

Population Demographics

The population demographics from this study are listed in Table 13 & 14 below

Table 13: Population Demographics

Demographic Characteristic	Treatment Group				Total N=117
	PBO N=29	30mg N=30	50mg N=30	75mg N=28	
Age, yrs Median	42	51	45	54.5	50.0
Min - Max	18 - 85	23 - 79	23 - 81	18 - 85	18 - 85
Sex, n (%)					
Female	16 (55)	16 (53)	21 (70)	20 (71)	73 (62)
Male	13 (45)	14 (47)	9 (30)	8 (29)	44 (38)
Race, n (%)					
African American/African	1 (3)	1 (3)	0	0	2 (2)
Asian - East Asian	2 (7)	1 (3)	8 (27)	2 (7)	13 (11)
Asian - South-East Asian	0	3 (10)	4 (13)	1 (4)	8 (7)
White - Arabic/North African	5 (17)	1 (3)	3 (10)	5 (18)	14 (12)
White - White/ Caucasian/European	20 (69)	24 (80)	15 (50)	20 (71)	79 (68)
Other/Mixed	1 (3)	0	0	0	1 (<1)
Ethnicity, n (%)					
Hispanic or Latino	0	0	2 (7)	2 (7)	4 (3)
Not Hispanic or Latino	29 (100)	30 (100)	28 (93)	26 (93)	113 (97)

Table 14: Current Medical Conditions Reported in 10% or more of Subjects

Preferred Term	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
Any condition	18 (62)	20 (67)	19 (63)	20 (71)
Hypertension	8 (28)	8 (27)	2 (7)	6 (21)
Hypercholesterolemia	4 (14)	2 (7)	1 (3)	5 (18)
Blood and lymphatic system disorders	3 (10)	6 (20)	3 (10)	3 (11)
Diabetes mellitus	2 (7)	2 (7)	0	3 (11)
Musculoskeletal and connective tissue disorders	0	2 (7)	0	3 (11)
Fatigue	0	1 (3)	0	3 (11)
Back pain	2 (7)	0	0	3 (11)
Osteoporosis	3 (10)	0	1 (3)	2 (7)
Gastrointestinal disorders	0	3 (10)	0	2 (7)
Hypothyroidism	3 (10)	2 (7)	0	2 (7)
Cardiac disorders	1 (3)	6 (20)	3 (10)	1 (4)
Headache	4 (14)	1 (3)	0	1 (4)
Gastro-esophageal reflux disease	3 (10)	0	1 (3)	0
Nausea	3 (10)	0	0	0

Results-Efficacy analysis:

Analysis of the primary endpoint using the primary dataset demonstrated that eltrombopag increased platelet counts in a dose dependent manner after up to 6 weeks of dosing (Table 15). Both the eltrombopag 50 and 75mg treatment groups achieved a statistical significant treatment effect compared to placebo ($p < 0.001$), and the odds of responding were significantly greater for each of the eltrombopag treatment groups compared to the PBO treatment group.

Table 15: Responders (Efficacy Population)

Responders at the Day 43 Visit (Efficacy Population)	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
N	27	29	27	26
Responders, n (%)	3 (11.1)	8 (27.6)	19 (70.4)	21 (80.8)

Odds ratio (Active relative to PBO)	NA	3.09	21.96	38.82
95% CI	NA	(0.69,13.75)	(4.72,102.23)	(7.62,197.73)
p-value (one-sided)	NA	0.070	<0.001	<0.001

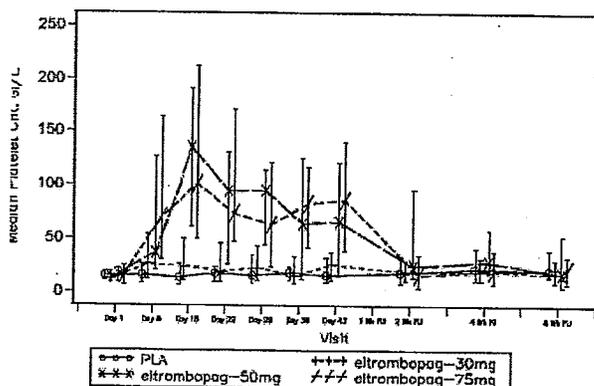
Results-PK analysis:

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

Results- Pharmacodynamic Analysis:

Baseline median platelet counts were similar across all four treatment groups and a dose dependent increase in the median platelet count was observed in the eltrombopag-treated subjects at each visit, suggesting a dose dependent increase in responders (Figure 2). Median platelet counts in the eltrombopag 50mg and 75mg treatment groups show an elevation of platelet counts as early as Day 8 and continue to rise to Day 15. A slight decrease in the median platelet count was observed after Day 15 in the eltrombopag 50mg and 75mg treatment groups. This decrease may be explained by the number of subjects withdrawn after Day 15 from the 50mg and 75mg treatment groups due to a platelet response >200Gi/L. Within two weeks following discontinuation of study medication, median platelet values returned to baseline levels.

Figure 2: Median Platelet Counts with 25th and 75th percentiles



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Reviewer Comment: While a trend toward a dose dependent increase was demonstrated the magnitude of the change was not proportional to the magnitude of the change in dose. It is also important to note the significant variability in these results.

The mean change in platelet count from baseline using the primary dataset was analyzed with an ANCOVA model, including actual baseline platelet count, ITP medication use at randomization, and splenectomy status as covariates (Table 15)

Table 16: Analysis of Change in Platelet Counts (Gi/L) From Baseline to the Day 43 Visit (Efficacy Population)

	Treatment Group			
	PBO N=27	30mgN=29	50mgN=27	75mgN=26
Baseline Mean (SD)	15.1 (7.00)	14.5 (6.26)	16.7 (8.63)	15.2 (9.79)
Day 43 Visit Mean (SD)	35.7 (78.12)	67.8 (99.64)	241.3 (296.32)	205.1 (163.55)
Change from Baseline Mean (SD)	20.6 (79.76)	53.3 (100.54)	224.5 (292.62)	189.9 (162.85)
Model-adjusted Change from Baseline Mean (SE)	27.3 (36.22)	57.9 (34.23)	224.9 (35.07)	192.8 (35.88)
Mean Difference from PBO Treatment		30.5	197.6	165.5
95% CI		(-65.36,126.39)	(98.90,296.26)	(66.02,264.91)

p-value		0.529	<0.001	0.001
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Reviewer Comment: Again, while a trend toward a dose dependent increase was demonstrated the magnitude of the change was not proportional to the magnitude of the change in dose. It is also important to note the significant variability in these results.

A trend toward a dose dependent increase in the number and percentage of subjects in each treatment group who achieved a platelet count >200Gi/L was observed in responders (Table 17).

Table 17: Subjects with Platelet Counts >200Gi/L at the Day 43 Visit (Efficacy Population)

Day 43 Visit	Treatment Group			
	PBO N=27	30mg N=29	50mg N=27	75mg N=26
Platelets >200Gi/L n	27	29	27	26
Responders, n (%)	1 (3.7)	4 (13.8)	10 (37.0)	13 (50.0)
Platelets >400Gi/L n	27	29	27	26
Responders, n (%)	1 (3.7)	1 (3.4)	6 (22.2)	4 (15.4)

Analysis of serum TPO levels showed that all four treatment groups had similar median serum levels at baseline, although a wide range of values was obtained for each treatment group, especially the PBO and 30mg treatment groups. At the Day 43 Visit there was a small decrease in median serum TPO levels for the 30 mg, 50 mg and 75 mg treatment groups; values returned to approximately baseline levels at the Day 85 Visit. Median serum TPO levels for the PBO treatment group remained level during the study.

Results of platelet aggregation measurements were summarized. In 10 subjects (30 mg:2 subjects; 50 mg: 5 subjects; 75 mg: 3 subjects) a change of platelet aggregation from abnormal to normal during the on-therapy period was observed, and in 9 out of those 10 subjects, a return from normal to abnormal aggregation after cessation of eltrombopag. No subject developed abnormal platelet aggregation while on-therapy. Although the results of platelet activation measurements were summarized, only 3 subjects had results from platelet activation assays; therefore, no trends or correlation with treatments could be discerned.

A decreased incidence of on-therapy bleeding (assessed via the World Health Organization [WHO] Bleeding Scale) relative to baseline at day 43 and to a lesser extent at day 57 was observed in subjects who received eltrombopag 30 mg, 50 mg and 75 mg.

Reviewer Comment: It is important to note that 1) these data are variable and 2) bleeding in the placebo group also declined at from baseline and should be considered when evaluating the change in bleeding associated with eltrombopag.

Results-Safety:

Overall, 63% of subjects reported at least one AE during the course of the study. During the treatment phase of the study, 53% of subjects reported at least one AE. Occurrences of AEs and related AEs by subject were similar across each of the treatment groups during the entire study (Table 18). No dose-dependent pattern of AEs or AE intensity was observed. Headache was the most commonly reported AE in all treatment groups. Fatigue and arthralgia were reported more frequently in the PBO group. Epistaxis was more frequently reported in the 30mg group, although the proportion of subjects with this AE was relatively low. Increased AST was reported in one subject in the 30mg treatment group and 2 subjects in the 75mg treatment group. On-therapy bleeding AEs were more frequent in the PBO and 30mg treatment groups (4 AEs and 6 AEs, respectively) compared to the 50 mg and 75 mg treatment groups (2 AEs and 1 AE, respectively).

Table 18: On-therapy Adverse Events Reported by 5% or More of Subjects in Any Treatment Group (Safety Population)

Incidence of AEs by Subject	Treatment Group, n (%)			
	PBO N=29	30mg N=30	50mg N=30	75mg N=28
Any AE	17 (59)	14 (47)	14 (47)	17 (61)
Headache	6 (21)	4 (13)	3 (10)	6 (21)

Fatigue	5 (17)	0	1 (3)	2 (7)
Constipation	2 (7)	1 (3)	0	2 (7)
Rash	1 (3)	1 (3)	0	2 (7)
AST increased	0	1 (3)	0	2 (7)
Anemia	2 (7)	1 (3)	1 (3)	1 (4)
Edema peripheral	2 (7)	0	1 (3)	1 (4)
Diarrhea	2 (7)	0	0	1 (4)
Dysgeusia	2 (7)	0	0	1 (4)
Epistaxis	0	4 (13)	0	0
Pain in extremity	1 (3)	2 (7)	0	0
Arthralgia	3 (10)	1 (3)	0	0
Abdominal distension	2 (7)	1 (3)	0	0
Hemorrhoids	2 (7)	0	0	0

The majority of subjects had AEs with a maximum CTCAE toxicity grade of Grade 1 or Grade 2. Overall 11% of subjects reported at least one SAE during the course of the entire study. SAEs occurred in 3% of subjects during the treatment course and 8% of subjects reported SAEs during the post-therapy follow up period. A total of seven on-therapy SAEs were reported during the on-therapy phase of the study in a total of four subjects, who were in the PBO and 50mg treatment groups. a total of 9 SAEs were reported in 7 subjects across the four treatment groups more than 24h after the last dose. A total of nine AEs were reported as leading to the withdrawal of six subjects from study medication. No AEs leading to withdrawal were reported in the 30mg treatment group. All but one of the AEs leading to withdrawal were considered by the investigator to be related to study medication.

There was one fatal SAE of cardiopulmonary failure reported in the study (Subject 144). Cardiopulmonary failure was considered to be not related to study medication. However, the subject experienced other SAEs including embolism, renal insufficiency, hepatitis, and pulmonary embolism, which were considered by the investigator as related to study medication.

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

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

There were 49 subjects (42%) in the study who had ocular assessments, out of the 117 subjects in the safety population (Category A, Figure 9). In these 49 assessed subjects, there were 14 reports of cataracts. Twenty subjects had a pre-therapy baseline ocular assessment. In these subjects, no new cataracts were reported during the study. In addition, no progression occurred during the study in the 3 subjects reported to have pre-existing cataracts.

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

Conclusions (sponsor):

- All current treatment options for patients with chronic ITP focus on the platelet destruction aspect of the disease, rather than on impaired platelet production. As a thrombopoietic agent, eltrombopag represents a novel, oral treatment option by stimulating platelet production.
- TRA100773A was a large randomized placebo-controlled study in subjects with chronic ITP. All eltrombopag treatment groups showed a similar safety profile compared to the placebo treatment group. All three eltrombopag treatment groups had a higher percentage of responders compared to placebo-treated subjects. The differences in the eltrombopag 50mg and 75mg treatment groups were statistically significant compared to placebo. These results demonstrate the efficacy and safety of eltrombopag in the relapsed or refractory setting of ITP, where there is an important unmet medical need.

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

4.3.3 Study SB-497115/001 Phase 1 Healthy PK/Dose escalation

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

Title: A single blind, randomized, placebo-controlled, parallel group, pharmacokinetics and pharmacodynamics of SB-497115-GR, a thrombopoietin agonist, when administered as an oral capsule at doses of 3 mg, 15 mg, 45 mg, 100 mg and 150 mg to healthy adult male and female subjects

Study period: 28 Oct 2002 - 10 Mar 2003

Objectives:

Primary

- To assess the safety and tolerability of single oral doses of SB-497115-GR in healthy male and female adult subjects.

Secondary

- To assess the pharmacokinetics of SB-497115-GR following administration of single oral doses of SB-497115-GR in healthy adult male and female subjects.
- To assess the pharmacodynamic effect of SB-497115-GR following administration of single oral doses of SB-497115-GR in healthy adult male and female subjects.

Methodology:

This was a single blind, single oral dose, dose-rising, placebo-controlled, randomized (with respect to placebo) study in healthy adult male and female subjects. Up to 6 subjects received a single dose of SB-497115-GR and up to 2 subjects received a single dose of placebo for each dose group studied. The decision to proceed to a higher dose of SB-497115-GR was made based on safety and tolerability observed at the lower dose, as well as drug exposure data (pharmacokinetics) through 72 hours post dose at the lower dose and platelet count data (pharmacodynamics) through Day 15. No subject received the next higher dose of SB-497115-GR until the preceding lower dose had been administered safely to at least 3 subjects. Dose escalation was limited due to higher than expected PK levels; the doses of SB-497115-GR administered were 3 mg, 6 mg, and 9 mg.

The planned and actual dosing regimens studied are displayed in Table 19

Table 19: Planned and Actual Dosing Regimens Studied

Planned		Actual	
P	Placebo	P	Placebo
A	3 mg	A	3 mg
B	15 mg	F	6 mg
C	45 mg	G	9 mg
D	100 mg		
E	150 mg		

Reviewer Comment: Dose escalation was curtailed due to higher than expected PK levels. As permitted by the protocol, dose escalation after Regimen A was modified to 6 mg (Regimen F) and 9 mg (Regimen G). Allometric scaling of SB-497115-GR systemic clearance (Cl) and volume of distribution (Vd) in animals was used to predict Cl and Vd in humans and quantify the expected dose concentration relationship. The predicted human clearance is 154 mL/min.

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

SB-497115-GR drug product was provided as _____ granules containing either 660 mg of SB-497115-GR per gram of granules (Formulation code AA, substance batch F033082 (Dartford), batch number U02107), 160 mg of SB-497115-GR per gram (Formulation code AB, substance batch F033082 (Dartford), batch number U02106), or 26 mg of SB-497115-GR per gram of granules (Formulation code AC, substance batch F033082 (Dartford) batch number U02105), equivalent to 517.4 mg per gram, 125.4 mg per gram or 20.4 mg per gram, of the free acid, respectively. The granules were packaged in an appropriate container closure system. As required, an appropriate amount of granules was filled into _____ gelatin capsules _____ by pharmacists at the clinical site prior to administration to patients. A matched placebo formulation was also provided (Formulation code YD, batch number U02104). The filled capsules will be stable for up to 6 days when stored under a controlled room temperature of 20-25 °C (68-77 °F) in _____ bottles.

b(4)

Subjects took a single oral dose of SB-497115-GR. Study medication was administered with 240 mL tepid water. Subjects fasted from all food and drink at least 4 hrs prior to any laboratory safety evaluations or 8 hrs prior to the beginning of pharmacokinetic sampling (Day 1). Water was permitted until 1 hour prior to study drug administration. No concomitant medications were permitted during the study. By exception, paracetamol at doses of ≤ 2 g/day was permitted up until 24 hrs prior to pharmacokinetic blood draws.

Reviewer Comment: Allowing paracetamol (APAP) may be significant given both APAP and eltrombopag undergo glutathione conjugation.

Criteria for evaluation:

- Sample size: Convenience sample. No formal sample size calculation made. For each dose level, a minimum of 4 subjects and a maximum of 8 subjects were enrolled. A sufficient number of subjects were to have been enrolled such that up to 40 subjects completed the study. Subjects were allocated to study treatment X or P, in a 3:1 ratio, where X represented an active dose of SB-497115-GR and P represented placebo,
- Pharmacokinetics: The focus of the statistical analysis was to characterize the preliminary pharmacokinetics of SB-497115-GR. The pharmacokinetics of SB-497115 were assessed by determining AUC(0- ∞), AUC(0-t), C_{max}, t_{max} and t_{1/2} following single oral dose administration of three capsules that consisted of SB-497115-GR (3, 6, or 9 mg).
 - Blood samples (approximately 2.7 mL) for SB-497115 pharmacokinetic analysis were collected over a 72 hr period at the following times: prior to dose administration of medication (predose) and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hr following SB-497115-GR administration on Day 1 (post-dose). The precise timing may vary, but no more than 16 samples per subject were to be obtained. Blood samples were collected into heparinized 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 20: Assay validation information

Eltrombopag is extracted from 500 μ L human plasma by protein precipitation using _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	10.0ng/mL
Validated Range	10.0 to 2500ng/mL
Within-run Precision (%CV)	$\leq 6.5\%$
Between-run Precision (%CV)	$\leq 2.2\%$
Accuracy (%Bias)	-0.3% \leq bias \leq 9.9%

b(4)

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

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 3.1 [WinNonlin, 2003]. Calculations were based on actual collection times recorded during the study. The maximum observed plasma concentration (C_{max}) was obtained directly from the SB-497115 concentration-time data, as was the time to C_{max} (t_{max}). 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-∞)). Areas under the concentration-time curve 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 C(t) divided by the elimination rate constant, where C(t) was the last observed concentration. The terminal elimination rate constant (λ_z) was derived from the log-linear disposition phase of the concentration-time curve using least-squares regression analysis. The elimination half-life (t_{1/2}) was calculated as ln 2/λ_z.
 - An assessment of dose proportionality was added, and made on AUC(0-∞), AUC(0-t), and C_{max} using the power model. Each parameter and the factor dose was loge-transformed prior to analysis. An estimate of slope (with corresponding 95% confidence interval [CI]) was provided as a measure of potential dose proportionality (slope of approximately 1 implies dose proportionality).
 - Following loge-transformation, AUC(0-∞), AUC(0-t), and C_{max} were separately analyzed by analysis of variance (ANOVA) with a term for regimen. Model based pooled between subject coefficients of variation (CVB%) were calculated for AUC(0-∞), AUC(0-t), and C_{max}.
 - Pharmacodynamics: The primary focus of the statistical analysis was to compare platelet counts between each active dose of SB-497115-GR relative to placebo.
 - Blood samples (approximately 2 mL) for platelet count and peripheral blood smear were obtained at screening, predose, Day 1, and Days 3, 5, 8, 10, 12, 14, 16, 18 and at follow-up (approximately Day 28). Blood samples (approximately 12 mL) were obtained predose on Day 1, and on Days 8, 12, 16 and at follow-up for platelet aggregation, TPO and P-selectin levels, reticulated platelet count, activation markers (PAC-1, P-selectin, and Annexin V binding). Additionally, the activation markers may be obtained at 2 hrs (or at approximately C_{max}) and 24 hrs post-dose.
 - TPO and P-selectin values were to have been determined by ELISA assays. Platelet activation was evaluated by flow cytometry for PAC-1, P-selectin and Annexin V binding. Reticulated platelet count was determined by flow cytometry using thiazole orange staining.

Platelet count, peripheral blood smear, neutrophil count, and platelet aggregation were determined. Platelet aggregation was determined from whole blood using thrombin receptor activation peptide (TRAP) as the agonist. Samples were assayed using the currently approved analytical methodology.
- Reviewer Comment: Insufficient information was provided by the sponsor to assess whether these methods were adequately validated.*
- Maximum post-dose platelet count data were analyzed by (ANCOVA), fitting a term for regimen. Baseline data was included in the analysis as a covariate. Point

estimates and 95% confidence intervals were constructed for the comparisons of interest (ie., Active – Placebo) for each dose of SB-497115. Within-subject and between-subject variability estimates were estimated for the platelet count data using a separate repeated measures model including terms for group, day and day*group.

Reviewer Comment: Rather than fitting the protocol defined mixed effects model, a decision was made by the sponsor to focus on maximum platelet count data, adjusting for baseline. Maximum post-dose platelet count data were analyzed by analysis of covariance (ANCOVA), fitting a term for regimen. Baseline data was included in the analysis as a covariate. This approach provides little insight into the dose response relationship. The sponsor does not provide a rationale for this change but it is irrelevant given the change in PD ultimately reported at these doses.

- **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 24 male subjects were enrolled in the study, all of which completed the study in accordance with the study protocol. All subjects were included in the evaluation of safety. All 18 subjects who received active drug were included in the analyses of pharmacokinetic parameters.

Population Demographics:

The population demographics from this study are listed in Table 21 below

Table 21: Population Demographics

Group	Parameter	Age (years)	Height (cm)	Weight (kg)
All Subjects n = 24	Mean	32	179	80.7
	SD	5.9	7	11.1
	Range	22-42	160-193	54.0-101.3
100% Male; 96% White, 4% "Oriental"				

Results-PK analysis:

Selected plasma PK parameters are listed in Table 22 below. Mean and median plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figures 3 and 4.

Table 22: Selected PK parameters

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

Figure 3: Mean plasma SB-497115 concentration

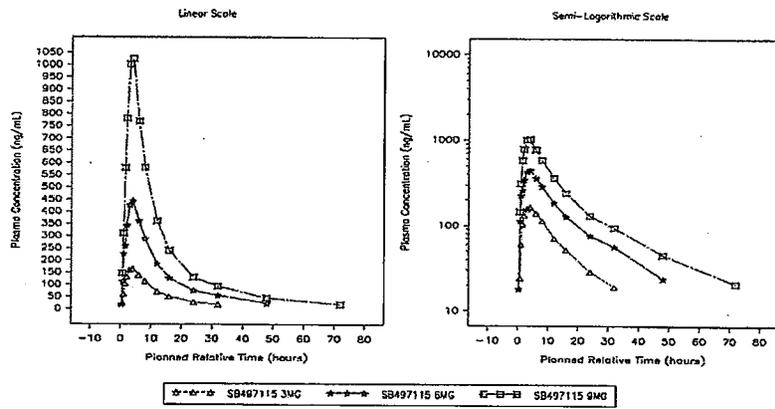
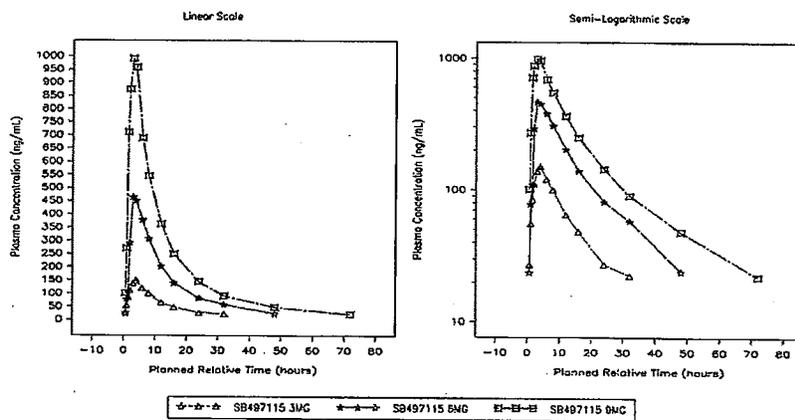


Figure 4: Median plasma SB-497115 concentration



Reviewer Comment:

- Two subjects (#12 & #13) received paracetamol (APAP) prior to or during the PK collection. Subject 12 received 1 g APAP on 1/22/03 @ 21:05 and was dosed 1/22/03 @ 08:45 (~ 12 hrs post dose). Subject 13 received 1 g APAP on 2/12/03 @ 17:27 and was dosed 2/12/03 @ 09:04 (~ 8 hrs post dose).
- The 6 mg cohort had the highest variability with regard to AUC which was not apparent based on the sponsor's reporting of mean (max, min) only. Upon close inspection Subject 13 had the highest and Subject 12 the third highest AUC values. The former playing a significant role in the observed variability. Further, subjects 12 & 13 had the highest $t_{1/2}$ in their cohort. The effect of APAP can not be ruled out given the temporal relationship, the higher variability in this cohort driven (in a large part, by these subjects) and the fact that both APAP and eltrombopag undergo phase 1 metabolism via CYP1A2 and phase 2 metabolism via glutathione conjugation.
- The variability with regard to $t_{1/2}$ was not apparent based on the Sponsor's reporting of median (max, min) only. It is not clear why this information was reported this way.

b(5)

Estimates of between-subject coefficients of variation for AUC(0-∞), AUC(0-t), and Cmax in SB-497115 are provided in Table 23

Table 23: Estimates of Between-Subject Coefficients of Variation Across Cohorts

Parameter	CVB(%)
AUC (0-∞) (ng.h/mL)	35.33
AUC(0-t) (ng.h/mL)	35.95
Cmax (ng/mL)	26.99

Plasma SB-497115 AUC and Cmax increased in a greater than dose proportional manner (See Table 24 and Figure 5)

Table 24: Summary of SB-497115 Dose Proportionality Assessment

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

Results- Pharmacodynamic Analysis:

Point estimates and 95% CIs for the comparison of the maximum platelet count are presented in Table 25. Active-Placebo Estimate was adjusted for baseline

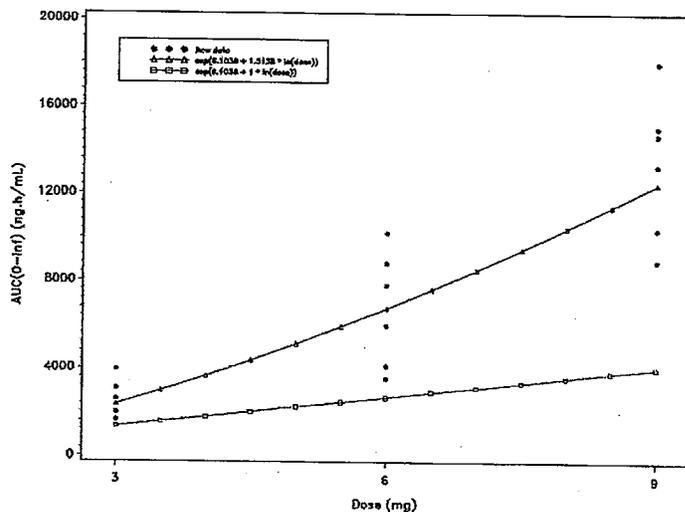
Table 25: Point Estimate and 95% CIs for Maximum Platelet Count

Parameter	Comparison	Estimate (Active-Placebo)	95% C.I.
Maximum Platelet Count (x10e9/L)	A-P	-17.26	(-44.38, 9.86)
	F-P	-17.09	(-43.74, 9.56)
	G-P	-26.31	(-53.22, 0.61)

P=Placebo; A= 3.0 mg; F= 6.0 mg; G= 9.0 mg

Reviewer Comment: While samples were collected for analysis of platelet aggregation, TPO and P-selectin levels, reticulated platelet count, and activation markers (PAC-1, P-selectin, and Annexin V binding), only platelet count was fully analyzed. The sponsor reports platelet aggregation and platelet activation markers were assayed, but were not remarkable and that TPO and P-selectin levels were not assayed due to non-availability of assay kits.

Figure 5: Prediction Plot for AUC(0-∞)



Results-Safety:

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Eighteen subjects received a single oral dose of SB-497115; 6 subjects received 3 mg (Regimen A), 6 subjects received 6 mg (Regimen F), and 6 subjects received 9 mg (Regimen G). A total of 39 adverse events were reported by subjects receiving SB-497115; 16 AEs were reported by subjects receiving placebo. The most common AEs were ecchymosis, 9/18 active subjects, 4/6 placebo subjects) and headache (7/18 active subjects, 4/6 placebo subjects). The number of AEs, as well as the number of subjects reporting AEs, appears to decrease with increasing dose of SB-497115. All AEs were mild with the exception of moderate headache and moderate dyspepsia each reported by 1 subject in the SB-497115 3 mg group, and moderate dizziness reported by 1 subject in the placebo group. There were no deaths, serious adverse events, or adverse events that led to discontinuation from the study and all AEs resolved by the end of the study. The specific adverse events are listed in Table 26 below:

Table 26: Post Dose Adverse Effects:

Adverse Event	SB-497115	SB-497115	SB-497115	Placebo
	3 mg	6 mg	9 mg	
Ecchymosis	4	3	2	4
Headache	3	2	2	4
Upper resp tract infection	1	1	1	1
Dizziness	1	0	0	2
Pharyngitis	2	1	0	0
Pruritus	1	0	1	1
Injury	1	1	0	0
Pain	1	0	0	1
Rhinitis	1	1	0	0
Abdominal pain	1	0	0	0
Asthenia	0	0	0	1
Bullus eruption	0	0	0	1
Chest pain	0	0	1	0
Diarrhea	0	0	0	1
Dyspepsia	1	0	0	0
Flushing	1	0	0	0
Hematoma	1	0	0	0
Injection site reaction	1	0	0	0
Insomnia	0	0	1	0
Nausea	1	0	0	0
Toothache	0	1	0	0
Total # of AEs	21	10	8	16
# of Subjects Exposed	6	6	6	6
# of Subjects with AE	6	5	2	6

Clinical laboratory values that were of potential clinical concern were all elevated glucose levels and are presented in Table 27

Table 27: Laboratory values of potential clinical concern

Subject	Treatment	Parameter	Reference Range	Time of Change	Value of Potential Concern
011	SB-497115 6 mg	Glucose	3.9-6.4 mmol/L	Final	8.3
017	SB-497115, 9 mg	Glucose	3.9-6.4 mmol/L	Day 1:24:0 h	7.0
019	Placebo	Glucose	3.9-6.4 mmol/L	Day 8:0:0 h	8.9
021	SB-497115, 9 mg	Glucose	3.9-6.4 mmol/L	Day1:24:0 h	9.2

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):

- SB-497115 was well tolerated following single oral administration of 3 mg, 6 mg, or 9 mg to healthy adult men.
- Following administration of single oral doses of 3, 6, and 9 mg of SB-497115-GR as granules in a capsule, median t_{max} was observed between 3 to 3.5 hours across the doses and median half-life was 14.1 to 15.9 hours across the doses.
- Following administration of single oral doses of SB-497115-GR as granules in a capsule, plasma SB-497115 exposure increased more than proportionally with dose over the range of 3 mg to 9 mg; the slope (95% CI) estimate was 1.59 (1.21, 1.97) for AUC(0-t), 1.51 (1.14, 1.88) for AUC(0- ∞), and 1.68 (1.39, 1.97) for C_{max} .
- Following single oral administration of 3, 6, and 9 mg SB-497115-GR, platelet count was not increased.

4.3.4 Study TRA104603 Phase 1 Healthy Japanese (Japan) Single Dose PK/Dose escalation

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

Title: Phase 1 study of SB-497115-GR -Single oral dose study in healthy Japanese male subjects

Study period: 21-Jun-2005 - 09-Mar-2006

Objectives:

Primary

- To investigate the safety and tolerability of SB-497115-GR following single oral doses in healthy Japanese adult male subjects.
- To investigate the pharmacokinetics of SB-497115-GR following single oral doses in healthy Japanese adult male subjects.

Secondary

- To investigate the pharmacodynamics of SB-497115-GR following single oral doses in healthy Japanese adult male subjects.

Methodology:

This was a single-center, placebo-controlled, double-blind, randomized, dose-escalation, 4-period crossover, single oral dose study in 16 healthy Japanese adult males. After screening, 16 eligible subjects were randomized to one of the four treatment sequences and received placebo and three of the four SB-497115-GR doses in four dosing periods. Each treatment was separated by 12 days. Investigational products were administered as single oral doses with 150 mL of water after fasting according to the treatment sequences given in Table 28.

Subjects were confined to the unit for 4 nights and 5 days during each dosing period. The use of any medication other than the investigational product was prohibited from 14 days before the first dose of the investigational product until the completion of post-study screen (follow-up examination) unless the investigator/subinvestigator allowed the use of other medications.

Table 28: Study Design

Group	Period 1	Period 2	Period 3	Period 4
A (n=4)	Placebo (Two placebo tablets)	50mg (Two 25mg tablets)	75mg (Three 25mg tablets)	100mg (Four 25mg tablets)
B (n=4)	30mg (One 25mg tablet and one 5mg tablet)	Placebo (Two placebo tablets)	75mg (Three 25mg tablets)	100mg (Four 25mg tablets)
C (n=4)	30mg (One 25mg tablet and one 5mg tablet)	50mg (Two 25mg tablets)	Placebo (Three placebo tablets)	100mg (Four 25mg tablets)
D (n=4)	30mg (One 25mg tablet and one 5mg tablet)	50mg (Two 25mg tablets)	75mg (Three 25mg tablets)	Placebo (Four placebo tablets)

Reviewer Comment: Carryover effect not evaluated although given the 12 day (288 hr) washout period and projected half-life for eltrombopag of 21-32 hrs there should theoretically not be a significant issue. However, the reviewer's analysis (Table 29) of the plasma concentration predose uncovered the following:

Table 29: Reviewer Generated Summary of Pre-Dose Quantifiable Concentrations

Dose (mg)	Subject	Period	Time	Plasma conc. (ng/mL)
50.00	0015	2	Pre-dose	
75.00	0011	3	Pre-dose	
75.00	0001	3	Pre-dose	
75.00	0002	3	Pre-dose	
75.00	0004	3	Pre-dose	
75.00	0010	3	Pre-dose	
100.00	0002	4	Pre-dose	
100.00	0003	4	Pre-dose	
100.00	0007	4	Pre-dose	
100.00	0001	4	Pre-dose	
100.00	0010	4	Pre-dose	
100.00	0006	4	Pre-dose	

b(4)

The investigator judged whether to make each subject and/or all the subjects proceed to the next treatment by reviewing the safety data (vital signs, 12-lead ECG, and laboratory tests) 72 hours after the previous dose and the platelet count at 144 hours after the previous dose and just before the next dose.

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

GSK used the investigational products (SB497115GR 5mg tablet, SB497115GR 25mg tablet and their placebo tablet) manufactured by Conshohocken and Collegeville Plants in GlaxoSmithKline US (R&D formulation) and packed by GlaxoSmithKline K.K. Takasaki Development Laboratory (Table 30).

Table 30: Investigational products

Investigational SB497115GR product	Formulation Code	Substance batch (site)	Batch number (expiration date)
5mg (free acid) tablet	AG	TPO-E-02C (Tonbridge)	041048099 (April 2006)
25mg (free acid) tablet	AL	TPO-E-02C (Tonbridge)	041048101 (October 2005)
placebo tablet	ALC	N/A	041048098 (October 2005)

b(4)

After fasting, subjects received three of four SB-497115-GR doses [30mg (one 25mg tablet+one 5mg tablet), 50mg (25mg tablet×2), 75mg (25mg tablet×3) and 100mg (25mg tablet×4)] and placebo (two to four placebo tablets) as single oral doses with 150mL of water in four dosing periods. Subjects fasted from 12 hours before dosing.

Reviewer Comment: It is important to note that this phase 2 formulation was shown to NOT be BE or dose proportional to the commercial phase 3 formulation in the biopharmaceutical studies reviewed below. These studies showed ~15% exposure increased exposure with the phase 2 formulation. This issue can not be ruled out as a possible confounding factor.

Criteria for evaluation:

- Sample size: Convenience sample. No formal sample size calculation made.
- Pharmacokinetics:
 - Blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours post-dose. Approximately 3mL of whole blood was collected into EDTA-2K containing vacuum tubes, and then centrifuged (4°C, 1500g, 10 min). The isolated plasma was divided into two pre-labeled 1.8mL tubes, and stored in a freezer at - 80°C or lower.
 - Plasma samples were analyzed for eltrombopag using a validated analytical method (Table 31) based on protein precipitation, followed by HPLC/MS/MS analysis. The LLQ for eltrombopag was 100 ng/mL, using a 50 µL aliquot of human plasma with a higher limit of quantification of 50,000 ng/mL.

Table 31: Assay Validation Information

Eltrombopag is extracted from 50µL human plasma by protein precipitation using _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	10.0ng/mL
Validated Range	10.0 to 10,000ng/mL
Within-run Precision (%CV)	≤6.5%
Between-run Precision (%CV)	≤8.5%
Accuracy (%Bias)	-10.0% ≤ bias ≤ 5.3%
Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 54 hours at ambient temperature

b(4)

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

- The following PK parameters were calculated from plasma SB-497115 concentration-time data for individual subjects using standard model independent methods. C_{max}, T_{max}, t_{1/2}, λ_z, AUC_{inf}, AUC_{last}, AUC₀₋₂₄, AUC₀₋₄₈, %AUC_{ex}, CL/F, Vz/F.

Dose-proportionality was evaluated using a power model. Dose-proportionality was assessed for AUC_{inf}, AUC_{last} and C_{max}. A linear mixed model was used with log-transformed dose as a fixed effect and subject as a random effect. Point estimates of slope and 90% confidence intervals for the differences were obtained and if 90% confidence interval included 1, dose-proportionality was assumed. In addition, dose-normalized AUC_{inf}, AUC_{last} and C_{max} were log-transformed and pairwise comparisons were made with the control group of 30mg or the minimum dose at which PK parameters of sufficient precision were obtained in all subjects. Differences between treatment groups were estimated using 90% confidence interval.

Reviewer Comment: The sponsor failed to provide adequate information to allow the reviewer to evaluate the method of analysis of the plasma PK data.

- Urine samples were collected at pre-dose (spot), 0-6, 6-12, 12-24, 24-48, 48-72 hours post-dose. Pooled urine collected (20% Tween20-added pooled urine containers) during each period was thoroughly stirred and injected into two pre-labeled 1.8mL tubes. Samples were stored in a freezer at - 80°C or lower. Measurement of urine samples from the subjects receiving SB-497115-GR was

started from the higher dose (100mg), and since samples from all subjects receiving 50 mg were below the lower limit of quantitation (LLQ), no samples after dosing of 30 mg were measured.

- Urine specimens were assayed using a validated analytical method Table 32)

Table 32: Assay validation information

Human urine samples containing eltrombopag are diluted with _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ*	10ng/mL
Validated Range	10 to 2500ng/mL
Within-run Precision (%CV)	≤3.9%
Between-run Precision (%CV)	≤1.1%
Accuracy (%Bias)	-1.7% ≤ bias ≤ 2.3%
Stability in Human Plasma	3 freeze-thaw cycles at approximately -80°C at least 25 hours at ambient temperature
Processed Extract Stability	at least 3 days at ambient temperature

b(4)

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

- The amount (Ae) and fraction (fe) of SB-497115 excreted in the urine for each urine sampling period and also as cumulative excretion over the entire sampling period were calculated from urinary SB-497115 concentrations and urine volumes up to 72 hours post-dose in individual subjects. Renal clearance (CLr) was not derived because urinary SB-497115 concentrations were quantifiable only one subject and fe were extremely is low (maximum 0.032%).
- Pharmacodynamics:
 - The change in platelet count was assessed.
 - Samples were collected at pre-dose, 24, 72, 144 and 288 hours post-dose. A .2mL of whole blood was collected from the antebraichial vein into vacuum tubes (containing EDTA-2K), and then thoroughly mixed. Platelet count was measured with an automatic cell counter (Direct current detection method). The counting was done within 24 hours after sampling.
 - Although the analysis of platelet counts between each dose of SB-497115-GR vs placebo using a mixed effects model and least square mean and 95% confidence interval of the difference from baseline were included in the planned analyses, it was not performed because no significant change of platelet count was observed at any dose. Summary statistics were presented.
- 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, ECG monitoring (12-lead), and ophthalmologic examination were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects: A total of 16 subjects were randomized and 15 completed the study. All subjects who participated in the study and received at least one dose of the investigational products were included in the safety analysis, PK analysis, and PD analysis. Since subject 0012 was withdrawn from the study due to an AE, all safety observations and examinations scheduled from 288 hours post-dose in Period 3 onward were handled as missing, and PK/PD data for period 4 was not included.

Population Demographics

The population demographics from this study are listed in the Table 33 below.

Table 33: Population Demographics

Demographic Factor	Overall
Sex, n (%)	Males 16 (100), Females 0 (0)
Age (years)	25.9±3.9 (20-33)
Race	Asian (Japanese): 100%
Body Weight (kg)	61.3±4.4 (55.5 - 69.6)
Height (cm)	170.9±3.4 (166.0 - 176.8)
BMI(kg/m ²)	21.0±1.3 (19.0 - 23.7)
mean±SD (minimum – maximum)	

Results-PK analysis:

Selected plasma PK parameters are listed in Table 34 below. Mean and median plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figures 6 and 7.

Table 34: Selected PK parameters

	30mg (n=12)	50mg (n=12)	75mg (n=12)	100mg (n=11)
C _{max} (µg/mL)	4.00±0.86 (2.83-5.44)	7.26±1.49 (5.32-10.2)	10.1±2.15 (7.86-14.5)	13.1±3.46 (8.51-20.7)
T _{max} (hr)	3.0 (2.0-5.0)	3.5 (2.0-5.0)	3.5 (1.5-4.0)	4.0 (2.0-5.0)
t _{1/2} (hr)	23.1±2.8 (20.1-28.4)	27.5±5.8 (18.7-36.8)	27.9±4.4 (21.2-34.8)	28.1±6.5 (17.8-41.6)
AUC _{inf} (µg·hr/mL)	64.5 ±14.6 (43.1-90.8)	130.8±22.3 (97.0-168.0)	182.7± 56.8 (114.9-272.4)	244.2± 53.6 (164.5-338.8)
AUC ₀₋₂₄ (µg·hr/mL)	40.3±8.6 (27.5-55.9)	74.1±11.7 (56.6-96.5)	102.0±23.3 (73.4-147.4)	134.8±24.2 (105.5-182.1)
PK parameters other than T _{max} : arithmetic mean±SD (range), T _{max} : median (range)				

Reviewer Comment:

- ~49 concentrations above the upper limit of quantification for the plasma eltrombopag assay. This may explain, in part, the overall wide ranges for C_{max}, AUC₀₋₂₄, & AUC_{inf}?
- Looking carefully at the raw data it is apparent that the subjects contained in the upper 25th percentile for AUC_{inf} were not consistent between the cohorts. 5/9 subjects were in the upper 25th percentile for AUC_{inf} in two cohorts but none were in the upper 25th percentile for AUC_{inf} for all three dosing cohorts. If a fixed effect was present (e.g., a genetic factor) you would expect subjects to be consistently high. This may suggest an assay or formulation problem in this study. It is also possible that the packaging of the doses at the GlaxoSmithKline K.K. Takasaki Development Laboratory or the methods of dispensing of dosing pouches to subjects resulted in patients getting incorrect doses. In addition, given that 4/5 subjects were in the upper 25th percentile for AUC_{inf} in two cohorts following a previous dose of eltrombopag, drug toxicity or inhibition (e.g., UGT1A1) can not be ruled out but the 12 day washout would make this unlikely.

b(5)

Figure 6: Mean Plasma SB-497115 Concentration

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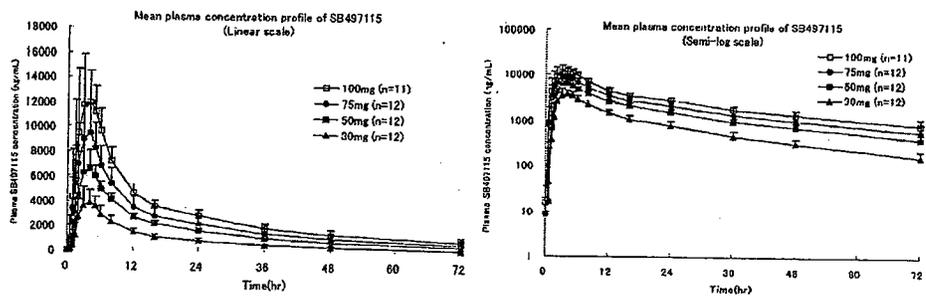
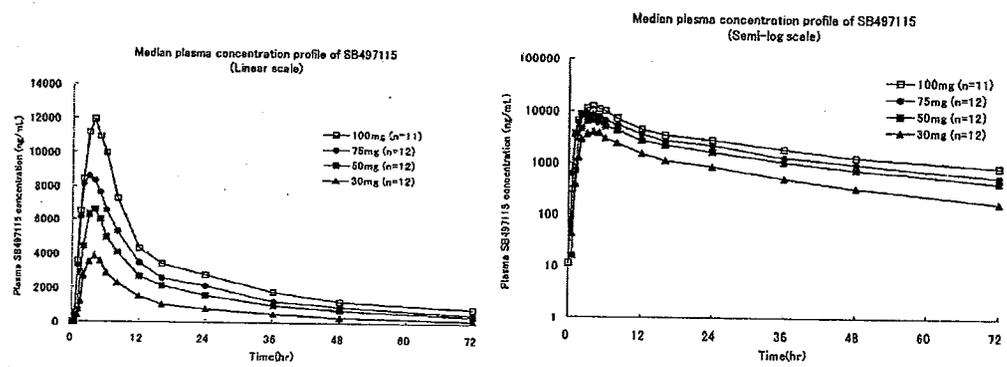


Figure 7: Median Plasma SB-497115 Concentration



The results of analysis of PK linearity using a power model and ANOVA are shown in Tables 35 & 36. Figure 8 shows linear scattergrams of PK parameters (C_{max}, AUC_{inf}) plotted against dose.

Table 35: Dose proportionality analysis (Power Model) by Treatment

Parameter	Slope Estimate	SE	90% CI-L	90% CI-U
C _{max}	1.0197	0.05205	0.9314	1.1081
AUC _{last}	1.0691	0.04679	0.9896	1.1485
AUC _{inf}	1.1126	0.05094	1.0261	1.1990

Parameters in red demonstrated dose proportionality based on a 90% CI of the slope Containing 1

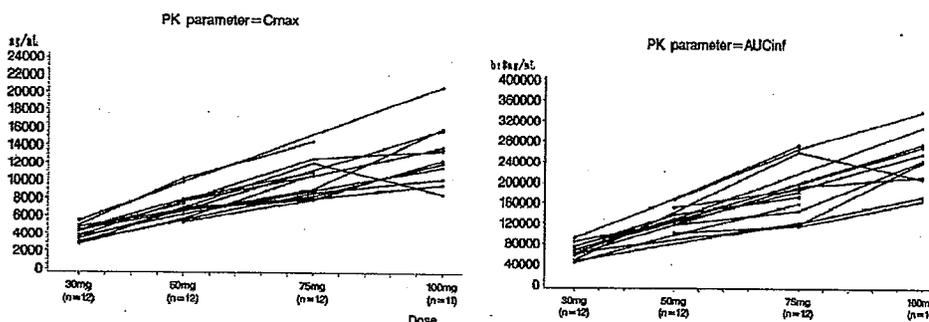
Table 36: Dose proportionality analysis (ANOVA) by Treatment compared to 30 or 50 mg Normalized Dose

Parameter	Contrast	difference of means (linear scale)	90% CI-L (linear scale)	90% CI-U (linear scale)
Normalized 30 mg dose				
C _{max}	50mg	1.0931	0.9404	1.2705
	75mg	1.0092	0.8682	1.1731
	100mg	0.9727	0.8340	1.1345
AUC _{last}	50mg	1.1762	1.0186	1.3582
	75mg	1.0610	0.9188	1.2251
	100mg	1.0732	0.9264	1.2432
AUC _{inf}	50mg	1.2301	1.0440	1.4492
	75mg	1.1113	0.9433	1.3093
	100mg	1.1380	0.9624	1.3457
Normalized 50 mg dose				

Cmax	30mg	0.9149	0.7871	1.0634
	75mg	0.9233	0.7943	1.0732
	100mg	0.8899	0.7630	1.0379
AUClast	30mg	0.8502	0.7363	0.9817
	75mg	0.9020	0.7812	1.0416
	100mg	0.9124	0.7876	1.0569
AUCinf	30mg	0.8130	0.6900	0.9578
	75mg	0.9035	0.7669	1.0644
	100mg	0.9252	0.7824	1.0940

Doses in red demonstrated dose proportionality based on a 90% CI between 0.8 and 1.25

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



Reviewer Comment: As indicated above dose proportionality was not demonstrated for AUCinf using a power model approach as well as 5/9 contrasts (30 mg) and 9/9 (50 mg) using the ANOVA approach. Upon careful inspection of the raw data it appears that several patients showed decreasing AUC (red) with increasing dose going from 50 mg to 75 mg and 75 to 100 mg (Table 37). Interestingly, this occurred in different subjects from 50 mg to 75 mg and 75 to 100 mg. This may suggest an assay or formulation problem in this study. It is also possible that the packaging of the doses at the GlaxoSmithKline K.K. Takasaki Development Laboratory or the methods of dispensing of dosing pouches to subjects resulted in patients getting incorrect doses.

Table 37: Reviewer generated analysis of AUCinf across doses by subject

Subject	30 mg hr*ng/mL	50 mg hr*ng/mL	30mg:50mg	75 mg hr*ng/mL	50mg:75mg	50mg:100mg	100 mg hr*ng/mL	75mg:100mg
1	62038.3	166703.9	2.69	265913.7	1.60	2.03	338830.7	1.27
2	90801.2	151175.5	1.66	187195	1.24	1.70	256604.4	1.37
3	43128.9	168044.5	3.90	118460.2	0.70	1.43	240180.3	2.03
6	57135.7	97015.4	1.70	272391.4	2.81	2.17	210984.1	0.77
7	48388.9	101356	2.09	158990.4	1.57	2.04	207084.8	1.30
8	73189.5	137544.3	1.86	192507.6	1.40	1.20	164541.5	0.85
10	67472.6	117314.7	1.74	259450.4	2.21	2.07	243350.2	0.94
12	66226.1	122523.2	1.85	114945.6	0.94	WD	WD	WD
13	83113.8	129663.8	1.56	171905.3	1.33	2.12	274743.5	1.60
14	61413.5	123541.9	2.01	145478.3	1.18	2.50	307946.7	2.12
15	74230.1	128488.7	1.73	182874.2	1.42	2.10	269477.3	1.47
16	46420	125670.4	2.71	121895.9	0.97	1.37	172506.3	1.42

Following dosing of 100 and 75 mg, urinary SB-497115 concentrations were quantifiable in subject 0016 but were all below LLQ (10ng/mL) in the other subjects. At 50 mg, urinary SB-

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497115 concentrations were below LLQ in all subjects. Accordingly, urine samples from the 30mg group were not measured based on the rule set in the protocol. Due to very low urinary SB-497115 concentrations as mentioned above, the amount (Ae) and fraction (fe) of SB-497115 excreted in the urine were calculated but renal clearance (CLr) was not calculated.

Results- Pharmacodynamic Analysis:

Following single oral doses of 30-100mg of SB-497115-GR tablet, the changes in platelet count were periodically evaluated up to 12 days post-dose. However, no clinically significant change was observed at either dose level (Tables 38 & 39)

Table 38: Platelet Count By Dosing Cohort and Sampling Times

Group	Observation time	N	Platelet Count (10E4/mcl)				
			Mean	S.D.	Minimum median	Maximum	
Screening (total)	Screening:	16	21.5	3.32	16.8	21.55	29.6
Placebo	Predose:	16	22.0	2.74	17	21.85	26.1
	Day 1:	16	21.4	3.18	16.8	22.15	26.4
	Day 3:	16	21.3	3.35	15.5	22.1	25.3
	Day 6:	16	20.7	3.00	15.5	20.85	26
	Day 12:	15	20.6	3.14	16.2	20.7	25.5
	Follow up:	4	20.2	3.85	16.2	19.9	24.8
30mg	Predose:	12	20.9	3.12	16	21.7	25.5
	Day 1:	12	20.20	2.437	16.5	20.9	23.6
	Day 3:	12	20.53	3.417	16.1	20.7	25.9
	Day 6:	12	21.5	3.22	16.1	22.25	25.2
	Day 12:	12	22.82	3.542	18	23.2	29.4
50mg	Predose:	12	22.48	3.694	18	21.85	29.4
	Day 1:	12	21.73	3.338	17.3	21.75	28.1
	Day 3:	12	22.6	4.13	17.1	22.85	30.3
	Day 6:	12	24.19	4.698	16.7	24.75	32.1
	Day 12:	12	23.15	3.954	17.3	22.8	31.2
75mg	Predose:	12	22.53	4.428	17.3	21.85	31.2
	Day 1:	12	22.1	4.45	16	21.5	29.7
	Day 3:	12	22.0	4.64	15.7	22.2	30.5
	Day 6:	12	24.2	4.40	18	25.75	31.5
	Day 12:	12	23.3	3.35	18.4	25.1	27.7
100mg	Predose:	11	22.85	3.518	16.6	24.4	27.7
	Day 1:	11	22.3	3.38	16.5	22.6	28.3
	Day 3:	11	22.95	3.401	18.9	23.1	27.9
	Day 6:	11	24.40	3.487	19.2	24.8	28.4
	Day 12:	11	24.81	3.279	20.4	25.1	29.8
Follow up:	11	24.8	3.28	20.4	25.1	29.8	

Table 39: Overall Change in Platelet Count By Dosing Cohort

Parameter	30mg (n=12)	50mg (n=12)	75mg (n=12)	100mg (n=11)	Placebo (n=15)
Maximum change from baseline (**10 ⁴ µL)	2.38±1.92	1.89±1.97	1.98±1.64	2.49±1.49	0.28±1.50
Maximum %change from baseline (%)	11.6±8.44	8.39±9.22	9.52±8.40	11.4±7.45	1.42±7.15

Results-Safety:

In this study, a total of 6 AEs were reported in 5 of 16 subjects. All these AEs were mild in severity except one subject who was withdrawn from the study before dosing in Period 4 due to the occurrence of acute pharyngitis of moderate severity after administration of placebo. Also only one AE of bilirubin total increased after dosing of 75mg was related

to the investigational product. No death or SAE occurred in this study. The specific adverse events are listed in Table 40 below:

Table 40: Post Dose Adverse Effects:

Adverse Event	30mg (n=12)	50mg (n=12)	75mg (n=12)	100mg (n=11)	Placebo (n=16)
Number of subjects with any AE(s)	1 (8.33%)	1 (8.33%)	2 (16.67%)	0	2 (12.5%)
Bilirubin total increased	0	0	1* (8.33%)	0	0
Total bile acids increased	0	1 (8.33%)	1 (8.33%)	0	0
Pyrexia	1 (8.33%)	0	0	0	0
ALT increased	0	0	0	0	1 (6.25%)
Acute pharyngitis	0	0	0	0	1 (6.25%)

Reviewer Comment: The frequency and type of ADR's reported appears to be different than that seen in similar western studies.

Clinical laboratory values that were of potential clinical concern were all elevated glucose levels and are presented in Table 41

Laboratory abnormalities judged as AEs during the study were one event each of total bile acids increased after dosing of 50 and 75mg, bilirubin total increased after dosing of 75mg and ALT increased after dosing of placebo (total 3 subjects with 4 events). All these events were mild in severity without accompanying symptoms, and had almost returned to the reference range or the subject's pre-dose values without treatment.

Table 41: Laboratory Values of Potential Clinical Concern

SC	Period 1			Period 2			Period 3			Period 4			Post-study
	Pre-dose	24hr	72hr	Pre-dose	24hr	72hr	Pre-dose	24hr	72hr	Pre-dose	24hr	72hr	
Subject 0001: Total bilirubin (reference range 0.2-1.0 mg/dL)													
0.9	1.4*	1.7*	1.5*	1.5*	1.7*	1.3*	1.4*	2*	2*	1.2*	1.8*	1.5*	0.8
Subject 0002: Total bile acids (reference range <10µmol/L)													
5.7	12.6*	12.1*	4.9	12.6*	19*	16.1*	13.3*	4.3	7.1	27.4*	5.9	6.8	14.2*
Subject 0008 ALT (reference range 5-40 IU/L/37°C)													
40	29	25	22	62*	49*	38	26	23	20	23	27	26	33
* Deviation from the reference range													

Reviewer Comment: This formulation was made from substance batch TPO-E-02C Study 497115/005 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. 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 during the study and 6 months after the final dose.

Conclusions (sponsor):

- SB-497115-GR was safe and well tolerated at doses up to 100mg when administered as single oral doses of 30-100mg of the tablet in 16 healthy Japanese adult males.
- Following single oral doses of 30-100mg of the SB-497115-GR tablet, maximum plasma concentrations of SB-497115 (free acid) were observed at 3 to 4 hours (median) post-dose and then declined with a mean elimination half-life of about 23 to 28 hours. Cmax and AUC increased approximately linearly with increasing dose over the dose range

examined. The urinary excretion of SB-497115 was 0.032% (maximum) of the dose even at the highest dose.

- No clinically significant changes in platelet counts were observed at either dose level following single oral doses of 30–100mg of the SB-497115-GR tablet.

Reviewer Comment: The reviewer disagrees that linearity was demonstrated for the reasons stated above. While there was a trend toward dose proportionality, it was possibly confounded by systematic error related to several factors (e.g., assay, formulation, etc.). These confounding factors also make a firm conclusion regarding the magnitude of the difference in PK between Japanese & Caucasian populations difficult unless these issues are resolved. As noted in the review below Japanese subjects in the study TRA105122 (conducted in the West) did not show PK characteristics similar to this study.

4.3.5 Study TRA105580 Phase 1 Healthy Japanese (Japan) Single Dose & Repeated Dose PK/PD/Dose Escalation Study

Reviewer: Joseph A. Grillo, Pharm.D.

Title: Phase I Study of SB-497115-GR - Single and Multiple Oral Dose Study in Healthy Japanese Male Subjects

Study period: 06-Jun-2006 - 30-Sep-2006

Objectives:

Primary

- To investigate the safety and tolerability of SB-497115-GR following single and multiple oral doses in healthy Japanese adult male subjects.
- To investigate the pharmacokinetics of SB-497115-GR following single and multiple oral doses in healthy Japanese adult male subjects.

Secondary

- To investigate the pharmacodynamics of SB-497115-GR following single oral and multiple doses in healthy Japanese adult male subjects.

Methodology:

This was a single-center, placebo-controlled, single-blind, randomized, dose-escalation, three doses, parallel group, single and multiple oral dose study in 42 healthy Japanese adult males (14/group). After screening, 14 eligible subjects in each dose group were randomized to an active drug group (n=10) or a placebo group (n=4), and received a single dose of SB-497115-GR or placebo (Table 42). After 5 days of washout, they received SB-497115-GR or placebo once daily for 10 days. Investigational products were orally administered with 150mL of water after fasting.

Table 42: Study Design

Treatment Group	SB-497115-GR (n=10)	Placebo (n=4)
25mg group	25mg tablet×1/time	Placebo tablet×1/time
50mg group	25mg tablet×2/time	Placebo tablet×2/time
75mg group	25mg tablet×3/time	Placebo tablet×3/time

Subjects were admitted to the unit the day before single dosing and confined there until 72 hours post-dose (Day 4 of single dosing) [for 4 nights]. Subjects were again admitted to the unit the day before the start of multiple dosing and confined there until 8 days after the final dose (Day 18 of multiple dosing) [for 18 nights]. If decreases in platelet count of individual subjects were confirmed 8 days after the final dose (Day 18), subjects were discharged from the unit.

Temporary daytime leaves 4 and 6 days after the final dose (Days 14 and 16) were permitted for subjects if the investigator judged that they had no safety problem on the basis of their platelet counts.

Dose escalation to the next dose level of multiple dosing proceeded following a satisfactory review of the platelet counts and safety data from the previous treatment 12 days after the final dose (Day 22). All dose groups underwent post-study screen (except ophthalmologic examination) 16 days after the final dose (Day 26) and ophthalmologic examination 28 days after the final dose (Day 38).

No medication other than the investigational products or non-drug therapy was allowed from 14 days before single dosing of the investigational product up to the completion of post-study screen (follow-up examination) unless the investigator/subinvestigator permitted the use of medications.

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

GSK supplied to the medical institution the investigational products manufactured by Ware Plant in the GlaxoSmithKline UK and packed by GlaxoSmithKline K.K. Takasaki Development Laboratory. In this study SB497115GR 25mg tablet and its matched placebo were used (Table 43).

Table 43: Investigational Products

Investigational SB497115GR product	Formulation Code	Substance batch (site)	Batch number (expiration date)
25mg (free acid) tablet	AS	F081601 (Tonbridge)	051109558
placebo tablet	APV	N/A	061114790

Subjects received one of three SB-0497115-GR oral doses [25 mg (25 mg tablet×1), 50 mg (25 mg tablet×2), 75 mg (25 mg tablet ×3)] or placebo (placebo tablet×1-3) with 150mL of water for single and 10 days in a fasted state. Subjects fasted from 10 hours before dosing until 4 hours post-dose.

Criteria for evaluation:

- Sample size: Convenience sample. No formal sample size calculation made.
- Pharmacokinetics:
 - PK parameters (C_{max}, T_{max}, t_{1/2}, λ_z, AUC_{inf}, AUC_{0-last}, %AUC_{ex}, AUC₀₋₂₄, AUC₀₋₄₈, CL/F, V_z/F) were calculated from plasma SB-497115 concentration data following single dosing and on Day 10 of multiple dosing in individual subjects using standard model independent methods. To evaluate possible accumulation of SB-497115, accumulation ratios (R₀, R_s, RC_{max}) were calculated by subject and summary statistics were calculated by dose.

Reviewer Comment: The sponsor failed to provide adequate information to allow the reviewer to evaluate the method of analysis of the plasma PK data.
 - Dose linearity of log transformed AUC and C_{max} was analyzed using a linear mixed effects model with dose, stage (single or multiple) and interaction of dose and stage as fixed effects and subject as a random effect. Point estimates of differences between multiple vs single dosing and their 90% CIs were calculated by dose. The AUC and C_{max} were then back transformed to calculate point estimates of R₀, R_s and RC_{max} and their 90% CIs.
 - Sampling for Single dosing and Day 10 of multiple dosing: pre-dose and 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose. During multiple dosing additional samples were collected pre-dose on Days 1-9. Approximately 3mL of whole blood was collected into EDTA-2K-containing vacuum tubes, and

then centrifuged (4°C, 1500g, 10 min). The isolated plasma was divided into two pre-labeled 1.8mL tubes, and stored in a freezer at - 80°C or lower.

- o Plasma specimens were assayed using a validated analytical method (Table 44)

Table 44: Assay Validation Information

Eltrombopag is extracted from 50uL human plasma by protein precipitation using as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	10.0ng/mL
Validated Range	10.0 to 10,000ng/mL
Within-run Precision (%CV)	≤6.5%
Between-run Precision (%CV)	≤8.5%
Accuracy (%Bias)	-10.0% ≤ bias ≤ 5.3%
Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 54 hours at ambient temperature

b(4)

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

- Pharmacodynamics:

- o Blood samples were collected at the following time-points to determine the changes in platelet count for PD assessment:
 - Single dosing: pre-dose and 24, 72 and 120 hours post-dose.
 - Multiple dosing: pre-dose on Days 1-3, 5-8 and 10 and at the times (18 points) corresponding to pre-dose on Days 11, 12, 14, 16, 18, 22 and 26.

Two milliliters of whole blood was collected from the antebraichial vein into EDTA-2K-containing vacuum tubes, and then thoroughly mixed.

- o Platelet count was measured with an automatic cell counter (Direct current detection method). The counting was done within 24 hours after sampling.
- o Platelet counts at each measurement time were summarized in tabular listings and graphical displays of changes in platelet count over time were prepared by subject. Summary statistics of platelet counts at each measurement time were calculated from individual subject data and graphical displays of changes in platelet count over time were prepared. Also pharmacodynamic parameters [maximum platelet counts (p-Cmax), area under the platelet count-time curve (p-AUC), observed time of maximum change (p-Tmax)] and the changes and percent (%) changes from baseline in these pharmacodynamic parameters were calculated using standard model independent methods and summarized in tabular listings. Also summary statistics were calculated by dose.
- o Dose linearity of maximum platelet counts (with and without log transformation) after dosing was analyzed using a liner mixed effects model with dose and baseline platelet counts (with and without log transformation) as fixed effects and subject as a random effect. Point estimates of differences between groups (dose of SB-497115-GR vs placebo) of interest and their 90% CIs were calculated.
- o As exploratory analysis, scattergrams of PK parameters (Cmax and AUC0-24) and PD parameters (p-Cmax, p-AUC, Δp-Cmax, %change p-Cmax, Δp-AUC and %change p-AUC) after multiple dosing were prepared.
- 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, ECG monitoring (12-lead), and ophthalmologic examination were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects: A total of 42 subjects were randomized (Placebo (12), 25 mg (10), 50 mg (10), 75 mg (10)) and 41 completed the study (Placebo (12), 25 mg (10), 50 mg (9), 75 mg (10)). All subjects who participated in the study and received at least one dose of the investigational products were included in the safety analysis, PK analysis, and PD analysis. Since subject 0024 was withdrawn by request from the study, all safety observations and examinations scheduled from 72 hours post-single 50 mg dose were handled as missing, PK data from 96 hours post-single 50 mg dose (half-life and AUCinf were calculated based on 3 terminal data points).

Population Demographics

The population demographics from this study are listed in the Table 45 below:

Table 45: Population Demographics

Demographic factor	Placebo	25mg	50mg	75mg	Total
Number of subjects	12	10	10	10	42
Sex: Male/Female n (%)	12 (100) / 0 (0)	10 (100) / 0 (0)	10 (100) / 0 (0)	10 (100) / 0 (0)	42 (100) / 0 (0)
Ethnicity: n (%) Not Hispanic/ Latin origin	12 (100)	10 (100)	10 (100)	10 (100)	42 (100)
Race: n (%) Asian-Japanese	12 (100)	10 (100)	10 (100)	10 (100)	42 (100)
Age (years)	25.0±3.22 (20 - 31)	26.0±4.19 (21 - 34)	26.1±4.01 (22 - 33)	25.5±2.72 (22 - 30)	25.6±3.46 (20 - 34)
Body weight (kg)	61.31±3.381 (55.8 - 66.9)	64.70±7.496 (56.6 - 82.0)	63.35±6.908 (56.9 - 77.4)	65.30±7.936 (56.1 - 77.3)	63.55±6.500 (55.8 - 82.0)
Height (cm)	173.0±5.44 (162 - 183)	173.4±5.19 (167 - 184)	176.0±4.85 (169 - 185)	177.5±7.38 (166 - 190)	174.9±5.88 (162 - 190)
BMI (kg/m ²)	20.498±1.0603 (19.25 - 23.18)	21.457±1.4320 (19.36 - 24.22)	20.407±1.4412 (18.80 - 22.62)	20.650±1.1337 (19.57 - 23.29)	20.741±1.2890 (18.80 - 24.22)
Smoking (smokers/ non-smokers)	6 (50) / 6 (50)	4 (40) / 6 (60)	7 (70) / 3 (30)	3 (30) / 7 (70)	20 (48) / 22 (52)

Reviewer Comment: Non-smokers or subjects smoking ≤10 cigarettes/day. Subjects had to refrain from smoking and taking products containing nicotine after signing informed consent till completion of post-study screen (follow-up examination). Smoking status was not verified by cotinine concentration. Number of smokers was not well balanced. Especially in the 50 mg repeated dose group

Results-PK analysis:

Selected plasma PK parameters are listed in Table 46 below for single and repeat dosing. Mean and plasma eltrombopag concentration-time profiles are displayed for single and repeat dosing with planned time on both semi-logarithmic and linear scales by treatment in Figures 9 and 10.

Table 46: Selected PK Parameters

Dose (mg)	Single / Multiple	n	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg.h/mL)	AUC _{inf} (µg.h/mL)	T _{max} (hr)	t _{1/2} (hr)
25	Single	10	3.56±1.13 (1.77-5.85) [31.7]	33.2±10.1 (16.3-55.2) [30.3]	55.4±23.2 (21.6-104.3) [41.8]	3.0 (2.0-5.0)	29.6±5.0 (21.0-37.5) [16.9]
	Repeated (Day 10)	10	4.83±1.17 (2.81-6.44) [24.3]	58.9±18.4 (29.7-78.0) [31.2]	135.0±56.5 (50.7-210.8) [41.9]	3.0 (1.5-5.0)	39.7±3.2 (36.0-44.5) [8.1]
50	Single	10	6.44±2.14 (2.64-8.88) [33.2]	63.9±17.6 (28.0-81.9) [27.6]	106.6±32.4 (47.1-145.9) [30.4]	3.0 (1.5-5.0)	31.0±5.9 (21.7-38.6) [19.1]
	Repeated (Day 10)	9	10.6±2.38 (7.06-14.77) [22.4]	133.8±33.6 (91.9-192.2) [25.1]	359.8±140.1 (218.5-655.0) [39.0]	4.0 (2.0-5.0)	51.3±12.2 (38.0-81.0) [23.8]
75	Single	10	8.39±2.84 (4.52-12.23)	80.7±20.7 (44.3-102.5)	134.9±37.4 (70.4-196.5)	3.0 (2.0-6.0)	32.4±7.6 (19.8-43.0)

			[33.8]	[25.7]	[27.7]		[23.3]
Repeated (Day 10)	10	12.78±2.84 (7.44-16.34) [22.2]	164.2±35.5 (117.3-225.4) [21.6]	460.6±159.8 (257.8-655.0) [34.7]	4.0 (2.0-5.0)		47.8±11.5 (30.9-63.7) [24.1]

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

Figure 9: Mean plasma SB-497115 concentration (Single-Dose)

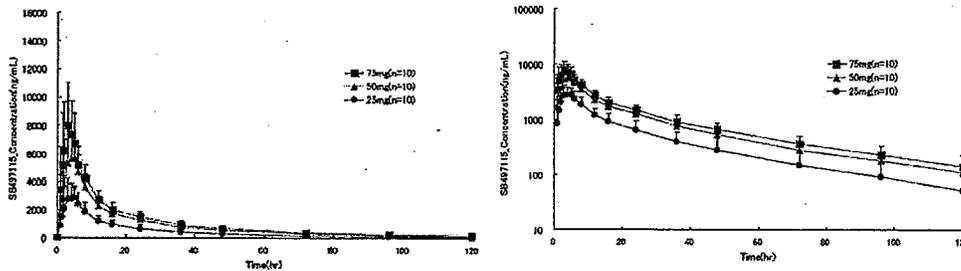
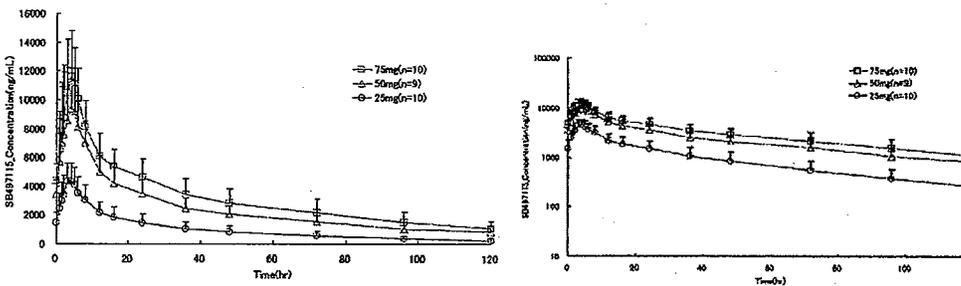


Figure 10: Mean plasma SB-497115 concentration (Repeat Dose)



Reviewer Comment:

- In this study PK samples were collected up to 120 hours post-dose in single dosing and on Day 10 of multiple dosing, providing sufficient data to calculate t_{1/2} and AUC_{inf} following single dosing. However, on Day 10 of multiple dosing, %AUC_{ex} exceeded 20% in one subject in the 50mg group and 3 subjects in the 75mg group.
- ~60 concentrations were above the upper limit of quantification for the plasma eltrombopag assay. Could this explain, in part, the increased %CVb noted for AUC_{inf} and the overall wide ranges for C_{max}, AUC₀₋₂₄, & AUC_{inf}?
- While the sponsor allowed smokers in this study, it failed to report information regarding the effect of this factor on PK. Despite the assay concerns above, a reviewer analysis showed a trend toward lower exposure in the smoking population (Table 47). Given smoking can induce UGT1A1 this may be significant and should be explored further.

Table 47: Reviewer Generated Effect of Smoking on Selected PK Parameters

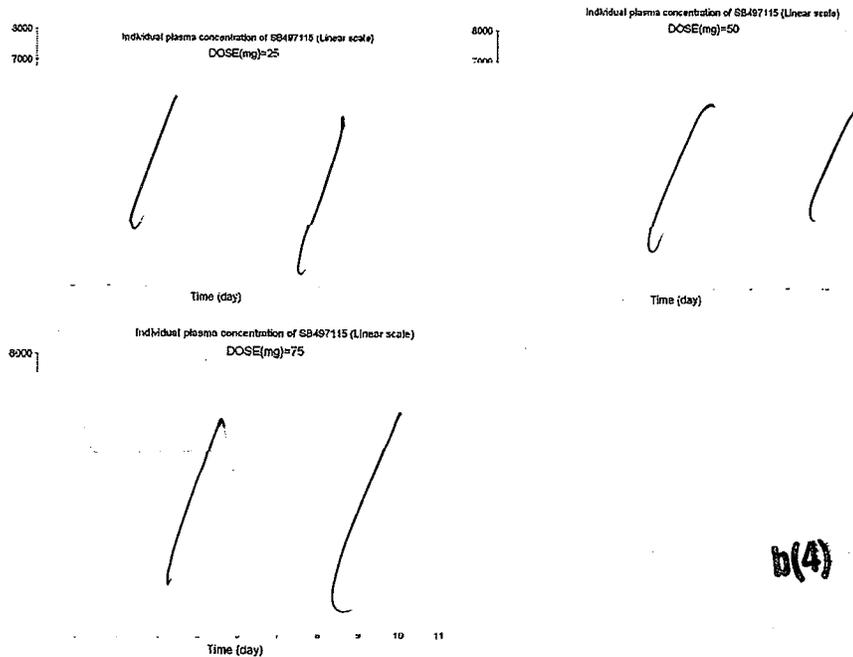
Parameter	Period	Dose	Smokers		Non-Smokers		S:NS
			Median	(25th, 75th)	Median	(25th, 75th)	
AUC _{inf} (µg.h/mL)	Single	25	46.5	(27.3, 71.2)	57.2	(42.2, 72.7)	0.81
	Repeat	25	139.7	(64.9, 202.4)	146.8	(91, 167.9)	0.95
	Single	50	101.5	(84.2, 122.3)	145.4	(47.1, 145.9)	0.7
	Repeat	50	332.3	(219.1, 354.1)	538.6	(422.3, 655)	0.62
	Single	75	156.2	(95.4, 169.4)	128.7	(113.8, 160.9)	1.21

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	Repeat	75	462.8	(275.6,751.9)	481.4	(313.7,517.5)	0.96
C _{max} (µg/mL)	Single	25	3.1	(2.1,3.5)	3.7	(3.2,5.1)	0.84
	Repeat	25	4.7	(3.2,5.4)	5.5	(3.9,5.9)	0.85
	Single	50	6.8	(5.4,8.1)	7.3	(2.6,8.9)	0.93
	Repeat	50	10.5	(8.2,11.2)	13.6	(12.5,14.8)	0.77
	Single	75	10.2	(9.3,10.2)	7	(4.7,10.7)	1.46
	Repeat	75	13	(12.4,15)	13.8	(9.6,15.5)	0.94

Plasma Steady State vs. Time profiles for trough concentrations following repeat dosing are shown in Figure 11 below. The slope and point estimates of log transformed trough values on Days 8, 9 and 10 of multiple dosing and their 90% confidence intervals are shown in Table 48. As a result, the 90% confidence interval of slope included 1, suggesting that the steady state was achieved by about 7 days after the start of multiple dosing (Day 8 of multiple dosing).

Figure 11: Individual plasma SB-497115 concentration profiles (Trough concentration) Following Repeat Dosing



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Table 48: Summary of Plasma SB-497115 Analysis of Steady State

Parameter	Treatment	Slope Estimate	90% CI
Predose Concentrations (Days 8, 9, and 10)	25mg	0.961	(0.783,1.178)
	50mg	1.062	(0.948,1.189)
	75mg	1.001	(0.909,1.103)

Reviewer Comment: Greater variability in trough concentrations noted with the higher doses.

Summary statistics of accumulation ratios calculated from the PK parameters following single dosing and on Day 10 of multiple dosing are presented in Table 49

Table 49: Accumulation ratios and 90% Confidence Interval

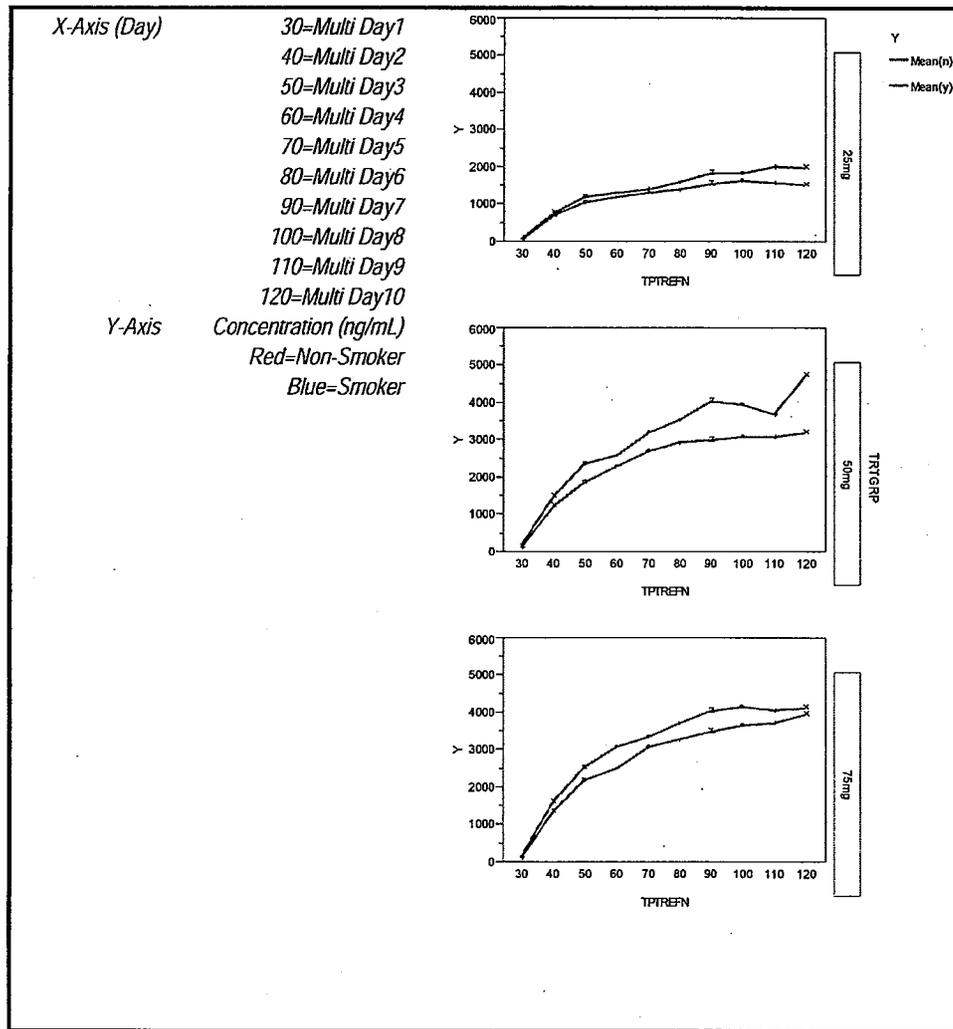
Dose	n	Ro	Rs	RCmax
25mg	10	1.752 (1.496, 2.052)	1.091 (0.932, 1.277)	1.376 (1.144, 1.654)
50mg	9	1.951 (1.642, 2.318)	1.178 (0.998, 1.391)	1.566 (1.275, 1.925)
75mg	10	2.060 (1.743, 2.435)	1.239 (1.059, 1.449)	1.577 (1.283, 1.939)

Point estimate (90% CI)
 Ro=Day 10 multiple dose AUC0-24/single dose AUC0-24
 Rs=Day 10 multiple dose AUC0-24/single dose AUCinf
 RCmax=Day 10 multiple dose Cmax/single dose Cmax

Reviewer Comment:

- Accumulation was shown with multiple dosing based on Ro and RCmax having 90% confidence interval did not include 1. This was particularly noted with the 75 mg dose.
- A slight trend toward lower accumulation at 50 mg & 75 mg with smokers was noted by a reviewer initiated review (Figure 12)

Figure 12: Reviewer Generated Effect of Smoking on Accumulation

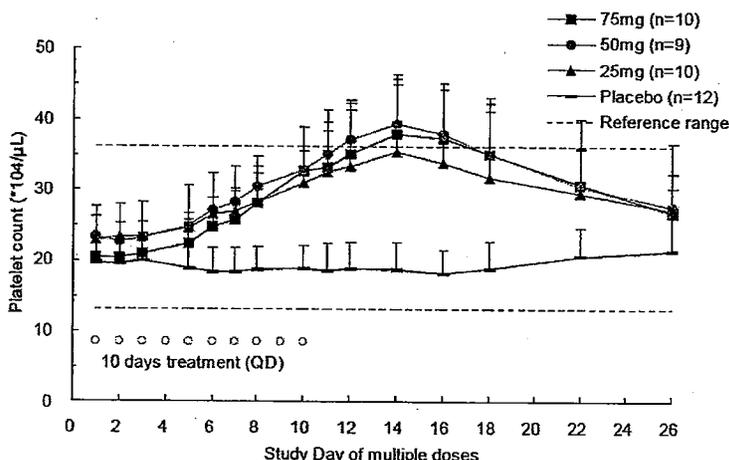


Results- Pharmacodynamic Analysis:

Peripheral blood smear test conducted at screening showed no platelet aggregation in any subject. There were no changes in platelet aggregation possibly related to study treatment at any dose level.

Platelet counts were periodically measured from before single dosing of 25, 50 and 75 mg of SB-497115-GR tablet and placebo up to 16 days after the final dose (Day 26 of 10-day multiple dosing). The changes in platelet count over time are shown by dose and subject in Figure 9-1 and the changes over time in mean platelet count by dose in Figure 13. Following single oral doses of 25, 50 and 75mg of SB-497115-GR tablet, there were no clinically significant changes in platelet count at either dose level. Following 10 days of multiple dosing, however, maximum platelet counts were reached 4 to 6 days after the final dose (Days 14-16 of multiple dosing) and had returned to the reference range by days after the final dose (Days 26 of multiple dosing) except one subject (0007 in the 25mg group).

Figure 13: Changes in Platelet Count over Time following Multiple Dosing (mean±SD)

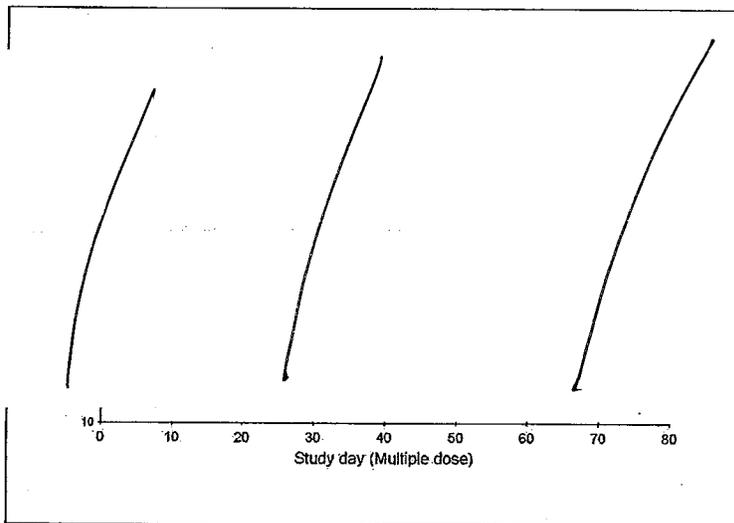


The platelet count of Subject 0007 reached a maximum value of 598,000/ μ L on Day 14 of multiple dosing, and took a long time to recover. The changes in platelet count in the 25mg group are shown in Figure 14. The platelet count returned to the reference range 64 days after the final dose (Day 74 of multiple dosing) without treatment. This subject had no subjective symptom, objective finding or abnormal platelet aggregation throughout the study period.

Figure 14: Changes in Platelet Count Over Time in 25mg Group by Subject (displayed up to Day 74 of multiple dosing)

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Summary statistics of PD parameters calculated from platelet counts are shown in Table 50. A comparison of maximum platelet change from baseline is displayed in Table 51.

Table 50: Selected PD parameters (mean±SD)

Dose	n	P0 (*104/ μ L)	p-Tmax (day)	p-Cmax (*104/ μ L)	Δ p-Cmax (*104/ μ L)	%change p-Cmax (%)	%change p-AUC (%)
Placebo	12	19.67±3.124	18.2±10.73	22.44±4.528	2.78±2.251	114±9.7	99±9.1
25mg	10	22.89±4.748	14.8±2.53	35.53±10.147	12.64±6.341	154±20.4	128±14.6
50mg	9	23.32±2.836	14.2±1.20	39.79±5.927	16.47±5.458	172±23.5	136±14.1
75mg	10	20.54±2.945	15.8±2.57	38.89±8.437	18.35±7.268	190±35.0	148±20.2

Table 51: Comparison of Maximum Change from Baseline in Platelet Count

Comparison	Ratio	90% CI
25mg/Placebo	3.51	2.248 - 5.475
50mg/ Placebo	4.61	2.892 - 7.354
75mg/ Placebo	5.67	3.718 - 8.638

Exploratory relationships between PK and PD parameters did not show an apparent relationship; however, data was limited.

Reviewer Comment:

- There were no obvious PK characteristics that could have explained the extreme change in platelet count for subject 0007.
- While a change in platelet count from baseline and relative to placebo is apparent, a dose proportional effect is not. There is a trend toward a slightly greater increase in platelet aggregation with increasing dose but this change is not proportional.
- Reviewer initiated assessment of smokers vs. non-smoker showed no apparent trends regarding platelet aggregation among the treatment groups.

Results-Safety:

In this study, a total of 6 AEs were reported in 6 of 42 subjects. All these AEs were mild in severity and there was no death, SAE or subject withdrawn from the study due to AE. There was no apparent relationship between the dose of SB-497115-GR and the occurrence of AEs. The specific adverse events are listed in Table 52 below:

Table 52: Post dose adverse effects:

AE	Dose			
	Placebo	25mg	50mg	75mg
Urticaria	0	0	1*	0
Amylase increased	0	1*	0	0
CK increased	0	0	1	1
Eosinophil percentage increased	0	0	0	1*
WBC count decreased	0	0	1*	0
Total number of AEs	0	1	3	2
Number of subjects treated	12	10	10a)	10
Number of subjects with AE (incidence)	0	1 (10%)	3 (30%)	2 (20%)
Number of subjects with ADR (incidence)	0	1 (10%)	2 (20%)	1 (10%)

Reviewer Comment: The frequency and type of ADR's reported appear to be different than that seen in similar western studies.

There were no clinically significant changes between pre-dose and post-dose values at any dose or between dose of SB-497115-GR and placebo. Laboratory abnormalities assessed as AEs during the study were 2 events of CK increased and 1 event each of amylase increased, eosinophil percentage increased and white blood cell count decreased (total 5 events, 5 subjects). All these abnormalities were mild and not accompanied by other symptoms and returned to the reference range or near the subject's pre-dose values without treatment. Clinical laboratory values that were of potential clinical concern are presented in Table 53

Table 53: Laboratory Values of Potential Clinical Concern

Screening	Single dose			Multiple dose					Post-study screen	Follow-up*	
	Pre-dose	24hr	72hr	Pre-dose	Day 5	Day 10	Day 14	Day 18			
Subject 0007: Amylase (Reference Range: 44 - 140 U/L)	60	82	98	140	107	110	164↑	198↑	234↑	215↑	77
Subject 0019: CK (Reference Range: 58 - 249 U/L)	115	108	105	97	99	112	108	116	137	1795↑	196
Subject 0020: WBC (Reference Range: 3900 - 9800 /MCB)	3800↓	3600↓	4000	3500↓	3900	2600↓	2700↓	3300↓	3300↓	6300	-
Subject 0029: CK (Reference Range: 58 - 249 U/L)	87	89	75	82	89	76	87	70	558↑	98	-
Subject 0042: Eosinophil (Reference Range: 0 - 6%)	5	9↑	11↑	15↑	11↑	15↑	15↑	14↑	12↑	11↑	-

Reviewer Comment: Interestingly no reported elevations in bilirubin or other LFT's. The substance batch for the formulation used in this study was different than that used in 104603.

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

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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 during the study and 6 months after the final dose.

Reviewer Comment: Interestingly sinus bradycardia also noted in 104603 but not to this degree in the Western studies.

Conclusions (sponsor)

- SB-497115-GR was safe and well tolerated when administered as single and multiple oral doses of 25, 50 and 75mg of the tablet in 42 healthy Japanese adult males (SB-497115-GR groups: 30, placebo group: 12).
- Following single and multiple oral dosing of SB-497115-GR tablets at 25, 50 and 75mg, maximum plasma concentrations of SB-497115 (free acid) were reached at 3 to 4 hours (median) post-dose. Mean elimination half-life was 30-32 hours after a single dose and 40-51 hours on Day 10 of multiple dosing. Systemic exposure (C_{max} and AUC) increased approximately linearly with increasing dose following single and multiple dosing. As judged from the changes in trough concentration of SB-497115 over the period of multiple dosing, the steady state was achieved by about 7 days of dosing. Although the accumulation ratio R_s exceeded 1 for the dose of 75mg, the change was slight.
- Following single oral doses of 25, 50 and 75mg of SB-497115-GR tablet, there were no clinically significant changes in platelet count at either dose level. In contrast, following multiple dosing, maximum platelet counts were reached 4 to 6 days after the final dose (Days 14-16 of multiple dosing) and had returned to the reference range by 16 days after the final dose (Day 26 of multiple dosing) in almost all subjects. Following multiple dosing of 25, 50 and 75mg of SB-497115-GR tablet, the mean maximum percent changes from baseline in platelet count (%change p-C_{max}) were 1.5, 1.7 and 1.9 folds, respectively, indicating that the platelet-increasing effect of SB-497115-GR tended to rise with increasing dose. Also there were 3.5- to 5.7- fold increases in maximum change from baseline in platelet count in the SB-497115- GR groups compared with placebo. Platelet aggregation was periodically measured from before single dosing up to 6 days after the final dose (Day 16 of multiple dosing), but there were no changes possibly related to study treatment at either dose level.

Reviewer Comment: I disagree with the sponsors conclusions regarding accumulation and dose-proportional PD for the reasons stated above. Assay problems, especially with the higher plasma concentrations can not be ruled out. The effect of smoking in relation to UGT1A1 induction and eltrombopag PK suggest the CYP1A2 pathway should be explored further. As noted in the review below Japanese subjects in the study TRA105122 (conducted in the West) did not show PK characteristics similar to this study.

4.3.6 Study SB-497115/002 Phase 1 Healthy PK/PD Dose escalation

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

Title: 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

Study period: 29 Sep 2003- 24 Aug 2004

Objectives:

Primary

- To assess the safety and tolerability of SB-497115-GR in healthy adult subjects of single oral dosing and after 10 days of repeat oral dosing at doses of 5, 10, 20, 30, 50 and 75 mg administered once daily.
- To describe the pharmacokinetics of SB-497115-GR in healthy adult subjects after single oral dose and after 10 days of repeat oral dosing at doses of 5, 10, 20, 30, 50 and 75 mg administered once daily.

Secondary

- To investigate the potential of SB-497115-GR to inhibit or induce cytochrome (CYP) P450 enzymes during 7 days of once daily repeat oral dosing.
- To estimate the effect of SB-497115-GR on platelet biomarkers in healthy adult subjects after a single oral dose and after 10 days of repeat oral dosing at doses of 5, 10, 20, 30, 50 and 75 mg administered once daily.

Methodology:

Study Part 1 was a single-blind, randomized (with respect to placebo), placebo-controlled, parallel group, dose-rising design. In Cohorts A–F, 9 subjects received active treatment, and 3 subjects received placebo (Table 54). There were 2 sessions. All subjects participated in a single dose session (Session 1) and 7 days later, a 10-day repeat dose session (Session 2). Subjects received the same active dose (or placebo) in each of the two sessions.

Study Part 2 was an open-label, single sequence design (Table 54). Twenty-four subjects were enrolled to examine the potential for SB497115-GR to inhibit or induce CYP activity using probe substrates for CYP1A2, CYP2C9, CYP2C19, and CYP3A4. Subjects were admitted on Day –1 and received probe substrates on Day 1 or 2 followed by 7 days of once daily, repeat oral dosing of 75 mg SB497115-GR. Subjects received probe substrates again on Day 8 or 9.

Reviewer Comment: Sponsor did not address the issue of potential interactions between the drugs contained in the cocktail so this potential confounding issue can not be ruled out.

Table 54: Dosing Scheme for Part 1 and Part 2

REGIMEN	N	Dose (mg)
P	18	Placebo
A	9	5
B	9	10
C	9	20
D	9	30
E	10	50
F	9	75
G (CYP450)	24	75

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

SB-497115-GR was supplied by GSK as _____, gelatin capsules containing SB-497115-GR equivalent to 5.0 mg or 25.0 mg of SB-497115-GR free acid (Table 55). A matching placebo capsule was also supplied. Midazolam, caffeine, omeprazole and flurbiprofen are all available commercially and were obtained by the study site.

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Table 55: The Batch and Formulation Information For The Study Products

IMP	Batch number	Formulation Code	Substance Batch	Expiry date
SB-497115-GR (placebo)	U02104	1CF	N/A	30 Jun 2004
SB-497115-GR (1.0 mg)	U03024	AD	F033082 (Dartford)	Not Reported
SB-497115-GR (5.0 mg)	U03025	AE	F033082 (Dartford)	31 May 2005
SB-497115-GR (25.0 mg)	U03026 & 041019400	AF	F033082 (Dartford)	30 Sep 2005 & 31 Aug 2005
Midazolam (10 mg/2 mL)	B1110	N/A	N/A	Nov 2007
Flurbiprofen (50 mg)	1RR	N/A	N/A	Dec 2005
Pro plus (50 mg caffeine)	4C076	N/A	N/A	Mar 2007
Omeprazole (20 mg)	CA271	N/A	N/A	Nov 2006

In part 1 a single and repeat oral doses of 5, 10, 20, 30, 50 and 75 mg SB-497115-GR, or matching placebo, were given once daily in the morning on Day 1 of Session 1 and on Days 1 through 10 of Session 2. In part 2 SB-497115-GR was administered as 75 mg QD on Days 3 through 9. Single 5 mg doses of midazolam were administered on Days 1 and 8, and single 100 mg doses of caffeine, 20 mg doses of omeprazole, and 50 mg doses of flurbiprofen were administered on Days 2 and 9.

Subjects fasted for 8 h before all pharmacokinetic samples. Standard meals were provided in Session 1 on Day 1, Session 2 Days 1–10, and CYP interaction cohort Days 1–9. Breakfast was provided in Session 2 Days 1–9, and Days 3–7 of the CYP interaction cohort only, at approximately 1 h after dosing. Lunch was provided approximately 4–5 h after dosing. Dinner was provided approximately 9–10 h after dosing. An evening snack was permitted until 2200.

Subjects had to abstain from prescription or non-prescription drugs, within 7 days or 5 half-lives (whichever was longer) before first dose of study medication, and until the completion of the follow-up visit. No concomitant medication was permitted during the study. By exception, acetaminophen at doses of 2 g/day was permitted up until 24 h before pharmacokinetic/pharmacodynamic blood draws.

Criteria for evaluation:

- Sample size:
 - In part 1 the target sample size was 12 subjects per dose cohort (9 active, 3 placebo). A total of at least 36 subjects were to be studied. Sample size was based on feasibility, as no prior estimates of variability were available for the pharmacokinetic endpoints. The pharmacodynamic analysis was considered as secondary. However, assuming that mean baseline mean baseline platelet count in healthy subjects is to be $254.3 \times 10^9/L$ with a standard deviation (SD) of $48 \times 10^9/L$ (according to the preliminary data from the 001 study), and that we wish to be able to show that the maximum post-dose platelet count in an active group would be 50% higher than that for the placebo group, then 9 active subjects and 12 placebo subjects would be enough to show that difference with at least 90% power. Calculations were done using a 2-sided t-test and an alpha level of 0.05. Table 56 gives the power for detecting differences smaller than 50%, with the 9 active subjects and 12 placebo subjects completing the study.

Table 56: Sample Size Assumptions: Power Calculations

Mean baseline placebo ($\times 10^9/L$)	SD ($\times 10^9/L$)	% Increase over placebo	Mean baseline active ($\times 10^9/L$)	Power (%)
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254.3	48.0	40	356.0	> 90
		30	330.6	> 90
		20	305.2	≈ 67

A sensitivity analysis suggests this model is sensitive to the standard deviation assumption and a doubling of SD results in 85% power assuming a 50% increase in platelet count but power rapidly declines as the presumed platelet increase is reduced.

- In part 2 the CYP interaction cohort, the target sample size was 24 subjects. Based on the largest estimate of within-subject variability for the CYP substrates being studied (81.05% for omeprazole/5'-hydroxyomeprazole ratio and a sample size of 24 subjects, the half-width of the 90% confidence interval (CI) about the ratio of interest SB-497115-GR+ CYP multi-drug cocktail: CYP multi-drug cocktail should be no more than 43% of the point estimate. A sensitivity analysis was done, in case the variability proved greater than estimated. An upper bound of the 90% CI for the variability of omeprazole/5'-hydroxyomeprazole ratio was determined to be 119.5%. Based on that larger variability, and a sample size of 24 subjects, the half-width of the 90% CI about the ratio of interest SB-497115-GR+ CYP multi-drug cocktail: CYP multi-drug cocktail should be no more than 60% of the point estimate.
- Pharmacokinetics:
 - Sampling
 - Blood samples (2.7 mL) for SB-497115 pharmacokinetics analysis were collected over a 24-h period on Day 1 Session 1, and Day 10 Session 2, at the following times: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 h after SB-497115-GR administration. In addition, PK samples were collected in Session 1 at 48 h, and in Session 2 at pre-dose, and 1, 2, and 4 h post-dose on Day 4 and Days 5, 8, and 9 (predose).

Reviewer Comment: Given the 21-32 hour half-life of eltrombopag, the ability to accurately characterize the terminal phase of the plasma concentration curve given the above sampling schedule is concerning.
 - Midazolam (CYP3A4): blood samples were collected on Days 1 and 8 at pre-dose, and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 h post-dose.
 - Caffeine and paraxanthine (CYP1A2): blood samples were collected on Days 2 and 9 at pre-dose, and 4 and 8 h post-dose.
 - Omeprazole and 5-hydroxyomeprazole (CYP2C19): blood samples were collected on Days 2 and 9 at pre-dose, and 2 and 3 h post-dose.
 - Flurbiprofen and 4-hydroxyflurbiprofen (CYP2C9): urine was collected on Days 2 and 9 over 0–8 h and 8–12 h post-dose.
 - Plasma pharmacokinetic parameters were calculated by non-compartmental methods using the computer program WinNonlin Professional, Version 4.1. Calculations were based on actual collection times recorded during the study. The maximum observed eltrombopag plasma concentration (C_{max}), time of C_{max} (t_{max}), and the concentration at the end of the dosing interval at steady-state (C_T) were obtained directly from the SB-497115 concentration-time data. Areas under the concentration-time curve (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. Area under the plasma concentration-time curve from the time of

dosing extrapolated to infinity ($AUC(0-\infty)$) was estimated as the sum of the AUC calculated from time zero until the last measurable concentration ($AUC(0-t)$) and C_t divided by the terminal elimination rate constant (λ_z). The AUC over a dosing interval ($AUC(0-\tau)$) was calculated from time zero to 24 hours after dosing. The terminal elimination rate constant 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 ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$.

- All SB-497115 pharmacokinetic parameters including single dose $AUC(0-\tau)$, $AUC(0-\infty)$, $\%AUC_{ex}$, C_{max} , t_{max} and $t_{1/2}$ and repeat dose $AUC(0-\tau)$, C_{max} , t_{max} , $t_{1/2}$, and C_T were descriptively summarized by dose and day. To assess accumulation of SB-497115 upon multiple dosing, an ANOVA model with effects for subject and day was fitted to loge-transformed R_o (Day 10 $AUC(0-\tau)$ / Day 1 $AUC(0-\tau)$) and RC_{max} (Day 10 C_{max} / Day 1 C_{max}) for each dose group. The accumulation ratios were estimated by exponentiating the difference in least squares means (Day 10 – Day 1) and the associated CI, to provide point and 90% CI estimates for the ratio Day 10: Day 1, as data permitted. To assess time invariance of SB-497115 pharmacokinetics, an ANOVA model with effects for subject and day was fitted to loge-transformed R_s (Day 10 $AUC(0-\tau)$ / Day 1 $AUC(0-\tau)$) for each dose group. Time invariance was estimated by exponentiating the difference in least squares means (Day 10 – Day 1) and the associated 90% CI, to provide point and 90% CI estimates for the ratio Day 10:Day 1, as data permitted. Dose proportionality was assessed by fitting the Power Model, relating log-transformed plasma SB-497115 single dose $AUC(0-\infty)$ and C_{max} and repeat dose $AUC(0-\tau)$ and C_{max} to log-transformed dose (log-transformed pharmacokinetic parameter = $\alpha + \beta * \log$ -transformed dose), by restricted maximum likelihood using SAS Version 8.2 MIXED procedure. The common slope was estimated and the associated 90% CI was constructed to examine linearity.
- Plasma caffeine and paraxanthine (CYP1A2) concentrations were collected predose and at 4 and 8 hours after dosing; no PK parameters were calculated. Similarly, plasma omeprazole and 5-hydroxyomeprazole (CYP2C19) concentrations were collected predose and at 2 and 3 hours after dosing; no PK parameters were calculated. Plasma midazolam (CYP3A4) $AUC(0-\infty)$, C_{max} , t_{max} , $t_{1/2}$, were calculated as described for SB-497115. In addition, plasma midazolam apparent clearance following oral administration (CL/F) was calculated as $Dose/AUC(0-\infty)$. Urine recovery of flurbiprofen and 4-hydroxyflurbiprofen (CYP2C9) were calculated by multiplying the observed concentration in urine by the total urine volume collected during the 12-h post dose period.
- The impact of SB-497115 on the various CYP isozymes was assessed as follows:
 - CYP1A2: comparing plasma paraxanthine/caffeine concentration ratios at 8 hours post-dose on Day 9 versus Day 2.
 - CYP2C9: comparing the urine total 4-hydroxyflurbiprofen recovery ratio over 12 hour post-dose on Day 9 versus Day 2.
 - CYP2C19: comparing plasma omeprazole/5'-hydroxyomeprazole concentration ratios at 2 and 3 hours post-dose on Day 9 versus Day 2.
 - CYP3A4: comparing plasma midazolam $AUC(0-\infty)$ on Day 8 versus Day 1.

After log_e-transformation, the endpoints were separately analyzed fitting an ANOVA model with terms for subject and regimen using the pharmacokinetic population. The point estimates of the regimen mean differences and associated 90% CI were then exponentially back-transformed to provide point and 90% CI estimates for the ratio SB- 497115-GR plus CYP multi-drug cocktail: CYP multi-drug cocktail alone, for each CYP probe substrate separately.

- Plasma samples were analyzed for SB-497115 using a validated analytical method based on protein precipitation followed by high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) employing positive-ion electrospray ionization (Table 57). The lower limit of quantification (LLQ) for SB-497115 was 10 ng/mL using a 50 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 2500 ng/mL

Table 57: Assay validation information

Eltrombopag is extracted from 50µL human plasma by protein precipitation using _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	10.0ng/mL
Validated Range	10.0 to 2500ng/mL
Within-run Precision (%CV)	≤6.5%
Between-run Precision (%CV)	≤2.2%
Accuracy (%Bias)	-0.3% ≤ bias ≤9.9%
Stability in Human Plasma	3 freeze-thaw cycles at -20°C at least 24 hours at ambient temperature
Processed Extract Stability	at least 24 hours at ambient temperature

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

- Plasma samples were analyzed for caffeine using a validated analytical method based on protein precipitation followed by HPLC/MS/MS. The LLQ for caffeine and paraxanthine was 50 ng/mL using a 100 µL aliquot of human plasma, with a HLQ of 5000 ng/mL

Reviewer Comment: Information regarding the validation of this assay was not provided by the sponsor. Therefore, whether or not this assay was validated in a manner consistent with the guidance "Bioanalytical Method Validation" could not be assessed.

- Plasma samples were analyzed for omeprazole and 5-hydroxyomeprazole a validated analytical method based on _____ followed by HPLC/MS/MS. The LLQ for omeprazole and 5-hydroxyomeprazole was 1 ng/mL using a 100 µL aliquot of human plasma, with a HLQ of 1000 ng/mL.

b(4)

Reviewer Comment: Information regarding the validation of this assay was not provided by the sponsor. Therefore, whether or not this assay was validated in a manner consistent with the guidance "Bioanalytical Method Validation" could not be assessed.

- Plasma samples were analyzed for midazolam using a validated analytical method based on protein precipitation followed by HPLC/MS/MS. The LLQ for midazolam was 0.5 ng/mL using a 100 µL aliquot of human plasma, with a HLQ of 500 ng/mL.

Reviewer Comment: Information regarding the validation of this assay was not provided by the sponsor. Therefore, whether or not this assay was validated in a manner consistent with the guidance "Bioanalytical Method Validation" could not be assessed.

- Urine samples were analyzed for flurbiprofen and 4-hydroxyflurbiprofen using a validated analytical method based on _____ followed by HPLC/MS/MS analysis. The LLQ for flurbiprofen was 0.25 µg/mL using a 50 µL aliquot of human urine, with a HLQ of 50 µg/mL. The LLQ for 4-hydroxyflurbiprofen was 0.5 µg/mL using a 50 µL aliquot of human urine with a HLQ of 25 µg/mL. Concentrations of flurbiprofen and 4-hydroxyflurbiprofen were determined for both untreated urine and urine treated with the enzyme β-glucuronidase, therefore giving estimates of free and total concentrations of these two analytes in human urine.

b(4)

Reviewer Comment: Information regarding the validation of this assay was not provided by the sponsor. Therefore, whether or not this assay was validated in a manner consistent with the guidance "Bioanalytical Method Validation" could not be assessed.

- Pharmacodynamics:

- Blood samples for platelet count, and peripheral blood smear and reticulated platelet count were obtained at screening, in Session 1 on Day 1 (pre-dose and 24 h post-dose), Day 3 and Day 5, and in Session 2 on Day 1 (pre-dose and 24 h post-dose) and Days 3, 5, 7, 8, 10 (pre-dose and 24 hrs post-dose), 12, 14, 16, 18, 22 and at follow-up. Blood samples were obtained in Session 1, on Day 1 (pre-dose) and Day 5, and in Session 2, on Days 1, 5, 10, and 12, and at follow-up for platelet aggregation, TPO serum levels, activation markers (P-Selectin and PAC-1).
- The primary focus of the statistical analysis of the pharmacodynamic data was to estimate the effect of each active dose of SB-497115-GR on the pharmacodynamic endpoints relative to placebo. Particular interest was given to platelet counts. Maximum post-dose platelet count was analyzed by ANOVA, fitting a term for regimen. Baseline data were included in the analysis as a covariate. Point estimates and 95% CI were derived for the comparisons of interest (i.e. Active-Placebo for each dose level of SB-497115-GR). Platelet data were loge-transformed as appropriate, and results were also presented as ratios (Active: Placebo) with 95% CI. Model-based pooled between-subject variability estimates were derived using a repeated measures model. No formal statistical analysis of the pharmacokinetic/pharmacodynamic data was planned or done.
- TPO was assayed by ELISA. Platelet activation was evaluated by flow cytometry for P-selectin and PAC-1 binding. Reticulated platelet count was determined by flow cytometry using thiazole orange staining. Platelet count, peripheral blood smear, neutrophil count, and platelet aggregation were determined. Platelet aggregation was determined in platelet rich plasma (PRP) and platelet poor plasma (PPP) samples. Samples were assayed using the currently approved analytical methods.

Reviewer Comment: Information regarding the validation of these methods was not provided by the sponsor. Therefore, it could not be assessed by the reviewer.

- 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: Seventy-three subjects entered and were randomized into Cohorts A-F. Four subjects were withdrawn from the study. Subject 3 was withdrawn because he was unable

to attend for the follow-up ultrasound. He had received all the planned doses of SB- 497115-GR. Subject 48 was withdrawn on Session 2, Day 8 but returned for all outpatient visits on Days 12–28. One subject (Subject 51) withdrew his consent after Session 1 and was replaced. Subject 67 was withdrawn because, after dosing in Session 1, his PK data came close to the toxicology threshold. The subject was unable to return at a later date for follow-up. Twenty-four subjects entered into Cohort G. There were no withdrawals from this group.

The 'Safety' population which was used for all safety summaries consisted of all 97 subjects (all available data) who received at least one dose of SB-497115-GR or placebo. The Pharmacokinetic population consisted of 52 subjects (part 1) and 24 subjects (part 2). All 73 subjects were included in the Pharmacodynamic population.

Population Demographics

The population demographics from this study are listed in the table below

Table 58: Population Demographics (mean (range))

	Part 1							Part 2	Total
	Placebo	5 mg	10 mg	20 mg	30 mg	50 mg	75 mg	75 mg (CYP cohort)	
Number of subjects	18	9	9	9	9	10	9	24	97
Race:									
Asian	0	0	0	0	1	0	0	1	2
Indian	0	0	0	1	0	0	0	0	1
Black	0	0	1	0	1	0	0	1	3
White	17	9	8	8	7	10	8	22	89
Other	1	0	0	0	0	0	1	0	2
Age (y)	25.8 (20–40)	24.6 (19–42)	25.6 (19–30)	25.6 (19–45)	24.2 (19–30)	24.8 (18–36)	26.3 (21–37)	25.3 (19–34)	25.3 (18–45)
Height (cm)	180.1 (170–194)	177.7 (163–187)	177.8 (164–186)	181.3 (174–190)	181.0 (170–200)	181.0 (164–196)	180.0 (171–195)	181.3 (170–198)	180.0 (163–200)
Weight (kg)	80.1 (64.1–91.4)	75.1 (61.8–94.0)	77.6 (65.9–93.9)	77.3 (64.4–94.8)	79.0 (69.0–92.2)	78.5 (57.4–90.7)	72.4 (59.0–87.2)	81.3 (62.8–97.7)	77.7 (57.4–97.7)

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Results-PK analysis:

Part 1

Selected plasma PK parameters are listed in Table 59 below. Mean plasma eltrombopag concentration-time profiles for single and repeat dosing are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figures 15 and 16.

Table 59: Selected PK parameters

Dose (mg)	Day	t _{max} (h) ^a	C _{max} (h) ^b	t _{1/2} (h) ^b	AUC(0–τ) (μg.h/mL) ^b	AUC(0–∞) (μg.h/mL) ^b
5	1	2.50 (2–4)	0.318 (25)	10.13 (36)	2.98 (30)	3.65 (35)
	10	4.00 (2–6)	0.333 (24)	8.63 (17)	3.44 (30)	
10	1	3.00 (2–6)	0.625 (32)	16.14 (27)	6.08 (30)	8.72 (35)
	10	3.00 (2–6)	0.700 (32)	12.48 (48)	7.67 (34)	
20	1	3.00 (2–6)	1.27 (28)	14.70 (21)	12.17 (31)	16.31 (41)
	10	4.00 (2–6)	1.53 (36)	12.65 (26)	16.80 (37)	
30	1	2.50 (1.5–4)	2.64 (31)	15.69 (11)	21.21 (27)	29.10 (28)
	10	3.00 (2–4)	2.97 (25)	12.30 (15)	28.99 (28)	
50	1	3.00	4.98	17.96	48.84	57.77

		(2-4)	(34)	(17)	(32)	(34)
	10	4.00 (2-6)	5.76 (29)	12.90 (12)	57.43 (28)	
75	1	4.00 (2.1-6)	6.03 (30)	16.05 (35)	50.72 (28)	71.84 (37)
	10	5.00 (2-10)	7.27 (15)	14.40 (49)	79.03 (23)	

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

Reviewer Comment:

- Greater than 50% of the subjects studied had AUCext > 10% (10.1(6.9, 12.6) (median (25th, 75th)). This was not reported by the sponsor.
- Given a pre-dose (time 0) sample was not collected prior to beginning session two the potential for carryover from session one could not be assessed by the reviewer. It is important to note that Japan study 104603 showed quantifiable concentrations following a 12 day wash-out period.
- ~16% (302/1923) of the plasma concentration samples were above the HLQ for the assay. This was not reported by the sponsor.
- The very small (n=4) number of Africa American subjects in this study showed a ~12-15% higher exposure compared to Caucasian subjects. While inconclusive by itself it does add to the findings of studies 105122, 102861, and 105120 where some African Americans showed a trend toward a 1.6-2 fold increase compared to Caucasians.

Figure 15: Mean plasma SB-497115 concentration (Single-Dose)

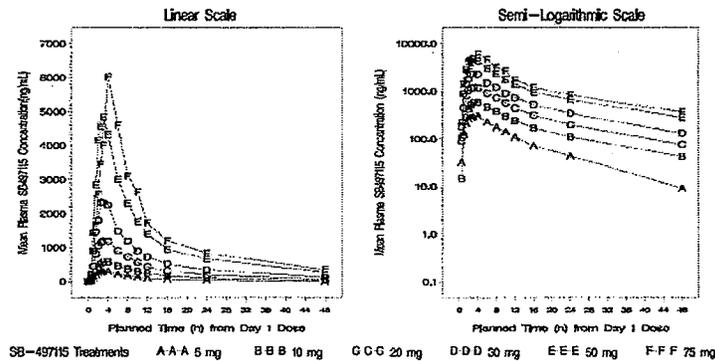
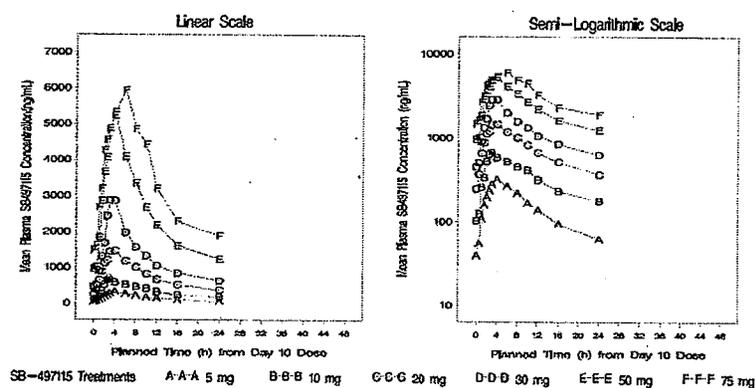


Figure 16: Mean plasma SB-497115 concentration (Repeat-Dose)

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Accumulation was assessed by comparing AUC(0-t) (Ro) and Cmax (Rmax) on Day 10, with comparable measures on Day 1, at each dose level. Time dependence in plasma SB-497115 pharmacokinetics was assessed by comparing AUC(0-t) on Day 10 with AUC(0-∞) on Day 1, at each dose level. See Table 60 for the analysis of accumulation and time invariance.

Table 60: Summary of Plasma SB497115 Analysis of Accumulation and Time Invariance (red values statistically significant)

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

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

Reviewer Comment: Sample size was based on the pharmacodynamic outcome so it can not be assumed that this analysis was adequately powered. The reviewer agrees that a trend toward accumulation and time invariance was demonstrated.

When comparing all cohorts, single dose plasma SB-497115 AUC(0-∞) and Cmax increased with increasing dose in a slightly greater than dose proportional manner (Table 61). However, when doses greater than 20 mg were evaluated there was a trend toward dose proportionality. A similar trend was noted for the evaluation of steady state.

Table 61: Summary of the Analysis of Dose Proportionality

	Parameter	90% CI		
		Slope	Lower	Upper
All Regimens				

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

Reviewer Comment: Sample size was based on the pharmacodynamic outcome so it can not be assumed that this analysis was adequately powered. The reviewer agrees that a trend toward accumulation and time invariance was demonstrated.

Part 2

The geometric least-squares mean (LS mean) for metabolic indices, and 90% CI for the ratio of the mean index after and before dosing with SB-497115-GR, for CYP 1A2, 2C9, and 2C19 are presented in Table 62. The ratio of the mean metabolic index, before and after treatment with SB-497115-GR, was were within the range of 0.80–1.25.

Table 62: Summary of Metabolic Indices

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

Summary statistics of the pharmacokinetic parameter estimates for midazolam before and after treatment with SB-497115-GR are presented in Table 63. The 90% CI for all parameters were contained within the range 0.8–1.25.

Table 63: Midazolam (CYP 3A4 probe) Pharmacokinetic Parameter Estimates

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

Reviewer Comment: The sponsor states that CYP 2C8 was not studied in vivo, but its in vitro potency for inhibition was similar to that for inhibition of CYP2C9 (IC50 values of 24.8 μM (CYP 2C8) and 20.2 μM (CYP 2C9)) and therefore "eltrombopag is not expected to interact with CYP2C8 substrates in vivo." While theoretically possible the reviewer believes the effect of eltrombopag on CYP 2C8 substrates to be unknown at this time.

Results- Pharmacodynamic Analysis:

The maximum changes in platelet count from baseline are summarized in Table 64. The log_e transformed ratios (active/placebo) of the maximum change in platelet count from baseline are summarized in Table 65. Single doses of SB-497115-GR had no consistent effect on platelet count. Repeated doses of SB-497115-GR caused a dose-related increase in platelet count, which reached a maximum at approximately Day 16, which was 6 days after the last dose of SB-497115-GR. There was no significant difference between 5, 10, or 20 mg repeat doses of SB-497115-GR and placebo. For the 30, 50, and 75 mg repeat dose SB-497115-GR versus placebo comparisons, the log_e transformed maximum change in platelet count from baseline showed a 2–3 fold increase, and a trend toward increasing with increasing dose.

Table 64: Summary of Platelet Count Maximum Change from Baseline (Platelet Count (10⁹/L))

Treatment		n	Mean	SD	Min.	Max.
P	Baseline	17	222.6	49.0	132	316
	Maximum Value Post-Baseline	17	270.5	52.9	180	337
	Maximum Change from Baseline	17	47.9	28.8	7	117
A	Baseline	9	206.1	40.9	121	246
	Maximum Value Post-Baseline	9	250.8	44.0	156	280
	Maximum Change from Baseline	9	44.7	17.9	20	80
B	Baseline	9	225.7	54.9	162	326
	Maximum Value Post-Baseline	9	290.9	77.0	192	440
	Maximum Change from Baseline	9	65.2	34.1	29	115
C	Baseline	9	223.9	30.4	176	257
	Maximum Value Post-Baseline	9	284.6	51.0	207	375
	Maximum Change from Baseline	9	60.7	31.7	23	122
D	Baseline	9	219.1	34.5	133	244
	Maximum Value Post-Baseline	9	322.8	44.2	266	381
	Maximum Change from Baseline	9	103.7	36.4	50	152
E	Baseline	10	209.0	42.1	155	292
	Maximum Value Post-Baseline	10	352.3	79.3	182	457
	Maximum Change from Baseline	10	143.3	51.6	27	211
F	Baseline	9	207.6	41.0	154	280
	Maximum Value Post-Baseline	9	359.6	42.0	286	401
	Maximum Change from Baseline	9	152.0	43.7	67	219

Table 65: Summary of log_e transformed platelet count maximum change from baseline

Comparison	Ratio (active/placebo)	95% CI
5 mg vs placebo	1.06	0.68–1.67
10 mg vs placebo	1.46	0.93–2.28
20 mg vs placebo	1.36	0.87–2.13
30 mg vs placebo	2.48	1.58–3.89
50 mg vs placebo	3.29	2.12–5.09
75 mg vs placebo	3.71	2.36–5.83

Reviewer Comment:

- Based on the sample size assumptions above the 5-20 mg cohorts may have been underpowered.
- The sponsor's log_e transformation makes the ratio appear greater than has been demonstrated (see table 66).

Table 66: Reviewer Generated Summary of non-log_e transformed platelet count maximum change from baseline

Comparison	Ratio (active/placebo)
5 mg vs placebo	0.933194
10 mg vs placebo	1.361169
20 mg vs placebo	1.267223
30 mg vs placebo	2.164927
50 mg vs placebo	2.991649
75 mg vs placebo	3.173278

There was no relevant change from baseline, in reticulated platelet count, at any dose level. After the single doses of active drug, there was a trend towards a decrease in serum TPO concentration from baseline, at all dose levels which was not evident in the placebo group. After the repeated doses, there was no consistent change from baseline, at any dose level. There was no significant change from baseline in PAC-1 %, at any dose level.

Results-Safety:

Fifty-eight subjects (59.8 %) reported 118 AEs after dosing during the study. The most common AE's were headache (19%), pharyngolaryngeal pain (8%), abdominal pain (5%), Fatigue (5%), cough (4%), nasal congestion (4%), rhinitis (4%), and epistaxis (3%). Most AE's were mild in intensity except for the following moderate intensity AE's: headache (2%), dyspepsia (2%), pharyngolaryngeal pain (1%), orthostatic hypotension (1%), backpain (1% (placebo)), and influenza (1%). No subjects experienced a non-fatal SAE or died.

Reviewer Comment: *There does not appear to be a dose-related change in the incidence or intensity of AE's in this relatively small study.*

There were no significant changes in any laboratory value over time. Sixteen subjects had at least one value outside any threshold range. Those values were flagged as abnormalities of potential clinical concern. Increased bilirubin (n=5), increased glucose (n=1), increased albumin (n=2), decreased protein (n=1), decreased sodium (n=1), decreased WBC (n=1), increased AST (n=1), increased WBC (n=1), increased sodium (n=1), and increased potassium (n=2) relative to the normal range were reported but not considered clinically significant.

Reviewer Comment: *There does not appear to be an exposure-related incidence of liver function test abnormalities in this relatively small study.*

SB-497115-GR had no consistent effect on mean systolic and diastolic blood pressure and there were no changes that were clinically significant. There were no clinically significant changes in heart rate. Three subjects reported significant orthostatic hypotension. One subject had orthostatic hypotension reported as an AE (moderate intensity), which occurred on Day 9, 6 h 6 min after dosing and lasted for 18 min. All 12-lead ECGs were judged by the study physician to

be within normal limits, and no ECG results gave cause for concern. All subjects had a QTc interval of ≤ 470 msec.

Conclusions (sponsor):

- Single and repeat oral doses of 5–75 mg SB-497115-GR were well-tolerated.
- No accumulation of plasma SB-497115 AUC(0- τ) was observed after QD dosing of 5 mg and 10 mg; however, 37–56% accumulation was observed after QD dosing of 20 mg, 30 mg, 50 mg, and 75 mg for 10 days.
- No time dependent changes in plasma SB-497115 pharmacokinetics were observed across the dose levels.
- Single dose plasma SB-497115 AUC(0- ∞) and Cmax values increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90% CI) 1.13 (1.04, 1.22) for AUC(0- ∞) and 1.15 (1.07, 1.24) for Cmax over a range of 5 mg to 75 mg.
- Steady-state plasma SB-497115 AUC(0- τ) and Cmax increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.19 (1.11, 1.26) for AUC(0- τ) and 1.20 (1.12, 1.27) for Cmax over a range of 5 mg to 75 mg QD.
- SB-497115, administered as 75 mg QD for 7 days, did not inhibit or induce the metabolism of probe substrates for CYP 1A2, 2C9, 2C19, and 3A4 in healthy male subjects.
- There were 2–3 fold, dose-related increases in platelet count after repeated 30, 50, and 75 mg oral doses of SB-479115. However, platelet function, as measured by platelet aggregation and activation, was not affected by the administration of eltrombopag, with similar results observed in subjects administered placebo and active study medication.

Reviewer Comment: The reviewer believes the effect of eltrombopag on CYP 2C8 substrates to be unknown at this time.

4.3.7 Study TRA102860 Phase 1 Healthy PK/PD/QTc Dose escalation

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

Title: A Two-Part, Randomized, Placebo-Controlled Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of Single, Oral Doses of the Thrombopoietin 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

Study period: 13 March 2006- 02 August 2007

Objectives:

Primary

Part 1:

- To assess the safety and tolerability of eltrombopag in healthy adult subjects after five daily oral doses of 100 mg, 150 mg and 200 mg.

Part 2:

- To determine the effect of repeat daily doses of 50 mg and 150 mg eltrombopag (therapeutic and supratherapeutic doses respectively) on QTcF as compared to placebo and an active comparator.

Secondary

Part 1

- To describe the pharmacokinetics (PK) of eltrombopag in healthy adult subjects at doses of 100 mg, 150 mg and 200 mg.
- To estimate the pharmacodynamic (PD) effect of eltrombopag in healthy adult subjects after five daily oral doses of 100 mg, 150 mg and 200 mg as measured by peripheral platelet count.

Part 2

- To characterize the effect of multiple daily oral dosing of 50 mg and 150 mg of eltrombopag and a single 400 mg dose of moxifloxacin on QT, QTc, QTcB and heart rate relative to placebo.
- To characterize the pharmacokinetics of eltrombopag and moxifloxacin.
- To assess the safety profile of eltrombopag at 50 mg and 150 mg dose levels.
- To estimate the pharmacodynamic effect of eltrombopag in healthy volunteers after multiple daily oral dosing of placebo, 50 mg and 150 mg of eltrombopag and a single 400 mg dose of moxifloxacin as measured by peripheral platelet count.

Methodology:

This was a two-part study conducted in healthy adult subjects enrolled at three study centers. Subjects participating in Part 1 did not participate in Part 2. Each part was composed of screening, treatment, and follow-up phases. For Part 1, the total duration of each subject's participation in the study, from screening through follow-up, was a maximum of eight weeks. For Part 2, the total duration of each subject's participation, from screening through follow-up, was a maximum of approximately 18 weeks.

Part 1 was a double-blind, placebo-controlled, randomized, parallel, repeat dose escalation study to investigate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of eltrombopag dosed as 100 mg, 150 mg, and 200 mg once daily (QD) for five days. At least ten subjects were to be enrolled at each dose level (8 active and 2 placebo). Subjects who were discontinued prior to completing the study in Part 1 were replaced. Sufficient subjects were enrolled in Part 2 so subjects who discontinued prior to completion of the study were not replaced.

The results from Part 1 were used to select the highest safe eltrombopag dose and regimen (single or repeat dose) for Part 2. The goal was not to exceed a mean observed platelet count of above $400 \times 10^9/L$ at any time on the study or during follow-up. Based on these platelet criteria and the absence of any other safety signal, eltrombopag 150 mg QD for five days was selected as the high-dose eltrombopag regimen for Part 2. Therapeutic dosing in current studies is 50 mg QD.

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. Subjects received each of four regimens in a randomized crossover fashion, as summarized in Table 67 below. There was a wash-out period of at least 14 days between each study period

Table 67: Study Design for Part 2 of TRA102860

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

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

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

Eltrombopag was supplied as 25 mg and 50 mg tablets and moxifloxacin was supplied as 400 mg tablets; matching placebo was provided for both eltrombopag and moxifloxacin. Investigational products and batch numbers used in this study are summarized in Table 68.

Table 68: Investigational Products and Batch Numbers

Drug	Strength	Formulation code	Substance Batch	Batch Number
Eltrombopag	25 mg	AS	F081598 F081601 (Tonebridge)	051109557 051109558
Eltrombopag	50 mg	AR	F081598 (Tonebridge)	051109563
Placebo (eltrombopag)	N/A	APV	N/A	051074350
Moxifloxacin	400 mg	N/A	N/A	5400L1H / 5400W1H / 5400W1H / 5400NL8 /
Placebo (moxifloxacin)	N/A	N/A	N/A	061084880.

b(4)

Criteria for evaluation:

- Sample Size:
 - Part 1: Convenience sample allowing a sufficient number of subjects to be enrolled to ensure at least eight subjects completed each eltrombopag dose level in Part 1 of the study.
 - Part 2: A sufficient number of subjects were enrolled to ensure at least 40 subjects completed Part 2 of the study. Based on assumed true mean difference of 0 msec and within-subject variability estimate of 10 msec, 40 subjects would provide overall power of at least 99% to demonstrate a lack of effect on the QTc interval at each time point. A power of 99% at each time point allowed the overall power to be retained at 90%. A lack of effect on any active dose as compared to placebo would be concluded if the upper 90% confidence interval (CI) was less than or equal to 10 msec. Calculations were based on one-sided testing procedure with a Type I error rate of 5%. No adjustment to the Type I error rate for multiple comparisons was made.
- Pharmacokinetics
 - Serial blood samples were collected for the determination of drug concentrations in plasma in Part 1 and Part 2 as presented in Table 69.

Table 69: PK Sample Collection

Day	Analyte	Planned Time Relative to Dose (hours)
Part 1: Day 1 and Day 5	eltrombopag	pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24 h post-dose
	placebo	
Part 2: Day 5	eltrombopag	pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 h post-dose
	moxifloxacin	

- PK analysis of plasma eltrombopag concentration-time data was conducted using the noncompartmental Model 200 of WinNonlin Professional Edition version 4.1. Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects.
 - Values for the following plasma eltrombopag PK parameters were estimated on Day 1 and 5 of Part 1 of the study:
 - The maximum observed plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were the actual observed values.
 - 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 the end of the dosing interval (AUC(0-τ)) were determined.
 - The observed accumulation ratio (R_o) and C_{max} ratio (R(C_{max})) were calculated as AUC(0-τ) Day 5 / AUC(0-τ) Day 1 and C_{max} Day 5 / C_{max} Day 1, respectively.
 - Values for the following plasma eltrombopag PK parameters were estimated on Day 5 of Part 2 of the study:
 - C_{max}, t_{max}, AUC(0-τ), and the concentration at the end of the dosing interval (C_τ)
 - Values for the following plasma moxifloxacin PK parameters were estimated following administration of a single dose of moxifloxacin on Day 5 of Part 2 of the study:
 - C_{max}, t_{max}, AUC(0-t)
- Plasma samples were analyzed for eltrombopag using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis (Table 70). The LLQ for eltrombopag was 100 ng/mL, using a 50 μL aliquot of human plasma with a higher limit of quantification of 50,000 ng/mL.

Table 70: Assay validation information

Eltrombopag is extracted from 50μL human plasma by protein precipitation using _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	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.

- Human plasma samples were analyzed for moxifloxacin concentrations using validated methods. Moxifloxacin was extracted from human plasma by protein precipitation. Extracts were analyzed by high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS). The assay was

validated over the moxifloxacin concentration range of 25 to 5,000 ng/mL in human plasma.

Reviewer Comment: Information regarding the validation of this assay was not provided by the sponsor. Therefore, whether or not this assay was validated in a manner consistent with the guidance "Bioanalytical Method Validation" could not be assessed.

- Pharmacodynamics:

- Blood samples were collected for PD assessments of platelet count, blood smears and platelet aggregation (Part 1 only) for subjects receiving eltrombopag and placebo; collection times are presented in Table x.

Table 71: PD Sample Collection: Platelet Count and Platelet Aggregation

Part 1 ¹	Day - 1; pre-dose on Day 2, 3, and 5; follow-up on Day 14 (± 3 days) and Day 28 (± 3 days); in addition, platelet count was obtained on Day 21 (± 3 days).
Part 2 ²	Day - 2; platelet counts were obtained pre-dose on Day 2, 3, and 5; follow-up on Day 14 (± 3 days) and Day 33 (± 3 days) following the last (4th) study period; platelet counts were also obtained on Day 14 after study period 1, 2, and 3.

1. If a subject had a change in PD parameters that had not returned to baseline by Day 28 (± 3 days), an additional follow-up visit was required between Day 40 to Day 45.

2. If a subject had a change in PD parameters that had not returned to baseline by Day 33 (± 3 days), an additional follow-up visit was required between Day 40 to Day 45.

- Platelet count, peripheral blood smear, and platelet aggregation were descriptively summarized by treatment and time point for Part 1; for Part 2, only platelet counts were performed.
 - In Part 1, maximum platelet count was analyzed by fitting an analysis of covariance (ANCOVA) after loge-transformation, including the period and regimen as fixed effect.
 - In Part 2, mixed effects ANCOVA was fitted after loge-transformation, including the period and regimen as fixed effect and subject as a random effect. Baseline data were included in the analysis as a covariate. Point estimates and 95% CIs were constructed for the comparisons of interest using ratio (Active/Placebo for each dose of eltrombopag).
- Definitive QTc Analyses (Part 2 Only)
 - Holter monitoring was performed for QTc analysis. The primary endpoints change from baseline QTcF were analyzed by analysis of covariance (ANCOVA) fitting terms appropriate to the study design, including sequence, period, regimen, time and time-by-regimen interaction as fixed effects and subject as a random effect. Baseline QTcF was included in the model as a covariate. Point estimates and 90% CIs were constructed for the difference, active vs. placebo, for 50 mg eltrombopag and 150 mg eltrombopag at each time point using the residual variance. A lack of effect on the QTcF interval was pre-specified as the upper 90% CI value less than or equal to 10 msec. Replicates at each time point were averaged first prior to the analysis. Secondary endpoints (including change from baseline QTcB and QTci) were similarly analyzed. Distributional assumptions underlying the analyses were assessed by residual plots. Homogeneity of variance was assessed by plotting the studentised residuals against the predicted values from the model, whilst normality was examined by normal probability plots. If assumptions were grossly violated, alternative analyses were performed. An outlier analysis to determine the number and percentage of subjects in which an increase from baseline in QTc greater than 30 msec and

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greater than 60 msec occurred for each regimen was performed when appropriate.

○ Cp/ddQTc Analysis

- Exploratory graphical displays assessed the shape of the potential relationship between plasma eltrombopag concentrations and ddQTcF. Linear correlations of plasma eltrombopag and moxifloxacin concentrations and ddQTcF were plotted with a fitted regression line superimposed.
- A population plasma drug concentration (Cp)-ddQTcF modeling approach was applied using the non-linear mixed effects modeling software NONMEM Version 5. A user defined control stream written in \$PRED was employed using first-order conditional estimation with interaction (FOCE).
- A linear relationship with no delay in the effect of concentration on ddQTcF was the base model evaluated for eltrombopag. The base model was: $ddQTcF = \Theta_1 + \eta_1 + \Theta_2 \cdot Cp + \eta_2 + \epsilon_1$
 - Where Θ_1 is the pre-dose ddQTc on Day 5 (intercept) and Θ_2 is the slope relating plasma drug concentration to ddQTc, η_1 is the inter-subject variability in pre-dose ddQTc and η_2 is the inter-subject variability in the slope, Cp is the plasma drug concentration, and ϵ_1 is random residual variability.
- The stability of the model parameter estimates for ddQTcF versus plasma eltrombopag concentration were examined using the bootstrap technique using Wings for NONMEM. The final Cp-ddQTcF model was fitted to bootstrap samples until 500 datasets successfully converged.
- Based on the final Cp-ddQTcF model, simulations were performed to predict ddQTcF at therapeutic and suprathreshold plasma eltrombopag concentrations (at Cmax). Simulations were performed to predict the mean (90% CI) for ddQTcF at eltrombopag doses of 50 mg QD, 150 mg QD, and 300 mg QD. Dose proportionality and constant coefficient of variation for Cmax were assumed for extrapolation to doses which were not studied (300 mg QD). Simulations of 1000 replicate studies were generated for each dose level. The mean ddQTcF was calculated for each study. The 5th and 95th percentiles of the distribution of study means were used to estimate the 90% CI.

• 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) (Table 72), were listed and summarized. No formal statistical analyses of the safety data were performed.

Table 72: ECG Assessments

Assessment	Day	Planned Time Relative to Dose
Part 1		
12-Lead ECG	1, 2, 3, 4, 5, 6	pre-dose, 1, 2, 4, 6 h
Telemetry	1 through 5	at least 6 h pre-dose on Day 1 until at least 24 h after last dose on Day 5
Part 2		
12-Lead ECG	1, 2, 3, 4, 5, 6	pre-dose, 1, 2, 3, 4, 6 h and 24 h post-dose

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Holter Monitoring	-1	pre-dose, 0.5, 1, 2, 3, 4, 6, 12, 23.25 h post-dose
	5	pre-dose, 0.5, 1, 2, 3, 4, 6, 12, 23.25 h post-dose
Telemetry	1 through 5	at least 6 h pre-dose on Day 1 until at least 24 h after last dose on Day 5

Number of Subjects

Subject disposition summarized for Part 1 in Table 73 and for Part 2 in Table 74:

Table 73: Summary of Subject Disposition for Part 1

Parameter	Placebo	Eltrombopag			Total
		100 mg	150 mg	200 mg	
Number of Subjects:					
Planned, N1:	6	8	8	8	30
Randomized, N:	6	10	9	8	33
Completed as Planned, n (%)	6 (100)	8 (80)	8 (89)	7 (88)	29 (88)
Withdrawn (any reason), n (%)	0	2 (20)	1 (11)	1 (13)	4 (12)
Adverse Event, n (%)	0	1 (10)	1 (11)	0	2 (6)
Decided to Withdraw from Study, n (%)	0	1 (10)	0	1 (13)	2 (6)

Table 74: Summary of Subject Disposition for Part 2

Parameter	DCAB	ADBC	BACD	CBDA	Total
Number of Subjects:					
Enrolled, N	21	20	23	23	87
Completed, n (%)	14 (67)	11 (55)	11 (48)	12 (52)	48 (55)
Withdrawn (any reason), n (%)	7 (33)	9 (45)	12 (52)	11 (48)	39 (45)
Adverse event, n (%)	2 (10)	3 (15)	1 (4)	0	6 (7)
Protocol violation, n (%)	3 (14)	1 (5)	1 (4)	1 (4)	6 (7)
Other, n (%)	2 (10)	5 (25)	10 (43)	10 (43)	27 (31)
Populations Analyzed, n (%):					
Safety	21 (100)	20 (100)	23 (100)	23 (100)	87 (100)
PK Concentration	20 (95)	20 (100)	22 (96)	22 (96)	84 (97)
PK Parameter	19 (90)	20 (100)	22 (96)	22 (96)	83 (95)
PD Population	18 (86)	11 (55)	11 (48)	22 (96)	62 (71)
ECG	19 (90)	11 (55)	11 (48)	22 (96)	63 (72)
PK/ECG	17 (81)	20 (100)	22 (96)	22 (96)	81 (93)
Cp/ddQTc	18 (86)	11 (55)	11 (48)	22 (96)	62 (71)

Treatment Sequences:
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

Population Demographics

The population demographics from parts 1 and 2 of this study are listed in Tables 75 & 76, respectively

Table 75: Population Demographics (Part 1)

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Parameter	Placebo	Eltrombopag			Total
		100 mg	150 mg	200 mg	
Age in Years, Mean (SD)	26.2 (7.91)	24.9 (6.19)	36.8 (12.5)	29.4 (8.48)	29.5 (9.96)
Sex, n (%)					
Female:	1 (17)	5 (50)	4 (44)	5 (63)	15 (45)
Male:	5 (83)	5 (50)	5 (56)	3 (38)	18 (55)
BMI (kg/m ²), Median (SD)	23.8 (3.09)	24.3 (3.64)	24.1 (3.44)	25.8 (2.40)	24.2 (3.20)
Ethnicity, n (%)					
Hispanic or Latino	2 (33)	2 (20)	0	2 (25)	6 (18)
Not Hispanic or Latino	4 (67)	8 (80)	9 (100)	6 (75)	27 (82)
Race, n (%)					
African American/African Heritage	2 (33)	3 (30)	2 (22)	2 (25)	9 (27)
American Indian or Alaska Native	0	0	1 (11)	0	1 (3)
Asian-Central/South Asian Heritage	0	1 (10)	0	0	1 (3)
White-White/Caucasian/European	4 (67)	6 (60)	6 (67)	6 (75)	22 (67)

Reviewer Comment: Presenting BMI as median (SD) does not communicate the differences in the mean BMI between the cohorts (24.4 (100mg) 25.7 (150 mg) 26.0 (200 mg))

Table 76: Population Demographics (Part 2)

Parameter	DCAB	ADBC	BACD	CBDA	Total
Age in Years, Mean (SD)					29.9 (9.17)
Sex, n (%)					
Female					25 (29)
Male					62 (71)
Ethnicity, n (%)					
Hispanic or Latino:					15 (17)
Not Hispanic or Latino:					72 (83)
BMI (kg/m ²), Median (Range)					25.8 (20.2 - 30)
Race, n (%)					
African American/African Heritage	8 (38)	1 (5)	4 (17)	2 (9)	15 (17)
American Indian or Alaska Native	1 (5)	0	2 (9)	1 (4)	4 (5)
Asian-Central/South Asian Heritage	1 (5)	0	0	0	1 (1)
Asian-East Asian Heritage	0	0	0	1 (4)	1 (1)
Asian-South East Asian Heritage	0	2 (10)	0	2 (9)	4 (5)
White-White/Caucasian/European	11 (52)	17 (85)	17 (74)	17 (74)	62 (71)
African American/African Heritage	8 (38)	1 (5)	4 (17)	2 (9)	15 (17)
American Indian or Alaska Native	1 (5)	0	2 (9)	1 (4)	4 (5)

Reviewer Comment: Sponsor failed to consistently report demographics for each sequence in part 2

Results-PK analysis:

Part 1

Twenty-seven subjects received eltrombopag in Part 1 of the study and underwent PK sampling (PK Concentration Population). Twenty-three subjects completed Part 1 and provided plasma

eltrombopag PK data for Day 1 and Day 5; however one subject (Subject 108) was excluded from the statistical analysis of the PK data due to incomplete sampling on Day 5.

Following single dose administration, plasma eltrombopag concentrations were quantifiable within 0.5 to 1.5 h and remained quantifiable through the 24-hour sampling period (Table 11.102). Following repeat dose administration for five days, plasma eltrombopag concentrations were quantifiable over the entire dosing interval for all doses.

Plasma eltrombopag PK parameters following single and repeat dose administration in Part 1 are summarized in Table 77 and Figures 17 & 18

Table 77: Summary of Plasma Eltrombopag PK Parameters

Day	Dose (mg)	N	AUC (0-τ) (μg hr/mL)	Cmax (μg/mL)	tmax (h)
1	100	8	97 (79, 119) [25.0]	10.3 (8.3, 12.8) [26.2]	3.50 (2.00, 6.00)
	150	8	142 (104, 193) [38.6]	17.3 (12.4, 24.1) [41.5]	2.28 (1.50, 6.00)
	200	7	167 (121, 231) [36.2]	18.3 (11.6, 28.8) [52.3]	4.00 (2.50, 4.00)
5	100	8	161 (116, 222) [40.0]	14.9 (10.9, 20.4) [38.7]	3.01 (2.50, 4.00)
	150	8	239 (187, 304) [29.6]	22.8 (18.2, 28.5) [27.3]	2.75 (1.50, 4.00)
	200	7	302 (198, 463) [48.5]	24.8 (16.2, 37.7) [48.1]	2.50 (2.50, 3.00)

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

Figure 17: Mean plasma SB-497115 concentration (Day 1)

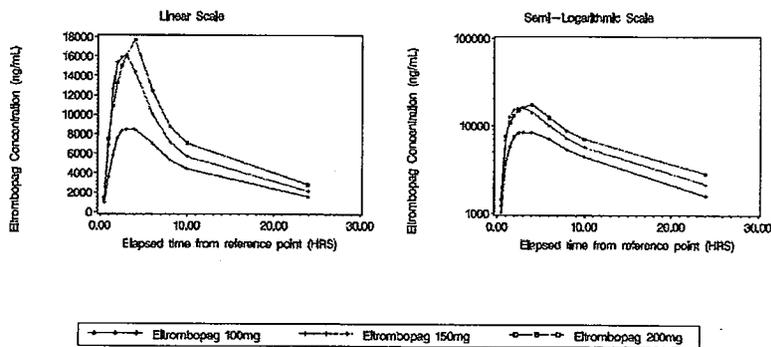
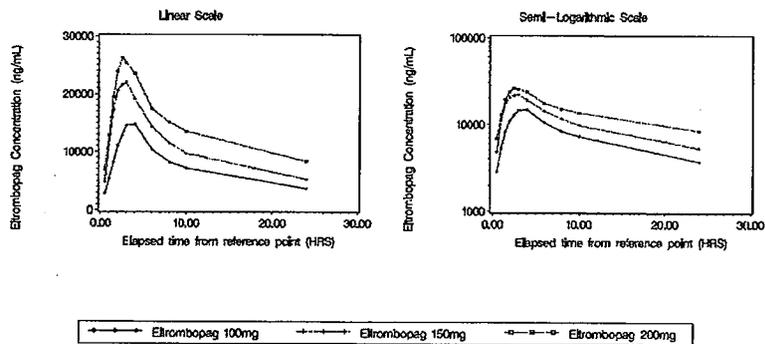


Figure 18: Mean plasma SB-497115 concentration (Day 5)



Reviewer Comment: Exposure between African American (n=9) and Caucasian (n=22) subjects appears similar in this small study.

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Ratios of Day 5 to Day 1 AUC(0- τ) (geometric mean [90% CI]) showed statistically significant accumulation at all doses; 100 mg: 1.66 (1.35, 2.04), 150 mg: 1.69 (1.39, 2.05), and 200 mg: 1.81 (1.30, 2.52). Ratios of Day 5 to Day 1 C_{max} also suggested accumulation across the doses, with point estimates of 1.32 to 1.45 across the doses; however, the 90% CIs for C_{max} included 1.00 for the 150 mg and 200 mg doses. These data are summarized in Table 78

Table 78: Summary of Results of Analysis of Dose Accumulation Ratio (red=significant accumulation)

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

Reviewer Comment: Given a sample size calculation was not reported, an underpowered study can not be ruled out for the lack of accumulation suggested for C_{max} at the 150 and 200 mg doses.

Following five days of repeat dosing, plasma eltrombopag AUC(0- τ) increased with increasing dose; whereas, C_{max} increased between 100 mg and 150 mg, but did not increase any further at the 200 mg dose. The dose proportionality slope estimate (90% CI) was 0.92 (0.45, 1.39) for AUC(0- τ) and 0.76 (0.29, 1.22) for C_{max} over a range of 100 mg to 200 mg QD.

Part 2

Eighty-four subjects who received eltrombopag in Part 2 of the study underwent PK sampling (PK Concentration Population). Sixty subjects provided plasma eltrombopag PK data for the 50 mg QD regimen and 73 subjects provided plasma eltrombopag PK data for the 150 mg QD regimen on Day 5.

Sixty-two subjects who received moxifloxacin in Part 2 of the study underwent PK sampling (PK Concentration Population). Sixty subjects provided plasma moxifloxacin PK data following administration of a single 400 mg dose.

Following repeat dose administration for five days, plasma eltrombopag concentrations were quantifiable over the entire dosing interval for all doses. Following single dose administration, plasma moxifloxacin concentrations were quantifiable within 0.5 hour and remained quantifiable through the 24-hour sampling period

Plasma eltrombopag PK parameters following repeat dose administration in Part 2 are summarized in Table 79 and Figure 19

Table 79: Summary of Plasma Eltrombopag PK Parameters

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

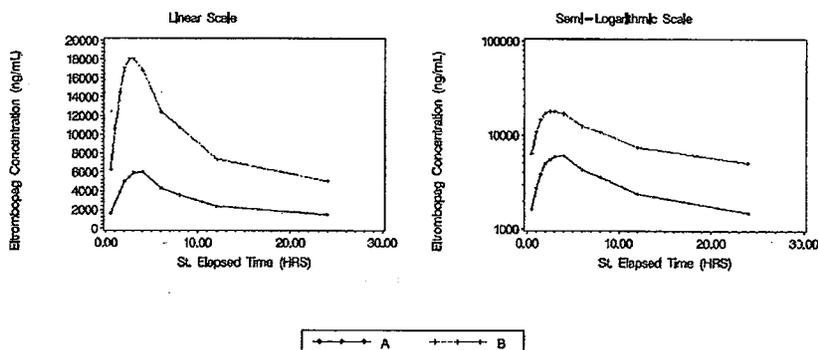
Data presented as geometric mean (95% CI) [P(CV)], except t_{max} presented as median (minimum-maximum)

Reviewer Comment: Exposure between African American (n=15) and Caucasian (n=62) subjects appears similar in this small study.

Figure 19: Mean plasma SB-497115 concentration (Day 5)

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

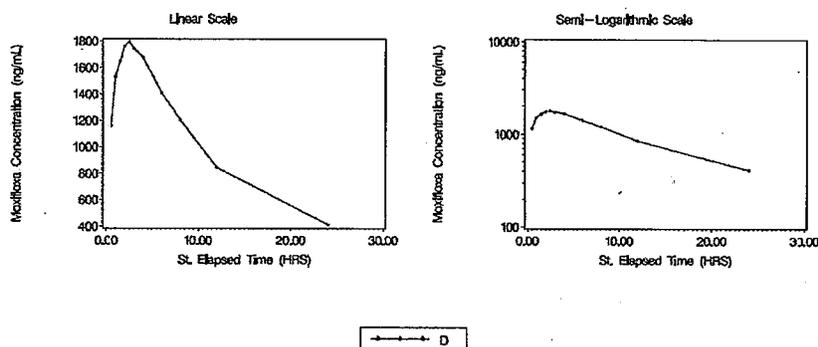
Plasma moxifloxacin PK parameters following single dose administration in Part 2 are summarized in Table 80 and Figure 20. Plasma moxifloxacin C_{max} values in this study were 2.05 µg/mL on average, which is lower than the C_{max} value of 3.1 µg/mL in the moxifloxacin product label

Table 80: Summary of Plasma Moxifloxacin PK Parameters

Dose (mg)	N	AUC(0-t) (µg hr/mL)	C _{max} (µg/mL)	t _{max} (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) [%CV], except t_{max} presented as median (minimum-maximum)

Figure 20: Mean plasma Moxifloxacin concentration (single dose)



Results- Pharmacodynamic Analysis:

Thorough QTc (Part 2)

The Fridericia's correction (QTcF) demonstrated slight undercorrection at lower RR values and slight overcorrection at higher RR values. The Bazett's correction (QTcB) and individualized correction (QTci) demonstrated more marked correction effect than the Fridericia's correction. The Bazett's correction demonstrated overcorrection at lower RR

values and undercorrection at higher RR values, while the individualized correction demonstrated the opposite effect.

Eltrombopag at both doses tested had no effect on cardiac repolarization. The upper limits of the 90% CI for the mean difference in QTc time matched change from baseline between eltrombopag and placebo (ddQTc) were below 10 msec for all time points in both 50 mg and 150 mg dosing groups, based on the results from QTcF, QTcB, and QTci. Assay sensitivity was established as moxifloxacin prolonged the mean QT interval by 10 to 11 msec between 2 and 4 h, in comparison to placebo, and the lower limits of 90% CI were greater than 5 msec for at least one timepoint, based on the results from QTcF, QTcB, and QTci.

The change from baseline in QTcF, QTcB, and QTci values were summarized. All of the changes from baseline were less than 30 msec in QTcF. Most change from baseline was less than 30 msec category and all were less than 60 msec in QTcB and QTci. Changes from baseline in QTcB that were greater than 30 msec, occurred in 2 subjects in the placebo group (3%) and 14 subjects in the moxifloxacin group (26%). Four subjects (8%), who received eltrombopag (50 mg or 150 mg), experienced a change from baseline in QTcB that was between 30 and 60 msec. None of the subjects experienced the change from baseline greater than 60 msec for any QTc. One subject (2%), administered with Moxifloxacin experienced the QTci change from baseline in the > 30 msec to ≤ 60 msec category

Reviewer Comment: IRT review pending

Platelets (part 1)

Eltrombopag increased platelet counts in a dose-dependant manner. Platelet counts reached peak level on Day 14 post-dose, and returned to baseline values by Day 28. The maximum change from baseline for platelet counts is summarized in Table 81, a median time plot for the platelet counts is presented in Figure 21, and the statistical analysis of maximum change from baseline of the platelet count and maximum platelet count are summarized in Table 82 and Table 83 respectively.

Table 81: Summary of Maximum Increase from Baseline Platelet Count (X10⁹/L)

Parameter	Placebo N=6	Eltrombopag		
		100 mg N=10	150 mg N=9	200 mg N=8
Mean (SD)	14.2 (22.5)	67.4 (26.2)	107 (51.8)	149 (99.3)
Median (Range)	19.5 (-25, 43)	57.5 (29, 111)	111 (12, 168)	141 (36, 304)

Figure 21: Median Platelet Count - Time Plots

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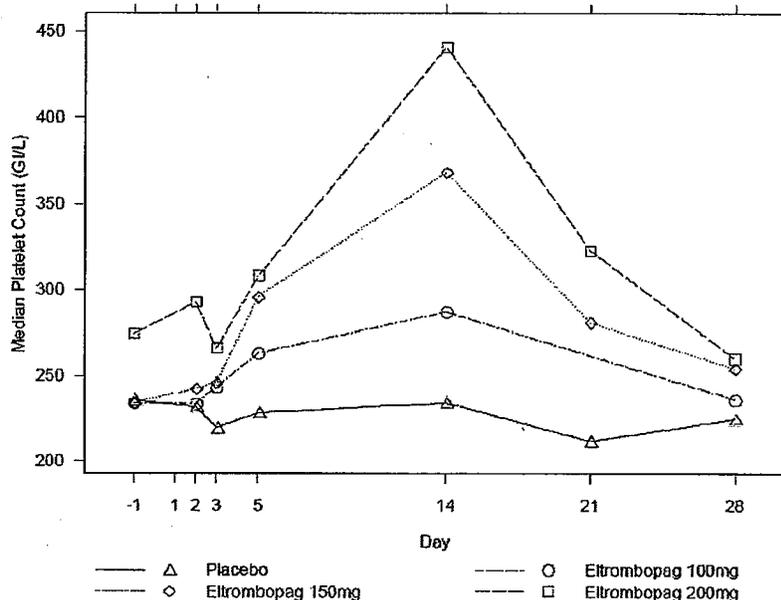


Table 82: Summary of Statistical Analysis of Maximum Increase from Baseline of Platelet Count

Treatment Comparison	Ratio (95% CI)	p-value	%CVb
100 mg vs Placebo	3.41 (1.83, 6.34)	0.0010	53.96
150 mg vs Placebo	4.67 (1.85, 11.81)	0.0037	87.60
200 mg vs Placebo	5.49 (2.61, 11.54)	0.0005	63.19

Significant increases in the platelet counts were observed in all eltrombopag dose groups in comparison to placebo. Maximum change from baseline of the platelet counts were 3.41-, 4.67-, and 5.49-fold higher than placebo from 100 mg, 150 mg, and 200 mg of eltrombopag, respectively.

Table 83: Summary of Statistical Analysis of Maximum Platelet Count

Treatment Comparison	Ratio (95% CI)	p-value	%CVb
100 mg vs Placebo	1.20 (1.09, 1.32)	0.0009	8.14
150 mg vs Placebo	1.33 (1.12, 1.56)	0.0029	14.43
200 mg vs Placebo	1.37 (1.14, 1.64)	0.0027	14.90

Maximum platelet counts were 20%, 33%, and 37% higher than placebo from 100 mg, 150 mg, and 200 mg of eltrombopag, respectively.

Platelet counts above $400 \times 10^9/L$ (upper limit of normal) were observed on Day 14 in one subject in the placebo group, none in the 100 mg dose group, three subjects in the 150 mg dose group, and five subjects in the 200 mg dose group; two subjects in the 200 mg dose group had platelet counts above $600 \times 10^9/L$ on Day 14.

Platelet function, as measured by platelet aggregation and activation, was not affected by the administration of eltrombopag; similar results were seen in subjects administered placebo and eltrombopag, regardless of dose. Mean platelet aggregation values for

Period 1 Day 5 and Follow-up Period Day 14 and 28 in each treatment are summarized in Table 84.

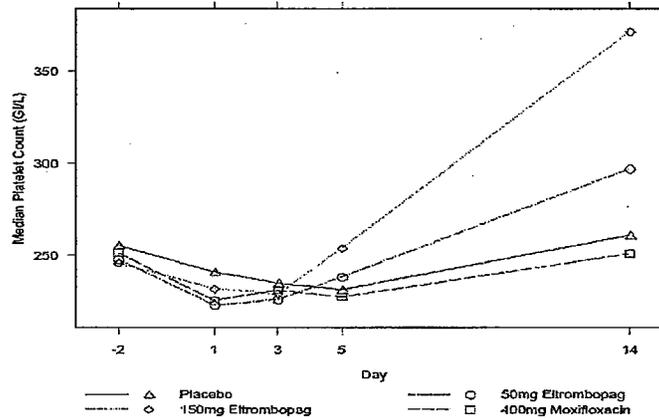
Table 84: Summary of Platelet Aggregation for Day 5, 14 and 28, Mean (SD)

Visit	Eltrombopag							
	Placebo N=6		100 mg N=10		150 mg N=9		200 mg N=8	
	n	Mean (%) (SD)	n	Mean (%) (SD)	n	Mean (%) (SD)	n	Mean (%) (SD)
Day 5	6	57.1 (31.0)	9	79.6 (16.1)	9	76.1 (18.3)	8	58.4 (37.5)
Day 14	5	66.6 (20.9)	8	58.9 (7.3)	9	61.0 (29.0)	8	74.3 (17.3)
Day 28	6	70.2 (12.0)	9	78.2 (11.8)	9	72.0 (24.4)	7	69.3 (15.8)

Platelets (Part 2)

Platelet counts did not return to baseline by the end of the 14-day washout period (Day -2) suggesting a carry-over effect (Figure 22). Eltrombopag increased platelet counts in a dose-dependant manner. Platelet counts reached peak level on Day 14 post-dose. The maximum change from baseline for platelet counts is summarized in Table 85 and a median time plot for the platelet counts is presented in Figure 22. The statistical analysis of maximum platelet count is summarized in Table 86

Figure 22: Median Platelet Count - Time Plots for Part 2



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Table 85: Summary of Statistical Analysis of Maximum Platelet Count

Treatment Comparison	Ratio (95% CI)	p-value	%CVw
50 mg vs Placebo	1.10 (1.04, 1.16)	0.0014	14.97
150 mg vs Placebo	1.31 (1.24, 1.38)	<0.0001	

Table 86: Summary of Maximum Increase from Baseline Platelet Count (X10⁹/L)

Parameter	Placebo N=64	Eltrombopag		Moxifloxacin 400 mg N=63
		50 mg N=62	150 mg N=77	
Mean (SD)	16.3 (32.7)	47.5 (44.2)	110 (79.9)	13.0 (32.0)
Median (Range)	8.0 (-58, 96)	46.0 (-39, 182)	116 (-69, 256)	5.5 (-63, 123)

Relationship Between Pharmacokinetic-and Pharmacodynamic Parameters

There was no relationship between individual maximum change from baseline in QTc (dQTc) and plasma eltrombopag AUC(0-τ) or Cmax. The final plasma concentration (Cp)-ddQTcF model for eltrombopag was a linear model with no delay in effect of concentration on ddQTcF; fixed effects for pre-dose ddQTcF on Day 5 (intercept, Θ1) and the slope relating plasma eltrombopag concentration to ddQTcF (Θ2) 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:

$$ddQTcF = \Theta1 + \eta1 + TRT1 * \eta3 + TRT2 * \eta4 + (\Theta2 + \eta2 + TRT1 * \eta5 + TRT2 * \eta6) * Cp + \epsilon1$$

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

Based on the final Cp-ddQTcF model, simulations were performed to predict ddQTcF at Cmax for therapeutic and supratherapeutic plasma eltrombopag concentrations (at Cmax). Simulations were performed to predict the mean (90% CI) ddQTc at eltrombopag doses of 50 mg QD, 150 mg QD, and 300 mg QD. The results of these simulations suggest that eltrombopag will not have a clinically significant effect on ddQTcF at concentrations predicted for a dose of 300 mg QD, as described in Table 87.

Table 87: Summary of Simulated ddQTcF at Cmax for Therapeutic and Supratherapeutic Eltrombopag Doses

Dose (mg) QD	Cmax (μg/mL) mean (95% CI) ¹	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 Comment: Also see IRT review Section 4.4

Results-Safety:

Adverse events (AEs) occurred in 24 of 33 subjects (73%) in Part 1 of the study: three of six subjects (50%) in the placebo group and 21 of 27 subjects (78%) in the eltrombopag dose groups. The majority of AEs were mild in intensity. The AEs reported in more than one subject total are summarized in Table 88. Two subjects were withdrawn for moderate gastroenteritis and herpes zoster.

AEs occurred in 58% of subjects in the placebo group, 66% of subjects in the 50 mg eltrombopag treatment group, 58 % of subjects in the 150 mg eltrombopag treatment and 52% of subjects in the moxifloxacin treatment group. The majority of AEs were mild in intensity. The AEs reported in more than one subject are summarized in Table 89. Six subjects were withdrawn due to AE's (Ventricular extrasystoles (2), Ventricular tachycardia (1), Gingival pain (2), Gingivitis (1), Oral discharge (1), Tooth Abscess (1), Eosinophil count increased (1).

Table 88: Summary of Adverse Events Occurring in Part 1 in More Than One Subject Total

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Preferred Term	Placebo N=6	Eltrombopag			Total N=33
		100 mg N=10	150 mg N=9	200 mg N=8	
Number of Subjects with Any AE	3 (50)	7 (70)	8 (89)	6 (75)	24 (73)
Headache	2 (33)	1 (10)	2 (22)	4 (50)	9 (27)
Dermatitis contact	0	1 (10)	4 (44)	1 (13)	6 (18)
Vessel puncture site hemorrhage	3 (50)	1 (10)	1 (11)	0	5 (15)
Ecchymosis	1 (17)	1 (10)	1 (11)	0	3 (9)
Vessel puncture site hematoma	0	0	3 (33)	0	3 (9)
Nausea	1 (17)	1 (10)	0	1 (13)	3 (9)
Conjunctivitis	0	1 (10)	1 (11)	0	2 (6)
Vomiting	1 (17)	1 (10)	0	0	2 (6)
Urinary tract infection	0	1 (10)	1 (11)	0	2 (6)
Excoriation	0	0	1 (11)	1 (13)	2 (6)

Table 89: Summary of Adverse Events Occurring in Part 2 in More Than One Subject Total

Preferred Term	Placebo N=64	Eltrombopag		Moxifloxacin 400 mg N=63
		50 mg N=62	150 mg N=77	
Number of Subjects with Any AE, n (%)	37 (58)	41 (66)	45 (58)	33 (52)
Application site dermatitis ¹	6 (9)	9 (15)	11 (14)	9 (14)
Ecchymosis ¹	8 (13)	10 (16)	9 (12)	5 (8)
Headache	7 (11)	7 (11)	10 (13)	8 (13)
Contusion	6 (9)	2 (3)	4 (5)	1 (2)
Vessel puncture site hemorrhage	4 (6)	4 (6)	4 (5)	4 (6)
Blood creatine phosphokinase increased	3 (5)	1 (2)	4 (5)	4 (6)
Excoriation	3 (5)	4 (6)	1 (1)	2 (3)
Application site erythema ¹	2 (3)	2 (3)	0	2 (3)
Application site pruritus	2 (3)	1 (2)	1 (1)	1 (2)
Pain in extremity	2 (3)	1 (2)	0	1 (2)
Vision blurred	2 (3)	1 (2)	0	1 (2)
Dermatitis contact	1 (2)	0	0	3 (5)
Nausea	1 (2)	2 (3)	3 (4)	4 (6)
Diarrhea	1 (2)	2 (3)	4 (5)	0
Nasal congestion	1 (2)	0	2 (3)	0
Hematuria	1 (2)	0	3 (4)	0
Dizziness	0	2 (3)	1 (1)	5 (8)
Atrioventricular block second degree	0	4 (6)	1 (1)	2 (3)
Abdominal pain	0	1 (2)	4 (5)	1 (2)
Pharyngolaryngeal pain	0	2 (3)	2 (3)	0
Throat irritation	0	1 (2)	2 (3)	1 (2)
Neutropenia	0	1 (2)	2 (3)	1 (2)
Fatigue	0	1 (2)	1 (1)	2 (3)

Rhinorrhea	0	0	2 (3)	2 (3)
Dermatitis	0	3 (5)	0	0
Musculoskeletal chest pain	0	1 (2)	0	2 (3)
Ventricular extrasystoles	0	1 (2)	0	2 (3)
Myalgia	0	0	2 (3)	1 (2)

Twenty-six subjects were withdrawn from the study due to elevated platelet counts greater than $400 \times 10^9/L$. The information for these subjects is summarized in Table 25. 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.

No treatment-related trends were seen in AEs, ECGs or vital signs. No deaths or SAEs were reported during the study. No drug-related changes in ocular status were seen in Part 1 or Part 2. A trend toward increase in platelet counts (pharmacological effect as expected) in higher doses was seen at the follow-up visits; otherwise, no notable treatment-related changes in laboratory parameters from pre-dose were noted.

Conclusions (sponsor):

- In Part 1 and Part 2 of the study, there were no deaths or SAEs. No treatment-related trends were seen in AEs, ECGs or vital signs; no notable treatment-related changes in laboratory parameters from pre-dose were noted, other than an expected dose-dependant increase in platelet count values.
- Significant accumulation of eltrombopag AUC(0- τ) was observed following administration of eltrombopag 100 mg, 150 mg, and 200 mg QD for five days.
- Following repeat dosing, plasma eltrombopag C_{max} and AUC(0- τ) increased in a dose proportional manner, with a dose proportionality slope estimate (90% CI) of 1.04 (0.987, 1.09) for AUC(0- τ) and 1.01 (0.942, 1.08) for C_{max} over a range of 50 mg QD to 150 mg QD. Proportional increases in plasma eltrombopag AUC(0- τ) were observed at 200 mg QD, but C_{max} values did not increase beyond 150 mg QD.
- 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 time-matched change from baseline between eltrombopag and placebo (ddQTcF) was below 10 msec at all timepoints in both 50 mg QD and 150 mg QD doses.
- The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QT prolongation as the lower limit of the 90% CI of ddQTcF was greater than 5 msec for at least one timepoint.
- Eltrombopag increased platelet counts in a dose-dependant manner. Platelet counts reached peak level on Day 14 post-dose, and returned to baseline values during follow-up periods in both parts of the study.
- The slope of eltrombopag concentration (range 0.224 $\mu\text{g/mL}$ to 31.4 $\mu\text{g/mL}$) effect on ddQTc was slight, with a model predicted value of 0.120 msec/ $\mu\text{g/mL}$.

Reviewer Comment: IRT review consistent with reviewer assessment (see IRT review Section 4.4)

4.3.8 Intrinsic Factor Study of Eltrombopag PK in Healthy Subjects and in Volunteers with Mild, Moderate or Severe Hepatic Impairment

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

Title: 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

Study period: 18-Apr-2006 - 07-Mar-2007

Objectives:

Primary

- Area under the plasma drug concentration-time curve from time 0 extrapolated to infinity [AUC(0-∞)] and maximum observed plasma drug concentration (C_{max}) of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.

Secondary

- Area under the plasma drug concentration-time curve from time 0 to the last quantifiable concentration [AUC(0-t)] of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.
- Time to achieve maximum plasma drug concentration (t_{max}) of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.
- Half-life (t_{1/2}) of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.
- Free fraction (% unbound) of eltrombopag.
- Evaluation of adverse events (AEs) and changes in vital signs and laboratory values from baseline.

Methodology:

This was an open-label, non-randomized study conducted at five investigative sites in which each subject received a single 50 mg oral dose of eltrombopag. Subjects with mild, moderate or severe hepatic impairment were enrolled in parallel. Once all subjects with moderate hepatic impairment completed the study, healthy subjects were enrolled to match subjects with moderate hepatic impairment based on sex, age (±5 years), and BMI (±15%). Subjects who withdrew prior to completing the study could be replaced.

Subjects remained in the clinical research unit (CRU) from the day prior to dosing until after the last PK blood sample was collected 120 hours following the dose of eltrombopag. Subjects were required to return to the CRU for a post-treatment follow-up visit 14 days after the dose of study medication.

The degree of hepatic impairment was based on clinical history and assessed using the Child-Pugh (CP) classification of liver disease.

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

The drug product used in this study is summarized in Table 90.

Table 90: Drug Product Administered in TRA103452

Drug	Dose/Form/Route	Frequency/Duration	Formulation Code	Substance Batch	Batch Number
SB-497115 (eltrombopag)	50 mg/tablet/oral	Single dose/1 day	AR	F074714 (Tonbridge)	051069268 (Ware)

Eltrombopag was administered as a single oral 50 mg dose with 240 mL of water. Subjects fasted for at least eight hours prior to dosing and for an additional four hours after dosing.

Criteria for evaluation:

- Sample size: Convenience sample. No formal sample size calculation made.
- Pharmacokinetics:
 - Blood samples were collected for the determination of plasma eltrombopag concentrations over a 120 hour period at the following times: pre-dose (within 60 minutes of the administration of eltrombopag) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108 and 120 hours after the administration of eltrombopag. Additional blood samples were collected pre-dose (within 60 minutes of the administration of eltrombopag) and 1, 2, 4, 12, 24 and 48 hours after the administration of eltrombopag for assessment of plasma protein binding.
 - Plasma samples were analyzed for eltrombopag using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis (Table 91). The LLQ for eltrombopag was 100 ng/mL, using a 50 μ L aliquot of human plasma with a higher limit of quantification of 50,000 ng/mL.

Table 91: Assay validation information

Eltrombopag is extracted from 50 μ L human plasma by protein precipitation using _____, as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	100 ng/mL
Validated Range	100 to 50,000 ng/mL
Within-run Precision (%CV)	$\leq 7.5\%$
Between-run Precision (%CV)	$\leq 8.1\%$
Accuracy (%Bias)	$-9.3\% \leq \text{bias} \leq 13.6\%$
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 non-compartmental Model 200 of WinNonlin Professional Edition, version 5.2 according to standard operating procedures. Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects. Values for the following PK parameters were estimated:
 - C_{max} and t_{max} were the observed values.
 - AUC was calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. $AUC(0-t)$ and $AUC(0-\infty)$ were determined. Values for $AUC(0-\infty)$ were estimated as the sum of $AUC(0-t)$ and C_t divided by the elimination rate constant, where C_t was the last observed quantifiable concentration.
 - Where possible, the terminal plasma elimination rate-constant (λ_z) was estimated from log-linear regression analysis of the terminal phase of the plasma concentration-time profile. The number of points included in the terminal phase was determined by visual inspection of the semi-log plots of the plasma concentration time profiles. The associated apparent terminal elimination $t_{1/2}$ was calculated as $\ln 2/\lambda_z$.
- Plasma eltrombopag PK parameters were compared between subjects with each level (mild, moderate or severe) of hepatic impairment and healthy subjects by

ANOVA, considering group as a fixed effect. The comparisons were evaluated by the differences in least squares means between groups, respectively and the corresponding 90% CI. Point and interval estimates of differences in means were exponentiated to give corresponding point and 90% CI estimates of the ratios of geometric means of the PK parameters for each of the hepatic impairment groups versus the healthy subjects group. The residuals from the ANOVA on PK endpoints were examined for violation of assumptions of normality and constant variance. Relationships between hepatic functional abnormalities (e.g., overall impairment) and selected PK parameters were sought using linear regression models. Plots of fitted models and the results of parameter estimates of the model and measures of their precision are presented.

- o Additional figures of plasma eltrombopag PK parameters versus measures of hepatic function including CP score, albumin, platelet count, bilirubin and prothrombin time were created in order to evaluate factors that may be predictive of eltrombopag PK. This information was provided in place of plasma unbound eltrombopag data which was not provided.

Reviewer Comment: The sponsor reports that attempts were made to determine plasma unbound eltrombopag concentrations in a portion of the plasma samples from subjects enrolled, using a 96 well plate equilibrium dialysis method. However, the results were deemed highly unreliable due to the large within- and between-run variability observed in the quality control plasma samples. Therefore, plasma unbound eltrombopag data is not provided.

- 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, ECG monitoring (12-lead), and ophthalmologic examination were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects: A total of 33 subjects were randomized (Healthy (8), Mild (8), Moderate (8), Severe (8)) and completed the study. One patient (severe) was excluded from the PK analysis because the subject had no detectable drug in the samples collected.

Population Demographics

The population demographics from this study are listed in Table 92 below.

Table 92: Population Demographics

Parameter	Healthy	Hepatic Impairment			Total
		Mild	Moderate	Severe	
Age: Median (range)	53.0 (38-59)	55.5 (43-59)	51.5 (41-64)	50.0 (43-60)	51.0 (38-64)
Sex					
Female, n (%)	1 (12%)	0	1 (12%)	1 (11%)	3 (9%)
Male, n (%)	7 (88%)	8 (100%)	7 (88%)	8 (89%)	30 (91%)
Weight (kg)	74.10 (69.6-87.8)	91.30 (58.6-111.0)	80.65 (65.8-105.7)	83.80 (60.9-105.8)	83.50 (58.6-111.0)
Height (cm)	173.0 (166-180)	175.5 (167-188)	174.0 (157-185)	174.0 (165-189)	173.0 (157-189)
BMI (kg/m ²): Median (range)	26 (23-30)	28 (20-34)	27 (20-35)	27 (21-34)	27 (20-35)
Ethnicity					
Hispanic or Latino:	1 (12%)	0	2 (25%)	0	3 (9%)
Not Hispanic or Latino:	7 (88%)	8 (100%)	6 (75%)	9 (100%)	30 (91%)
Race					
African American/African Heritage:	1 (13%)	0	0	0	1 (3%)
American Indian or Alaskan Native:	1 (13%)	0	0	0	1 (3%)
Asian - Central/South Asian Heritage:	0	1 (13%)	0	0	1 (3%)

Native Hawaiian or Other Pacific Islander	0	1 (13%)	0	0	1 (13%)
White – White/Caucasian/European Heritage:	6 (75%)	6 (75%)	8 (100%)	9 (100%)	29 (88%)

Results-PK analysis:

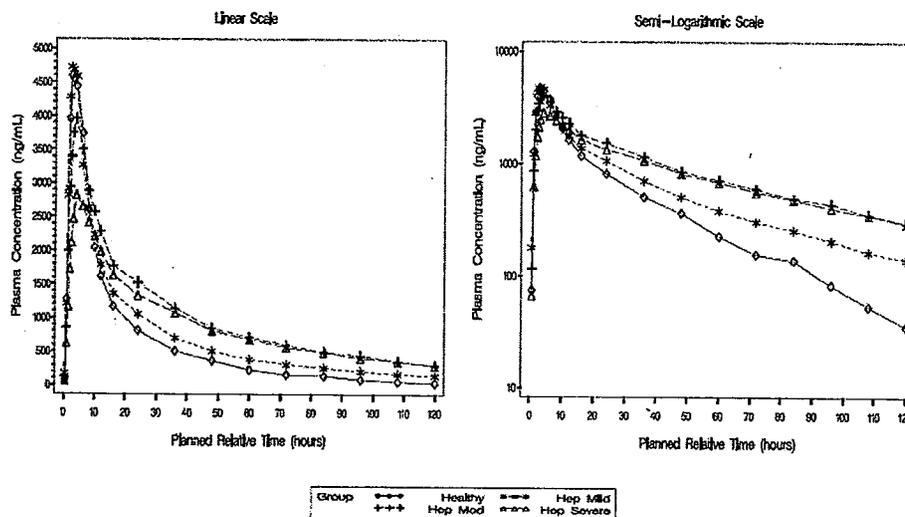
Selected plasma PK parameters are listed in Table 93 below. Mean plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figures 23.

Table 93: Selected PK parameters

Parameter	Healthy (N=8)	Hepatic-Impaired Mild (N=8)	Hepatic-Impaired Moderate (N=8)	Hepatic-Impaired Severe (N=8)
AUC(0-t) ^a (ng h/mL)	61,377 (59.2)	82,661 (41.6)	107,835 (54.3)	99,331 (83.3)
AUC(0-∞) ^a (ng h/mL)	66,026 (57.9)	92,814 (42.9)	127,211 (60.9)	118,752 (83.0)
C _{max} (ng/mL)	5,427 (47.0)	4,677 (49.5)	3,843 (63.3)	2,754 (86.9)
t _{1/2a} (h)	21.3 (39.9)	36.4 (56.7)	44.4 (34.4)	45.6 (12.3)
T _{max} ^b (h)	3.0 (2.5, 6.0)	3.5 (2.5, 4.0)	4.9 (2.0, 7.0)	4.0 (3.0, 8.0)

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

Figure 23: Mean plasma eltrombopag concentration-time profile



Reviewer Comment:

- Data highly variable with moderate to high-between-subject variability
- Difficult to interpret this data without knowing the free concentration of this highly protein bound drug. A reviewer generated analysis of albumin and total protein (TP) concentrations (see Table 94) shows a trend toward lower albumin concentrations with worsening liver function. Half of the albumin and TP concentrations were below normal in the moderate to severe groups. This is significant given this could mean higher free (active) concentrations in patients with moderate to severe liver disease.

Table 94: Reviewer Generated Analysis of Albumin and Total Protein by Liver Function

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

The statistical comparisons of selected eltrombopag PK parameters between the subjects with mild, moderate or severe hepatic impairment versus healthy subjects are summarized in Table 95

Table 95: Summary of Plasma Eltrombopag PK Parameters for Subjects with Hepatic Impairment versus Healthy Subjects

Parameter	Comparison (Test/Reference)	Ratio	90% CI
AUC(0-∞) (ng·h/mL)	Severe/Healthy	1.80	(1.11, 2.92)
	Moderate/Healthy	1.93	(1.19, 3.13)
	Mild/Healthy	1.41	(0.87, 2.28)
Cmax (ng/mL)	Severe/Healthy	0.51	(0.31, 0.83)
	Moderate/Healthy	0.71	(0.43, 1.15)
	Mild/Healthy	0.86	(0.53, 1.40)
t1/2 (h)	Severe/Healthy	2.14	(1.56, 2.93)
	Moderate/Healthy	2.08	(1.52, 2.86)
	Mild/Healthy	1.71	(1.24, 2.34)

Reviewer Comment: *It is difficult to interpret these data given the high variability and without knowing the free concentration of eltrombopag. I agree there is a trend toward increased exposure especially with moderate to severe liver impairment but the magnitude can not be quantified by this study.*

Correlation results from PK parameters versus measures of hepatic function including CP score, albumin, platelet count, bilirubin and prothrombin time are listed in Table 96. Plasma eltrombopag PK parameters were not correlated with CP score. Plasma eltrombopag AUC(0-∞) was positively correlated with bilirubin: Pearson's correlation coefficient (p-value) of 0.4882 (0.0046); Cmax was positively correlated with albumin: 0.4445 (0.0108) and platelet count: 0.5048 (0.0032); t1/2 was negatively correlated with albumin: -0.4858 (0.0048) and platelet count: -0.5406 (0.0014), and positively correlated with bilirubin: 0.4669 (0.0071).

Table 96: Correlation results from PK parameters versus measures of hepatic function

Parameter	Statistic	n	AUC(0-inf) (ng*hr/mL)	Cmax (ng/mL)	t1/2 (hr)
Child-Pugh Score	Coefficient	24	0.2404	-0.3663	0.1659
	P-value		0.2579	0.0783	0.4386
Albumin (G/L)	Coefficient	32	-0.2829	0.4445	-0.4858
	P-value		0.1167	0.0108	0.0048
Platelets (G/L)	Coefficient	32	-0.2900	0.5048	-0.5406
	P-value		0.1074	0.0032	0.0014
Bilirubin (umol/L)	Coefficient	32	0.4882	-0.2232	0.4669
	P-value		0.0046	0.2194	0.0071
Prothrombin Time (seconds prolonged)	Coefficient	16	-0.2790	-0.4961	0.0287
	P-value		0.2953	0.0506	0.9158

Reviewer Comment: *Interesting but exploratory. The positive correlation with bilirubin may also show this compounds dependency on conjugation and UGT1A1.*

Results-Safety:

All reported AEs are summarized in Table 97. The majority of AEs reported were mild in intensity. Eight AEs were reported as moderate in intensity: diarrhea (moderate hepatic impairment), muscle spasms (severe hepatic impairment), restless legs syndrome (mild hepatic impairment), 2 episodes of back pain occurring on the same day (moderate hepatic impairment), influenza-like illness (healthy), headache (mild hepatic impairment) and back pain (moderate hepatic impairment). All AEs resolved with the exception of one event of back pain (Subject 205). No serious adverse events (SAEs), non-fatal SAEs or deaths were reported during the study.

Table 97: Post dose adverse effects:

Adverse Event	Healthy(N=8)	Hepatic Impaired		
		Mild (N=8)	Moderate (N=8)	Severe (N=8)
.Any Event	7 (88%)	5 (63%)	7 (88%)	4 (44%)
Back Pain	1 (13%)	1 (13%)	1 (13%)	0
Myalgia	2 (25%)	0	0	0
Headache	2 (25%)	1 (13%)	1 (13%)	3 (33%)
Nausea	2 (25%)	0	1 (13%)	0
Diarrhea	1 (13%)	0	1 (13%)	0

The following AEs were reported once during the study: arthralgia, joint stiffness, muscle spasms, musculoskeletal stiffness, pain in extremity, restless legs syndrome, abdominal distension, asthenia, chills, influenza-like illness, ear pain, tinnitus, localized infection, muscle strain and increased CPK, hyperglycemia, hematuria and pharyngolaryngeal pain.

There were no changes in clinical chemistry variables that were considered to be clinically significant and reported as an AE in the healthy group or the mild or severe hepatic impairment groups. Two subjects (Subject 204 and Subject 402) in the moderate hepatic impairment group had changes in clinical chemistry variables that were considered to be clinically significant and were reported as AEs: Subject 204 had one report of elevated CPK and Subject 402 had one report of elevated glucose level. There were no changes in the hematology laboratory values that were considered to be clinically significant and reported as an AE in any treatment group.

A total of 27 subjects [six healthy subjects and 21 hepatic impaired subjects (four mild, eight moderate and nine severe)] had hematology and clinical chemistry laboratory values that met the protocol-defined criteria for potential clinical importance. The majority of the hematology laboratory values of potential clinical importance were reported in the moderate and severe hepatic impairment groups. The hematology laboratory values of potential clinical importance were decreased lymphocyte, platelet, neutrophil and WBC counts, and elevated hemoglobin. Clinical chemistry laboratory values of potential clinical importance included: elevated ALT, AST, bicarbonate, glucose, potassium and total bilirubin, decreased albumin and calcium, and mixed elevated/decreased inorganic phosphorus. Two subjects had clinical chemistry laboratory values of potential clinical importance that were reported as AEs (elevation in creatine phosphokinase (CPK) (moderate hepatic impairment) and hyperglycemia (moderate hepatic impairment).

There were no notable changes in median values from baseline (Day -1, pre-dose) to the end of the study period (follow-up visit) for systolic or diastolic blood pressure in any treatment group. Median heart rate was slightly higher at the end of Day 6 compared to baseline (Day -1, pre-dose) in both the healthy and moderately hepatic impaired groups and lower in the mild and severe groups. No vital sign (blood pressure or heart rate) results were reported as AEs.

One subject (moderate hepatic impairment) experienced clinically significant ECG abnormalities (prolonged QT using Bazette's correction) prior to dosing of eltrombopag. This continued throughout the study.

Visual acuity changes from baseline (Day -1) were noted in six subjects: one healthy subject, 2 moderately hepatic-impaired subjects and three severely hepatic-impaired subjects. None of these changes reported were due to cataracts. The ophthalmic examinations by direct ophthalmoscopy were reported as normal in the majority of subjects. Slit lamp examinations were reported as normal in the majority of subjects. Slit lamp biomicroscopy was reported as

normal in all subjects in the healthy, mildly hepatic-impaired and severely hepatic-impaired groups.

Reviewer comment: *These ophthalmic findings are not consistent with other studies and the effect of liver disease on these findings can not be ruled out.*

Conclusions (sponsor):

- Subjects with mild, moderate or severe hepatic impairment had mean increases in eltrombopag AUC(0-∞) of 41%, 93% and 80%, respectively, when compared with healthy subjects. These increases were statistically significant in the moderate and severe hepatic impairment groups. However, there was significant overlap in the data between groups potentially due to the high inter-subject variability, particularly in subjects with moderate or severe hepatic impairment.
- Subjects with mild, moderate or severe hepatic impairment had mean decreases in eltrombopag Cmax of 14%, 29%, and 49%, respectively, when compared with healthy subjects. These decreases were statistically significant in the severely hepatic-impaired group only.
- Subjects with mild, moderate or severe hepatic impairment had mean increases in eltrombopag t1/2 values of 71%, 108%, and 114%, respectively, when compared with healthy subjects. These increases were statistically significant in all groups of hepatic impairment.
- Administration of a single oral 50 mg dose of eltrombopag in subjects with mild, moderate or severe hepatic impairment was well tolerated.
- No significant difference in the type or frequency of AEs reported was noted between subjects with mild, moderate or severe hepatic impairment following the administration of a single oral 50 mg dose of eltrombopag.

Reviewer Comment:

- *It is difficult to interpret these data given the high variability and without knowing the free concentration of eltrombopag. I agree there is a trend toward increased exposure especially with moderate to severe liver impairment but the magnitude can not be quantified by this study. The validity of the "statistical significance" of these findings is questionable given the extreme variability. Since the hepatobiliary route is the major elimination pathway for eltrombopag, which is also highly protein bound, the effect of hepatic impairment of free concentration should be explored further.*
- *Based on these data, a starting dose of 25 mg once daily should be considered for patients with moderate hepatic impairment. Eltrombopag should be used with great caution in severe hepatic impairment.*
- *(/ (/ / / / /*
- *Tolerability is hard to qualify given the co-morbidities present in this population*

b(5)

4.3.9 Intrinsic Factor Study of Eltrombopag PK in Healthy Subjects and in Volunteers with Mild, Moderate or Severe Renal Impairment

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

Title: 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

Study period: 26-Sep-2006 - Ongoing

Objectives:

Primary

- To compare the pharmacokinetics (PK) of eltrombopag 50 mg following a single dose in subjects with renal impairment (mild, moderate or severe) to healthy subjects matched to the moderate group.

Secondary

- To describe the safety profile of a single 50 mg oral dose of eltrombopag in healthy subjects and those with renal impairment.
- To assess the effect of renal impairment on the plasma protein binding of eltrombopag.

Methodology:

This is an ongoing open-label, non-randomized study being conducted at two investigative sites in which each subject receives a single 50 mg oral dose of eltrombopag. Subjects remain in the clinical research unit from the day prior to dosing until the last PK blood sample is collected 120 hours after dosing. Subjects are required to return to the CRU within 14 days of the dose of study medication for a follow-up visit.

The degree of renal impairment was based on 24-hour urine creatinine clearance levels and assessed using the criteria outlined in the FDA Guidance document, "Guidance for Industry: Pharmacokinetics in Patients with Limited Renal Function – Study Design, Data Analysis and Impact on Dosing and Labeling (May 1998)." Subjects with mild, moderate or severe renal impairment were defined by a creatinine clearance of 50 to 80 mL/min, 30 to 49 mL/min or less than 30 mL/min, respectively.

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

The drug product used in this study is summarized in Table 98.

Table 98: Drug Product Administered in TRA10412

Drug	Dose/Form/Route	Frequency/Duration	Formulation Code	Substance Batch	Batch Number
SB-497115 (eltrombopag)	50 mg/tablet/oral	Single dose/1 day	AR	F074714 (Tonbridge)	051069268 (Ware)

Each subject received a single oral 50 mg dose of eltrombopag. Subjects fasted for two hours prior to and after administration of eltrombopag.

Criteria for evaluation:

- Sample size: Convenience sample. No formal sample size calculation made.
- Pharmacokinetics:
 - Serial blood samples were collected within one hour prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108 and 120 hours after dosing.
 - Plasma samples were analyzed for eltrombopag using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis (Table 99). The LLQ for eltrombopag was 100 ng/mL, using a 50 µL aliquot of human plasma with a higher limit of quantification of 50,000 ng/mL.

Table 99: Assay validation information

Eltrombopag is extracted from 50µL human plasma by protein precipitation using _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and
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b(4)

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

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

- The following plasma eltrombopag PK parameters were calculated by "standard" non-compartmental methods: AUC(0-∞), AUC(0-t), the percent of AUC(0-∞) obtained by extrapolation (%AUCex), Cmax, CL/F, tmax and t1/2. Pharmacokinetic parameters from plasma SB-497115-GR concentration-time data were derived using non-compartmental methods with WinNonlin Version 4.1 or higher.

Reviewer Comment:

- The sponsor failed to provide adequate information to allow the reviewer to evaluate the method of analysis of the plasma PK data.
- Sponsor states that prior to completion of this study, attempts were made to determine unbound eltrombopag concentrations in plasma samples from subjects enrolled in a previous study (TRA103452, hepatic impairment), using a 96 well plate equilibrium dialysis method. However, the results were deemed highly unreliable due to the large within- and between-run variability observed in the quality control plasma samples. Therefore, no attempt was made to measure plasma unbound eltrombopag data in this study.
- Following log_e-transformation, AUC(0-∞), AUC(0-t), Cmax, CL/F and t1/2 were separately analyzed by analysis of variance (ANOVA). The model included group and day as fixed effects and subject as a random effect. The endpoints were compared between healthy subjects and subjects with each level (mild, moderate or severe) of renal impairment. The comparisons were evaluated by the differences in least squares means between groups and the corresponding 90% confidence intervals (CI). Point and interval estimates of the differences in means were exponentiated to give corresponding point and 90% CI estimates of the ratios of geometric means of the PK parameters. The residuals from the ANOVA on pharmacokinetic endpoints will be examined for violation of assumptions of normality and constant variance.
- 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, ECG monitoring (12-lead), and ophthalmologic examination were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects: A total of 25 subjects (32 planned) were enrolled thus far (Healthy (6), Mild (8), Moderate (8), Severe (3)) and completed the study.

Reviewer Comment: One patient (healthy) was excluded from the PK analysis because but the reason was not provided by the sponsor.

Population Demographics

The population demographics from this study are listed in Tables 100 and 101 below.

Table 100: Population Demographics

Parameter	Healthy Subjects	Renal Impaired			Total
		Mild	Moderate	Severe	
Age: Median (range)	65.5 (55 - 70)	68.0 (39 - 74)	64.5 (48 - 73)	47.0 (41 - 53)	64.0 (39 - 74)
Sex					
Female, n (%):	4 (67%)	4 (50%)	4 (50%)	2 (67%)	14 (56%)
Male, n (%):	2 (33%)	4 (50%)	4 (50%)	1 (33%)	11 (44%)
Ethnicity					
Hispanic or Latino:	0	0	1 (13%)	0	1 (4%)
Not Hispanic or Latino:	6 (100%)	8 (100%)	7 (88%)	3 (100%)	24 (96%)
Race					
Central/South Asian Heritage:	0	1 (13%)	0	0	1 (4%)
African American/African Heritage:	0	0	2 (25%)	0	2 (8%)
White/Caucasian/European Heritage:	6 (100%)	7 (88%)	6 (75%)	3 (100%)	22 (88%)
BMI (kg/m ²): Median (range)	28 (20 - 30)	28 (22 - 37)	28 (23 - 36)	25 (23 - 29)	28 (20 - 37)
Height (cm): Median (range)	166.5 (152-181)	163.0 (157-177)	165.5 (160-180)	168.0 (164-186)	166.0 (152-186)
Weight (kg): Median (range)	81.25 (46.7-91.2)	74.40 (57.7-108.5)	76.65 (58.2-97.5)	71.70 (61.1-100.0)	76.60 (46.7-108.5)

Table 101: Summary of Creatinine Clearance in Subjects with Renal Impairment at Screening

Renal Impairment Treatment Group	Creatinine Clearance (mL/min)		
	Mean	SD	Min. - Max.
Mild	65.8	9.24	50 - 80
Moderate	42.0	7.75	30 - 49
Severe	21.3	5.03	15 - 26

Results-PK analysis:

Selected plasma PK parameters are listed in Table 102 below. Median plasma eltrombopag concentration-time profiles are displayed with planned time on both semi-logarithmic and linear scales by treatment in Figure 24.

Table 102: Selected PK parameters

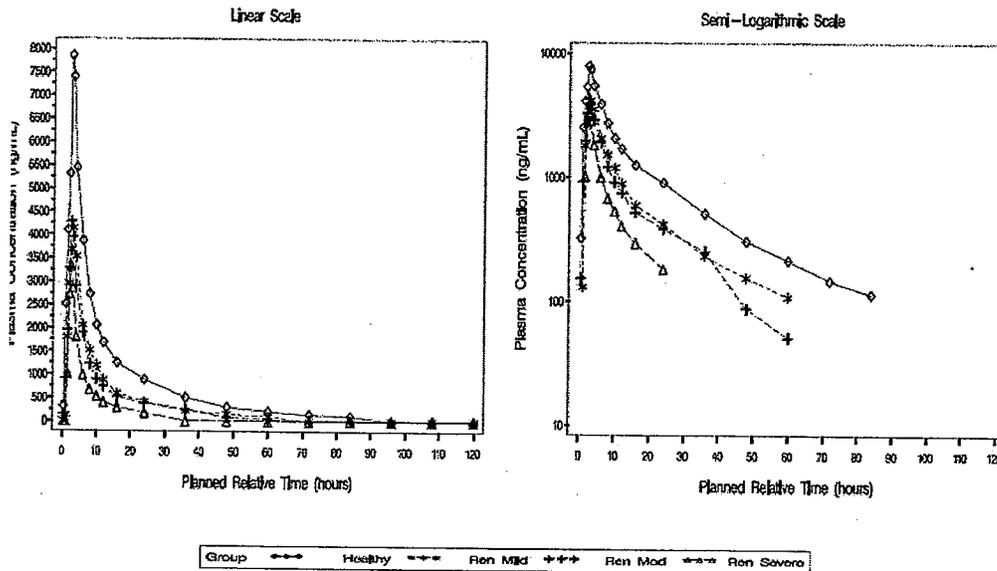
Parameter	Healthy Subjects	Renal Impaired		
		Mild	Moderate	Severe

AUC(0-t) (ng.h/mL) [CVb%] ^a	68.0 (42.1, 110) [40.2]	40.0 (24.8, 64.7) [62.6]	37.5 (22.1, 63.5) [69.9]	16.9 (0.162, 1763) [567]
AUC(0-∞) (ng.h/mL) [CVb%] ^a	72.7 (46.2, 115) [37.9]	44.9 (28.5, 70.7) [58.6]	41.0 (24.9, 67.5) [65.4]	19.7 (0.245, 1588) [465]
C _{max} (ng/mL) [CVb%] ^a	6.94 (4.58, 10.5) [34.4]	4.29 (3.00, 6.11) [44.5]	5.01 (3.03, 8.29) [66.1]	2.12 (0.042, 107) [333]
CL/F (L/h) [CVb%] ^a	0.69 (0.44, 1.08) [37.9]	1.11 (0.71, 1.75) [58.6]	1.22 (0.74, 2.01) [65.4]	2.53 (0.03, 204) [465]
t _{1/2} (h) [CVb%] ^a	26.9 (21.4, 33.8) [18.5]	19.6 (14.0, 27.4) [42]	15.5 (10.4, 22.9) [49.8]	11.3 (0.70, 180) [158]
t _{max} ^b (h)	2.55 (2.50, 3.00)	3.00 (2.50, 4.00)	2.74 (1.00, 4.00)	3.00 (2.50, 6.00)

a. Geometric mean (95% CI [Coefficient of variation as a percentage, CVb%])

b. Presented as median and (minimum, maximum).

Figure 24: Median plasma eltrombopag concentration-time profile



The statistical comparisons of selected eltrombopag PK parameters between the subjects with mild, moderate or severe hepatic impairment versus healthy subjects are summarized in Table 103 & Figure 25

Table 103: Summary of Plasma Eltrombopag PK Parameters for Subjects with Hepatic Impairment versus Healthy Subjects

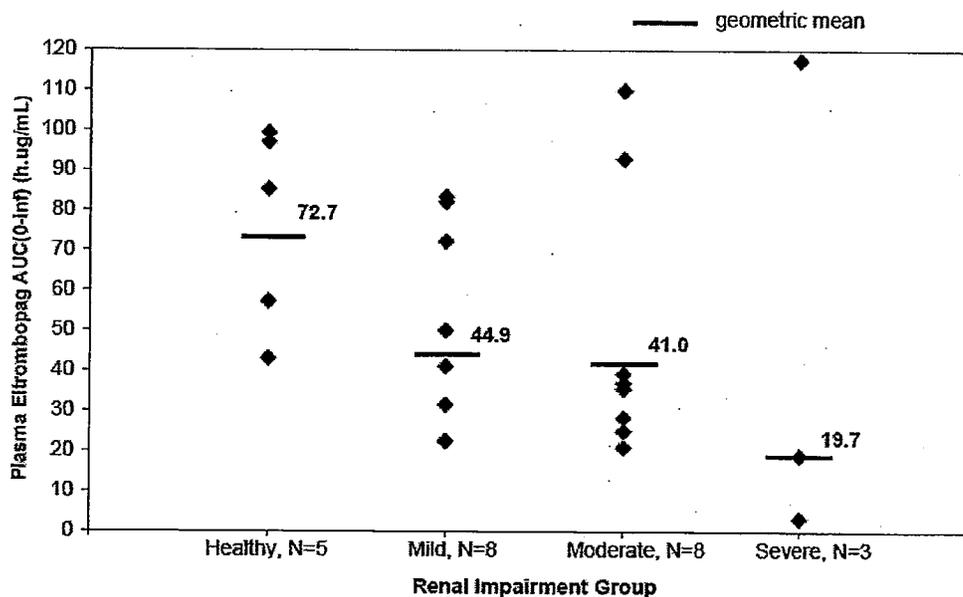
Plasma Eltrombopag PK Parameter	Comparison (Test/Reference)	Ratio	90% CI
AUC(0-∞) (ng.h/mL)	Severe/Healthy	0.27	(0.11, 0.70)
	Moderate/Healthy	0.56	(0.27, 1.18)
	Mild/Healthy	0.62	(0.29, 1.29)
C _{max} (ng/mL)	Severe/Healthy	0.31	(0.13, 0.72)
	Moderate/Healthy	0.72	(0.37, 1.41)

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	Mild/Healthy	0.62	(0.32, 1.20)
t _{1/2} (h)	Severe/Healthy	0.42	(0.22, 0.80)
	Moderate/Healthy	0.58	(0.35, 0.96)
	Mild/Healthy	0.73	(0.44, 1.21)

a. Data presented as geometric least squares mean ratio (90% CI).

Figure 25: Plasma Eltrombopag AUC(0-inf) Values Versus Group following Single-Dose Administration of 50 mg Etlrombopag



Reviewer Comment:

- These data highly variable with high-between-subject variability. This is especially apparent in the "severe" group. There was also and significant overlap in exposures between subjects with renal impairment and healthy subjects
- %AUC_{ex} values were less than 10% for all but six subjects (two subjects each with mild, moderate and severe renal impairment) and less than 20% for all but two subjects (one subject each with mild and severe renal impairment)
- It is difficult to interpret this data without knowing the free concentration of this highly protein bound drug. A reviewer generated analysis of albumin and total protein (TP) concentrations was not possible because these data were not provided by the sponsor. This issue is significant given the known changes in albumin concentration and binding characteristics associated with renal disease which can result in higher free (active) drug concentrations.

Based on analysis of seven subjects, there were no qualitative differences in circulating metabolites between healthy and renal impaired subjects, and the metabolites detected were qualitatively similar to those found in previous human studies (Study 05DMM155). The metabolite screen was qualitative, thus no statistical analysis was conducted.

Reviewer Comment: The sponsor did not provide the method or validation for the assay used to qualify these metabolites.

Plasma eltrombopag C_{max} and CL/F were significantly correlated with serum creatinine (SCr); C_{max} decreased and CL/F increased with increasing level of renal impairment. There were also

trends for AUC(0-∞) and t1/2 to decrease with increasing level of renal impairment. Pearson's correlation coefficient for Cmax: -0.407 (p=0.05), CL/F: 0.406 (p=0.05), AUC(0-∞): -0.369 (p=0.08), and t1/2: -0.381 (p=0.07) (Table 104).

Table 104: Correlation Results From PK Parameters Versus Measures of Hepatic Function

	Statistics	AUC(0-inf) (ng*hr/mL)	AUC(0-t) (ng*hr/mL)	AUC(ext) (%)	Cmax (ng/mL)	CL/F (L/hr)	t1/2 (hr)	tmax (hr)
Serum Creatinine at Day -1	Pearson's r	-0.367	-0.369	0.442	-0.407	0.406	-0.381	0.196
	P-value	(0.0779)	(0.0763)	(0.0307)	(0.0486)	(0.0491)	(0.0659)	(0.3591)

Results-Safety:

The specific adverse events reported in this study are listed in Table 105 below. All drug-related AEs reported were mild in intensity with the exception of one event of nausea reported as moderate. The majority of drug-related AEs were reported in the severe renal impairment group. No drug-related AEs were reported in subjects with moderate renal impairment. All drug-related AEs resolved without any action taken. No serious adverse events (SAEs), non-fatal SAEs or deaths were reported during this study. No subjects experienced an AE leading to premature discontinuation of investigational product and/or the study.

Table 105: Post dose adverse effects:

Parameter	Healthy Subjects	Renal Impaired		
		Mild	Moderate	Severe
Headache	0	3 (38%)	0	2 (67%)
Dyspepsia	0	1 (13%)	2 (25%)	0
Nausea	0	0	0	2 (67%)
Nasopharyngitis	1 (17%)	0	0	1 (33%)
Hypoglycemia	0	1 (13%)	0	1 (33%)

The following AEs were reported once during the study: dizziness, paraesthesia, diarrhea, subcutaneous abscess, urinary tract infection, hyperglycemia, increased creatine phosphokinase, eczema, rash, leukocytosis, polyuria, sinus congestion, frequent bowel movements and hematoma.

Reviewer Comment: Safety information regarding abnormalities seen in vital signs, ECG values, and ophthalmic exams for each treatment regimen were not reported by the sponsor and therefore could not be reviewed.

Conclusions (sponsor):

- Based on these data, which are variable and inconclusive regarding the impact of renal impairment on plasma eltrombopag PK, careful monitoring of platelet response is suggested in patients with renal impairment.
- No significant difference in the type or frequency of AEs reported was noted between subjects with mild or moderate renal impairment following the administration of a single oral 50 mg dose of eltrombopag. The most frequently reported AE across all treatment groups was headache.
- To date, no SAEs or deaths have been reported during this study.

Reviewer Comment: I agree that the data are variable and inconclusive. Although parent drug is not thought to be eliminated via the renal route, given the high protein binding associated with eltrombopag and the known changes in albumin related to renal disease,

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patients with renal impairment.

Careful monitoring is reasonable for

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4.3.10 Intrinsic Factor Phase I & II Pharmacogenetic Investigation From Pooled Studies

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

Genomics Reviewer: Silvana Borges, M.D., Genomics Group

Title: Pharmacogenetic Investigation of Associations with Pharmacokinetic and Pharmacodynamic Outcomes Observed in Subjects Exposed to Eltrombopag

Study period: 06Oct2003 - 27Jul2007

Objectives:

Primary

The primary objective of this investigation was to identify polymorphisms in the 135 ADME panel gene regions that were associated with PK variability as measured by AUC(0-infinity) or AUC(0-tau) in Asian and/or White subjects treated with eltrombopag and to explore any possible pharmacogenetic basis for differential exposure between Asian and White Subjects.

Secondary

The secondary objective of this investigation was to identify any possible associated with variability in PD response in Asian and/or White subjects treated with eltrombopag as measured by the change in maximum platelet count from baseline. This objective included two analyses. In the first analysis, polymorphisms identified as associated with variability in PK in Asians and/or White subjects were evaluated for association with variability in PD response. In the second analysis, the association of polymorphisms within six genes in the thrombopoietin signaling pathway with variability in PD response was explored and the DNA sequences of MPL (encoding amino acids key to thrombopoietin receptor agonist mechanism of action) were determined.

Methodology:

This investigation utilized data from ten clinical studies: TRA104603, TRA105580, 497115/002, 497115/005, TRA104631, TRA105122, TRA102863, TRA102860 Part 1, TRA100773A and TRA100773B. All analyses were conducted when (1) the relevant clinical study databases were cleaned and validated and (2) the corresponding polymorphism data was available and confirmed for accuracy. The analyses focused on Asian and White populations. For other racial groups with at least 5 HVT and/or ITP subjects, only polymorphisms associated with PK or PD variability in Asian or White subjects were assessed.

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

See individual study reviews for clinical studies: TRA104603, TRA105580, 497115/002, 497115/005, TRA104631, TRA105122, TRA102863, TRA102860 Part 1, TRA100773A and TRA100773B.

Criteria for evaluation:

No formal sample size calculation reported. Two analysis populations were defined. The Intent to Treat (ITT) PGx population consisted of all subjects with PK or PD data in the nine clinical studies. The PGx analysis population, a subset of the ITT PGx population, consisted of all randomized subjects in the PK, PK/PD, and PD populations who consented to genotyping, provided a blood sample, and were successfully genotyped for at least one of the polymorphisms under investigation. Subjects with gender discrepancy between self-reported data and results from PGx assays were excluded from the PGx analysis population. The PGx analysis population was divided into HVT subjects and ITP patients in the corresponding race groups.

Race categories in the clinical studies were based on subject self-report. Because these categories varied extensively by clinical trial, it was necessary to initially group subjects into

uniformly-defined racial categories including Asian, White, African American, American Indian, and Other.

A total of approximately 5,000 polymorphisms from gene regions encoding 135 proteins involved in ADME are included in the GSK ADME Panel, v. 1.5. The panel included all known fSNPs describing ADME phenotypes as well as pfSNPs and selected tSNPs to capture known common variations for these ADME gene regions. Genes in the panel have been divided into eight modules according to their biological mechanisms. The eight modules are: 1) Cytochromes and their upstream regulators, 2) Other Phase I enzymes, 3) UDP-glucuronosyltransferase (UGTs), 4) Glutathione S-transferases (GSTs), 5) Other Phase II enzymes such as N-acetyl transferases (NATs) and Thiopurine Smethyltransferases (TPMT), 6) ABC Transporters, 7) Other Transporters, and 8) Miscellaneous. Included are 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.

The primary PK endpoint is the area under the plasma concentration curve (AUC). For HVT subjects who received a single dose of eltrombopag, the AUC is extrapolated to infinity, AUC(0- ∞). For HVT subjects and ITP patients who received repeated doses of eltrombopag, the AUC is measured to dosing interval, AUC(0- τ).

Secondary endpoints involved the PD parameter, change in maximum platelet count from baseline. This parameter was only measured in subjects (HVT and ITP) exposed to repeat doses of eltrombopag. Baseline was defined as the platelet count level before the first dose of repeated doses of eltrombopag. For studies (TRA105580 and 497115/002) in which subjects received single dose and repeat doses of eltrombopag after a washout period, the baseline is the platelet count level before the single dose.

Although summary statistics were calculated to assess the association of each polymorphism with the primary and secondary investigation endpoints, no formal hypothesis testing was conducted. The analyses described herein are exploratory in nature with results and conclusions considered hypothesis generating rather than confirmatory. Association analyses to determine polymorphisms associated with PK, PK/PD, and PD response variability were conducted through a series of evaluations. In each approach, a regression model was fitted with PK (AUC(0- ∞), AUC(0- τ)) or PD response (change in maximum platelet count from baseline) as the dependent variable and the genotype at each marker as the independent variable. Two analysis strategies assigning pre-specified critical p-values using different populations were employed to select polymorphisms for PK and PK/PD evaluation (i.e., a tiered approach, and threshold significance (0.05) approach). To select polymorphisms associated with variability in PD response, polymorphisms in the selected TPO signaling pathway regions associated with PD were identified using two analysis strategies (i.e., threshold significance (0.05) approach and Box Whisker plots/linkage disequilibrium mapping).

Genotyping assays were performed for both the ADME panel gene regions and the six candidate gene regions using standard Sanger-based sequencing techniques, a single base chain extension protocol (FAST), and ~~methodologies~~ methodologies. All assays were validated against the HapMap cohort of subjects. Assays were removed from analysis if less than 80% of subjects returned genotypes, if more than one duplicate error was detected (~10% of samples were duplicated), if assays had less than 99% concordance with published HapMap data (when available), or if they could not be uniquely mapped. 2,828 unique SNPs that were polymorphic in this sample set were detected and used for analyses.

Reviewer Comments:

- 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.
- There is insufficient information about the conditions of blood collection, storage of the blood samples before DNA extraction and DNA extraction procedures.
- It is not possible to calculate the power of the study without knowing the frequency of the variants in the studied population. However, the exploratory nature of this study, make this over inclusive approach acceptable.
- The genotyping procedures as well as the quality control are adequate. However, the exclusion of the assays from the analysis due to low performance is questionable and a source of bias.
- Analysis primarily focused around differences between Asian and Caucasian population. Exposure differences between African American and Caucasian population noted in some studies was not part of the analysis plan.

Demographics

Genotyping assays were performed to evaluate 5129 SNPs comprised of 525 fSNPs, 2757 pfSNPs, and 1847 tSNPs for both the ADME panel gene regions and the six candidate gene regions. For ADME panel gene regions, 202 fSNPs, 969 pfSNPs, and 1,588 tSNPs were polymorphic in this sample set. Only 38 pfSNPs and 31 tSNPs in the PD genes were polymorphic. Monomorphic SNPs for selected MPL sites of interest for PD impact were evaluated separately from the association analysis.

Only a small proportion of the HVT subjects enrolled in the relevant clinical studies had samples available (Table 106) with a combination of genotypic and phenotypic data. Approximately 67% (193/290) of the ITT subjects consented to PGx analysis. Of this set, genotyping data was obtained for ~90% (173/193) of these subjects. PK data (AUC(0-∞)) was available for 159 subjects with AUC(0-τ) data available for 48 subjects. PD data (change in maximum platelet count from baseline) was available for 49 subjects. The ratio of White to Asian samples with PK data available was ~3:1. The ratio of White to Asian samples with PD data available was approximately 1:1. There were insufficient samples available from African American subjects to identify polymorphisms associated with PK variability.

Table 106: HVT population Availability¹

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.

The Intent to treat population is described in Table 107. Approximately 65% (103/159) of the ITT subjects consented to PGx analysis. Within this subset, genotypic data was obtained for ~97% (100/103) of these subjects. PK data (AUC(0-τ)) were available for 54 subjects and PD data (change in maximum platelet count from baseline) was available for 96 subjects. The ratio of White to Asian samples with PK data available was ~ 4:1. The ratio of White to Asian samples with PD data available was ~ 4:1. There were insufficient sample numbers available from African American subjects for group analysis to identify markers associated with variable PK responses.

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Table 107: ITP population Availability

Racial Group	ITT	PGx Consent	Genotype Data2	PK AUC(0-τ)3	PK/PD4	PD5
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.

The PGx HVT and ITP populations were similar to the corresponding ITT HVT and ITP populations in age and weight parameters and in the ratio of male to female subjects. In each population the mean and median weights for Asians were less than the mean and median weights for Whites (~10 kg difference)

For PGx HVT subjects (Table 12), race and dose were significantly associated with AUC(0-∞). Race, baseline platelet count, AUC(0-τ), body weight, and number of repeat dosing days were all significantly associated with PD response in the HVT subjects. For PGx ITP subjects, race, sex, and dose were significantly associated with PK as measured by AUC(0-τ).

Reviewer Comment: Although higher exposure in Japanese reported the true magnitude of the difference is difficult to assess given concerns regarding systematic error in studies 104603 and 105580 (Japan).

Results-Genotyping

Eight polymorphisms were identified as significantly associated with PK variability (Table 108) using the tiered approach in Asian or White HVT subjects. However, none of these polymorphisms was associated with PK variability in both Asian and White HVT samples. Two of these eight polymorphisms were significantly associated with PK variability in Asian HVT subject samples only. These included polymorphisms in the candidate genes NAT1 (RS4986783) and NAT2 (RS1801280). Both of these polymorphisms were defined as fSNPs. Of these two polymorphisms, only one, RS1801280 (in NAT2), was subsequently identified as significant in a combined sample set of Asian and White ITP subjects. The remaining six polymorphisms were associated with variable PK in White HVT samples only by the tiered analysis. These included polymorphisms in five ADME panel genes. RS6976017 and RS28365067 map to the CYP3A5 gene region. RS11590802, maps to the DPYD gene region.

Table 108: Association of SNPs with PK Variability using the Tiered Analysis Approach

Gene / Gene Region	SNP Category	Polymorphism	Association with PK (AUC 0-∞), p-value		Pre-Specified Significance p-Value	Association with PK3 in Combined Sample Sets, p<0.05	
			Asian	White		Asian & White HVT	Asian & White ITP
CYP3A5	fSNP	RS6976017	0.4083	0.006	0.01	0.012	NS1
	fSNP	RS28365067	0.4083	0.0009	0.01	0.002	NS
DPYD	fSNP	RS11590802	-2	0.00008	0.0001	<0.0001	NS
NAT1	Candidate fSNP	RS4986783	0.0239	0.2332	0.05	NS	NS
NAT2	Candidate fSNP	RS1799931	0.5364	0.0292	0.05	NS	NS
	Candidate fSNP	RS1801280	0.0239	0.3658	0.05	NS	0.044

SLC10A2	rSNP	RS7987433	0.7345	0.0002	0.01	<0.001	NS
SLC15A2	rSNP	RS1143671	0.7139	0.0063	0.01	NS	NS

1. NS, not significant
2. Genetic marker was monomorphic in this sample set
3. HVT PK = AUC(0-∞), ITP PK = AUC(0-1).

Polymorphisms in ADME Panel candidate gene regions were evaluated for association with AUC(0-∞) in Asian and in White HVT subjects, $p < 0.05$. One hundred fifty four polymorphisms were identified in 52 distinct gene regions that were associated with PK variability in White HVT subjects. One hundred and five polymorphisms in 40 distinct gene regions were identified that were associated with PK variability in Asian HVTs. Although polymorphisms identified in 22 shared ADME gene regions were associated with variable PK in both Asian and White HVT subjects, only four of these polymorphisms in three gene regions were shared by both Asian and White HVT subjects. None of the four polymorphisms significantly associated with variable PK in both Asian HVT and White HVT groups were associated with variable PK in the corresponding ITP subject sample groups. Of the 154 polymorphisms originally identified as associated with variable PK in White HVT samples, five were significantly associated with variable PK in White ITP samples. Two of these markers, RS6976017 and RS6977165, map to the CYP3A5 gene region covered by the ADME Panel. The other three markers (RS2380570, RS4633, and RS174696) and corresponding gene regions (SLCO5A1 and COMT) are distinct from those identified in HVT samples using the tiered approach followed by secondary analyses in the combined sample sets.

In total, 10 polymorphisms were selected for additional evaluation using either the tiered or the uniform 5% significance threshold approaches. Each of these polymorphisms found to be associated with variability in PK in either Asian or White HVT subject samples was replicated in a secondary analysis using a significance level of $p < 0.05$. No polymorphisms were associated with PK variability in both Asian and White subjects. Eight of the 10 polymorphisms were associated with PK variability in White subject samples. One polymorphisms associated with variable PK in the Tiered Analysis approach, mapping to the CYP3A5 gene region, RS6976017, was identified by both strategies. Two of the 10 polymorphisms were associated with PK variability in Asian subject samples, RS1801280 (NAT2) and RS3758953 (ABCC8).

Three polymorphisms identified in the CYP3A5 gene region were associated with PK variability in White subject samples. The distribution for each of these polymorphisms was consistent between HVT and ITP subjects. For each of the three polymorphisms, only two genotypes were detected in our dataset with the homozygote genotype detected at a higher frequency in both HVT and ITP samples. The genomic context of these associated polymorphisms in the CYP3A5 gene region was examined (Figure 7). Evaluation of linkage disequilibrium for these three polymorphisms indicated that these markers are strongly linked and likely represent the same association.

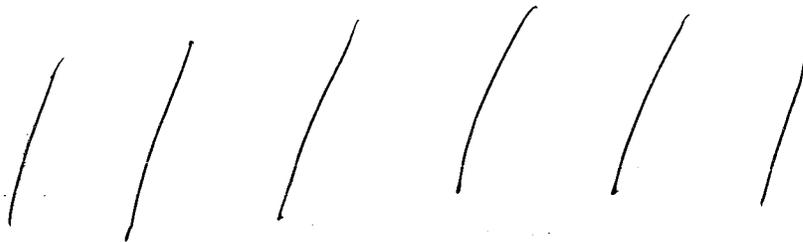
None of the four polymorphisms identified as significantly associated with eltrombopag PK variability in HVT and ITP subjects that demonstrated consistency in genotype distributions (RS6976017, RS28365067, RS6977165, and RS2380570) were associated with PD variability.

Polymorphisms from the thrombopoietin signaling pathway were not associated with variability in PD response. The investigation did confirm, however, that mutations shown with in vitro site-directed mutagenesis studies to negatively impact thrombopoietin receptor agonist interactions with the thrombopoietin receptor are not detected in a large cohort of subjects representing several ethnic groups.

Reviewer Comments:

- 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 and no polymorphisms in the six genes analyzed in the thrombopoietin signaling pathway were associated with variability in PD.

- *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.*
- *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.*
- *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.*



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Conclusions (sponsor):

- No polymorphisms were associated with differences in eltrombopag exposure between Asian and White subjects.
- Three polymorphisms in CYP3A5 were associated with variability in eltrombopag AUC in both White HVT and ITP subjects. However, all these markers are in complete linkage disequilibrium with each other and more than a dozen known genes, making it difficult to define causative associations. The p-values reported here were not adjusted for multiplicity.
- One polymorphism in SLCO5A1, encoding the organic anion transporter, OATPJ (OATPRPM) was associated with variability in AUC in both White HVT and ITP subjects.
- Although it is possible that variability in eltrombopag AUC is the result of polygenic contributions, it was not possible to demonstrate this with the existing sample sets.
- While dose of eltrombopag was associated with PD response, none of the polymorphisms associated with PK variability in White subjects was subsequently shown to be associated with PD variability.
- No polymorphisms in the six genes analyzed in the thrombopoietin signaling pathway were associated with variability in PD.
- All sequences encoding amino acids in MPL (the thrombopoietin receptor) that have been shown to impact interaction of the receptor with its cognate ligand (TPO) were monomorphic in this sample set.
- Confirmation of polymorphisms associated with observed variability in PK and PD responses between Asian and White subjects would require substantially more samples with relevant genotypic and phenotypic datasets than was currently available at the time this investigation.

Reviewer Comment:

- 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.

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4.3.11 Extrinsic Factor Study of Eltrombopag OATP1B1 inhibition in Healthy Subjects

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

Title: 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

Study period: 18 May 2006 – 02 October 2006

Objectives:

Primary

- To examine the pharmacokinetics (PK) of single-dose (SD) rosuvastatin when coadministered with eltrombopag as compared to rosuvastatin alone.

Secondary

- To examine the PK of rosuvastatin metabolites of SD rosuvastatin coadministered with eltrombopag compared to rosuvastatin alone.
- To assess the safety and tolerability of eltrombopag when co-administered with rosuvastatin.

Methodology:

This was an open-label study in healthy subjects, evaluating the potential drug interaction of eltrombopag (SB-497115-GR) with rosuvastatin. A total of 42 healthy subjects received rosuvastatin and eltrombopag orally in the following sequence (Table 109):

Table 109: Treatment Sequence

Study Day	Study Drug
Day 1	Rosuvastatin 10 mg once daily (QD)
Day 6 through Day 9	Eltrombopag 75 mg QD
Day 10	Eltrombopag 75 mg QD + Rosuvastatin 10 mg QD

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

Batch numbers for eltrombopag supplied to study sites are as follows (Table 110):

Table 110: Eltrombopag Product Information

Batch Number	Strength	Formulation Code	Substance Batch	Site
051109557	25 mg	AS	F081598 (ToneBridge)	Singapore
051109563	50 mg	AR	F081598 (ToneBridge)	Singapore

051109558	25 mg	AS	F081601 (ToneBridge)	—
051109563	50 mg	AR	F081598 (ToneBridge)	—

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Subjects received rosuvastatin and eltrombopag orally as follows:

- Rosuvastatin alone: 10 mg once daily (QD) on Day 1
- Eltrombopag alone: 75 mg QD on Day 6 through Day 9
- Combination: Eltrombopag 75 mg QD + Rosuvastatin 10 mg QD on Day 10

Subjects were required to fast from food and drink (except water) from eight hours prior to dosing until four hours after dosing. Subjects will be allowed water up to one hour prior to dosing and starting from one hour after dosing.

Reviewer Comment: Information regarding the Rosuvastatin product not provided by the sponsor

Criteria for evaluation:

- Sample Size:
 - The target sample size was at least 30 evaluable subjects. Based on results from a previous rosuvastatin study in healthy volunteers to assess the dose proportionality of rosuvastatin estimated within-subject coefficients of variation are 33.0% and 35.4% for C_{max} and AUC(0-24), respectively. The largest of these estimates (35.4%) translated to a standard deviation of 0.344 on the natural log scale. When the sample size is 30 evaluable subjects, the upper 90% confidence limit for the true ratio of statin alone and with eltrombopag for the most variable PK parameter of primary interest would be no more than 15% greater than the observed ratio of the means of the two formulations.

Reviewer Comment: Sensitivity analysis was not provided by the sponsor

- Pharmacokinetics:
 - Blood samples for eltromboag, rosuvastatin, and rosuvastatin metabolites (3 mL) were collected on Day 1 through Day 5, and Day 10 through Day 14 as listed in Table 111

Table 111: PK Sample Collection Schedule

Study Day	Analyte	Planned Time Relative to Dosing (hours)
1	Rosuvastatin and metabolites	pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 hours post-dose
2	Rosuvastatin and metabolites	24 and 36 hours post-dose
3	Rosuvastatin and metabolites	48 and 60 hours post-dose
4	Rosuvastatin and metabolites	72 and 84 hours post-dose
5	Rosuvastatin and metabolites	96 hours post-dose
8	Eltrombopag	pre-dose
9	Eltrombopag	pre-dose
10	Eltrombopag + Rosuvastatin and metabolites	pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 hours post-dose
11	Eltrombopag + Rosuvastatin and metabolites	24 and 36 hours post-dose
12	Eltrombopag + Rosuvastatin and metabolites	48 and 60 hours post-dose
13	Eltrombopag + Rosuvastatin and metabolites	72 and 84 hours post-dose
14	Eltrombopag + Rosuvastatin and metabolites	96 hours post-dose

- Plasma samples were analyzed for eltrombopag using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) analysis (Table 112). The lower limit of quantification (LLQ) for eltrombopag was 100 ng/mL,

using a 50 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 50000 ng/mL

Table 112: Assay validation information

Eltrombopag is extracted from 50µL human plasma by protein precipitation using _____ as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
LLQ	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.

- Plasma samples were analyzed for rosuvastatin using a validated analytical method based on _____, followed by high-performance liquid chromatography/mass spectroscopy (HPLC/MS/MS) analysis. The LLQ was 0.2 ng/mL for rosuvastatin, using a 100 µL aliquot of human EDTA plasma, and the HLQ was 30 ng/mL for rosuvastatin.

b(4)

Reviewer Comment: The sponsor failed to provide adequate information to allow the reviewer to evaluate the method of analysis of the plasma rosuvastatin samples.

- PK analysis of plasma rosuvastatin and eltrombopag concentration-time data was conducted using the noncompartmental Model 200 of WinNonlin Professional Edition version 4.1 Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects.
 - Values for the following single dose plasma rosuvastatin PK parameters were estimated:
 - The maximum observed plasma concentration (C_{max}) and the first time to reach C_{max} (t_{max}) were the actual observed values.
 - 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 after single dosing (AUC_(0-∞)) were determined. Values for AUC_(0-∞) were estimated as the sum of AUC_(0-t) and C_t divided by the elimination rate constant, where C_t was the last observed quantifiable concentration.
 - Values for the following steady-state plasma eltrombopag PK parameters were estimated:
 - C_{max}
 - T_{max}
 - Area under the plasma concentration-time curve over a dosing interval (AUC_(0-τ))

- The terminal elimination rate constant (λ_z) 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 terminal elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$.
 - Plasma rosuvastatin PK was compared between treatments for all subjects combined and for subgroups based on race (Asian vs. non-Asian) and on genotypes for OATP1B1, BCRP, and NTCP. In addition, plasma rosuvastatin PK was compared between Asian and non-Asian subjects and between the transporter genotypes for each treatment separately. No hypothesis testing was planned. Point estimates and associated 90% confidence intervals were constructed for each comparison of interest.
- Genetic analysis
 - Genetic analysis of transporters was conducted. Genotypes were determined for the following transport proteins: OATP1B1 A388G, OATP1B1 T521C, BCRP C421A, NTCP*2 C800T, NTCP*3 T688C, NTCP*4 T836C, and NTCP*5 A940G.

Reviewer Comment: The sponsor failed to provide adequate information to allow the reviewer to evaluate the method of genotyping.
- 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, ECG monitoring (12-lead), and ophthalmologic examination were listed and summarized. No formal statistical analyses of the safety data were performed.

Number of Subjects

Subject number and disposition are summarized in Table 113.

Table 113: Subject Number and Disposition

	Total
Number of Subjects Planned ¹ :	36
Number of Subjects Enrolled:	42
Number of Subjects included in safety analysis, n (%):	42 (100)
Number of Subjects included in pharmacokinetic analysis, n (%):	
PK Concentration population	42 (100)
PK Parameter population	39 (93)
Number of Subjects Completed as Planned, n (%):	40 (95)
Number of Subjects Withdrawn (any reason), n (%):	2 (5)
Number of Subjects Withdrawn for AE, n (%) *	1 (2)
Subject decided to withdraw from the study, n (%):	1 (2)
*Subject 7 was withdrawn on Day 10 after receiving study drug following a diagnosis of herpes zoster. The Investigator considered the herpes zoster not related to study drug.	

Population Demographics

The population demographics from this study are listed in Table 114 below.

Table 114: Population Demographics

Parameter	Total
Age in Years, Mean (SD)	33.6 (7.80)
Sex	
Female: Male	9:33
Ethnicity, n (%)	
Hispanic or Latino:	4 (10)
Not Hispanic or Latino:	38 (90)
Race, n (%)	
African American/African Heritage	12 (29)
American Indian or Alaska Native	4 (10)
Asian – Central/South Asian Heritage	2 (5)
Asian – East Asian Heritage	19 (45)
Asian – South East Asian Heritage	1 (2)
White – White/Caucasian/European Heritage	4 (10)

Table 115: Summary of Genotype Frequencies

Genotype	n	African American/ African Heritage	American Indian or Alaskan Native	Asian - Central/ South Asian Heritage	Asian - East Asian Heritage	Asian - South East Asian Heritage	White - White/Cau- casian/Eu- ropean Heritage	Total
		(N=12)	(N=4)	(N=2)	(N=19)	(N=1)	(N=4)	(N=42)
OATP1B1 (A388G)	n	12	4	2	19	1	3	41
	AA	2 (17%)	3 (75%)	0	2 (11%)	1 (100%)	0	8 (20%)
	AG	3 (25%)	1 (25%)	2 (100%)	6 (32%)	0	2 (67%)	14 (34%)
	GG	7 (58%)	0	0	11 (58%)	0	1 (33%)	19 (46%)
OATP1B1 (T521C)	n	12	4	2	19	1	3	41
	TT	10 (83%)	3 (75%)	2 (100%)	15 (79%)	1 (100%)	1 (33%)	32 (78%)
	TC	2 (17%)	1 (25%)	0	4 (21%)	0	1 (33%)	8 (20%)
67	CC	0	0	0	0	0	1 (33%)	1 (2%)
BCRP (C421A)	n	12	4	2	19	1	3	41
	CC	11 (92%)	2 (50%)	1 (50%)	11 (58%)	0	1 (33%)	26 (63%)
	CA	1 (8%)	2 (50%)	1 (50%)	7 (37%)	1 (100%)	2 (67%)	14 (34%)
	AA	0	0	0	1 (5%)	0	0	1 (2%)
NTCP*2 (C800T)	n	12	4	2	19	1	3	41
	CC	12 (100%)	4 (100%)	2 (100%)	16 (84%)	1 (100%)	3 (100%)	38 (93%)
	CT	0	0	0	3 (16%)	0	0	3 (7%)
NTCP*3 (T688C)	n	12	4	2	19	1	3	41
	TT	12 (100%)	4 (100%)	2 (100%)	19 (100%)	1 (100%)	3 (100%)	41 (100%)
NTCP*4 (T836C)	n	12	4	2	19	1	3	41
	TT	11 (92%)	4 (100%)	2 (100%)	19 (100%)	1 (100%)	3 (100%)	40 (98%)
	CC	1 (8%)	0	0	0	0	0	1 (2%)
NTCP*5 (A940G)	n	12	4	2	19	1	3	41
	AA	12 (100%)	4 (100%)	2 (100%)	19 (100%)	1 (100%)	3 (100%)	41 (100%)

Reviewer Comment:

- Weight, Height, and BSA not provided by the sponsor. This information is significant given the sponsor's assertion that ethnic differences may be related to body weight.
- Difficult to identify genotypic differences between Asians and Caucasians due to the small number of Caucasians. African Americans and East Asians appeared similar except for BCRP.

Results-PK analysis:

Asian subjects had 2.09-fold higher plasma rosuvastatin AUC(0-∞) compared to non-Asian subjects when rosuvastatin was given alone. In addition, Asian subjects had 46% higher plasma rosuvastatin AUC(0-∞) compared to non-Asian subjects when rosuvastatin was coadministered with eltrombopag. Plasma rosuvastatin Cmax values were similarly higher in Asian compared to non-Asian subjects (See Table 116 & Figure 26). OATP1B1 A388G GG variant tended to have slightly higher plasma rosuvastatin exposure.

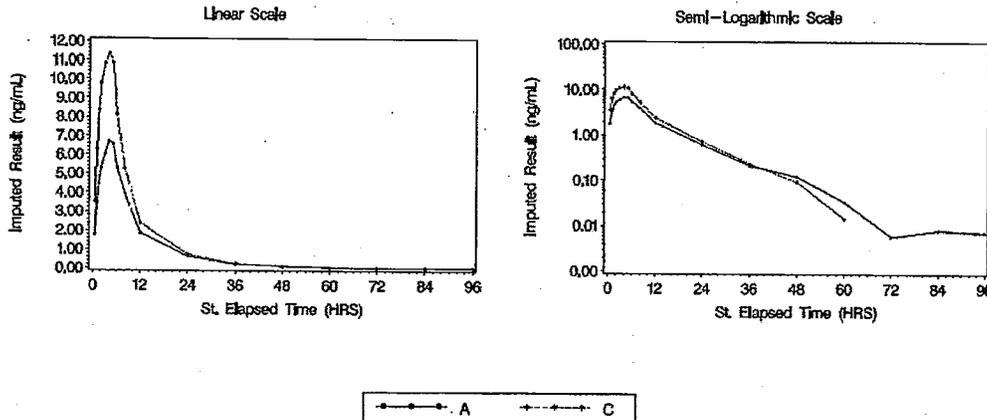
Table 116: Summary of Plasma Rosuvastatin PK by Race

PK parameter	Rosuvastatin (Treatment A)			Rosuvastatin + Eltrombopag (Treatment C)		
	Asian (n=21)	Non-Asian (n=18)	Asian vs. Non-Asian	Asian (n=21)	Non-Asian (n=18)	Asian vs. Non-Asian
AUC(0-∞) (ng-hr/mL)	87.0 (58)	41.6 (58)	2.09 (1.60, 2.72)	114 (47)	78.2 (45)	1.46 (1.12, 1.91)
Cmax (ng/mL)	8.93 (63)	3.74 (59)	2.39 (1.81, 3.16)	14.4 (51)	9.91 (47)	1.45 (1.10, 1.92)

Reviewer Comment:

- Three subjects (Subjects 9, 58, and 65) were excluded from the PK parameter population for the following reasons: 1) Subject 65 completed only one treatment; 2) AUC(0-∞) could not be appropriately determined for Subject 9 because the Cmax value was included as the third point in the terminal phase rate constant (λz) estimate; and 3) AUC(0-∞) could not be appropriately determined for Subject 58 because the elimination phase was flat, which resulted in a t½ estimate of >56h which was not supported by the PK sample collection interval.
- Although planned as an objective of the study, rosuvastatin metabolites were not analyzed in this study, due to an oversight in the requirement for metabolite quantification.

Figure 26: Mean plasma Rosuvastatin Concentration-Time Profile



Reviewer Comment:

- Reviewer generated analysis (Table 117) of three populations of interest showed similar exposure between African Americans and Caucasians for rosuvastatin alone. There was a trend toward African Americans having a lower exposure when rosuvastatin was coadministered with eltrombopag compared to the other two groups. Perhaps this is related to differences in BCRP CC?

Table 117: Reviewer Generated Analysis of PK in Selected Ethnic Groups

Parameter	Period	White/Caucasian	African American	East Asian
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AUC _{inf} (ng*hr/mL)	A	40.6 (28.4,73.7)	40.9 (38.6,57.9)	90.4 (62.7,148.7)
	C	107.6 (48.3,117.3)	84.3 (59.1,115.2)	109 (90,142)
C _{max} (ng/mL)	A	3.6 (3.5)	3.7 (3.5,8)	8.6 (6,13.7)
	C	12.8 (6.2,15.4)	11.7 (7.5,14.1)	15.1 (10.3,19)
Auc _{last} (ng*hr/mL)	A	38.1 (26.2,64.4)	36.9 (33.2,54.3)	88.1 (57.5,145.9)
	C	102.5 (46.4,113.3)	82.4 (56.1,112)	104.3 (77.1,128)

Data as median (25th, 75th)

Co-administration of eltrombopag with rosuvastatin increased plasma rosuvastatin C_{max} by 2.03-fold and AUC(0-∞) by 55% (Table 118).

Table 118: Summary of Eltrombopag-Rosuvastatin Drug Interaction Results

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

Reviewer Comment: The 90% CI based on the ratio of C:A for both parameters are outside the 80%-125% range and the absence of a drug interaction has not been proven.

When eltrombopag was co-administered, plasma rosuvastatin exposure was increased to a greater extent in non-Asian than Asian subjects. For Asian subjects, plasma rosuvastatin AUC(0-∞) increased 32% and for non-Asian subjects, AUC(0-∞) increased 88% when eltrombopag was co-administered (Table 119).

Table 119: Summary of Eltrombopag-Rosuvastatin Drug Interaction Results by Race

Plasma Rosuvastatin PK parameter	Rosuvastatin+Eltrombopag (Treatment C) vs. Rosuvastatin (Treatment A)	
	Asian (n=21)	Non-Asian (n=18)
	AUC(0-∞) (ng·hr/mL)	1.32 (1.19, 1.46)
C _{max} (ng/mL)	1.61 (1.44, 1.80)	2.65 (2.35, 3.00)

Reviewer Comment: It appears from the reviewer generated analysis that the ratio of ratio of C:A showed a trend of Caucasians>African Americans>East Asians.

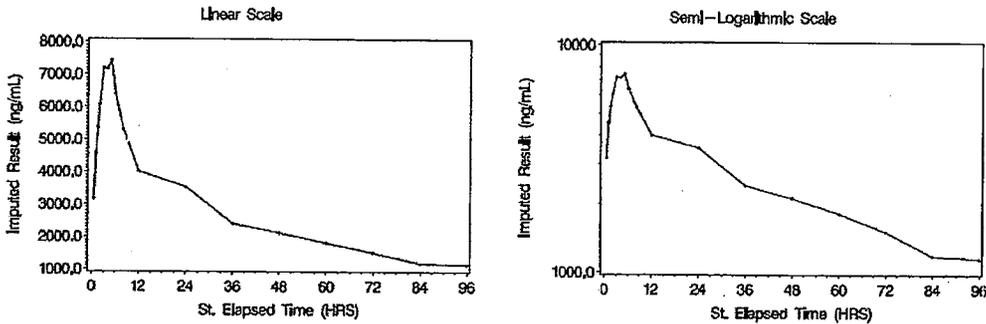
Plasma eltrombopag PK were similar between Asian and non-Asian subjects (Table 120 & Figure 27)

Table 120: Summary of Plasma Eltrombopag PK by Race

Plasma Eltrombopag PK Parameter	Rosuvastatin + Eltrombopag (Treatment C)		
	Overall (N=39)	Asian (n=21)	Non-Asian (n=18)
AUC(0-τ) (μg·hr/mL)	102 (44)	105 (48)	99.7 (39)
C _{max} (μg/mL)	8.00 (39)	8.14 (43)	7.83 (35)

Figure 27: Mean plasma Eltrombopag concentration-time profile

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Reviewer Comment:

- Although the sponsor reports similar eltrombopag exposure between Asians and non Asians, a reviewer generated analysis (Table 121) of three populations of interest showed a trend toward lower eltrombopag exposure Caucasians and higher exposure in African Americans and Asians. Comparisons to Caucasians would be inconclusive given the small sample size. However this does provide additional evidence (see Study TRA 105122) to suggest possibly higher exposure in African Americans.

Table 121: Reviewer Generated Analysis of PK in Selected Ethnic Groups

Parameter	African American	East Asian	White/Caucasian
Cmax (mcg/mL)	8.7(7.8,9.7)	9.4(5.9,10.7)	7.6(3.1,8.9)
T1/2 (hr)	37.3(33.4,44.2)	46.4(38.7,52.3)	29.9(26.4,42.4)
AUC _{0-∞} (mcg*hr/mL)	116.4(96.3,132.6)	111.3(83,146.8)	58.5(41,117.1)

Data as median (25th, 75th)

- This possible 2 fold difference in exposure between African American/Asian and Caucasian subjects was further analyzed by the pharmacometrics reviewer using information from the pop-PK analysis looking specifically at differences in clearance (CL). This analysis showed that the small number of Caucasian subjects (N=3) in this study had a median clearance almost double that of other studies (see Figure 27a). For African American subjects the reported clearance was similar to that reported in other studies with the exception of study 122. For the Asian population clearance in this study is higher relative to other studies. Based on this the effect of African American ethnicity on exposure in this study is not clear.

Figure 27a: PM Reviewer Generated Analysis of Apparent Clearance by Ethnic Groups Across Studies

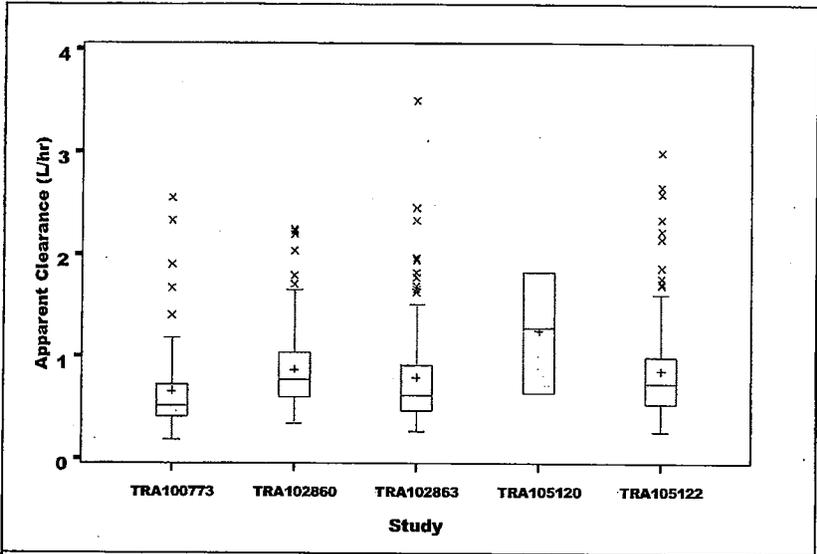
Caucasian

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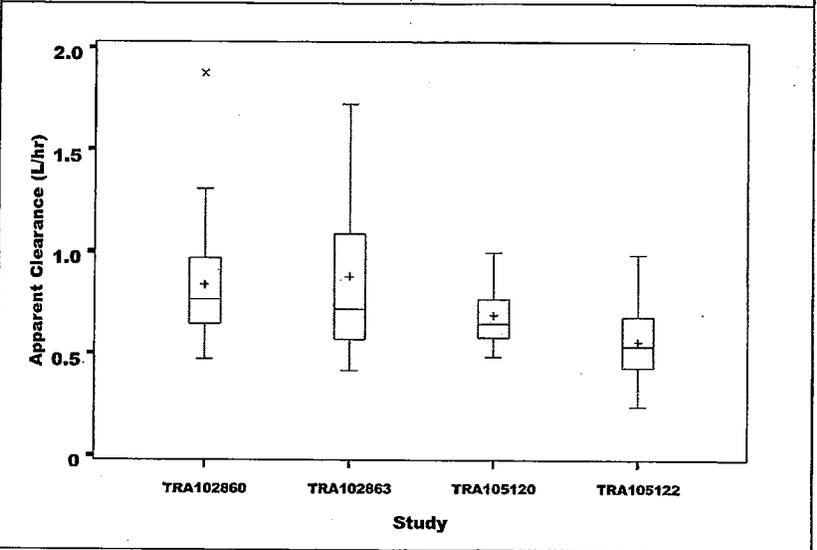
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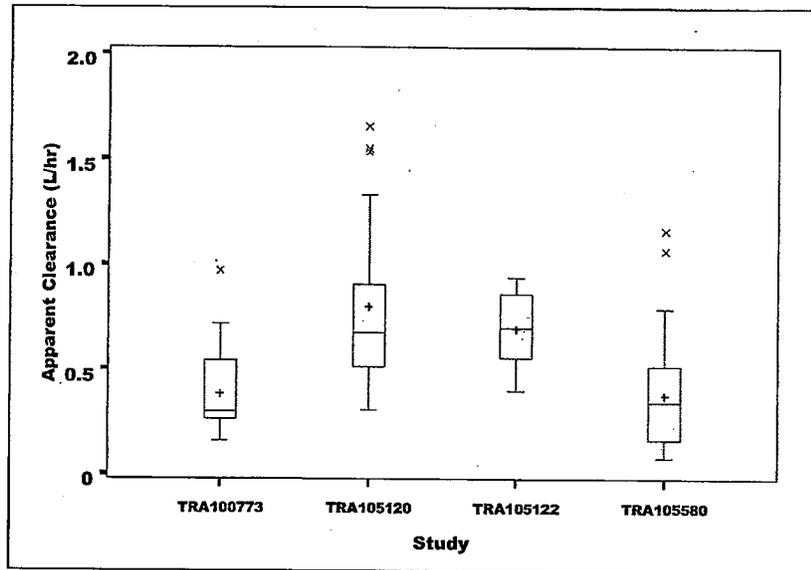
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African-American



Asian



Results-Safety:

The specific adverse events that occurred in this study are listed in Table 122 below:

Table 122: Post Dose Adverse Effects:

SOC Preferred Term	Rosuvastatin	Eltrombopag	Rosuvastatin + Eltrombopag
	n=42 n (%)	n=41 n (%)	n=41 n (%)
Number of Subjects with Any AE	9 (21)	4 (10)	5 (12)
Infections & infestations, any event	6 (14)	1 (2)	3 (7)
Gastroenteritis	2 (5)	0	1 (2)
Upper respiratory tract infection	3 (7)	0	0
Herpes zoster	0	0	1 (2)
Hordeolum	0	0	1 (2)
Pharyngitis streptococcal	0	0	1 (2)
Rash pustular	0	1 (2)	0
Viral upper respiratory tract infection	1 (2)	0	0
Gastrointestinal disorders, any event	3 (7)	1 (2)	1 (2)
Abdominal pain	1 (2)	0	0
Diarrhea	0	0	1 (2)
Flatulence	0	1 (2)	0
Gastritis	1 (2)	0	0
Nausea	1 (2)	0	0
Nervous system disorders, any event	2 (5)	0	1 (2)
Headache	2 (5)	0	1 (2)
Eye disorders, any event	0	1 (2)	0
Vision blurred	0	1 (2)	0
Injury, poisoning and procedural complications, any event	0	0	1 (2)
Excoriation	0	0	1 (2)
Musculoskeletal and connective tissue disorders, any event	0	1 (2)	0
Musculoskeletal pain	0	1 (2)	0