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Study No: TRA102863
Title : A randomized, open-label, two-period, period-balanced, crossover study with three parallel groups to evaluate the relative bioavailability of single oral doses of SB-497115-GR (eltrombopag) phase III tablets [50 mg, 75 mg, 100 mg] compared to SB-497115-GR phase II tablets [25mg and 50 mg] in healthy volunteers
Rationale: The purpose of the current study was to evaluate the relative bioavailability of 50 mg, 75 mg and 100 mg strength tablets manufactured at the commercial facility for use in phase III studies relative to the same dose administered using 25 mg and 50 mg tablets, which were manufactured at the R&D facility and have been used in phase II studies. It also evaluated the safety and tolerability of eltrombopag up to 100 mg in healthy subjects.
Phase: I
Study Period: 18 August 2005 – 26 October 2005
Study Design: Randomized, open-label, two-period, period-balanced, crossover study with three parallel groups
Centres: PPD Development, LP; 7551 Metro Center Drive, Suite 200; Austin, TX 78744
Indication: none
Treatment: Group 1: Regimen A=One Phase II 50 mg eltrombopag tablet; Regimen B=one Phase III 50 mg eltrombopag tablet; Group 2: Regimen C= concomitant dosing of one Phase II 25 mg eltrombopag tablet and one 50 mg eltrombopag tablet; Regimen D= one Phase III 75 mg eltrombopag tablet; Group 3: Regimen E= two Phase II 50 mg eltrombopag tablets; Regimen F= one Phase III 100 mg eltrombopag tablet
Objectives: To evaluate the relative bioavailability of phase III SB-497115-GR (eltrombopag) 50 mg tablet relative to phase II eltrombopag 50 mg tablet. To evaluate the relative bioavailability of one phase III eltrombopag 75 mg strength tablet relative to concomitant administration of one phase II eltrombopag 25 mg tablet and one eltrombopag 50 mg tablet (total dose 75 mg). To evaluate the relative bioavailability of one phase III eltrombopag 100 mg tablet relative to two phase II eltrombopag 50 mg tablets.
Statistical Methods: The primary endpoint for analysis were PK parameters, AUC(0-∞), and Cmax for the comparison of the Phase III test formulation to Phase II reference formulation. The primary endpoints were log-transformed prior to the primary analyses. No adjustments for multiple comparisons were made. To estimate the relative bioavailability of eltrombopag Phase III tablets compared to eltrombopag Phase II tablets for each primary PK endpoint, a mixed effects linear analysis of variance (ANOVA) model was fit to the natural logarithm of the PK parameter. Effects associated with treatment sequence, period, and treatments were assumed to be fixed; effects associated with subjects within each treatment sequence were assumed to be random. Point and 90% interval estimates of the difference in least-squares means of the test minus the reference treatment were derived using a SAS code such as that described below. The difference was then exponentiated (back-transformed) to provide the comparison based on the ratios on the

original scale. The final estimates therefore represent the ratio of the geometric least squares (GLS) mean of the test treatment to the GLS mean of the reference treatment. Group 2 (C vs D) and Group 3 (E vs. F) were analyzed separately in a similar manner. No formal statistical comparisons were made for the safety data. All safety data were reported according to the actual treatment the subject received. Safety analysis included extent of exposure, adverse events, clinical laboratory evaluations, vital signs, and ECGs.

Study Population: Healthy male or female subject 18-64 years of age, with Body Mass Index (BMI) $19 \leq 30$ kg/m² and body weight ≥ 50 kg for males and ≥ 45 kg for females.

Number of Subjects:	
Planned N	60
Dosed N	66
Completed n (%)	63 (95.5)
Total Number Subjects Withdrawn N (%)	3 (4.5)
Withdrawn due to Adverse Events n (%)	1 (1.5)
Withdrawn due to Lack of Efficacy n (%)	N/A
Withdrawn for Other Reasons n (%)	2 (3.0)
Demographics	
N (Safety)	66
Females: Males	46:20
Mean Age in Years (sd)	42.9 (13.5)
Mean Weight in Kg (sd)	70.0 (12.9)
White n (%)	55 (83)

Pharmacokinetics (PK) Endpoints:

The geometric mean AUC (0- ∞) and C_{max} values appeared similar at corresponding doses of Phase II and Phase III formulations. The t_{1/2} of eltrombopag was similar among all treatments and was approximately 18-21 hours post dose.

Bioavailability, based on AUC (0- ∞) and C_{max}, of the Phase II and Phase III formulations was similar for the total dose of 75 mg and 100 mg, but not at the lower dose of 50 mg.

Summary of Selected eltrombopag PK Parameters

Dose (mg)	Regime n	N	AUC(0- ∞) (ng.hr/ml) ¹	C _{max} (ng/ml) ¹	t _{max} (hr) ²	t _{1/2} (hr) ¹
50 mg	A	22	74457.7 (34.9)	6111.0 (29.0)	3.00 (1.48,4.15)	18.9 (19.6)
	B	22	63160.1 (54.6)	5093.7 (54.3)	3.00 (1.50,6.00)	18.3 (24.8)
75 mg	C	22	98606.4 (52.8)	8184.3 (43.8)	3.00 (1.50, 6.00)	18.2 (23.4)
	D	22	100488.5 (46.4)	8679.0 (38.1)	3.00 (1.50,4.00)	17.8 (21.5)
100 mg	E	20	178988.2 (58.5)	12320.4 (56.6)	3.34 (2.00,6.00)	21.5 (16.1)
	F	20	154189.3 (73.7)	11176.0 (65.5)	3.00 (2.00,8.00)	21.3 (20.9)

1 geometric mean (CVb%)

2 median (min, max)

A: phase II 50 mg tablet

B: phase III 50 mg tablet

C: phase II 75 mg (one 25 mg and one 50 mg dose)

D: phase III 75 mg tablet

E: phase II 2 x 50 mg tablets

F: phase III 100 mg tablets

Safety results:

An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as an SAE with onset on or after the start date of study

medication and up to 30 days after the last dose of medication.						
Adverse Events:	Regime n A	Regime n B	Regime n C	Regime n D	Regime n E	Regime n F
N (Safety)	22	22	22	22	22	20
No. subjects with AEs n (%)	9 (41)	7 (32)	9 (41)	5 (23)	2 (9)	3 (15)
Most Frequent AEs						
Headache	3 (14)	3 (14)	2 (9)	1 (5)	0	0
Syncope vasovagal	2 (9)	0	0	0	0	0
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:	Regime n A	Regime n B	Regime n C	Regime n D	Regime n E	Regime n F
N (Safety)	22	22	22	22	22	20
No. subjects with SAEs n (%)	1 (5%) [0]	0	0	0	0	0
Most Frequent SAEs						
Severe abdominal pain*	1 (5) [0]	0	0	0	0	0
*Subject experienced severe abdominal pain and was hospitalized 8 days after receiving the last dose (Regimen A, during Period 2). This subject was not withdrawn from the study, as she had received the final dose of study medication.						

Publications: None