except tmax presented as median (minimum, maximum)
Source Data: Table 29 of sponsor report tra102860-report-body.pdf

Following five days of repeat dosing, plasma eltrombopag C_{max} and $AUC_{(0-\tau)}$ increased in a dose proportional manner between the 50 mg and 150 mg dose levels. The dose proportionality ratio estimate (90% CI) was 1.04 (0.987, 1.09) for $AUC_{(0-\tau)}$ and 1.01 (0.942, 1.08) for C_{max} over a range of 50 mg QD to 150 mg QD
Plasma moxifloxacin PK parameters following single dose administration in Part 2 are summarized in

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

Dose (mg)	N	AUC(0-t) (µg hr/mL)	Cmax (µg/mL)	tmax (h)
400	60	22.6 (21.4, 23.9) [21.1]	2.05 (1.93, 2.18) [23.7]	2.17 (0.63, 6.17)

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

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

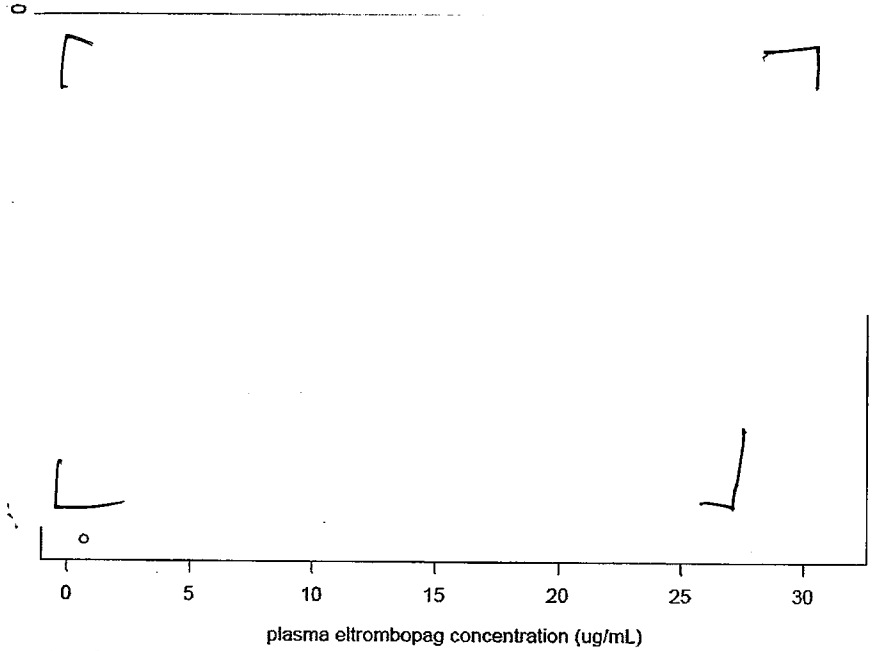
Plasma moxifloxacin C_{max} values in this study were 2.05 µg/ml on average, which is lower than the C_{max} value of 3.1 µg/ml in the moxifloxacin product label [Avelox, Package Insert, 2005].

Exposure-Response Analysis

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

A plot of ΔΔQTcF and plasma eltrombopag concentrations showed no relationship as shown in Figure 1 .

Figure 1: ΔΔQTcF versus Plasma Concentration following Repeat Dose Administration of 50 mg QD and 150 mg QD Eltrombopag for Five Days



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

The final Cp-ΔΔQTcF model for eltrombopag was a linear model with no delay in effect of concentration on ΔΔQTcF; fixed effects for pre-dose ΔΔQTcF on Day 5 (intercept, Θ_1) and the slope relating plasma eltrombopag concentration to ΔΔQTcF (Θ_2) were included, along with inter-individual variability and inter-occasion variability (TRT1=50 mg and TRT2=150 mg) for both fixed effects, and additive random residual variability, as defined by the following equation:

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

The slope of eltrombopag concentration effect on ΔΔQTc 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-ΔΔQTcF model, simulations were performed to predict the mean (90% CI) ΔΔQTc 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 ΔΔQTcF at concentrations predicted for a dose of 300mg QD as shown in Table 10.

Table 10: Summary of ΔΔQTcF at C_{max} for Therapeutic and Supratherapeutic Eltrombopag Doses

Dose (mg) QD	Plasma eltrombpag Cmax (μg/mL) mean (95% CI)	Predicted ddQTcF (msec) mean (90% CI)[1]
50	6.72 (6.35, 7.10)	0.02 (-1.92, 2.42)
150	20.2 (19.0, 21.3)	1.60 (-0.50, 4.03)
300[2]	40.3 (38.1, 42.6)	4.03 (1.55, 6.79)

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

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

REVIEWERS' ASSESSMENT

Statistical Assessments

Primary Analysis

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

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

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

Table 11: Summary of ΔQTcF analysis: Eltrombopag 50 mg versus Placebo (A vs. C)

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

Table 12: Summary of ΔQTcF analysis: Eltrombopag 150 mg versus Placebo (B vs. C)

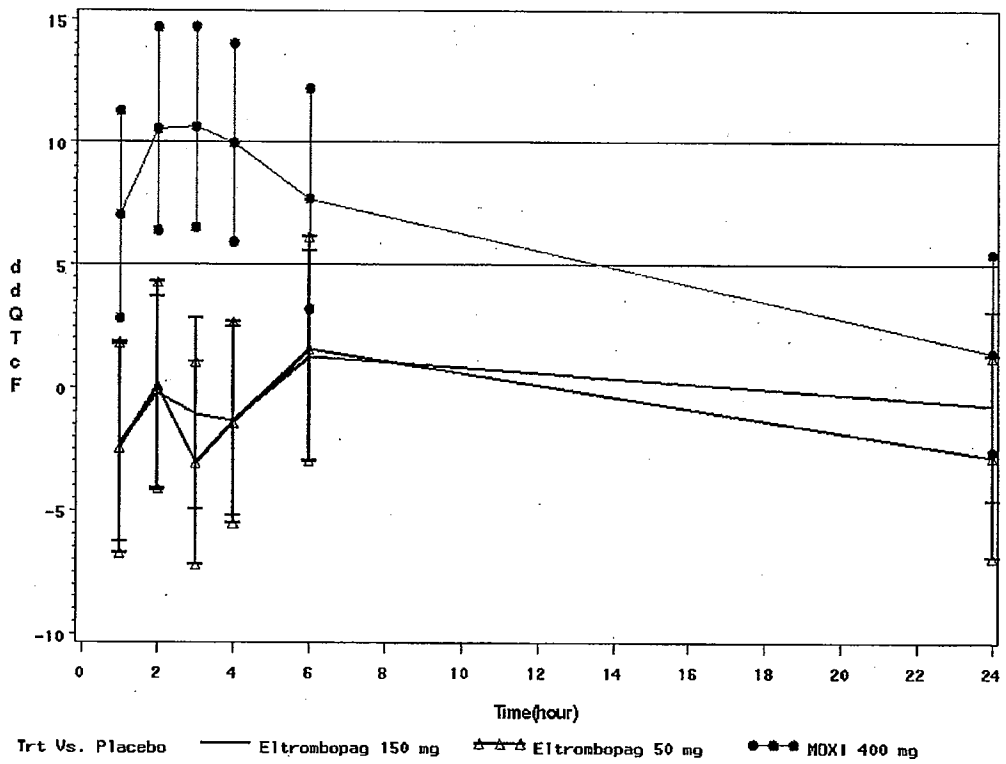
Day	Time	Mean ΔQTcF		Treatment Difference: ΔΔQTcF		
		TRT: B	TRT: C	Estimate	S.E.	90% CI
5	1	–2.06	0.21	–2.2653	2.4346	(–6.2920, 1.7614)
	2	–2.23	–1.98	–0.2478	2.3883	(–4.1978, 3.7022)
	3	–2.47	–1.40	–1.0682	2.3545	(–4.9624, 2.8261)
	4	–2.47	–2.21	–1.3683	2.3293	(–5.2208, 2.4842)
	6	–6.18	–7.45	1.2636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

Table 13: Summary of ΔQTcF analysis: Moxifloxacin 400 mg versus Placebo (D vs. C)

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

The time course of ΔΔQTcF for the study drug Eltrombopag and moxifloxacin is displayed in Figure 2.

Figure 2: ΔΔQTcF for Eltrombopag and Moxifloxacin



Categorical Analysis

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

Table 14: Subjects with ΔQTcF over 30 ms (FDA)

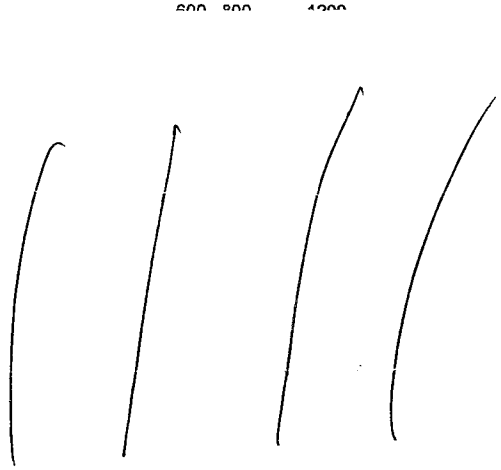
SUBJID	TREATMENT	dQTcF	SUBJID	TREATMENT	dQTcF
5001	C	32	5120	C	31
5019	B	41	5122	C	31
5022	B	41	5124	B	39
5023	D	37	5127	C	34
5025	A	36	5128	A	39
5026	D	34	5131	B	47
5030	B	33	5134	C	34
5031	C	40	5139	B	37
5032	D	40	5142	C	32
5102	D	40	5143	A	32
5105	C	33	5145	C	40
5106	A	40	5201	D	40
5108	D	32	5202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

Clinical Pharmacology Assessments

QT Corrections

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

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



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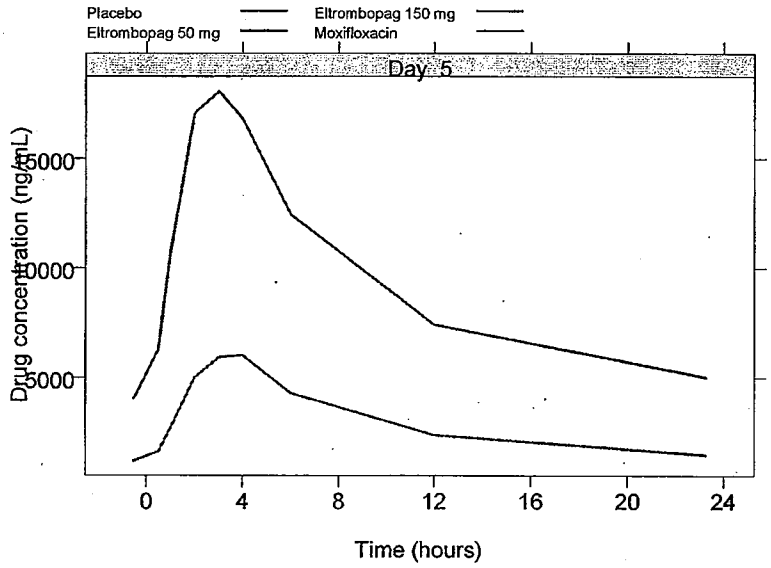
QTcF and Eltrombopag Concentration Time Profiles

Please refer to Figure 2 of the Reviewer's Statistical Assessment for time course of ΔΔQTcF for eltrombopag and moxifloxacin.

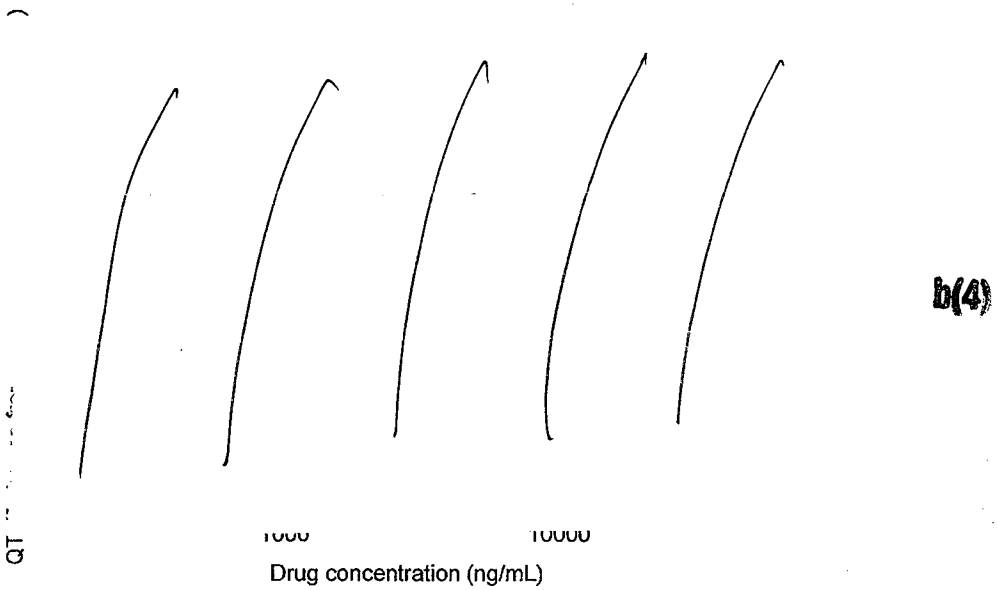
Figure 4. Mean Drug concentration - time profiles for Eltrombopag 50 mg (blue line), Eltrombopag 150 mg (red line),



Eltrombopag Concentration-QTcF Analysis

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

Figure 5. ΔΔ QTcF vs. Eltrombopag concentration



Clinical Assessments

Safety assessments

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

ECG assessments

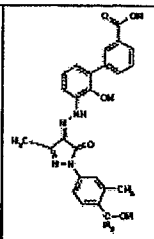
Waveforms submitted to the ECG warehouse were reviewed. ECGs were predominantly read in Lead II (96%) with V2 or V5 as alternate leads. Per QT analysis scores computed by the warehouse, there was no significant QT bias. Overall ECG acquisition and interpretation in this study appears acceptable.

APPENDIX

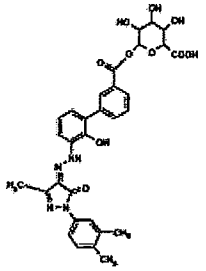
Highlights of Clinical Pharmacology

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

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

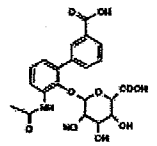


METABOLITE K (glucuronide metabolite; three isomers, together 0.6% plasma radioactivity at 4 hours)

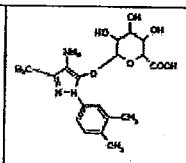


Metabolites M14 and AE have been identified in urine; representing the radiolabeled and unlabeled portion of the molecule following hydrazine cleavage, these glucuronide metabolites account for 20% of the administered dose.

METABOLITE M14

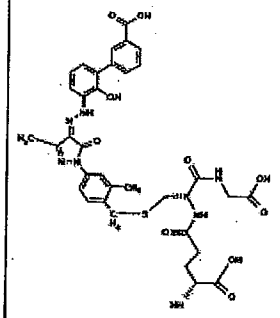


METABOLITE AE

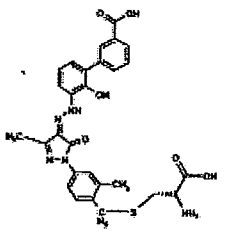


Metabolites F, G, and M9 have been identified in feces. These three glutathione-related metabolites co-elute and together account for 21% of the administered dose.

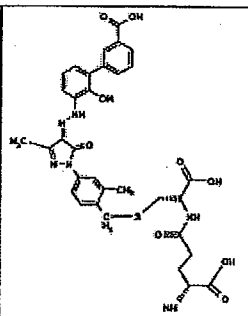
METABOLITE F



METABOLITE G



METABOLITE M9

		
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability data are not available due to [redacted] b(4) Relative bioavailability of tablet compared to capsule formulation geometric least squares mean ratio (90% CI): Cmax: 0.82 (0.70, 0.96) AUC(0-∞): 0.85 (0.75, 0.97)
	Tmax	Healthy Adult Subjects: Parent (eltrombopag): median 3 to 4 hours range: 2 to 6 hours Metabolites: not determined.
Distribution	Vd/F or Vd	From the population PK analysis, the typical value for Vc/F was 11L (inter-individual %CV of 41.8).
	% bound	>99%
Elimination	Route	Primary route: feces, 59% of dose (20% of dose as parent drug in feces) Other route: urine, 31% of dose (no parent drug in urine)
	Terminal t½	Parent: geometric mean ranged from 21 to 32 hours across four studies. %CVb ranged from 18 to 40%. Metabolites: not determined.

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

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

Table of Study Assessments

Appendix 2: Time and Events Table – Part 2

Study Procedure	Screen1	Treatment Periods 1, 2, 3, and 411									Follow-Up Visits	
		Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 14	Day 14 (± 1 day)	Day 33 (± 3 days)
Informed Consent	X											
Medical History/Medication History2	X											
Physical Examination3	X	X									X	X
Physical Examination to Assess Evidence of Bruising				X	X	X	X	X	X		X	X
Ophthalmology examination18	X											X
Blood Pressure and Heart Rate21	X	X		X	X	X	X	X	X		X	X
Safety 12-lead ECG	X4			X14	X14	X14	X14	X14	X14		X4	X4
Holter Monitoring			X15					X15				
Telemetry18				X	X	X	X	X	X			
Height and Weight	X											
Clinical Chemistry5	X	X			X	X		X			X	X
Hematology5	X	X			X	X		X		X23	X	X
Coagulation Tests22	X											
Lipid Panel8	X											
Urinalysis5, 6	X	X			X	X		X			X	X
Urine drug screen (including alcohol and cotinine)	X	X19										
HBsAG, Hep C antibody and HIV Screening	X											
Pregnancy Test7	X	X										X
Serum FSH and serum estradiol20	X											
Study Drug Dosing12				X	X	X	X	X				
ELTROMBOPAG PK Samples9, 13								X	X			
Moxifloxacin PK Samples13, 17								X	X			
Pharmacogenetics Sample10		X										
Adverse Events		Continuous									X	X
Concomitant Medications		Continuous									X	X
Outpatient	X										X	X

Continued

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

1. Subjects should be fasting from all food and drink for 4 hours prior to screening assessments being performed.
2. Medical history and medication history should include full history of drug, alcohol and nicotine-containing product use, complete history of all medications (including vitamin and herbal supplements) taken within 30 days prior to screening.
3. Physical examination, performed at screening, Day -2 of each treatment period and at follow-up visits, will include vital signs (supine blood pressure and heart rate) and assessment of vascular bruits and spleen. Height, weight, and calculation of body mass index (BMI) will be performed at screening only.
4. Three consecutive 12-lead ECGs will be taken at least 5 minutes apart.
5. Hematology, clinical chemistry and urinalysis will be performed on Day -2, pre-dose on Day 2 (24 hr post-dose on Day 1) and pre-dose on Days 3 and 5. Any safety lab results outside the normal range will be repeated at the discretion of the Investigator.
6. Urinalysis should include a microscopic evaluation if dipstick urinalysis is positive for blood or protein.
7. For female subjects of childbearing potential only: Serum β-hCG or urine pregnancy test is to be performed at screening, on Day -2 of each treatment period and at the Day 28 Follow-up visit.
8. Lipid panel includes total cholesterol, triglycerides, LDL and HDL.
9. Serial blood samples (approximately 3 mL) for PK analysis will be collected pre-dose (within 30 minutes prior to the administration of study medication) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours post-dose of Day 5 of each ELTROMBOPAG treatment period (treatment regimen A, B and C).
10. Pharmacogenetics sample (approximately 10 mL) may be taken at any time during the study but it is recommended that the sample be taken on Day -1.
11. Each subject will participate in all 4 treatment periods in the order designated at randomization. Each treatment period will be separated by a 14-day wash-out period.
12. Study medication will be administered by Unit personnel. Subjects must remain in a quiet room (no TV, no radio and minimal talking) in the supine position for 4 hours.
13. An intravenous cannula may be inserted for approximately 24 hours for collection of PK samples.
14. Single 12-Lead ECGs will be taken pre-dose (within 30 minutes prior to first dose of study medication) and 1, 2, 4 and 6 hours post-dose.
15. On Day -1 and Day 5, subjects will be fitted with a H12+ Holter recording device. ECGs will be extracted at the following timepoints within a five minute time window: Day -1 of each treatment period: 0.5, prior to planned dosing, 0.5, 1, 2, 3, 4, 6, 12 and 23.5 hours post planned dosing and Day 5 of each treatment period: pre-dose (30 minutes prior to administration of study medication) and 0.5, 1, 2, 3, 4, 6, 12 and 24 hours post-dose. Subjects should be kept in a supine position at least 10 - 15 minutes prior to the collection timepoints. Whenever 12-lead ECGs are obtained at the same nominal time as blood draw or blood pressure/pulse rate measurement, the 12-lead ECG MUST be obtained first.
16. On Day 1 of each treatment period, continuous dual-lead cardiac monitoring (telemetry) will be performed for at least 6 hours pre-dose and continue until at least 24 hours after the last dose of study medication for each treatment period.
17. Serial blood samples (approximately 3 mL) for PK analysis will be collected pre-dose (within 30 minutes prior to administration of study medication) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours post dose of Day 5 of moxifloxacin treatment period (treatment regimen D).
18. Refer to Appendix 9 for procedures to be followed for ophthalmology exam.

Continued

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

4.4.3 Pharmacometrics Review

Pharmacometrics Review

NDA	22291
Submission Date(s)	12/19/2007
PDUFA Due Date	06/19/2008
Brand Name	PROMACTA®
Generic Name	Eltrombopag
Pharmacometrics Reviewer	Yaning Wang, Ph.D.
Pharmacometrics Secondary Reviewer	Jogarao V Gobburu, Ph.D.
Clinical Pharmacology Reviewer	Joseph Grillo, Ph.D.
Clinical Pharmacology Review Team Leader	Young M Choi, Ph.D.
Sponsor	GlaxoSmithKline
Submission Type	Original NDA (NME)
Formulation	Tablet
Proposed indication	Short-term treatment of chronic idiopathic thrombocytopenic purpura
Proposed Dosage and Administration	50 mg QD starting Dose; 75 mg QD after — week if needed

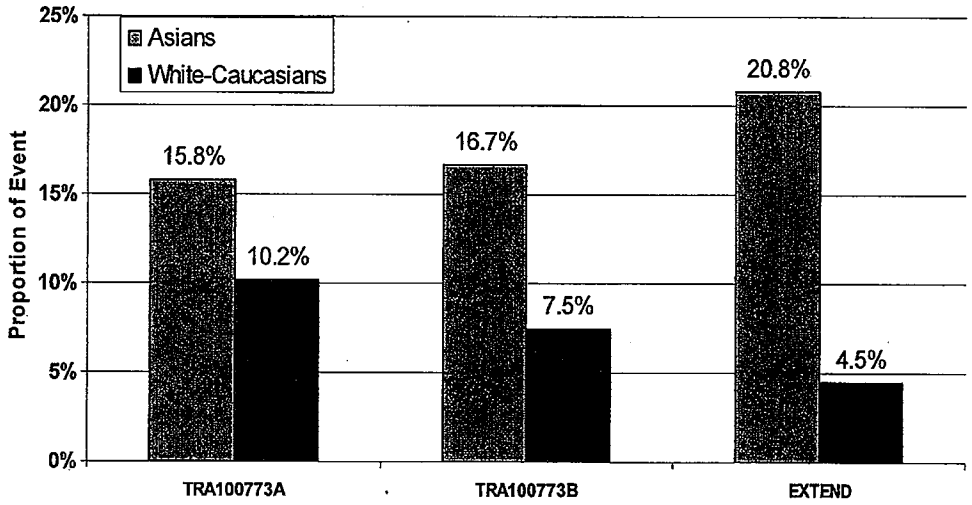
b(4)

4.4.3.1 Executive Summary

In the present submission, the following key question was addressed by the reviewer:

1. **Is it reasonable to reduce the starting dose from 50mg QD to 25 mg QD in East Asian patients?** Yes. Population pharmacokinetic analysis showed that the exposure (area under the concentration curve, AUC) of eltrombopag is 71% higher for Asian patients than that for non-Asian patients (mainly Caucasian patients). This result is consistent with the non-compartment analysis results derived from a pooled analysis across multiple clinical trials. The increased exposure in Asian patients and the higher rate of increased liver laboratory values in Asian patients (**Error! Reference source not found.**) in the long-term studies provide reasonable justification for the reduced starting dose for East Asian patients.

Figure 1. Comparison of Hepatobiliary Laboratory Abnormalities Between Asians and White-Caucasians Across Three Studies



Signatures:

Yaning Wang, Ph.D.

Pharmacometrics Reviewer

Office of Clinical Pharmacology

Joga Gobburu, Ph.D.

Pharmacometrics Director

Office of Clinical Pharmacology

4.4.3.2 Table of Contents

4.4.3.3 List of Tables

4.4.3.4 List of Figures

4.4.3.5 Introduction

Eltrombopag olamine is a thrombopoietin receptor agonist (platelet growth factor) indicated for short-term treatment of chronic idiopathic thrombocytopenic purpura (ITP). ITP is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a low peripheral blood platelet count (<150Gi/L). The clinical hallmark of the disease is an increased, pathological tendency to bleed, spontaneously or after minimal trauma.

The recommended daily dose of eltrombopag is one 50mg tablet given once daily. Dose adjustment to 75mg is allowed ——— days of dosing if platelet counts are <50Gi/L. A reduced dose of 25mg once daily ——— ——— for patients of East Asian ancestry (such as Japanese, Chinese, Taiwanese or Korean ancestry), because higher plasma concentrations of eltrombopag are achieved in this population. b(5)

Eltrombopag is an orally administered drug. The absolute oral bioavailability of eltrombopag in humans has not been established. Absorbed eltrombopag is extensively metabolized, predominately through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. The predominant route of eltrombopag excretion was via feces (59%), and 31% of the dose was found in the urine. Unchanged eltrombopag in feces accounted for approximately 20% of the dose; unchanged eltrombopag was not detectable in urine. The plasma elimination half-life of eltrombopag is approximately 21 to 32 hours.

The efficacy of eltrombopag in the treatment of ITP was mainly supported by two double-blind, randomized, and placebo-controlled trials (TRA100773A and TRA100773B). TRA100773A was a dose-ranging (30mg, 50mg or 75mg) phase II trial that used an adaptive sequential design and TRA100773B was a phase III trial. The starting dose of 50 mg QD in TRA100773B was based on the lowest effective dose in TRA100773A. The primary efficacy endpoint in both trials was the proportion of subjects who responded with a platelet count of ≥50Gi/L after up to 42 days of dosing.

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis was conducted based on five studies to quantify the PK of eltrombopag and explore the relationship between plasma PK and the platelet response.

4.4.3.6 Sponsor's Analysis

4.4.3.7 Objectives

The main objectives of the population PK/PD analyses were to:

- To characterize the PK parameters of eltrombopag following single and repeat oral doses in male and female, Japanese and non-Japanese, healthy and ITP subjects
- To explore the relationship between plasma PK and the platelet response

4.4.3.8 Data

A total of 4093 plasma concentrations from 199 subjects were included in the final dataset. The distribution of the subject population is described in **Error! Reference source not found.**.

Table 1. Summary of subject demographics by Study
(per sponsor report poppk; Table 4-1)

Study	Statistic or category	TRA102860	TRA105580	SB-497115/002	TRA100773A	TRA100773B	All
Total Number		26	30	55	83	5	199
Age (yrs)	Mean (SD)	30.5 (10.4)	25.9 (3.58)	25.2 (5.54)	51.0 (15.7)	57.8 (16.2)	37.6 (16.9)
Weight (kg)	Mean (SD)	72.7 (11.5)	64.5 (7.24)	76.7 (9.57)	75.8 (18.0)	73.1 (27.9)	73.9 (14.7)
Body mass index (kg/m2)	Mean (SD)	25.3 (3.27)	20.8 (1.37)	23.7 (2.49)	27.4 (5.95)	26.5 (7.40)	25.1 (4.96)
Creatinine clearance (mL/min)	Mean (SD)	114 (21.3)	123 (16.1)	113 (16.3)	99.3 (31.0)	85.5 (24.6)	108 (25.8)
Alanine aminotransferase (IU/L)	Mean (SD)	27.0 (10.4)	14.8 (6.23)	20.9 (9.25)	31.8 (27.3)	24.2 (4.15)	25.4 (19.8)
Aspartate aminotransferase (IU/L)	Mean (SD)	22.7 (6.16)	16.3 (3.31)	21.5 (5.16)	28.5 (21.0)	23.8 (4.82)	23.9 (14.7)
Albumin (g/dL)	Mean (SD)	4.37 (0.283)	4.69 (0.240)	5.00 (0.267)	4.19 (0.412)	3.58 (0.753)	4.50 (0.510)
Total bilirubin (mg/dL)	Mean (SD)	0.615 (0.248)	0.930 (0.269)	0.915 (0.471)	0.652 (0.354)	0.728 (0.219)	0.764 (0.369)
Age (yrs)	Mean (SD)	30.5 (10.4)	25.9 (3.58)	25.2 (5.54)	51.0 (15.7)	57.8 (16.2)	37.6 (16.9)
Sex	Female	14	0	0	54	3	71
	Male	12	30	55	29	2	128
Race	Japanese	0	30	0	0	0	30
	Non-Japanese Asian	1	0	0	18	0	19
	Caucasian	17	0	50	55	3	125
	Black	7	0	2	1	2	12
	Others	1	0	3	9	0	13
Immune thrombocytopenia purpura (ITP)	Healthy	26	30	55	0	0	111
	ITP patient	0	0	0	83	5	88
Formulation	Capsule	0	0	55	0	0	55
	Tablet	26	30	0	83	5	144
Total No. of samples		553	1230	1844	404	62	4093

4.4.3.9 Methods

A population pharmacokinetic model was developed utilizing the nonlinear mixed effects program (NONMEM, Version VI level 1.0). A two-compartment open model with first-order absorption and elimination was used as a starting point of the analysis based on a previously available model. Pharmacokinetic parameters were estimated using the first order conditional estimation (FOCE) method with interaction (FOCEI). Other absorption

models were attempted in order to improve the prediction of the peak concentrations: A) a combined first and zero order absorption with lag-time and B) a dual sequential first-order absorption with lag-time.

Effects of the following covariates were investigated in the analysis:

- Age
- Race (Japanese=0, non-Japanese Asian=1, Caucasian=2, Black=3, Others=4)
- Gender (Male=1, Female=0)
- Immune thrombocytopenia purpura (ITP=1, healthy=0)
- Body weight
- Body mass index (BMI)
- Serum creatinine (used to estimate creatinine clearance but not used directly as a covariate)
- Creatinine clearance (CRCL): Calculated based on the Cockcroft-Gault equation3
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Albumin (ALB)
- Total bilirubin (TBIL)
- Concomitant medications (individual and class): The inclusion of an individual concomitant medication required at least a 10% presence or shows potential influence on PK by exploratory techniques as described below. Candidates from the same class may have been pooled if none met the 10% presence inclusion criteria. Concurrent medications of interest included: corticosteroids, vitamin/supplements, statins, gastrointestinal agents (e.g., H2 blockers and proton pump inhibitors), 1A2 inhibitors/inducers, and 2C9 inhibitors/inducers.
- Formulation (Tablet=1, Capsule=0)
- Doses

A full model was first developed based on step-wise forward addition procedure. The full model was reduced to the final model based on a step-wise deletion procedure.

Other details of the method can be found in the sponsor report (\\Cdsesub1\evsprod\NDA022291\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poppk\).

4.4.3.10 Results

- The PK of eltrombopag following oral administration can be described by a 2-compartment model with dual sequential first-order absorption and lag-time (**Error! Reference source not found.**).
- In patients with ITP, plasma eltrombopag AUC(0-τ) was approximately 71% higher in subjects of East Asian ancestry as compared to non-Asian subjects (**Error! Reference source not found.**).

Table 2. Population pharmacokinetic parameters of the final population model

Parameter (Unit)	Final Estimate	%RSE	Lower 95% CI	Upper 95% CI
CL/F Healthy Non-Japanese [L/hr]	0.794	8.26	0.665	0.923
CL/F Healthy Japanese [L/hr]	0.490	12.2	0.373	0.607
CL/F ITP w/o CORT [L/hr]	0.607	7.35	0.520	0.694
CL/F ITP with CORT [L/hr]	0.458	7.55	0.390	0.526
CL/F ~ WT	0.750 Fixed	-	-	-
CL/F~SEX	1.27	6.13	1.12	1.42
Vc/F [L]	11.0	5.42	9.83	12.2
Vc/F ~ WT	0.821	16.6	0.554	1.09
Ka1 [hr-1]	0.272	15.9	0.187	0.357
Ka2 [hr-1]	1.40	8.71	1.16	1.64
MTIME [hr]	1.40	1.44	1.36	1.44
Q/F [L/hr]	0.395	4.20	0.362	0.428
Vp/F [L]	12.1	6.60	10.5	13.7

ALAG [hr]	0.460	0.452	0.456	0.464
F1 ~ FORM	1.21	4.35	1.11	1.31
$\omega^2\eta_{CL}$	0.196	8.67	0.163	0.229
$\omega^2\eta_{Vc}$	0.175	11.4	0.136	0.214
$\omega^2\eta_{Vp}$	0.146	36.2	0.0425	0.249
$\omega^2\eta_{Ka1}$	0.481	83.6	-0.307	0.0796
$\omega^2\eta_{IOV\ Ka1}$	3.64	15.0	2.57	4.71
$\omega^2\eta_{\varepsilon}$	0.0651	11.4	0.0506	0.0796
Corr η_{CL}, η_{Vc}	0.135	12.1	0.103	0.167
$\sigma^2\varepsilon_{prop}$	0.0626	4.97	0.0565	0.0687
$\sigma^2\varepsilon_{add}$	682	12.0	521	843

%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 = lagtime,
CI = confidence interval, $\omega^2\eta$ = variance for eta, random effects between individuals, $\sigma^2\varepsilon$ = variance for epsilon, random effects from residual variability.

Table 3. Summary of Plasma Eltrombopag AUC(0-τ) for Asian and non-Asian Patients with ITP

Population	Eltrombopag Dose (QD)	N	AUC(0-τ) (μg.h/mL)
Non-Asian ITP Patients	50mg	23	77.3 (59.6, 100)
Asian ITP patients	50mg	11	132 (89.9, 194)

Data based on population PK post-hoc estimates and are presented as geometric mean (95% CI)

To explore the relationship between PK and platelet response, the sponsor conducted exploratory graphical PK/PD analysis, which indicated a relationship between eltrombopag exposure and increase in platelet count.

b(4)

4.4.3.11 Reviewer's Comments

- The population pharmacokinetic analyses are acceptable.
- The estimated difference (71%) in plasma eltrombopag AUC(0-τ) between Asian ITP patients and non-asian ITP patients is consistent with the non-compartmental analysis result (80%) based on healthy subjects.

4.4.3.12 Reviewer's Analysis

Question Based Review

1. Is it reasonable to reduce the starting dose from 50mg QD to 25 mg QD in East Asian patients?

Yes. Population pharmacokinetic analysis showed that the exposure (area under the concentration curve, AUC) of eltrombopag is 71% higher for Asian patients than that for non-Asian patients (mainly Caucasian patients). This result is consistent with the non-compartment analysis results derived from a pooled analysis across multiple clinical trials. In addition, the proportion of Asians that met the FDA criteria for assessment of hepatobiliary toxicity for transaminases >3x ULN, bilirubin>1.5x ULN or alkaline phosphatase (AP) >1.5x ULN were 15.8%, 16.7%, and 20.8%, as compared to 10.2%, 7.5%, and 4.5% of White-Caucasian subjects, in TRA100773A, TRA100773B, and EXTEND, respectively (**Error! Reference source not found.**). The increased frequency of hepatobiliary laboratory abnormalities could be related to an increased exposure to eltrombopag in Asians or a higher sensitivity to hepatobiliary toxicity for Asians. The increased exposure in Asian patients and the higher rate of increased liver laboratory values in Asian patients provide reasonable justification for the reduced starting dose for East Asian patients.

Since the clinical pharmacology reviewer believes that the drug exposure measurements from study TRA105580 may not be reliable due to assay problem, the population pharmacokinetic analysis was rerun after data from study TRA105580 were excluded. The parameter estimates from this new analysis are listed in **Error! Reference source not found.** and they are generally consistent with the sponsor's point estimates. The difference (71%) in plasma eltrombopag AUC(0-τ) between Asian ITP patients and non-asian ITP patients is consistent with the sponsor's estimate even though the point estimates for each group are slightly higher (**Error! Reference source not found.**).

Table 4. Population pharmacokinetic parameters of the final population model (excluding study TRA105580)

Parameter (Unit)	Sponsor's Estimate	Reviewer's Estimate
CL/F Healthy Non-Japanese [L/hr]	0.794	0.736
CL/F Healthy Japanese [L/hr]	0.490	-
CL/F ITP w/o CORT [L/hr]	0.607	0.546
CL/F ITP with CORT [L/hr]	0.458	0.41
CL/F ~ WT	0.750 Fixed	0.750 Fixed
CL/F~SEX	1.27	1.27
Vc/F [L]	11.0	9.42
Vc/F ~ WT	0.821	0.804
Ka1 [hr-1]	0.272	0.261
Ka2 [hr-1]	1.40	1.22
MTIME [hr]	1.40	1.40
Q/F [L/hr]	0.395	0.499
Vp/F [L]	12.1	10.1
ALAG [hr]	0.460	0.455
F1 ~ FORM	1.21	1.02
$\omega^2\eta_{CL}$	0.196	0.235
$\omega^2\eta_{Vc}$	0.175	0.230
$\omega^2\eta_{Vp}$	0.146	0.384
$\omega^2\eta_{Ka1}$	0.481	0.08
$\omega^2\eta_{IOV\ Ka1}$	3.64	3.50
$\omega^2\eta_{\varepsilon}$	0.0651	0.0626
Corr η_{CL}, η_{Vc}	0.135	0.175
$\sigma^2\varepsilon_{prop}$	0.0626	0.0717
$\sigma^2\varepsilon_{add}$	682	185

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 = lagtime, CI = confidence interval, $\omega^2\eta$ = variance for eta, random effects between individuals, $\sigma^2\varepsilon$ = variance for epsilon, random effects from residual variability.

Table 5. Summary of Plasma Eltrombopag AUC(0-τ) for Asian and non-Asian Patients with ITP (excluding study TRA105580)

Population	Eltrombopag Dose (QD)	N	AUC(0-τ) (μg.h/mL)
Non-Asian ITP Patients	50mg	23	90 (70, 115)

Asian ITP patients	50mg	11	154 (110, 216)

Data based on population PK post-hoc estimates and are presented as geometric mean (95% CI)

In addition to the higher PK exposure observed in Asians, the proportions of Asians that met the FDA criteria for assessment of hepatobiliary toxicity (transaminases >3x ULN, bilirubin>1.5x ULN or alkaline phosphatase (AP) >1.5x ULN) were also higher than those for White-Caucasian subjects when the patients were taking eltrombopag in three studies (**Error! Reference source not found.**). The increased frequency of hepatobiliary laboratory abnormalities could be related to an increased exposure to eltrombopag in Asians or a higher sensitivity for hepatobiliary toxicity in Asians. A summary of hepatobiliary toxicity data from study TRA100773A indicated that the hepatobiliary toxicity is not dependent on eltrombopag dose/exposure for White-Caucasian subjects (**Error! Reference source not found.**). The numbers of Asian subjects at Placebo, 30 mg and 75 mg are too small to draw a conclusion about the dose-response relationship. The proportion at 50 mg, however, is consistent with the result form study TRA100773B. Even though the higher PK exposure observed in Asians may contribute to the higher proportion of hepatobiliary toxicity, a comparison between 50 mg for Asians and 75 mg for Whites (comparable PK exposure) suggests that Asians may be more sensitive to hepatobiliary toxicity.

Table 6. Proportions of Hepatobiliary Toxicity (FDA Criteria) at Different Doses Stratified by Race

Study	Race	Dose Group, n/N* (%)			
		Placebo	30 mg	50 mg	75 mg
TRA100773A	White	3/25(12%)	3/25(12%)	2/18(11.1%)	1/25(4%)
	Asian	0/2(0%)	0/4(0%)	2/12(16.7%)	1/3(33.3%)
TRA100773B	White	0/26(0%)		4/58(6.9%)	
	Asian	0/8(0%)		2/12(16.7%)	

*n: number of subjects with hepatobiliary toxicity; N: total number of subjects

4.5 Cover sheet and OCPB Filing/Review Form

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-291	Brand Name	Promacta™
OCPB Division (I, II, III)	5	Generic Name	eltrombopag
Medical Division	OND/OODP/DMIHP	Drug Class	Thrombopoietin receptor agonist
OCPB Reviewer	Joseph A. Grillo, Pharm.D.	Indication(s)	The short-term treatment of previously-treated patients with chronic ITP
OCPB Team Leader	Young Moon Choi, Ph.D.	Dosage Form	Tablet
		Dosing Regimen	50 mg qd (25 mg E. Asian)
Date of Submission	12/19/2007	Route of Administration	Oral
Estimated Due Date of OCPB Review	4/21/2008	Sponsor	GSK
PDUFA Due Date	6/19/2008	Priority Classification	Priority Review
Division Due Date	6/5/2008		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5	[redacted]	
I. Clinical Pharmacology				
Mass balance:	X	2	2	
Isozyme characterization:	X	14	14	
Blood/plasma ratio:	X	0		
Plasma protein binding:	X	2	2	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	2	2	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	0		
In-vivo effects of primary drug:	X	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:	X	3	3	
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	

PD:				
Phase 2:	X	3	3	
Phase 3:	X	2	3	
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	2	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X	1	1	
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References	X (79)			
Studies unrelated to indication	X	7	2	
Total Number of Studies		50	45	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	See attached comments to be sent to Sponsor
QBR questions (key issues to be considered)	-Increased exposure in East Asian/Japanese population, hepatic disease, corticosteroid use -Decreased exposure with renal disease -Inhibition of Cyp 2C8 & 2C9 -Substrate of CYP 1A2 & 2C8 -Substrate of UGT1A1 and UGT1A3 -OATP1B1 inhibitor & potential statin interaction -Weak PXR activator -Antacid/Ca2+ effects on BA	
Other comments or information not included above		
Primary reviewer Signature and Date	/s/ Joseph A. Grillo, Pharm.D.	
Secondary reviewer Signature and Date	/s/ Young Moon Choi, Ph.D.	

Attachment: NDA 22-291 Filing Questions

Joseph A. Grillo, Pharm.D., Clinical Pharmacology Reviewer
Young Moon Choi, Ph.D., Team Leader

STUDY	Question/Comment to Sponsor
We note that most of your non clinical PK studies relating to protein binding, metabolism and the evaluation hepatic microsomes and transporters fail to provide information regarding the validation of the assay methods utilized. Please provide detailed information regarding your validation of the assay used in these studies or provide justification why assay validation was not necessary.	
We note that your PK studies relating to the evaluation hepatic microsomes and transporters provide inhibition data in terms of IC50 rather than Ki. Please provide inhibition data in terms of Ki rather than IC50 wherever possible.	
The Validation of a Method for the Determination of SB-497115 in Human Plasma (range 10 - 10000 ng/mL) using LC-MS/MS [JBA/SB-497115/02]	• Please provide information regarding your assessment of Freeze/thaw samples or provide justification why this parameter was not evaluated as part of your assay validation.
An In Vitro Evaluation of the Glucuronidation of SB-497115 by Heterologously Expressed UGT's (uridine diphosphoglucuronyltranferases) [CD2007/00777/00]	• It appears assay CD2004/00830/00 was developed for use in rabbits. Please provide information regarding cross validation to human samples or provide justification why assay validation was not necessary.
A preliminary In vitro investigation of the metabolism of [14C]SB-497115 in the rat, dog, cynomolgus monkey and man [SB-497115/RSD-101TJJ/1]	• Please provide raw and summary data for the radio-HPLC and LC/MS analyses for Human #2, #3, #4
An In Vitro Investigation of the Hepatic Metabolism of an Alternate Labelled [14C]SB-49115 in the Mouse, Rat, Female Rabbit, Dog, Cynomolgus Monkey and Human [CD2006/00906/00]	• Please provide structural information for Metabolites of [14C] SB-497115 in Human #1 • Please provide origin and demographics, if available, for all human subject hepatocytes used in the study. • Please provide Radio-HPLC chromatogram for human #2
A Preliminary Screen of the In Vitro Inhibitory Potential of SB-497115 on Human Cytochrome P450 Enzymes [SB-497115/RSD-101TKH/1]	• Please provide a measure of variability for estimates used in tables
An In Vitro Evaluation of the Inhibitory Potential of SB-497115 on Human Cytochrome P450 Enzymes [CD2003/00990/00]	• Please provide a measure of variability for estimates used in tables
In Vitro Investigation of Human and Rat PXR Activation by SB-497115-GR [CD2003/00721/00]	• Please provide a reference to justify the "rough guidelines" used to interpret PAX inhibition
In Vitro Investigation of Transport via Human P-glycoprotein and the Passive Membrane Permeability of [14C]SB-497115 in MDCKII-MDR1 Cells [CD2003/01046/00]	• Please provide a reference to justify the use of amprenavir as a positive control and justify why only a single concentration SB-497115 was evaluated.
In Vitro Investigation of the Potential of SB-497 1 15-GR to Inhibit P-glycoprotein Mediated Transport in MDCKII Cells Heterologously Expressing Human P-glycoprotein [CD2003/00637/00]	• This Pdf document is not rendered properly. For example you can not cut & paste from it. Please revise

STUDY	Question/Comment to Sponsor
Preliminary investigation of the protein binding of SB-497115 to rat, dog, monkey and human plasma proteins by equilibrium dialysis and also to determine the blood to plasma ratio of SB-497115 in each species [SB-497115/RSD-101TJK/1]	• Please provide demographics for pooled human subjects if available
Assessment of SB-497115 Protein Binding in Male Mouse, Rat, Dog, Human and Female Rabbit Plasma by Equilibrium Dialysis In Vitro [CD2004/01516/00]	• Please provide the source of human plasma
A single-blind, randomized (with respect to placebo), placebo controlled, parallel group, dose rising study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and repeat oral doses of SB-497115-GR, a thrombopoietin receptor agonist, in healthy adult subjects [SB-497115/002]	• Links within report are not always correct (e.g. p63 to 13.14). Please revise
An Open-label Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Rosuvastatin when Co-administered with Eltrombopag (SB-497115-GR) in Healthy Adult Subjects [TRA105120]	• Please provide summary and raw data for group "B" (Eltrombopag alone).
An Open-,Label, Non-Randomized Pharmacokinetic and Safety Study of a Single Oral Dose of 50 mg Eltrombopag in ,Healthy Subjects and in Subjects with Mild, Moderate or Severe Renal Impairment [TRA104412]	• Please provide synopsis, amendments, consent form, sample CRF, signatures etc. that are associated with this study in a manner consistent with the other submitted studies • Please provide summary and raw data for free/bound drug. We note your comment that you believe it to be unreliable • Please provide demographic information (including race) by subject in addition to the summary provided in your submission. • Please provide individual laboratory data by subject in your report
An Open-Label, Non-Randomized Pharmacokinetic and Safety Study of a Single Oral Dose of 50 mg Eltrombopag in Healthy Subjects and in Volunteers with Mild, Moderate or Severe Hepatic Impairment [TRA103452]	• Please provide synopsis, amendments, consent form, sample CRF, signatures etc. that are associated with this study in a manner consistent with the other submitted studies.
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 [TRA100773A]	
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 [TRA100773B]	
Population Pharmacokinetic and Pharmacodynamic Analysis of Eltrombopag in Healthy Subjects and Subjects with Chronic Idiopathic Thrombocytopenic Purpura [RA018135]	

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