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.: TPL102357
Title: A double-blind, randomized, placebo-controlled, multi-centre, dose-ranging, parallel group, phase II study to assess efficacy, safety/tolerability, and pharmacokinetics of a thrombopoietin receptor agonist, SB-497115-GR, when administered as 30, 50, and 75mg once daily for 12 weeks in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with pegylated interferon and ribavirin.
Rationale: Thrombocytopenia is reported in patients with chronic HCV infection and can be as a consequence of both their underlying liver disease (hypersplenism resulting from portal hypertension and low production of endogenous thrombopoietin in the damaged liver) and as a result of myelosuppressive effects of antiviral therapy (peginterferon-alpha and ribavirin) used to treat HCV infection. The current gold standard therapy for HCV infection, peginterferon-alpha and ribavirin, has not been adequately studied in subjects with platelet counts of <100Gi/L due to the increased risk of severe thrombocytopenia and life-threatening hemorrhagic events. Peginterferon alpha treatment may lead to thrombocytopenia in hepatitis C-infected subjects. Current clinical management of thrombocytopenia in patients with chronic HCV relies primarily on the reduction of peginterferon alpha dose. The product label information from the pivotal Phase III studies for the pegylated interferons indicates that approximately 20 to 30% of subjects had a reduction in platelet count during treatment with a combination of peginterferon plus ribavirin. However, such treatment modifications, particularly if occurring during the initial 12 weeks of treatment, may be associated with a reduced ability to successfully clear HCV virus. The purpose of this study was to determine if eltrombopag could increase platelet counts to levels allowing the initiation and maintenance of antiviral therapy with peginterferon-alpha and ribavirin at efficacious doses. The study was designed to assess the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of once daily oral administration of eltrombopag 30mg, 50mg, 75mg or matching placebo in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with peginterferon and ribavirin and had baseline platelet counts 20 to <70Gi/L.
Phase: II
Study Period: 05Apr2005 - 20Oct2006
Study Design: Double-blind, Randomized, Placebo-controlled, Multi-center, Dose-ranging, Parallel Group
Centers: Sites from the United States and Europe (France, Germany, United Kingdom, and Greece) participated in the study.
Indication: Hepatitis C-related thrombocytopenia
Treatment: Subjects were randomly allocated (1:1:1:1) to 1 of 4 treatment groups (30mg, 50mg, or 75mg eltrombopag or matching placebo). Randomization was stratified according to baseline platelet count (20 to <50Gi/L or ≥50 to <70Gi/L). In Part 1 (pre-antiviral treatment phase), subjects received eltrombopag tablets once daily for 4 weeks. Dosing with eltrombopag was interrupted if the platelet count exceeded 200Gi/L and reinstated on an individual basis, but generally when platelet counts returned to ≤100Gi/L. Subjects who completed Part 1 could enter Part 2 (antiviral treatment phase) by attaining a predefined platelet count (≥70Gi/L for peginterferon alpha-2a or ≥100Gi/L for peginterferon alpha-2b). In Part 2, peginterferon and

ribavirin were administered for 8-12 weeks concomitant with maintenance of eltrombopag or placebo. Dose reductions/cessation of these approved peginterferon therapies were required in accordance with the appropriate product labels. At the end of Part 2 (eltrombopag/placebo treatment), antiviral therapy continued at the investigator's discretion according to local standard of care.

Objectives: The primary objective was to evaluate the effect of eltrombopag on platelet counts when administered once daily for 4 weeks (Part 1, pre-antiviral phase) to subjects with chronic hepatitis C virus (HCV)-related thrombocytopenia, prior to receiving antiviral therapy.
Secondary objectives of the study were:

- To evaluate the effects of eltrombopag on platelet counts when administered once daily for 12 weeks (Part 2) to subjects with chronic HCV-related thrombocytopenia, during antiviral therapy.
- To evaluate the effects of eltrombopag on markers of thrombopoiesis, when administered once daily for 16 weeks to subjects with chronic HCV-related thrombocytopenia.
- To evaluate the effects of eltrombopag on antiviral treatment outcome measures during and after antiviral therapy in subjects with chronic HCV.
- To evaluate the safety and tolerability of eltrombopag when administered once daily for 16 weeks to subjects with chronic HCV.
- To evaluate the population pharmacokinetic profile of eltrombopag when administered once daily for 16 weeks to subjects with chronic HCV.

Primary Outcome/Efficacy Variable: The primary endpoint was the proportion of subjects with a shift from baseline platelet count (between 20Gi/L and <70Gi/L) to ≥100Gi/L after 4 weeks (Part 1) of administration of eltrombopag prior to receiving antiviral therapy.

Secondary Outcome/Efficacy Variable(s): Secondary endpoints included platelet response throughout the study, serum endogenous TPO levels, peginterferon and ribavirin dose modifications, HCV RNA levels, safety and tolerability and pharmacokinetic analyses.

Statistical Methods: The planned sample size for the study was 160 subjects, with 40 subjects randomized to each treatment group. The sample size was estimated assuming a placebo response rate of 20% and an active response rate of 60%. The power to detect the anticipated treatment effect was 90% at the overall 5% level of significance (two-sided). The primary endpoint was analyzed using multiple logistic regression. Each dose was compared to placebo using a closed testing procedure. Efficacy analyses were performed on two datasets. The primary dataset used a last observation carried forward (LOCF) analysis. The secondary dataset had no imputations for premature withdrawals or missing data (Observed dataset).

There were 3 analysis populations: The Intent-to-treat (ITT) population was used as the primary population for the analysis of efficacy, pre-defined as all randomized subjects who received at least one dose of study medication; the Per-protocol (PP) population was also used for the analysis of efficacy and was pre-defined to exclude major protocol violators; and the Safety population was used for the analysis of safety and was pre-defined as all subjects who received at least one dose of study medication. In this study, all subjects who were randomized received at least one dose of study medication; hence, the Safety population was the same as the ITT population.

The analyses generally included all randomized subjects. Since the primary endpoint was defined as a shift from baseline platelet count of between 20 and <70 to ≥100Gi/L after 4 weeks (defined as a responder), the primary endpoint analysis excluded subjects whose baseline platelet count was ≥70Gi/L. Missing data for the primary endpoint analysis were imputed using the last observation carried forward (LOCF) approach.

Two interim analyses were conducted and based on the results of a second interim analysis, the study was terminated early (n=74) because the protocol-defined statistical stopping criterion was met ($p<0.0001$ for the analysis of the primary endpoint).

Study Population: Eligible male and female subjects were ≥18 years of age with chronic HCV (defined as the presence of HCV antibodies and detectable HCV RNA [ribonucleic acid]) who had compensated liver disease and pre-existing thrombocytopenia (defined as a platelet count of 20 to <70Gi/L). Subjects were required to have a liver biopsy indicative of chronic hepatitis, or radiographic evidence of cirrhosis or endoscopic evidence of portal hypertension. Subjects were excluded if they were pregnant, had a history of thrombosis, or were co-infected with human immunodeficiency virus or hepatitis B virus.

Number of Subjects		**PBO**	**30mg**	**50mg**	**75mg**	**Total**
Part 1:	Randomized to Part 1, n (%)	18	14	19	23	74
	Completed Part 1, n (%)	4 (22)	10 (71)	14 (74)	21 (91)	49 (66)
	Total Withdrawn, n (%)	14 (78)	4 (29)	5 (26)	2 (9)	25 (34)
	Lack of Efficacy, n (%)	7 (39)	2 (14)	2 (11)	1 (4)	12 (16)
	Other, n (%)	5 (28)	1 (7)	1 (5)	1 (4)	8 (11)
	Subject's Decisio n, n (%)	2 (11)	0	2 (11)	0	4 (5)
	Adverse Event, n (%)	0	1 (7)	0	0	1 (1)

Part 2:	Entering Part 2, n (%)	4 (22)	10 (71)	14 (74)	21 (91)	49 (66)
	Completed Part 2 (Entire Study), n (%)	1 (6)	5 (36)	10 (53)	15 (65)	31 (42)
	Total Withdrawn, n (%)	3 (17)	5 (36)	4 (21)	6 (26)	18 (24)
	Other, n (%)	2 (11)	1 (7)	1 (5)	4 (17)	8 (11)
	Adverse Event, n (%)	0	2 (14)	1 (5)	1 (4)	4 (5)
	Lost to Follow-up, n (%)	0	1 (7)	0	1 (4)	2 (3)
	Subject's Decisio n, n (%)	0	1 (7)	1 (5)	0	2(3)
	Lack of Efficacy, n (%)	1 (6)	0	1 (5)	0	2 (3)

Demographics (ITT Population):

	PBO N=18	**30mg N=14**	**50mg N=19**	**75mg N=23**	**Total N=74**
Age: Median (Min, Max)	52 (41, 71)	56 (43, 74)	50 (30, 72)	51 (38, 60)	51 (30, 74)
Gender –F emales:Males	7:11	4:10	7:12	4:19	22:52
White/Caucasian/European, n (%)	16 (89)	13 (93)	15 (79)	20 (87)	64 (86)
Genotype, n (%)					
1	9 (50)	9 (64)	11 (58)	11 (48)	40 (54)
2	0	1 (7)	2 (11)	2 (9)	5 (7)
3	7 (39)	3 (21)	6 (32)	6 (26)	22 (30)
4	1 (6)	1 (7)	0	3 (13)	5 (7)
Missing	1 (6)	0	0	1 (4)	2 (3)

Primary Efficacy Results (ITT Population, LOCF):

Responders by Visit in Part 1

	PBO N=18	**30mg N=14**	**50mg N=19**	**75mg N=23**
Day 28 Visit (Week 4), n (%)	0	9 (75)	15 (79)	20 (95)
Analysis of Responders at Week 4				
Odds ratio	NA	26	32	86
95% Confidence interval	NA	(4, 166)	(5, 190)	(12, 616)
p-value versus placebo (two-sided test)	NA	0.00067	0.00015	<0.0001

Secondary Efficacy Results (ITT Population, Observed Data):

Median Platelet Counts (Gi/L) for All Subjects by Visit in Part 1

Baseline (Day 1), n	18	14	19	23
Median (Min, Max)	55 (38, 75)	61 (42, 94)	55 (26, 66)	56 (28, 75)
Day 8 Visit	18	14	19	22
Median (Min, Max)	57 (26, 86)	77 (53, 259)	80 (23, 180)	92 (44, 156)
Day 15 Visit	18	14	17	22
Median (Min, Max)	54 (34, 74)	111 (52, 798)	130 (36, 376)	157 (68, 395)
Day 22 Visit	17	12	16	22
Median (Min, Max)	54 (34, 87)	125 (70, 778)	196 (44, 551)	234 (82, 576)
Day 28 Visit	14	11	15	20
Median (Min, Max)	53 (34, 77)	125 (40, 214)	212 (47, 599)	204 (78, 527)

Median Platelet Counts (Gi/L) for All Subjects by Visit in Part 2

Number of Subjects Entering Part 2	4	10	14	21
Visit 7 (Day 36), n	3	10	12	18
Median (Min, Max)	51.0 (32, 85)	95.5 (10, 161)	173.5 (62, 330)	162.0 (102, 304)

Visit 8 (Day 43), n Median (Min, Max)	3 54.0 (22, 59)	10 90.0 (37, 152)	14 106.5 (57, 246)	20 138.0 (76, 207)
Visit 9 (Day 57), n Median (Min, Max)	4 38.0 (25, 40)	9 97.0 (52, 203)	12 71.5 (22, 188)	18 87.5 (50, 163)
Visit 10 (Day 85), n Median (Min, Max)	2 39.0 (38, 40)	7 80.0 (30, 103)	10 111.0 (42, 182)	17 106.0 (29, 198)
Visit 11 (Day 113), n Median (Min, Max)	1 39.0 (39, 39)	6 105.5 (43, 164)	10 100.0 (46, 156)	15 92.0 (38, 245)

Number of Viral Responders

HCV RNA Response Baseline/Endpoint	Viral Response	PBO N=18	30mg N=14	50mg N=19	75mg N=23
Early viral response (Day 28/Day 113)	Yes No Exclusions	1 1 16	4 4 6	3 4 12	9 3 11
Modified viral response (Screening or Day 28/Day 113)	Yes No Exclusions	1 2 15	4 4 6	3 7 9	10 3 10
Any viral response (Screening or Day 28/Day 85 or 113)	Yes No Exclusions	1 2 15	4 6 4	4 7 8	11 3 9

Safety Results: AEs during Part 1 were events starting prior to antiviral therapy or, if antiviral therapy was not started, ≤30 days after the last day of double-blind study medication. AEs during Part 2 were events starting during antiviral therapy or ≤30 days after the last day of double-blind study medication. An on-therapy serious adverse event (SAE) was defined as any SAE starting during active double-blind treatment (Part 1 or Part 2) or ≤30 days after the last day of double-blind study medication.

On-Therapy AEs During Part 1 (Pre-antiviral Therapy) Reported by 2 or More Subjects

Preferred Term	PBO N=18	30mg N=14	50mg N=19	75mg N=23
Any AE	10 (56)	11 (79)	10 (53)	13 (57)
Headache	3 (17)	5 (36)	3 (16)	4 (17)
Dry mouth	1 (6)	2 (14)	2 (11)	2 (9)
Pruritus	0	0	0	2 (9)
Nausea	0	1 (7)	2 (11)	1 (4)
Fatigue	0	0	2 (11)	1 (4)
Upper abdominal pain	0	2 (14)	2 (11)	0
Insomnia	0	0	2 (11)	0
Arthralgia	0	2 (14)	1 (5)	0
Preferred Term Number of Subjects Entering Part 2	PBO N=4	30mg N=10	50mg N=14	75mg N=21
Any AE	3 (75)	9 ((90)	13 (93)	17 (81)
Influenza like illness	1 (25)	4 (40)	5 (36)	8 (38)
Fatigue	1 (25)	4 (40)	5 (36)	5 (24)
Depression	0	2 (20)	1 (7)	4 (19)
Headache	0	3 (30)	3 (21)	3 (14)
Diarrhea	1 (25)	0	1 (7)	3 (14)
Decreased appetite	0	0	0	3 (14)
Chills	1 (25)	0	6 (43)	2 (10)
Pyrexia	0	1 (10)	3 (21)	2 (10)
Myalgia	0	3 (30)	2 (14)	2 (10)
Anemia	0	2 (20)	2 (14)	2 (10)
Arthralgia	1 (25)	3 (30)	1 (7)	2 (10)
Asthenia	0	1 (10)	0	2 (10)
Nausea	0	3 (30)	3 (21)	1 (5)
Rash	0	0	3 (21)	1 (5)
Irritability	1 (25)	2 (20)	0	1 (5)
Abdominal pain	0	2 (20)	0	1 (5)
Neutropenia	0	0	3 (21)	0
Pruritus	1 (25)	1 (10)	2 (14)	0
Anorexia	1 (25)	0	2 (14)	0
Influenza	0	2 (20)	0	0
Serious Adverse Events - On-Therapy **n (%) [number of events considered by the investigator to be related to study medication]**				
Preferred Term	PBO N=18 n (%) [related]	30mg N=14 n (%) [related]	50mg N=19 n (%) [related]	75mg N=23 n (%) [related]
Subjects with Any SAE	1 (6) [0]	2 (14) [1]	0	1 (4) [0]
Retinal exudates	0	0	0	1 (4) [0]
Ascites	0	1 (7) [0]	0	0
Thrombocytopenia	0	1 (7) [1]	0	0
Abdominal pain	1 (6) [0]	0	0	0
Renal failure	1 (6) [0]	0	0	0
Subjects with Any Fatal SAE	1 (6) [0]	0	0	0
Abdominal pain	1 (6) [0]	0	0	0
Renal failure	1 (6) [0]	0	0	0

Conclusion: Refer to Publications

Publications:

McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, Berg T, Gordon SC, Campbell FM, Theodore D, Blackman N, Jenkins J, Afdhal NH; TPL 102357 Study

Group. Eltrombopag for thrombocytopenia in patients with cirrhosis associated hepatitis C. *N Engl J Med*. 2007;357(22) :227-36.