

Study No: TRA104631	
Title : An open-label, randomized, five-period, period-balanced, crossover study to assess the effect of food and antacid on the pharmacokinetics of a single dose of SB-497115-GR (eltrombopag) in healthy volunteers	
Rationale: The current study was designed to investigate the effect of food and metal cations on the pharmacokinetics of eltrombopag by testing a variety of meals (high-fat and low-fat, both consisting of foods with low calcium content [40-50 mg of calcium] and no dairy products) consumed with eltrombopag, altering the timing of meal consumption (high fat meal consisting of foods with low calcium content [40-50 mg of calcium] and no dairy products consumed 1 hour after study drug administration) and concomitantly administering antacids.	
Phase: I	
Study Period: 01 Aug 2005 – 02 Nov 2005	
Study Design: open-label, randomized, five-period, period-balanced, crossover study	
Centres: Covance Clinical Research Unit Inc 3402 Kinsman Boulevard Madison, WI 53704	
Indication: none	
Treatment: Regimen A: 75mg eltrombopag while fasting Regimen B: 75mg eltrombopag with low-fat meal (low calcium/no dairy) Regimen C: 75mg eltrombopag while fasting with cation-containing antacid (GAVISCON™) Regimen D: 75mg eltrombopag with high-fat meal (low calcium/no dairy) Regimen E: 75mg eltrombopag administered one hour prior to consumption of high-fat meal (low calcium/no dairy)	
Objectives: To evaluate the effects of high- and low-fat meals consisting of foods with low calcium content (40-50mg calcium) and no dairy products on the pharmacokinetics of a single oral dose of 75mg eltrombopag in healthy volunteers To evaluate the effect of cation-containing antacid on the pharmacokinetics of a single oral dose of eltrombopag 75mg in healthy volunteers To evaluate the effect of timing of meal consumption in relation to study drug administration on the pharmacokinetics of eltrombopag.	
Statistical Methods: The SB-497115 PK parameters, except tmax, will be log-transformed prior to the primary analyses, and treatment comparisons were expressed as ratios on the original scale. No adjustments were to be made for multiple comparisons. To assess the effect of food on the bioavailability of SB-497115 for each primary PK endpoint (AUC and Cmax), a mixed effects linear analysis of variance (ANOVA) model was fitted to the natural logarithm of the derived endpoint. Effects associated with period, and treatment were assumed fixed; effects associated with subject were assumed random. The geometric least-squares mean ratios (B:A, C:A, D:A, E:A, E:D) and associated 90% confidence interval for each treatment comparison were estimated using the SAS mixed linear models procedure.	
Study Population: Subjects in this study were healthy adults with a mean age of 35.6±11.3 years.	
Number of Subjects:	
Planned N	26
Dosed N	26
Completed n (%)	23
Total Number Subjects Withdrawn N (%)	3
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	3
Demographics	
N (Safety)	26
Females: Males	12 : 14
Mean Age in Years (sd)	35.6 (11.3)
Mean Weight in Kg (sd)	76.0 (12.1)
White n (%)	17 (65)
Pharmacokinetics (PK), pharmacodynamics (PD), PK/PD Endpoints:	

Regimen	N	AUC(0-∞) (ng·hr/mL) ¹	C _{max} (ng/mL) ¹	T _{max} (hr) ²	t _{1/2} (hr) ¹
A	24	76876 (48.58)	6198 (44.00)	4.00 (2.00-6.00)	16.8 (15.8)
B	24	70871 (44.15)	5362 (43.97)	4.00 (2.07-6.00)	17.0 (15.1)
C	25	23057 (95.08)	1875 (102.99)	4.00 (1.00-8.00)	15.0 (20.8)
D	25	79829 (43.97) ³	6218 (46.32)	4.00 (2.00-6.00)	17.1 (18.0) ³
E	25	68414 (43.83)	5306 (44.35)	3.00 (2.00-5.00)	17.5 (17.4)

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

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

Parameter	Comparison	Ratio	90% CI
AUC(0-∞)	B vs. A	0.928	(0.763, 1.127)
	C vs. A	0.295	(0.243, 0.358)
	D vs. A	1.025	(0.843, 1.247)
	E vs. A	0.874	(0.720, 1.060)
	E vs. D	0.852	(0.703, 1.034)
C _{max}	B vs. A	0.874	(0.699, 1.094)
	C vs. A	0.302	(0.241, 0.377)
	D vs. A	1.010	(0.808, 1.262)
	E vs. A	0.854	(0.684, 1.067)
	E vs. D	0.846	(0.679, 1.053)

Safety results:

All adverse events (AEs) occurring after the administration of study medication and on or before the follow-up visit was to be reported as Adverse Events.

Adverse Events:	Regimen				
	A	B	C	D	E
N (Safety)	24	24	25	25	26
No. subjects with AEs n (%)	9 (38)	6 (25)	8 (32)	6 (24)	8 (31)
Most Frequent AEs					
Headache	7 (29)	3 (13)	3 (12)	3 (12)	4 (15)
Dizziness	0	0	2 (8)	0	0
Nausea	0	1 (4)	2 (8)	1 (4)	0

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

All serious adverse events (SAEs) occurring after the administration of study medication and on or before the follow-up visit was to be reported as Serious Adverse Events.

There were no SAEs.

Publications: None.