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Study No.: TRA100773B
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
<p>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.</p> <p>First-line treatment of adult ITP with corticosteroids or intravenous immunoglobulins (anti-D and IVIg) is effective in increasing platelet counts in about 70% of ITP patients, approximately 50% of whom will achieve platelet counts in the normal range. Intravenous immunoglobulins elevate platelet counts for approximately 2-3 weeks to allow short-term management of a hemostatic challenge, or for repeated administration every 2-3 weeks for patients requiring long-term platelet elevation. The side effects of corticosteroids are often rate-limiting for further treatment 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. Following splenectomy, patients are less able to clear infections and thus are more susceptible to sepsis for the rest of their lives.</p> <p>Relapsed or refractory disease is a significant clinical management problem, as all treatments to date are associated with significant morbidity, and for some agents, mortality. Therefore, patients with relapsed or refractory ITP represent a patient population with an unmet medical need.</p> <p>A global, randomized, double-blind, placebo-controlled, dose-ranging (eltrombopag 30mg, 50mg and 75mg) Phase II trial (TRA100773A) was performed in 118 adults with chronic ITP and platelets <30Gi/L. A dose dependent increase in the proportion of responders was observed: placebo (PBO) (11%), 30mg (28%), 50mg (70%) and 75mg (81%). The odds-ratio of treatment response to PBO was statistically significant in the 50mg and 75mg arms ($p < 0.001$). A decreased incidence of on-therapy bleeding (assessed via the World Health Organization [WHO] Bleeding Scale) was observed relative to baseline in subjects who received eltrombopag. Overall, the safety profile was similar across the treatment groups and no dose dependent safety concerns were identified.</p> <p>The current study was designed to assess the efficacy, safety, and tolerability of eltrombopag 50mg (with dose increases up to 75mg permitted), compared to PBO when administered for up to 6 weeks in adults with chronic ITP and platelet counts <30Gi/L. The up to 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 treatment options, consistent with an ITP patient population with the greatest unmet medical need. The objective of the study was to confirm the efficacy and safety of short-term administration of eltrombopag observed in TRA100773A.</p>
Phase: III

Study Period: 06Feb2006 -3 1Jan2007
Study Design: double-blind, randomized, placebo-controlled, parallel group
Centers: Sixty-three study centers were located in a total of 23 countries in North America, Europe, Asia, Africa, South America, and Australia.
Indication: Chronic idiopathic thrombocytopenic purpura (ITP)
Treatment: The treatment phase of the study involved once-daily dosing with eltrombopag 50 mg or matching placebo for up to 6 weeks. Subjects with platelet counts <50Gi/L could have had their dose increased to eltrombopag 75mg (or matching PBO) on or after Day 22. Subjects who attained a platelet count >200Gi/L were required to discontinue treatment, but continued to attend follow-up visits. After the dosing period, subjects were assessed at 1, 2, 4 and 6 weeks to assess the durability of the platelet response.
<p>Objectives: The primary objective of the study was to determine the efficacy of eltrombopag as a thrombopoietic agent, when administered once daily for up to 6 weeks to previously treated adult subjects with chronic immune thrombocytopenic purpura (ITP).</p> <p>Secondary objectives of the study were:</p> <ul style="list-style-type: none"> • To assess the safety and tolerability of eltrombopag when administered once daily for up to 6 weeks to previously treated adult subjects with chronic ITP; • To characterize the population pharmacokinetic profile of oral eltrombopag using a serial pharmacokinetic sampling strategy when administered once daily for up to 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 up to 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 up to 6 weeks to previously treated adult subjects with chronic ITP.
Primary Outcome/Efficacy Variable: The primary endpoint for the study was a platelet count of ≥ 50 Gi/L after up to 42 days of dosing (compared to a baseline count of <30Gi/L).
<p>Secondary Outcome/Efficacy Variable(s):</p> <ul style="list-style-type: none"> • Platelet counts; • Proportion of subjects responding to treatment during Weeks 2 to 6 of the study • Proportion of subjects with platelet counts ≥ 50Gi/L and at least twice their baseline • Incidence and severity of symptoms associated with chronic ITP, including bleeding, bruising, and petechiae, were measured using the WHO Bleeding Scale and the ITP Bleeding Score; and • Physical and mental health status using the Short Form-36, version 2 (SF-36v2) health-related quality of life (HR-QoL) tool and Patient Preference Assessment.
<p>Statistical Methods: Assuming 25% and 60% of subjects respond to PBO and eltrombopag 50mg, respectively, 87 evaluable subjects (58, eltrombopag 50mg; 29, PBO) were needed in order to provide 90% power at the 5% level of significance (two-sided). However, in order to provide additional safety data, 66 subjects were to be recruited to the eltrombopag treatment group and 33 subjects to the PBO treatment group. The ratio of the odds of responding in the eltrombopag treated group relative to PBO was provided together with 95% confidence limits. The overall type I error was no more than 5% (two-sided).</p> <p>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 analysis of the primary 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 applied following agreement with regulatory authorities:</p> <ul style="list-style-type: none"> • Subjects were classified as responders if they achieved a platelet count of ≥ 50Gi/L (from a

- baseline platelet count of $<30\text{Gi/L}$ at the Day 43 Visit;
- Subjects were also classified as responders if they responded with a platelet count $>200\text{Gi/L}$ 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 ($\leq 15\text{Gi/L}$ vs. $>15\text{Gi/L}$).

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 who had chronic ITP for at least 6 months and who were previously treated with at least one ITP therapy and had a platelet count of $<30\text{Gi/L}$ on Day 1 (or within 24h prior to dosing).

Subject Disposition	PBO	Eltrombopag	Total
All randomized subjects	38	76	114
Efficacy Population	38	74	112
Safety Population	38	76	114
ITT Population	38	76	114
Completed study, n (%)	30 (79)	52 (68)	82 (72)
Discontinued prematurely from study medication	8 (21)	24 (32)	32 (28)
Platelets >200Gi/L	1 (3)	18 (24)	19 (17)
Adverse Event	2 (5)	3 (4)	5 (4)
Protocol Violation	1 (3)	2 (3)	3 (3)
Lack of efficacy	2 (5)	0	2 (2)
Subject decision	0	1 (1)	1 (<1)
Other	2 (5)	0	2 (2)
Demographics (ITT Population)	PBO	Eltrombopag	Total
Age, yrs, Median (Min-Max)	51.0 (21-79)	47.0 (19-84)	48.0 (19-84)
Females:Males	27:11	43:33	70:44
Race, n (%)			
African American/African	0	1 (1)	1 (<1)
American Indian/Alaskan Native	2 (5)	4 (5)	6 (5)
Asian - East Asian	1 (3)	0	1 (<1)
Asian - South-East Asian	3 (8)	7 (9)	10 (9)
Asian - Central/South Asian	4 (11)	5 (7)	9 (8)
White - Arabic/North African	3 (8)	5 (7)	8 (7)
White - White/ Caucasian/European	23 (61)	53 (70)	76 (67)
Mixed Race	2 (5)	1 (1)	3 (3)
Ethnicity, n (%)			
Hispanic or Latino	6 (16)	10 (13)	16 (14)
Not Hispanic or Latino	32 (84)	66 (87)	98 (86)
Primary Efficacy Results (Efficacy Population):			
Responders, Day 43 Visit	PBO N=38	Eltrombopag N=74	
Number of Subjects at Day 43 Visit	37	73	
Responders, n (%)	6 (16.2)	43 (58.9)	
Odds ratio (Active relative to PBO)	NA	9.61	
95% CI	NA	(3.31, 27.86)	
p-value (two-sided)	NA	<0.001	
Secondary Outcome/Efficacy Variable(s):			
Subjects with a Platelet Count of 50Gi/L or More and at Least 2x Baseline (Efficacy Population)	PBO N=38	Eltrombopag N=74	
n	37	73	
Responders, n (%)	5 (13.5)	42 (57.5)	
Odds ratio (Active relative to PBO)	NA	11.18	
95% CI	NA	(3.63, 34.36)	
p-value (two-sided)	NA	<0.001	
Median Platelet Counts (Gi/L) by Visit (Efficacy Population, Observed Dataset)	PBO N=38	Eltrombopag N=75	
Day 1 Visit, N	29	65	
Median (Min-Max)	17.0 (3-29)	18.0 (0-30)	
Day 8 Visit, N	37	74	

Median (Min-Max)	26.0 (2-250)	29.5 (0-216)
Day 15 Visit, N	34	71
Median (Min-Max)	18.0 (2-155)	53.0 (0-532)
Day 22 Visit, N	34	59
Median (Min-Max)	20.5 (0-145)	47.0 (1-280)
Day 29 Visit, N	32	55
Median (Min-Max)	19.0 (0-161)	49.0 (3-333)
Day 36 Visit, N	32	52
Median (Min-Max)	18.5 (3-123)	50.5 (2-193)
Day 43 Visit, N	29	51
Median (Min-Max)	20.0 (2-120)	53.0 (4-268)
WHO Bleeding Scale Assessment of Subjects by Visit (Efficacy Population)	PBO N=38	Eltrombopag N=74
Baseline, n	35	70
Grade 0	12 (34.3)	27 (38.6)
Grade 1 – Grade 4	23 (65.7)	43 (61.4)
Day 43 Visit, n	30	51
Grade 0	12 (40.0)	31 (60.8)
Grade 1 – Grade 4	18 (60.0)	20 (39.2)
Day 50 Visit, n	29	65
Grade 0	17 (58.6)	46 (70.8)
Grade 1 – Grade 4	12 (41.4)	19 (29.2)
Day 57 Visit, n	34	72
Grade 0	14 (41.2)	43 (59.7)
Grade 1 – Grade 4	20 (58.8)	29 (40.3)
On-therapy AEs Reported by 2 or More Subjects (Safety Population)	PBO N=38	Eltrombopag N=76
Subjects with Any AE, n (%)	14 (37)	45 (59)
Headache	4 (11)	6 (8)
Nasopharyngitis	3 (8)	5 (7)
Nausea	0	6 (8)
Diarrhea	1 (3)	4 (5)
Vomiting	0	4 (5)
Protein total increased	1 (3)	3 (4)
Fatigue	0	3 (4)
Myalgia	0	3 (4)
Arthralgia	1 (3)	2 (3)
Alanine aminotransferase increased	0	2 (3)
Anemia	0	2 (3)
Aspartate aminotransferase increased	0	2 (3)
Constipation	0	2 (3)
Menorrhagia	0	2 (3)
Upper respiratory tract infection	0	2 (3)
Urinary tract infection	0	2 (3)
Vertigo	0	2 (3)
Abdominal distension	1 (3)	1 (1)
Abdominal pain upper	1 (3)	1 (1)
Cerebral hemorrhage	1 (3)	1 (1)
Gastrointestinal hemorrhage	1 (3)	1 (1)
Paresthesia	1 (3)	1 (1)
Pharyngitis	1 (3)	1 (1)
Pharyngolaryngeal pain	1 (3)	1 (1)

Sinusitis	1 (3)	1 (1)
Gingival bleeding	3 (8)	0
On-Therapy SAEs, n (%) [n considered by the investigator to be related to study medication] (Safety Population)	PBO N=38 n (%) [related]	Eltrombopag N=76 n (%) [related]
Subjects with non-fatal SAEs	2 (5) [1]	2 (3) [0]
Gastrointestinal hemorrhage	1 (3) [1]	1 (1) [0]
Cerebral hemorrhage	1 (3) [1]	1 (1) [0]
Hematuria	1 (3) [1]	0
Face injury	1 (3) [0]	0
Subjects with fatal SAEs	0	0

Conclusion: See Publications

Publications: Bussel J, Provan D, Shamsi T, Cheng G, Kovaleva L, Stone N, Mayer B, Poulin R, Arning M. Eltrombopag raises platelet count and reduces bleeding compared with placebo during short-term treatment in chronic idiopathic thrombocytopenic purpura: a phase III study. *Haematologica*. 2007;92(suppl 1):143.