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Study No.: TRA104603				
Title: Phase I Study of SB-497115-GR – Single Oral Dose Study in Healthy Japanese Male Subjects – <Clinical Pharmacology Study>				
Rationale: Thrombopoietin (TPO) is an endogenous stimulator of platelet production. SB-497115-GR is a TPO receptor (TPO-R) agonist. Overseas, single and repeat doses of 5–75mg of SB-497115-GR have been assessed in healthy adult males. The results demonstrate that SB-497115-GR is safe and well tolerated over the dose range examined and there is no apparent relationship between the dose of SB-497115-GR and the incidence of adverse events. Pharmacodynamically, SB-497115-GR has been shown to increase platelet counts in a dose-dependent manner at doses of ≥ 30 mg administered for 10 days. Based on these data, Phase II studies of 30–100mg of SB-497115-GR were ongoing or planned overseas in patients with idiopathic thrombocytopenic purpura (ITP), one type of immune thrombocytopenic purpura, patients with chronic hepatitis C-related thrombocytopenia, and patients with chemotherapy-induced thrombocytopenia. On the basis of the above, this Phase I study of SB-497115-GR was conducted in healthy Japanese adult males investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of single oral doses of 30, 50, 75 and 100mg of SB-497115-GR as tablets.				
Phase: I				
Study Period: 21 June 2005 to 9 March 2006				
Study Design: A single-center, placebo-controlled, double-blind, randomized, dose-escalation, 4-period crossover, single oral dose study in 16 healthy Japanese adult males				
Centres: One center in Japan				
Indication: Thrombocytopenia				
Treatment: Subjects were randomized to one of the four treatment sequences (A to D) and received placebo and three of the four SB-497115-GR doses (30, 50, 75 and 100mg) in four study periods.				
Sequence	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+one 5mg tablet)	Placebo (two placebo tablets)	75mg (three 25mg tablets)	100mg (four 25mg tablets)
C (n=4)	30mg (one 25mg tablet+one 5mg tablet)	50mg (two 25mg tablets)	Placebo (three placebo tablets)	100mg (four 25mg tablets)
D (n=4)	30mg (one 25mg tablet+one 5mg tablet)	50mg (two 25mg tablets)	75mg (three 25mg tablets)	Placebo (four placebo tablets)
Study periods were separated by 12 days.				
Objective(s): Primary				

<ul style="list-style-type: none"> To investigate the safety and tolerability of single oral doses of SB-497115-GR in healthy Japanese adult males. To investigate the pharmacokinetics of single oral doses of SB-497115-GR in healthy Japanese adult males. 	
<p>Secondary</p> <ul style="list-style-type: none"> To investigate the pharmacodynamics of single oral doses of SB-497115-GR in healthy Japanese adult males. 	
<p>Primary Outcome/Efficacy Variable:</p> <ul style="list-style-type: none"> Adverse events, clinical laboratory tests (hematology, clinical chemistry, urinalysis), vital signs, 12-lead ECG, ophthalmologic examinations Pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, AUC_{inf}, AUC_{last}, AUC_{0-24}, AUC_{0-48}, CL/F, Vz/F, and if possible, fe and CLr) 	
<p>Secondary Outcome/Efficacy Variable(s):</p> <ul style="list-style-type: none"> Pharmacodynamics (platelet count) 	
<p>Statistical Methods:</p> <ul style="list-style-type: none"> Safety <p>The safety of SB-497115-GR was evaluated using data collected until the post-study visit or additional follow-up visit. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Terminology Version 8.1J. All adverse events reported post-dose were summarized in listings by dose, together with dates of onset and resolution, outcome, severity, frequency, and causality.</p> <p>Clinical laboratory tests (hematology, clinical chemistry, urinalysis) were summarized in listings using summary statistics (mean, SD, minimum, median, maximum). Clinical laboratory test values outside the reference range were summarized in listings.</p> <p>Body weight, vital signs, and 12-lead ECG were summarized in listings using summary statistics.</p> <p>The results of ophthalmologic examinations were listed for each subject.</p> <ul style="list-style-type: none"> Pharmacokinetics <p>For pharmacokinetic analyses, plasma SB-497115 concentrations were determined to derive pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, λ_z, AUC_{inf}, AUC_{last}, AUC_{0-24}, AUC_{0-48}, $\%AUC_{ex}$, CL/F, Vz/F). Urinary SB-497115 concentrations were also determined to derive Ae and fe. Since the urinary excretion of SB-497115 was very low, CLr was not calculated. Linearity of AUC and C_{max} for SB-497115 was assessed using a power model, and figures were produced by plotting parameter estimates (AUC and C_{max}) against dose.</p> <ul style="list-style-type: none"> Pharmacodynamics <p>For pharmacodynamic analyses, platelet counts were measured to derive the maximum and percent changes from baseline.</p>	
<p>Study Population:</p> <p>Healthy Japanese adult males 20–35 years of age with BMI 18.5–<25.0.</p>	
	Total
Number of Subjects:	16
Planned, N	16
Randomised, N	16
Completed, n (%)	15 (93.75%)
Total Number Subjects Withdrawn, N (%)	1 (6.25%)
Withdrawn due to Adverse Events n (%)	1 (6.25%)
Withdrawn due to Lack of Efficacy n (%)	N.A.

Withdrawn for other reasons n (%)	0 (0%)				
Demographics	Total				
N (FAS)	16				
Males / Females	16/0				
Mean Age, years (SD)	25.9 (3.9)				
Race, n (%)	Asian (Japanese) (100%)				
Primary Efficacy Results: Pharmacokinetic Parameters of SB-497115					
	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)	
fe ₀₋₇₂ (%)	NA ^{a)}	0.000 ^{b)}	0.007 ^{c)}	0.032 ^{c)}	
C _{max} , t _{max} , t _{1/2} , AUC _{inf} , AUC ₀₋₂₄ : mean±SD (range), t _{max} : median (range)					
a) NA = Not determined, b) Below LLQ in all subjects, c) Values from one subject in whom SB-497115 was quantifiable					
Secondary Outcome Variable(s): Platelet Counts					
	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 percent change from baseline (%)	11.6±8.44	8.39±9.22	9.52 ±8.40	11.4±7.45	1.42±7.15
Mean±SD					
Safety Results: On-Therapy Adverse Events					
	30mg	50mg	75mg	100mg	Placebo
Subjects with any AE(s), n (%)	1 (8.33%)	1 (8.33%)	2 (16.67%)	0 (0%)	2 (12.5%)
Bilirubin total increased			1*		
Total bile acids increased		1	1		
Pyrexia	1				
ALT increased					1
Acute pharyngitis					1
* The causal relationship to study medication was judged "yes".					
Serious Adverse Events - On-Therapy					
n (%) [n considered by the investigator to be related to study medication]					
	30mg	50mg	75mg	100mg	Placebo

Subjects with non-fatal SAEs, n (%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
n (%) [number of subjects who had "related" events]	[0(0%)]	[0(0%)]	[0(0%)]	[0(0%)]	[0(0%)]
Subjects with fatal SAEs, n (%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
n (%) [number of subjects who had "related" events]	[0(0%)]	[0(0%)]	[0(0%)]	[0(0%)]	[0(0%)]

Conclusion:

- SB-497115-GR was 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. Systemic exposure (C_{max} and AUC) increased approximately proportionally with increasing dose over the dose range examined. The urinary excretion of SB-497115 was <0.1% 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.

Publications: None