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.: SB-497115/003
Title: A Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group, Dose Ranging Study to Assess the Efficacy, Safety, and Pharmacokinetics of an Oral Thrombopoietin Receptor Agonist (SB-497115-GR) Administered at 50, 75, and 100 mg to Cancer Patients receiving Multiple Cycles of Chemotherapy
Rationale: Chemotherapy-induced myelosuppression affects platelets, neutrophils, and erythrocytes, and one of the major risks of chemotherapy-induced thrombocytopenia (CIT) is hemorrhage as a consequence of low platelet counts. Thrombocytopenia can potentially increase morbidity and mortality in subjects undergoing chemotherapy, and in the presence of significant thrombocytopenia, the benefits of anticancer therapy at optimal doses and schedules may be limited. Currently, the primary treatment for severe or life-threatening CIT is platelet transfusion. This study focused on the effect of eltrombopag olamine, an orally bioavailable, small molecule thrombopoietin receptor agonist, for the treatment of CIT.
Phase: II
Study Period: 07Feb2005 –2 8Feb2007
Study Design: Randomized, double-blind, four-arm, parallel group, placebo-controlled, multi-center
Centers: A total of 87 centers enrolled subjects for this study: 22 in the United States, 49 in Europe, and 16 in South America and Asia.
Indication: Chemotherapy-induced thrombocytopenia
Treatment: Subjects were randomized to treatment (placebo, eltrombopag 50mg, 75mg, or 100mg) in a 1:1:1:1 ratio. Eltrombopag was supplied as 25mg and/or 50mg tablets, and matching placebo tablets were supplied. All subjects self-administered study medication every day during the 10-day dosing period of each chemotherapy cycle (starting on day 2 through day 11). All subjects were to receive study medication and to complete all visits (Day 1, 2, 5, 8, 11, 15, 18) through Cycle 2 unless the subject was withdrawn before Cycle 2. Subjects were also allowed to continue to receive chemotherapy and study medication after Cycle 2 and for up to a maximum of 8 cycles provided that the subject was not required to withdraw from treatment due to the inability to continue to meet inclusion / exclusion criteria, non-compliance with the protocol, adverse experiences, rescue treatment for chemotherapy-induced thrombocytopenia, or non-receipt of scheduled chemotherapy. If a subject experienced a platelet count >400Gi/L, the subject was to temporarily discontinue study medication; however a subject was allowed to restart study medication during the next cycle of chemotherapy provided that their platelet count was <400Gi/L.
Objectives: The primary objective was to evaluate the efficacy of oral eltrombopag at doses of 50, 75, and 100mg compared with placebo in cycle 2 of carboplatin/paclitaxel chemotherapy, administered to subjects with an advanced solid tumor.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the change in platelet count from Day 1 in Cycle 2 (baseline) to Cycle 2 nadir. During Cycle 2 of carboplatin/paclitaxel administration, efficacy assessments (platelet count) were performed on Day 1 prior to chemotherapy and on Days 2, 5, 8, 11, 15, and 18 post-chemotherapy, throughout the cycle.
Secondary Outcome/Efficacy Variable(s): • Safety and tolerability; • Pharmacodynamic parameters; • Change in platelet count from Day 1 to nadir during the first cycle and beyond the second cycle of carboplatin/paclitaxel; • Population PK of SB-497115; • Dose intensity (percent of intended dose) of carboplatin/paclitaxel; and

- Carboplatin/paclitaxel-associated thrombocytopenia-related AEs.

Statistical Methods: The planned sample size for this study was 164 subjects and 41 subjects were to be randomized to each treatment group: 50mg, 75mg, 100mg of eltrombopag and placebo. The study was powered at 90% to detect a difference of at least 83Gi/L in the mean difference in change in platelet count from Day 1 in Cycle 2 to Cycle 2 nadir for each dose group (50, 75, and 100 mg of oral eltrombopag) compared with placebo.

- The primary efficacy population for analysis was the modified Intent-to-Treat (mITT) population which was comprised of all subjects that were randomized and treated with at least one dose of the study treatment in Cycle 1 and had both baseline (Day 1 of Cycle 1) and at least one on therapy platelet count. The primary endpoint was the change in platelet count from Day 1 of Cycle 2 to Cycle 2 nadir.
- Safety analyses were reported using the safety population which was comprised of all subjects randomized and who received at least one dose of study medication (eltrombopag/placebo in any cycle).

The null hypothesis versus a two-sided alternative was that there is no difference in primary endpoint between each of the dose groups (50, 75 and 100mg of oral eltrombopag) and placebo. A closed test procedure was used for multiplicity consideration. The analysis of covariance was employed at the 5% significance level (2-sided) for treatment effect testing. In addition, 95% confidence intervals for the difference in primary efficacy parameter between each dose of eltrombopag and placebo were also calculated.
Demographic and baseline characteristics were summarized using descriptive statistics. Qualitative and quantitative results were summarized for all AEs, drug-related AEs, all SAEs, and events leading to withdrawal from the study. Other assessments were summarized for hematology, clinical chemistry, urinalysis, vital signs, 12-lead ECG, ocular examinations, and ECOG Performance Status. The PK population included all subjects who underwent PK sampling during the study and results were summarized in a separate PK report. Pharmacodynamic results included a summarization of platelet count data, TPO data, and platelet aggregation and activation data.

Study Population: Eligible subjects were ≥18 years old, were chemotherapy naïve, had a histologically or cytologically confirmed advanced solid tumor (leukemia and lymphoma were excluded), had at least 6 months life expectancy, were scheduled to receive carboplatin/paclitaxel, and had no history of platelet disorders, platelet dysfunction or bleeding disorder. For the purpose of this study, advanced tumors were defined as tumors that were being treated with palliative intent. Eligible subjects also had an ECOG-Zubrod performance status of zero or one, had adequate organ function (hematologic, liver, and kidney), were practicing contraception if appropriate, were able to ingest and retain oral medications, and were able to understand study procedures and sign informed consent.

	PBO	50mg	75mg	100mg	Total
Number of Subjects:					
Planned, N	41	41	41	41	164
Randomized, N	47	45	45	46	183
mITT Population, N (%)	45 (96)	41 (91)	41 (91)	43 (93)	170 (93)
Completed first 2 cycles, n (%, based on mITT Population)	36 (80)	34 (83)	29 (71)	29 (67)	128 (75)
Safety Population, N (%)	46 (98)	44 (98)	44 (98)	46 (100)	180 (98)
Total Number Subjects Withdrawn, n (%) (% based on Safety Population)	40 (87)	38 (86)	40 (91)	42 (91)	160 (89)
Withdrawn due to Adverse Events, n (%)	8 (17)	3 (7)	8 (18)	13 (28)	32 (18)
Withdrawn due to Subject Decision, n (%)	7 (15)	6 (14)	8 (18)	3 (7)	24

					(13)
Withdrawn due to Complete/End Chemotherapy, n (%)	5 (11)	2 (5)	5 (11)	12 (26)	24 (13)
Withdrawn due to Physician Decision, n (%)	4 (9)	5 (11)	7 (16)	5 (11)	21 (12)
Withdrawn due to Disease Progression, n (%)	3 (7)	10 (23)	4 (9)	3 (7)	20 (11)
Withdrawn due to Other Reasons, n (%)	4 (9)	7 (16)	3 (7)	4 (9)	18 (10)
Withdrawn due to Lack of Efficacy, n (%)	4 (9)	4 (9)	1 (2)	1 (2)	10 (6)
Withdrawn due to Need for Surgery, n (%)	3 (7)	0	2 (5)	1 (2)	6 (3)
Withdrawn due to Protocol Violation, n (%)	2 (4)	1 (2)	2 (5)	0	5 (3)
Demographic/Baseline Characteristics (Safety Population)					
Females: Males	30:16	21:23	28:16	22:24	101:79
Median Age, years (min – max)	58.0 (23-73)	58.5 (35-75)	59.0 (33-75)	58.0 (34-81)	58.0 (23-81)
White/Caucasian/European, n (%)	35 (78)	36 (88)	33 (80)	37 (86)	141 (83)
Tumor Type, n (%)					
NSCL	27 (59)	29 (66)	28 (64)	28 (61)	112 (62)
Ovarian	14 (30)	8 (18)	10 (23)	14 (30)	46 (26)
Breast	2 (4)	3 (7)	1 (2)	1 (2)	7 (4)
Other					
Median Carboplatin Dose, mg (min –max)	2176.3 (370-5154)	2355.0 (450-5570)	2085.0 (310-6187)	1950.0 (406-8070)	2146.8 (310-8070)
Median Paclitaxel Dose, mg (min – max)	1220.0 (234-4055)	1290.0 (263-3570)	1250.0 (243-3283)	1184.2 (240-3675)	1261.8 (234-4055)

Primary Efficacy Results:					
Change in Platelet Count (Gi/L) from Day 1 of Cycle 2 to Nadir of Cycle 2 (mITT Population)		**PBO**	**50mg**	**75mg**	**100mg**
Day 1	n	41	38	33	35
	Mean (SD)	291.5 (106.53)	376.1 (154.04)	397.8 (163.28)	447.9 (217.19)
Nadir	n	38	38	31	32
	Mean (SD)	178.3 (55.43)	218.3 (75.67)	214.9 (87.48)	210.9 (73.03)
Change from Day 1 to Nadir in Cycle 2	n	38	38	31	32
	Mean (SD)	115.0 (98.38)	157.8 (114.00)	171.1 (119.10)	227.7 (216.88)
Model adjusted change from Day 1 to Nadir in Cycle 2	Mean (SD)	114.6 (22.53)	164.0 (22.65)	166.3 (25.01)	225.5 (24.57)

Difference from placebo	Mean	-	49.4	51.7	111.0
	95% CI	-	-13.8, 112.6	-14.9, 118.3	45.0, 176.9
	p-value	-	0.125	0.127	0.001
Secondary Outcome Variable(s):					
Summary of Platelet Counts (Gi/L) by Visit in Cycle 1 (mITT Population)		**PBO**	**50mg**	**75mg**	**100mg**
Visit 1, Day 1	n	45	41	41	43
	Mean (SD)	321.8 (115.64(	290.6 (89.32)	317.7 (78.47)	324.0 (112.47)
Visit 4, Day 8	n	44	40	38	40
	Mean (SD)	262.5 (63.99)	248.4 (96.96)	83.18 (261.0)	93.39 (245.5)
Visit 5, Day 11	n	42	40	37	39
	Mean (SD)	273.5 (69.83)	314.5 (107.71)	336.8 (129.25)	335.7 (130.18)
Visit 7, Day 18	n	41	37	36	37
	Mean (SD)	272.3 (80.47)	401.1 (145.58)	441.4 (211.36)	445.4 (171.71)

Safety Results: Adverse event s (AEs) and Serious Adverse Events (SAEs) were collected on or after Day 1, Cycle 1 and up to 30 days following the end of the last cycle of treatment. Neutropenia was the most commonly reported hematologic AE, an expected effect from treatment with carboplatin and paclitaxel chemotherapy. Nausea and alopecia were the most commonly reported non-hematologic AEs reported and are expected events when subjects are given chemotherapy.

Most Frequent Adverse Events	**PBO N=46**	**50mg N=44**	**75mg N=44**	**100mg N=46**	**Total N=180**
Subjects with any AE, n (%)	**39(85)**	**37(84)**	**38(86)**	**42(91)**	**156 (87%)**
Hematologic AEs, n (%)					
Neutropenia	17 (37)	8 (18)	12 (27)	13 (28)	50 (28)
Anemia	11 (24)	6 (14)	10 (23)	8 (17)	35 (19)
Leukopenia	7 (15)	9 (20)	5 (11)	4 (9)	25 (14)
Thrombocytosis	3 (7)	2 (5)	4 (9)	6 (13)	15 (8)
Non-hematologic AEs					
Nausea	19 (41)	18 (41)	14 (32)	13 (28)	64 (36)
Alopecia	10 (22)	19 (43)	8 (18)	12 (26)	49 (27)
Vomiting	9 (20)	5 (11)	4 (9)	11 (24)	29 (16)
Fatigue	8 (17)	7 (16)	8 (18)	5 (11)	28 (16)
Arthralgia	3 (7)	10 (23)	4 (9)	5 (11)	22 (12)
Diarrhea	4 (9)	5 (11)	6 (14)	4 (9)	19 (11)
Asthenia	4 (9)	7 (16)	2 (5)	4 (9)	17 (9)
Pain in extremity	7 (15)	4 (9)	1 (2)	3 (7)	15 (8)
Headache	3 (7)	6 (14)	2 (5)	3 (7)	14 (8)
Pyrexia	3 (7)	6 (14)	1 (2)	4 (9)	14 (8)
Peripheral sensory neuropathy	2 (4)	3 (7)	1 (2)	5 (11)	11 (6)
Serious Adverse Events - n (%) [n considered by the investigator to be related to study medication]					

	PBO N=46 n (%) [related]	50mg N=44 n (%) [related]	75mg N=44 n (%) [related]	100mg N=46 n (%) [related]
Subjects with any SAE – includes both fatal and non-fatal events	**7 (15) [3]**	**4 (9) [1]**	**7 (16) [2]**	**10 (22) [2]**
Anemia	0	0	0	2 (4) [0]
Cardiac arrest	0	0	0	2 (4) [0]
Metastases to CNS	0	0	0	1 (2) [0]
Myalgia	0	0	0	1 (2) [0]
Pulmonary embolism	0	0	0	1 (2) [1]
Overdose	0	0	0	1 (2) [1]
Ischemic stroke	0	0	0	1 (2) [0]
DVT	0	1 (2) [0]	0	1 (2) [0]
Cardio-respiratory arrest	1 (2) [1]	0	1 (2) [0]	0
Respiratory tract infection	0	0	2 (4) [0]	0
Hyperglycemia	0	0	1 (2) [0]	0
Hyponatremia	0	0	1 (2) [0]	0
Intestinal obstruction	0	0	1 (2) [0]	0
Acute renal failure	0	0	1 (2) [0]	0
Diarrhea	0	0	1 (2) [1]	0
Cerebral infarction	0	0	1 (2) [0]	0
Febrile neutropenia	0	0	1 (2) [0]	0
COPD	0	0	1 (2) [1]	0
Ileus	0	1 (2) [0]	0	0
Duodenal stenosis	0	1 (2) [0]	0	0
Bilirubin increase	0	1 (2) [1]	0	0
Pulmonary hemorrhage	1 (2) [0]	0	0	0
Embolism	1 (2) [0]	0	0	0
Hyponatremia	1 (2) [0]	0	0	0
Right bundle branch block	1 (2) [1]	0	0	0
Pancytopenia	1 (2) [1]	0	0	0
Thrombocytopenia	1 (2) [1]	0	0	0
Hypotension	1 (2) [0]	0	0	0
Subjects with fatal SAEs	**3 (7) [1]**	**1 (2) [0]**	**3 (7) [1]**	**3 (7) [0]**
Cardiac arrest	0	0	0	1 (2) [0]
Ischemic stroke	0	0	0	1 (2) [0]
Metastases to CNS	0	0	0	1 (2) [0]
Acute renal failure	0	0	1 (2) [0]	0
Cardio-respiratory arrest	1 (2) [1]	0	1 (2) [0]	0
COPD	0	0	1 (2) [1]	0
Disease progression	1 (2) [0]	0	0	0
Embolism	1 (2) [0]	0	0	0
Hemoptysis	0	1 (2) [0]	0	0

Conclusion: Treatment with eltrombopag 50mg, 75mg, and 100mg failed to meet the study-defined primary endpoint compared to placebo in cancer patients receiving carboplatin/paclitaxel chemotherapy.

Publications: None