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<b>Study No:</b> TRA105122					
<b>Title :</b> Phase I Bioequivalence Study for SB-497115-GR (eltrombopag) Phase II and Phase III Tablets					
<b>Rationale:</b> The aim of the study was to demonstrate bioequivalence between SB- 497115-GR (eltrombopag) oral film-coated tablets manufactured at the Research and Development (R&D) and commercial sites. Bioequivalence was assessed for both 25 mg and 50 mg tablet strengths.					
<b>Phase:</b> I					
<b>Study Period:</b> 23 March 2006 – 06 July 2006					
<b>Study Design:</b> This was an open-label, single dose, randomized, two-period, period balanced, crossover study with two parallel groups conducted in healthy subjects.					
<b>Centers:</b> Three centers in the United States					
<b>Indication:</b> Thrombocytopenia					
<p><b>Treatment:</b> Subjects were randomized to a treatment sequence, participating in two dosing periods which were separated by a washout period of <math>\geq 10</math> days. During each dosing period, subjects received a single dose of oral eltrombopag according to the following treatment sequence:</p> <ul style="list-style-type: none"> <li>• Regimen A: one Phase II 25 mg tablet</li> <li>• Regimen B: one Phase III 25 mg tablet</li> <li>• Regimen C: one Phase II 50 mg tablet</li> <li>• Regimen D: one Phase III 50 mg tablet</li> </ul>					
<p><b>Objectives:</b> The primary objectives of this study were to:</p> <ul style="list-style-type: none"> <li>• Demonstrate the bioequivalence of 25 mg eltrombopag Phase III to the Phase II formulation of eltrombopag in fasted healthy subjects.</li> <li>• Demonstrate the bioequivalence of 50 mg eltrombopag Phase III to the Phase II formulation of eltrombopag in fasted healthy subjects.</li> </ul>					
<p><b>Statistical Methods</b>            Analysis of variance (ANOVA), using SAS (Version 8.2) Mixed Linear Models procedure, considering treatment sequence, period, and treatment as fixed effects and subject within sequence as a random effect was performed on log-transformed plasma eltrombopag AUC(0-<math>\infty</math>) and Cmax to assess, separately, the bioequivalence of eltrombopag 25 mg oral film-coated tablets and the bioequivalence of eltrombopag 50 mg oral film-coated tablets. The results from these analyses were exponentiated to obtain a point estimate and 90% CI estimate of the test-to-reference ratio of geometric least-squares (GLS) means. Data from the combination of sequences AB and BA were used to assess bioequivalence for the 25 mg tablets and data from the combination of sequences CD and DC were used to assess bioequivalence for the 50 mg tablet. The statistical criteria to conclude bioequivalence was that the 90% CI for the ratio of GLS means was completely contained within the range of 0.80-1.25 for AUC(0-<math>\infty</math>) and Cmax.</p> <p>Safety data were listed and summarized.</p>					
<b>Study Population: Eltrombopag Treatment Sequence<sup>1</sup></b>					
<b>Number of Subjects:</b>	<b>AB</b>	<b>BA</b>	<b>CD</b>	<b>DC</b>	<b>Total</b>
Planned, N	26	26	26	26	104
Enrolled, N	25	25	25	25	100
Completed, n (%)	23 (92)	25 (100)	22 (88)	24 (96)	94 (94)
Total Number Subjects Withdrawn, n (%)	2 (8)	0	3 (12)	1 (4)	6 (6)
Withdrawn Due to Adverse Events, n (%)	0	0	2 (8)	1 (4)	3 (3)
Withdrawn for Other Reasons, n (%)	2 (8)	0	1 (4)	0	3 (3)
<b>Demographics</b>	<b>AB</b>	<b>BA</b>	<b>CD</b>	<b>DC</b>	<b>Total</b>
N (Total)	25	25	25	25	100
Females: Males	11:14	6:19	10:15	5:20	32:68
Mean Age in Years (SD)	27.3 (8.70)	27.4 (7.84)	25.7 (8.44)	26.2 (7.41)	26.7 (8.02)

Mean Weight in Kg (SD)	70.5 (14.9)	75.6 (14.2)	73.5 (9.50)	75.6 (11.1)	73.8 (12.6)	
White n (%)	20 (80)	19 (76)	16 (64)	19 (76)	74 (74)	
1. A=Phase II 25 mg eltrombopag; B=Phase III 25 mg eltrombopag; C=Phase II 50 mg eltrombopag; D=Phase III 50 mg eltrombopag						
Pharmacokinetics (PK) Endpoints:						
Summary of Plasma Eltrombopag PK Parameters and Bioequivalence Results in Study TRA105122						
Plasma Eltrombopag PK Parameter	Eltrombopag 25 mg (N=48)			Eltrombopag 50 mg (N=46)		
	Phase II Tablet Treatment A	Phase III Tablet Treatment B	Phase III vs Phase II Treatment B/A	Phase II Tablet Treatment C	Phase III Tablet Treatment D	Phase III vs Phase II Treatment D/C
AUC(0-∞) (µg.h/mL)	31.0 (26.9, 35.7) [52]	33.9 (29.8, 38.5) [47]	1.10 (0.992, 1.22)	75.6 (65.9, 86.7) [49]	79.5 (69.2, 91.4) [50]	1.05 (0.943, 1.17)
Cmax (µg/mL)	2.47 (2.13, 2.86) [54]	2.85 (2.51, 3.23) [46]	1.16 (1.04, 1.30)	5.73 (4.99, 6.58) [49]	6.36 (5.64, 7.17) [42]	1.11 (0.989, 1.24)
PK summary = geometric mean (95% CI) [CVb%]						
Treatment comparisons = geometric least square (GLS) mean ratio (90% CI)						
Safety results: An adverse event (AE) was defined as an AE that occurred after screening through the end of the study or early withdrawal.						

**Summary of AEs Occurring in More Than One Subject in any Treatment Regimen Group (Safety Population)**

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

Source Data: Table 10.6

1. A=Phase II 25 mg eltrombopag; B=Phase III 25 mg eltrombopag;  
C=Phase II 50 mg eltrombopag; D=Phase III 50 mg eltrombopag
2. Data represents the number of subjects with any AE; some subjects may have experienced the same AE more than once.

**Summary of Drug-Related AEs (Safety Population)**

Preferred Term	Treatment Regimen <sup>1</sup>			
	A N=50	B N=48	C N=49	D N=47
	n (%)	n (%)	n (%)	n (%)
Number of Subjects with Any Drug-Related Event <sup>2</sup>	4 (8)	4 (8)	5 (10)	5 (11)
Headache	3 (6)	3 (6)	3 (6)	2 (4)
Dizziness	1 (2)	0	0	1 (2)
Dizziness postural	0	1 (2)	0	0
Somnolence	1 (2)	0	0	0
Abdominal pain upper	0	0	1 (2)	0
Nausea	0	0	0	1 (2)
Viral infection	0	0	1 (2)	0
ECG signs of myocardial ischemia <sup>3</sup>	0	0	0	1 (2)

**Serious adverse events:**

No serious adverse events were reported in this study.

**Publications: None**