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Study No: TRA105580		
Title: Phase I Study of SB-497115-GR - Single and Multiple 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. Phase II studies (doses: 30-100 mg) in patients with idiopathic thrombocytopenic purpura (ITP), thrombocytopenia comorbid with chronic hepatitis C (HCV), and chemotherapy-induced thrombocytopenia (CIT) are in progress outside Japan. In Japan, the development of SB-497115-GR was initiated in 2005 with a single oral dose study (doses: 30, 50, 75 and 100 mg) in 16 Japanese healthy male subjects. The study demonstrated well tolerability of a single dose up to 100 mg. The plasma concentrations of SB-497115 following a single dose 30 - 100 mg in Japanese were higher than those in overseas data. On the basis of the above, in the present multiple does study in Japanese subjects, the safety/tolerability, pharmacokinetics and pharmacodynamics of SB-497115-GR were investigated at three doses levels, 25, 50 and 75 mg.		
Phase: I		
Study Period: 6 June 2006 to 30 September 2006		
Study Design: A single-centre, placebo-controlled, single-blind, randomised, parallel-group single and multiple oral dose, dose-escalation study using three dose levels in 42 healthy Japanese male subjects.		
Centres: One centre in Japan		
Indication: Thrombocytopenia		
Treatment: Subjects were randomly divided into the active treatment and placebo groups. Each subject received SB-497115-GR or placebo given as a single dose, and after a 5-day off-dose period, SB-497115-GR or placebo given as once daily for 10 days. Subjects took each oral dose with 150 mL of wafer in a fasted condition.		
	SB-497115-GR group	Placebo group
A (n=14)	25mg (n=10)	Placebo (n=4)
B (n=14)	50mg (n=10)	Placebo (n=4)
C (n=14)	75mg (n=10)	Placebo (n=4)
Objectives:		
Primary To determine the safety and tolerability of SB-497115-GR following single and multiple oral doses in healthy Japanese male subjects. To determine the pharmacokinetics of SB-497115-GR following single and multiple oral doses in healthy Japanese male subjects.		
Secondary To determine the pharmacodynamic (PD) effects of SB-497115-GR following single and multiple oral doses in healthy Japanese male subjects.		

Statistical Methods:**Safety:**

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 9.0J. All adverse events reported post-dose were summarised in listings by dose, together with date of onset and resolution, outcome, severity, frequency, and causality.

Clinical laboratory tests (haematology, clinical chemistry, urinalysis) were summarised in listings using summary statistics (mean, S.D., minimum, median, maximum). Clinical laboratory test values outside the reference range were summarised in listings.

Body weight, vital signs and 12-lead ECG were summarised in listings using summary statistics.

The results of ophthalmologic examinations were listed for each subject.

Pharmacokinetics:

Pharmacokinetic parameters (C_{max} , T_{max} , $t_{1/2}$, λz , AUC_{inf} , AUC_{last} , $\%AUC_{ex}$, AUC_{0-24} , AUC_{0-48} , CL/F , Vz/F) for individual subjects were calculated from plasma SB-497115 concentration data following the single dose and on Day 10 of the multiple dose phase in a model independent manner, and summary statistics for each parameter calculated by dose. Furthermore, accumulation co-efficients (R_o , R_s , RC_{max}) for individual subjects were calculated for evaluation of accumulation, and summary statistics calculated by dose.

For each of the derived parameters described above, the summary statistics were calculated for each treatment group. Log transformed AUC and C_{max} were analysed in a mixed effects model with dose group, stage (single dose or multiple dose), and dose group-by-stage interaction as fixed effects and subject as a random effect. Point estimate and their 90% confidence intervals for differences between data after single dosing and those after multiple dosing were displayed for each dose group. Subsequently data were inverse transformed and to display point estimates and their 90% confidence intervals for the R_o , R_s , and RC_{max} .

Pharmacodynamics:

Pharmacodynamic parameters (P_0 : baseline of platelet counts, $p-T_{max}$: Time of $p-C_{max}$ observed, $p-C_{max}$: Maximum platelet counts, $\Delta p-C_{max}$: Maximum changed from baseline, $\%change\ p-C_{max}$: Maximum percent change from baseline, $\%change\ p-AUC$: percent change from baseline of time-platelet counts area were derived from platelet counts data.

$P-C_{max}$ (untransformed and log transformed) were analysed in a mixed effects model with dose group and baseline platelet counts as fixed effects and subject as a random effect. Point estimates and their 95% confidence intervals were displayed for inter-group differences of interest.

Study Population: Healthy Japanese adult males 20 - 35 years of age with BMI 18.5-<25.0.

Number of Subjects:	Total
Planned N	42
Dosed N	42
Completed n (%)	41 (98%)
Total Number Subjects Withdrawn N (%)	1 (2%)
Withdrawn due to Adverse Events n (%)	0 (0%)
Withdrawn due to Lack of Efficacy n (%)	N.A.
Withdrawn for Other Reasons n (%)	Personal reason: 1 (2%)
Demographics	Total
N (ITT)	42
Females: Males	42/0
Mean Age in Years (sd)	25.6 (3.46)
Mean Weight in Kg (sd)	63.55 (6.500)
Race n (%)	Asian (Japanese): 42 (100%)

Pharmacokinetics (PK), pharmacodynamics (PD), PK/PD Endpoints: PK parameters of SB-497115									
Dose (mg)	Single /multiple	n	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg.hr/mL)	AUC _{inf} (µg.hr/mL)	T _{max} (hr)	t _{1/2} (hr)	Ro	Rs
25	Single	10	3.56 ±1.13 (1.77-5.85)	33.2±10.1 (16.3-55.2)	55.4±23.2 (21.6-104.3)	3.0 (2.0-5.0)	29.6±5.0 (21.0-37.5)	1.752	1.091
	Multiple Day 10	10	4.83±1.17 (2.81-6.44)	58.9±18.4 (29.7-78.0)	-	3.0 (1.5-5.0)	39.7±3.2 (36.0-44.5)		
50	Single	10	6.44±2.14 (2.64-8.88)	63.9±17.6 (28.0-81.9)	106.6±32.4 (47.1-145.9)	3.0 (1.5-5.0)	31.0±5.9 (21.7-38.6)	1.951	1.178
	Multiple Day 10	9	10.6±2.38 (7.06-14.77)	133.8±33.6 (91.9-192.2)	-	4.0 (2.0-5.0)	51.3±12.2 (38.0-81.0)		
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)	2.060	1.239
	Multiple Day 10	10	12.78±2.84 (7.44-16.34)	164.2±35.5 (117.3-225.4)	-	4.0 (2.0-5.0)	47.8±11.5 (30.9-63.7)		
C _{max} , AUC and t _{1/2} : mean±S.D. (range), T _{max} : median (range) Ro=Multiple Day 10 AUC ₀₋₂₄ /Single AUC ₀₋₂₄ , Rs=Multiple Day 10 AUC ₀₋₂₄ /Single AUC _{inf} : point estimate									
PD parameters (platelet counts)									
Dose (mg)	n	P ₀ (*10 ⁴ /µL)	p-T _{max} (day)	p-C _{max} (*10 ⁴ /µL)	Δp-C _{max} (*10 ⁴ /µL)	%change p-C _{max} (%)	%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		
25	10	22.89±4.748	14.8±2.53	35.53±10.147	12.64±6.341	154±20.4	128±14.6		
50	9	23.32±2.836	14.2±1.20	39.79±5.927	16.47±5.458	172±23.5	136±14.1		
75	10	20.54±2.945	15.8±2.57	38.89±8.437	18.35±7.268	190±35.0	148±20.2		
Mean±S.D.									
Safety results:									
Adverse Events:									
		Placebo	25mg	50mg	75mg				
N (ITT)		12	10	10 ¹⁾	10				
No. subjects with AEs n (%)		0 (0%)	1 (10%)	3 (30%)	2 (20%)				
Urticaria		0	0	1 ²⁾	0				
Blood amylase increased		0	1 ²⁾	0	0				
Blood creatine phosphokinase increased		0	0	1	1				
Eosinophil percentage increased		0	0	0	1 ²⁾				
White blood cell count decreased		0	0	1 ²⁾	0				
1): One subject was withdrawn due to personal reason at 72 hours after single dose. 2): The causal relationship to study medication was judged "yes".									
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:									
		Placebo	25 mg	50 mg	75 mg				
Subjects with non-fatal SAES, n(%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)				
n (%) [number of subjects who had "related" events]		[0 (0%)]	[0 (0%)]	[0 (0%)]	[0 (0%)]				
Subjects with fatal SAES, n(%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)				
n (%) [number of subjects who had "related" events]		[0 (0%)]	[0 (0%)]	[0 (0%)]	[0 (0%)]				
Publications: None									