

Study No.: TRA108109
Title: Clinical Evaluation of SB-497115-GR in Chronic Idiopathic Thrombocytopenic Purpura (ITP) -A Multicenter Study in Subjects with Chronic ITP Receiving a Double-Blind, Placebo-Controlled, Short-Term Treatment Followed by an Open-Label, Uncontrolled, Long-Term Treatment-
Rationale: This was a study to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of SB-497115-GR in Japanese subjects with chronic ITP.
Phase: II/III
Study Period: 18 September 2007 - 12 December 2008
Study Design: The study consisted of a double-blind phase, followed by an open-label phase. The double-blind phase was a multicenter, placebo-controlled, double-blind, randomized, parallel-group, comparative study of 7 weeks duration. The open-label phase was a multicenter, open-label, uncontrolled study where all subjects received SB-497115-GR for 19 weeks in the SB-497115-GR group or 26 weeks in the placebo group.
Centers: 7 centers in Japan
Indication: chronic idiopathic thrombocytopenic purpura (ITP)
Treatment: The study medication was administered orally once daily in the fasted state. <u>Double-Blind Phase:</u> Subjects received SB-497115-GR 12.5 mg or matching placebo for the first 3 weeks of the double-blind phase. The dose of study medication was adjusted at Week 3 based on the subject's platelet count and then continued up to Week 7. The primary data for each subject was fixed at Week 6 and his/her treatment assignment was unblinded at Week 7 on an individual subject basis. <u>Open-Label Phase:</u> Subjects who had completed the double-blind phase entered the open-label phase (19 Weeks for SB-497115-GR Group or 26 Weeks for Placebo Group, hence Total 26 Weeks of SB-497115-GR Treatment). During the open-label phase, all subjects received SB-497115-GR regardless of their treatment assignment during the double-blind phase. Dose adjustment to 12.5, 25 or 50 mg/day was allowed based on the subject's platelet count.
Objectives: To evaluate the efficacy, safety, PK and PD of SB-497115-GR in previously treated subjects with chronic ITP. <u>Primary Objectives:</u> Subjects diagnosed with ITP for at least 6 months prior to screening who had a platelet count of <30,000/ L at screening (Week -4 or -3) and at the start of the double-blind phase (Day 1) were included in the following assessments. <u>Short-Term Efficacy:</u> The proportion of subjects achieved a platelet count of $\geq 50,000/ L$ and $\leq 400,000/ L$ after 6 weeks of study medication was compared between SB-497115-GR and placebo. <u>Long-Term Efficacy:</u> The percentage of assessment visits during 26 weeks of dosing with SB-497115-GR of each subject achieved a platelet count of $\geq 50,000/ L$ and $\leq 400,000/ L$ was calculated.
Primary Outcome/Efficacy Variable: <u>Assessments at Week 6 (Short-Term Efficacy):</u> Proportion of responders* at Week 6 (Day 43) for SB-497115-GR compared with placebo. <u>Assessments after 26 Weeks of SB-497115-GR Treatment (Long-Term Efficacy):</u> Proportion of subjects for whom at least 75% of their assessments during 26 weeks of SB-497115-GR treatment meet the definition of responders* * Responders: A shift from <30,000/ L at baseline to $\geq 50,000/ L$ and $\leq 400,000/ L$ at any given assessment.
Secondary Outcome/Efficacy Variable(s): <u>Short-Term Efficacy:</u> Proportion of responders at each visit and over time, proportion of subjects assessed as responders in at least 4 assessments between Week 2 and Week 6, platelet counts, platelet change from baseline, proportion of subjects at baseline and during Weeks 1-6 of treatment by platelet category. <u>Long-Term Efficacy:</u> Proportion of responders at each visit and over time, proportion of subjects receiving rescue treatment for ITP, maximum duration for which a subject maintained a platelet count $\geq 50,000/ L$ and $\leq 400,000/ L$, proportion of subjects with a reduction in use of concomitant

ITP medications from baseline, average concomitant ITP medication use per month, platelet counts, platelet change from baseline, total duration of time a subject had a platelet count $\geq 50,000/L$ and $\leq 400,000/L$ during the 26 weeks of SB-497115-GR dosing, platelet function and plasma thrombopoietin (TPO) levels, the pharmacokinetics (PK: C_{max} , t_{max} , $t_{1/2}$, λ_z , AUC_{0-last} , AUC_{0-24} , CL/F , V_z/F) and the pharmacodynamics (PD) of SB-497115-GR.

Statistical Methods:

The Safety population (SP) was used for safety analysis and the Full Analysis Set (FAS) was used for efficacy analysis.

The SP was defined as all subjects who had been randomized and received at least one dose of the investigational product. The FAS was defined as all randomized subjects with the exception of: 1) those who did not receive any dose of study medication; and 2) those with no valid platelet count measurements on therapy. The populations for efficacy and safety were identical in this study. For PK analysis, the PK population was defined as all subjects with valid PK data following SB-497115-GR treatment.

The primary comparison was SB-497115-GR vs. placebo during the double-blind phase. The proportion of responders (i.e., subjects with a shift from $<30,000/L$ at baseline to $\geq 50,000/L$ and $\leq 400,000/L$ at Week 6 [Day 43]) and a 95% confidence interval were calculated for each group. The difference between SB-497115-GR and placebo in the proportion of responders and a 95% confidence interval were calculated. No comparison was performed during the open-label phase, because all subjects received active SB-497115-GR treatment.

Secondary efficacy endpoints (except platelet function and plasma TPO levels) and safety during the double-blind phase were summarized for each treatment group (SB-497115-GR or placebo). No comparison was performed during the open-label phase, because all subjects received active SB-497115-GR treatment. Platelet function and plasma TPO levels were listed. PK, PD and PK/PD analyses were performed by dose of SB-497115-GR.

Study Population: Subjects who were diagnosed with ITP had a platelet count of $<30,000/L$ at Screening and Week 0 despite one or more prior therapies, male or female, aged ≥ 20 . Subjects also had to have a complete blood count within the reference range, with the following exceptions: 1) Hemoglobin: females ≥ 9 g/dL and males ≥ 10 g/dL were eligible for inclusion if hemorrhage was present; 2) Neutrophil count $\geq 1,500/\mu L$ ($1.5 \times 10^9/L$) was required for inclusion.

A subject was not allowed to participate in the study if he/she had suspected platelet aggregation abnormality or blood disorder other than ITP.

Number of Subjects:	Placebo	SB-497115-GR	
Planned, N	8	12	
Randomized, N	8	15	
Completed 26 Weeks of SB-497115-GR Treatment, n (%)	6 (75)	14 (93)	
Total Number Subjects Withdrawn, n (%)	2 (25)	1 (7)	
Withdrawn due to Adverse Events, n (%)	0	1 (7)	
Withdrawn due to Lack of Efficacy, n (%)	2 (25)	0	
Withdrawn for other reasons, n (%)	0	0	
Demographics:	Placebo (Week 0-7)	SB-497115-GR (Week 0-7)	SB-497115-GR (Week 0-26)
N (FAS/SP)	8	15	23
Females: Males	7 : 1	8 : 7	15 : 8
Mean Age, years (SD)	58.4 (11.72)	53.7 (13.72)	55.3 (12.98)
Race Asian - Japanese Heritage, n (%)	8 (100)	15 (100)	23 (100)
Primary Efficacy Results:			
Short-Term Efficacy: (Observed Case)	Placebo (N=8)	SB-497115-GR (N=15)	
No. of responders at Week 6, n (%)	0 (0.0)	9 (60.0)	
Difference between treatments, %	60.0		

95% Confidence Interval		35.21, 84.79	
Long-Term Efficacy: (Observed Case)		SB-497115-GR (N=23)	
No. of subjects for whom at least 75% of their assessments during 26 weeks of SB-497115-GR treatment meet the definition of responders, n (%)		10 (43.5)	
95% Confidence Interval		23.19, 65.51	
Secondary Outcome Variable(s):			
Short-Term Efficacy: (Observed Case)		Placebo (N=8)	SB-497115-GR (N=15)
Responders at each visit and over time, n/N (%)	Day 8	0/8 (0.0)	1/15 (6.7)
	Day 15	0/8 (0.0)	4/15 (26.7)
	Day 22	0/8 (0.0)	5/15 (33.3)
	Day 29	0/8 (0.0)	9/15 (60.0)
	Day 36	0/8 (0.0)	10/15 (66.7)
	Day 43	0/8 (0.0)	9/15 (60.0)
Subjects assessed as responders in at least 4 assessments between Week 2 and Week 6, n/N (%)		0/8 (0.0)	5/14 (35.7)
Platelet counts, Mean±SD, Gi/L	Baseline	12.6±8.65	19.3±6.79
	Day 8	14.3±12.26	26.9±17.77
	Day 15	13.5±12.15	54.9±55.84
	Day 22	11.6±9.50	54.4±46.88
	Day 29	10.6±9.04	73.3±46.72
	Day 36	11.9±10.79	99.4±78.62
	Day 43	9.9±4.76	95.1±100.25
Change from baseline in Platelet counts, Mean±SD, Gi/L	Day 8	1.6±6.05	7.6±16.47
	Day 15	0.9±5.46	35.5±56.11
	Day 22	-1.0±3.02	35.0±46.52
	Day 29	-2.0±4.17	53.9±46.02
	Day 36	-0.8±7.94	80.1±77.06
	Day 43	-2.8±9.41	75.8±99.93
Subjects with bleeding episode, n/N (%)	Day 1	6/8 (75)	5/15 (33)
	Day 8	5/8 (63)	2/15 (13)
	Day 15	5/8 (63)	2/14 (14)
	Day 22	6/8 (75)	4/14 (29)
	Day 29	3/8 (38)	0/14
	Day 36	5/8 (63)	1/14 (7)
	Day 43	6/8 (75)	2/14 (14)

Subjects at baseline and during Weeks 16 of treatment by platelet category, n	platelet category (Gi/L)	Placebo (N=8)						SB-497115-GR (N=15)					
		≤15	>15 to <30	≥30 to ≤50	≥50 to ≤200	>200 to ≤400	>400	≤15	>15 to <30	≥30 to ≤50	≥50 to ≤200	>200 to ≤400	>400
	Baseline	6	2	0	0	0	0	3	12	0	0	0	0
	Day 8	5	2	1	0	0	0	3	6	5	1	0	0
	Day 15	6	1	1	0	0	0	2	3	5	3	1	0
	Day 22	5	3	0	0	0	0	3	3	3	5	0	0
	Day 29	6	2	0	0	0	0	1	0	4	9	0	0
	Day 36	7	0	1	0	0	0	2	0	2	9	1	0
	Day 43	7	1	0	0	0	0	2	2	1	7	2	0
Long-Term Efficacy: (Observed Case)							SB-497115-GR (N=23)						
Responders at each visit and over time, n/N (%)							Day 8	1/23 (4.3)					
							Day 15	4/23 (17.4)					
							Day 22	5/23 (21.7)					
							Day 29	11/23 (47.8)					
							Day 36	13/23 (56.5)					
							Day 43	12/23 (52.2)					
							Week 10	12/21 (57.1)					
							Week 14	14/23 (60.9)					
							Week 18	11/22 (50.0)					
							Week 22	11/21 (52.4)					
							Week 26	16/23 (69.6)					
Platelet counts, Mean±SD, Gi/L							Baseline	16.5±8.45					
							Day 8	23.0±16.77					
							Day 15	41.5±48.32					
							Day 22	41.0±41.80					
							Day 29	55.3±45.75					
							Day 36	78.1±72.76					
							Day 43	78.0±88.31					
							Week 10	88.9±81.15					
							Week 14	121.6±121.20					
							Week 18	87.3±80.09					
							Week 22	78.5±57.58					
							Week 26	86.2±49.62					

Change from baseline in Platelet counts, Mean±SD, Gi/L	Day 8	6.4±13.53	
	Day 15	25.1±46.73	
	Day 22	24.6±39.37	
	Day 29	38.9±42.37	
	Day 36	61.7±69.53	
	Day 43	61.6±86.72	
	Week 10	71.4±80.01	
	Week 14	104.5±120.20	
	Week 18	69.4±80.23	
	Week 22	61.1±54.85	
	Week 26	68.4±46.49	
Maximum duration subjects maintained platelet counts ≥ 50,000/L and ≤400,000/L, Mean±SD, days		59.5±46.99	
Total Time subjects maintained platelet counts ≥ 50,000/L and ≤400,000/L, Mean±SD, days		78.4±54.56	
Subjects with bleeding episode, n/N (%)	Day 1	11/23 (48)	
	Day 8	8/23 (35)	
	Day 15	6/22 (27)	
	Day 22	8/22 (36)	
	Day 29	4/22 (18)	
	Day 36	5/22 (23)	
	Day 43	6/22 (27)	
	Week 10	2/19 (11)	
	Week 14	3/21 (14)	
	Week 18	5/19 (26)	
	Week 22	5/18 (28)	
Week 26	1/20 (5)		
Subjects with a reduction in use of concomitant ITP medications from baseline, n/N (%)		7/19 (36.8)	
Subjects receiving rescue treatment for ITP, n/N (%)		2/23 (9)	
Average concomitant ITP medication use per month, Mean±SD		25.14±11.796	
SB-497115 (free acid) PK Results:			
	SB-497115-GR 12.5 mg (N=8)	SB-497115-GR 25 mg (N=5)	SB-497115-GR 50 mg (N=4)
C _{max} , Mean±SD, ng/mL	2992.4±1253.14	6776.4±2619.62	11877.8±3926.21
t _{max} , Median (range), hr	3.192 (2.004, 17)	4.000 (2.004, 00)	2.967 (1.924, 17)
t _{1/2} ^{a)} , Mean±SD, hr	19.50±7.164 ^{b)}	26.96±7.664	18.19±4.938
λ _z , Mean±SD, 1/hr	0.04021±0.015558 ^{b)}	0.02724±0.006881	0.04040±0.011422
AUC _{last} , Mean±SD, hr•ng/mL	41671.5±24344.64 ^{b)}	92556.2±41095.63	171523.2±75250.93

AUC ₀₋₂₄ , Mean±SD, hr•ng/mL	41637.2± 24361.51 ^{b)}	92527.5± 41122.30	171551.0± 75242.59
CL/F, Mean±SD, L/hr	0.37156± 0.154284 ^{b)}	0.30923± 0.114096	0.33035± 0.124401
Vz/F, Mean±SD, L	5.6267±2.00964 ^{b)}	5.3870±1.75077	5.0391±1.76091
a) reference value; calculated with data up to 24 hrs.			
b) N=7			

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 a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.		
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
6 Weeks of Placebo/SB-497115-GR Treatment	Placebo (N=8)	SB-497115-GR (N=15)
Subjects with any AE(s), n (%)	2 (25)	11 (73)
Nasopharyngitis	0	4 (27)
Alanine aminotransferase increased	0	3 (20)
26 Weeks of SB-497115-GR Treatment	SB-497115-GR (N=23)	
Subjects with any AE(s), n (%)	21 (91)	
Nasopharyngitis	10 (43)	
Alanine aminotransferase increased	4 (17)	
Aspartate aminotransferase increased	3 (13)	
Headache	3 (13)	
Cystitis	2 (9)	
Gastroenteritis	2 (9)	
Herpes simplex	2 (9)	
Rhinitis	2 (9)	
Nausea	2 (9)	
Platelet count increased	2 (9)	
Myalgia	2 (9)	
Fatigue	2 (9)	
Conjunctival haemorrhage	2 (9)	
Limb injury	2 (9)	
Hypokalaemia	2 (9)	
Haemorrhagic diathesis	2 (9)	
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
6 Weeks of Placebo/SB-497115-GR Treatment	Placebo (N=8)	SB-497115-GR (N=15)
Subjects with non-fatal SAEs, n (%) [related]	0	1 (7) [1]
Transient ischaemic attack	0	1 (7) [1]
26 Weeks of SB-497115-GR Treatment	SB-497115-GR (N=23)	
Subjects with non-fatal SAEs, n (%) [related]	6 (26) [1]	
Haemorrhagic diathesis	2 (9) [0]	
Transient ischaemic attack	1 (4) [1]	
Thrombocytopenia	1 (4) [0]	
Prostate cancer	1 (4) [0]	
Renal impairment	1 (4) [0]	
6 Weeks of Placebo/SB-497115-GR Treatment	Placebo (N=8)	SB-497115-GR (N=15)
Subjects with fatal SAEs, n (%) [related]	0	0
26 Weeks of SB-497115-GR Treatment	SB-497115-GR (N=23)	

Subjects with fatal SAEs, n (%) [related]	0
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Conclusion:

The proportion of responders at Week 6 showed a difference between the treatment groups in favour of SB-497115-GR-treated subjects (SB-497115-GR 60%, placebo 0%). The proportion of subjects for whom at least 75% of their assessments during 26 weeks of SB-497115-GR treatment meet the definition of responders was 43.5%.

During the 6 weeks of placebo/SB-497115-GR treatment, 11 subjects (73%) in SB-497115-GR group and 2 subjects (25%) in placebo group reported AEs. The most commonly reported AEs for SB-497115-GR group were nasopharyngitis (27%) and alanine aminotransferase increased (20%). During the 26 weeks of SB-497115-GR treatment, 21 subjects (91%) reported AEs. The most commonly reported AEs were nasopharyngitis (43%), alanine aminotransferase increased (17%), aspartate aminotransferase increased (13%) and headache (13%). A total of 6 subjects (26%) reported SAEs on therapy. No death occurred during the study.

The pharmacokinetics of SB-497115 were investigated at the steady state after oral administration of SB-497115-GR 12.5 mg, 25 mg and 50 mg. C_{max} was observed at 3 to 4 hours after administration and $t_{1/2}$ was calculated as 18 to 27 hours. C_{max} and AUC_{0-24} increased in a generally dose proportional manner in the dose range of 12.5 to 50 mg.