The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: TRA100773A
Title: A double-blind, randomized, placebo-controlled, parallel group study to investigate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of SB-497115-GR, a thrombopoietin receptor agonist, administered at 30, 50 and 75 mg as oral tablets once-daily for 6 weeks to adult male and female subjects with refractory, chronic immune thrombocytopenic purpura
Rationale: Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by autoantibody-induced platelet destruction and reduced platelet production, leading to a chronically low peripheral blood platelet count (<150Gi/L). Persistently low platelet counts of <30Gi/L are associated with an increased incidence of spontaneous and induced bleeding, such as bruising, mucosal bleeding and intra-cranial hemorrhage. First-line treatment of adult ITP includes corticosteroids or intravenous immunoglobulins (anti-D and IVIg), and these agents are effective in increasing platelet counts in about 70% of ITP patients, approximately 50% of whom will achieve platelet counts in the normal range. However, the side effects of corticosteroids are often rate-limiting and many patients suffer relapse when the corticosteroid dose is lowered or when regular administration of IVIg is discontinued. Second-line therapy typically involves splenectomy, the safety and efficacy of which has not been assessed in well-controlled clinical studies in patients with chronic ITP. Furthermore, splenectomized patients are less able to clear infections. Goals of this study were to determine the efficacy and safety of a 6-week treatment administration of three eltrombopag doses in adults with chronic ITP and platelet counts <30Gi/L and to define an optimal starting dose for further evaluation in a phase III setting. The 6-week treatment period was chosen to allow 1-2 weeks for platelet count elevation followed by continued platelet elevation for 3-4 weeks, thereby meeting or exceeding the duration of platelet count elevation observed with currently available short-term treatments (intravenous immunoglobulins) with the convenience of oral administration. The study population was comprised of subjects who were refractory to, or had relapsed following standard first- and second-line treatment options, consistent with an ITP patient population with the greatest unmet medical need.
Phase: II
Study Period: 02Feb2005 –2 6Aug2006
Study Design: Double-blind, randomized, placebo-controlled, parallel group, dose ranging, adaptive sequential design.
Centres: Forty-four study centers were located in a total of 14 countries in North America, Europe, Africa, and Asia.
Indication: Chronic idiopathic thrombocytopenic purpura (ITP)
Treatment: The treatment phase of the study involved once-daily dosing with placebo (PBO) or eltrombopag (30mg, 50mg, 75mg) for up to 6 weeks. Subjects who attained a platelet count >200Gi/L discontinued treatment, but continued in the study with their follow-up visits. After the dosing period, subjects were assessed every 2 weeks for up to 6 weeks to assess the durability of the platelet response.
Objectives: The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once-daily for 6 weeks to previously treated adult subjects with chronic idiopathic thrombocytopenia (ITP). Secondary objectives of the study were: • To assess the safety and tolerability of eltrombopag when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP; • To characterize the population pharmacokinetic profile of oral eltrombopag using a

combined sparse and serial pharmacokinetic sampling strategy when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP;
- To determine the pharmacodynamic effect of eltrombopag on markers of thrombopoiesis when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP;
- To assess the impact of eltrombopag on the incidence and severity of symptoms of thrombocytopenia when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP; and
- To assess the impact of eltrombopag on the health-related quality of life when administered once-daily for 6 weeks to previously treated adult subjects with chronic ITP.

Primary Outcome/Efficacy Variable: The primary efficacy endpoint was a shift from a baseline platelet count of <30Gi/L to ≥50Gi/L after up to 42 days of dosing with study medication.

Secondary Outcome/Efficacy Variable(s):
- Platelet counts;
- Incidence and severity of symptoms associated with chronic ITP, including bleeding, bruising, and petechiae, measured using the WHO bleeding scale; and
- Physical and mental health status using the SF-36v2 health-related quality of life (HR-QoL) tool.

Statistical Methods: Assuming 30% and 60% of subjects were to respond on placebo and eltrombopag, respectively, the maximum planned sample size required to provide 90% power at the 2.5% level of significance (one-sided) was 272 evaluable subjects; 68 were to be randomized to each treatment group in a 1:1:1:1 ratio.

Two interim analyses were planned to be conducted when on-therapy platelet count data were available from approximately one-third (~90) and two-thirds (~180) of the subjects. The primary comparisons of interest were between the eltrombopag treatment groups and PBO. In order to protect the overall Type I error at 2.5% (1-sided) a closed testing procedure was applied.

The first scheduled interim analysis in 104 subjects determined that the results from the eltrombopag 50mg and 75mg treatment groups met the pre-defined efficacy stopping criteria for superiority compared to PBO. The pre-specified stopping criteria at the first interim was $p<0.0113$ for superiority compared to PBO and $p\geq0.333$ for futility. The results from the eltrombopag 30mg group did not meet the pre-specified stopping criteria for either efficacy or futility. The study design indicated eltrombopag 30mg should continue to be tested on additional subjects until the second interim analysis. However, based on the overwhelming efficacy in the eltrombopag 50mg and 75mg treatment groups, the decision was made to stop the study and not continue the 30mg treatment group. Stopping the 30mg treatment group was a deviation from the planned statistical conduct of the study but had no bearing on the dose chosen as the starting dose for phase III studies in subjects with chronic ITP.

Following the decision to stop the study, a final analysis of data up to Day 43 was performed including data from all subjects enrolled between the interim cut-off date and the decision to stop the study. The final analysis was performed on 118 subjects.

The Efficacy Population was the primary population for efficacy analyses and was comprised of all randomized subjects treated with at least one dose of study medication, who had a baseline platelet count of <30Gi/L. The primary analysis of this endpoint was performed on a dataset which classified subjects as either responders or non-responders (primary dataset). For this primary analysis of response, only on-therapy platelet counts were included. The criteria to determine response in the primary dataset were prospectively stated in an amendment to the Reporting and Analysis Plan (RAP) following agreement with regulatory authorities:
- Subjects were classified as responders if they achieved a platelet count of ≥50Gi/L (from a baseline platelet count of <30Gi/L) at the Day 43 Visit;

- Subjects were also classified as responders if they responded strongly with a platelet count >200Gi/L and discontinued study medication prior to Day 43; their last on treatment platelet count was used to determine response; and
- Subjects were classified as non-responders if they discontinued treatment with study medication prior to the Day 43 Visit for any other reason, irrespective of their last on treatment platelet count.

The proportion of responders was compared between treatments using a logistic regression model adjusted for ITP medication use at randomization, splenectomy status and baseline platelet count (≤15Gi/L vs >15Gi/L).

Some analyses were performed using the Intent-to-Treat (ITT) population, which was comprised of all randomized subjects who received at least one dose of study medication and had at least one platelet count post-dosing. Supportive data analyses were performed using a dataset of all platelet counts during the treatment and follow-up periods, whether or not the subject discontinued treatment prematurely (observed dataset). This dataset was used to address other aspects of the pharmacodynamic response of platelet counts to study medication, such as duration of response and comparison of bleeding episodes during and after treatment with study medication. All safety analyses were reported using the Safety Population, which included all randomized subjects who received at least one dose of the study medication.

Study Population: The study was conducted in subjects with chronic ITP who had not responded to or had relapsed within 3 months of the most recent therapy for ITP and had a platelet count of <30Gi/L on Day 1 (or within 24h prior to dosing).

Subject Disposition	PBO	30mg	50mg	75mg	Total
All randomized subjects	29	30	30	29	118
Efficacy Population	27	29	27	26	109
Safety Population	29	30	30	28	117
ITT Population	29	30	30	28	117
Completed study, n (%)	22 (76)	23 (77)	17 (57)	12 (43)	74 (63)
Completed study or discontinued prematurely due to platelets ≥ 200Gi/L, n (%)	23 (79)	27 (90)	28 (93)	24 (86)	102 (87)
Discontinued prematurely from study medication, n (%)	7 (24)	7 (23)	13 (43)	16 (57)	43 (37)
Platelets >200Gi/L, n (%)	1 (3)	4 (13)	11 (37)	12 (43)	28 (24)
Adverse Event, n (%)	3 (10)	0	2 (7)	1 (4)	6 (5)
Lack of efficacy, n (%)	0	2 (7)	0	1 (4)	3 (3)
Other, n (%)	1 (3)	1 (3)	0	1 (4)	3 (3)
Subject decision, n (%)	2 (7)	0	0	0	2 (2)
Protocol Violation, n (%)	0	0	0	1 (4)	1 (<1)
Demographics (ITT Population)	**PBO**	**30mg**	**50mg**	**75mg**	**Total**
Age, yrs, Median (Min -Max)	42 (18-85)	51 (23-79)	45 (23-81)	54.5 (18-85)	50.0 (18-85)
Females:Males	16:13	16:14	21:9	20:8	73:44
Race, n (%)					
African American/African	1 (3)	1 (3)	0	0	2 (2)
Asian - East Asian	2 (7)	1 (3)	8 (27)	2 (7)	13 (11)
Asian - South-East Asian	0	3 (10)	4 (13)	1 (4)	8 (7)
White - Arabic/North African	5 (17)	1 (3)	3 (10)	5 (18)	14 (12)
White - White/ Caucasian/European	20 (69)	24 (80)	15 (50)	20 (71)	79 (68)
Other/Mixed	1 (3)	0	0	0	1 (<1)
Ethnicity, n (%)					
Hispanic or Latino	0	0	2 (7)	2 (7)	4 (3)
Not Hispanic or Latino	29 (100)	30 (100)	28 (93)	26 (93)	113 (97)

Primary Efficacy Results (Efficacy Population):				
Responders, Day 43 Visit	**PBO**	**30mg**	**50mg**	**75mg**
n	27	29	27	26
Responders, n (%)	3 (11.1)	8 (27.6)	19 (70.4)	21 (80.8)
Odds ratio (Active relative to PBO)	NA	3.09	21.96	38.82
95% CI	NA	(0.69,13.75)	(4.72,102.23)	7.62,197.73)
p-value (one-sided)	NA	0.070	<0.001	<0.001
Secondary Outcome/Efficacy Variable(s) (Efficacy Population, Observed Dataset):				
Median Platelet Counts (Gi/L) by Visit	**PBO**	**30mg**	**50mg**	**75mg**
Baseline, N	27	28	27	26
Median (Min-Max)	14.7 (2-36)	15.0 (1-37)	19.0 (1-29)	13.5 (1-38)
Day 8 Visit, N	27	28	27	25
Median (Min-Max)	16.2 (3-73)	26.0 (5-243)	37.0 (3-406)	70.0 (4-491)
Day 15 Visit, N	27	28	25	19
Median (Min-Max)	14.0 (2-110)	24.5 (1-413)	135.0 (1-652)	101.0 (4-447)
Day 22 Visit , N	24	26	18	14

Median (Min-Max)	18.0 (2-41)	20.0 (1-110)	94.5 (1-1312)	73.6 (4-556)
Day 29 Visit, N	23	24	17	12
Median (Min-Max)	16.0 (3-114)	23.0 (8-156)	95.0 (3-148)	63.0 (6-159(
Day 36 Visit, N	22	22	17	12
Median (Min-Max)	18.5 (1-419)	15.5 (3-119)	64.0 (3-169)	83.0 (5-203)
Day 43 Visit, N	21	23	16	11
Median (Min-Max)	16.0 (4-70)	26.0 (5-211)	66.0 (2-258)	86.0 (4-533)
WHO Bleeding Scale Assessment of Subjects by Visit (Efficacy Population)	**PBO**	**30mg**	**50mg**	**75mg**
Baseline	27	29	27	25
Grade 0	12 (44.4)	10 (34.5)	10 (37.0)	7 (28.0)
Grade 1 – Grade 4	15 (55.6)	19 (65.5)	17 (63.0)	18 (72.0)
Day 43 Visit	22	24	16	12
Grade 0	11 (50.0)	14 (58.3)	12 (75.0)	9 (75.0)
Grade 1 – Grade 4	11 (50.0)	10 (41.7)	4 (25.0)	3 (25.0)
Day 57 Visit, N	25	26	26	26
Grade 0	11 (44.0)	12 (46.2)	14 (53.8)	10 (38.5)
Grade 1 – Grade 4	14 (56.0)	14 (53.8)	12 (46.2)	16 (61.5)
On-therapy AEs Reported by 2 or More Subjects (Safety Population)	**PBO N=29**	**30mg N=30**	**50mg N=30**	**75mg N=28**
Subjects with Any AE	17 (59)	14 (47)	14 (47)	17 (61)
Headache	6 (21)	4 (13)	3 (10)	6 (21)
Fatigue	5 (17)	0	1 (3)	2 (7)
Constipation	2 (7)	1 (3)	0	2 (7)
Rash	1 (3)	1 (3)	0	2 (7)
AST increased	0	1 (3)	0	2 (7)
Anemia	2 (7)	1 (3)	1 (3)	1 (4)
Edema peripheral	2 (7)	0	1 (3)	1 (4)
Diarrhea	2 (7)	0	0	1 (4)
Dysgeusia	2 (7)	0	0	1 (4)
Epistaxis	0	4 (13)	0	0
Pain in extremity	1 (3)	2 (7)	0	0
Arthralgia	3 (10)	1 (3)	0	0
Abdominal distension	2 (7)	1 (3)	0	0
Hemorrhoids	2 (7)	0	0	0
On-Therapy SAEs, n (%) [n considered by the investigator to be related to study medication] (Safety Population)	**PBO N=29 n (%) [related]**	**30mg N=30 n (%) [related]**	**50mg N=30 n (%) [related]**	**75mg N=28 n (%) [related]**
Subjects with non-fatal SAEs	3 (10) [2]	0	2 (7) [2]	1 (4) [1]
Toxic hepatitis	1 (3) [1]	0	0	0
Ruptured varicose vein	1 (3) [0]	0	0	0
Convulsion	1 (3) [1]	0	0	0
Herpes zoster	0	0	1 (3) [0]	0
Hepatitis	0	0	1 (3) [1]	0
Renal failure	0	0	1 (3) [1]	0
Urticaria	0	0	0	1 (4) [1]

Subjects with fatal SAEs	0	0	1 (3) [2]	0
Cardiopulmonary failure	0	0	1 (3) [0]	0
Embolism	0	0	1 (3) [1]	0
Pulmonary embolism	0	0	1 (3) [1]	0

Conclusion: See Publications
Publications: Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, Kloczko J, Hassani H, Mayer B, Stone NL, Arning M, Provan D, Jenkins JM. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007;357(22):2237-47.