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Study No.: TPL104054
Title: Clinical Study Report for Study TPL104054, a Randomised, Double-Blind, Placebo-Controlled, Multi-Centre Study to Evaluate the Safety and Efficacy of Eltrombopag to Reduce the Need for Platelet Transfusion in Thrombocytopenic Subjects with Chronic Liver Disease Undergoing Elective Invasive Procedures. ELEVATE: Eltrombopag Evaluated for its Ability to overcome Thrombocytopenia and Enable procedures
Rationale: Eltrombopag olamine (SB-497115-GR) is a thrombopoietin receptor agonist being developed for the treatment of thrombocytopenia of various aetiologies. The use of eltrombopag to elevate platelet count in chronic liver disease patients with thrombocytopenia may eliminate the need for a platelet transfusion on the day and up to seven days following the elective invasive procedure. Avoidance of platelet transfusion eliminates the risk of a patient developing transfusion-related complications. In addition, the use of an oral thrombopoietic agent may reduce the occurrence and severity of bleeding during the pre- and post-procedural period in thrombocytopenic patients with liver disease. The study was designed to determine if eltrombopag is a safe and effective means to elevate platelet counts thereby reducing the need for platelet transfusions in chronic liver disease patients with thrombocytopenia, undergoing elective invasive procedures.
Phase: III
Study Period: 02 June 2008 to 15 October 2009
Study Design: Randomised, double-blind, placebo-controlled, 2-arm study
Centres: 76 centres in US (20 centres), Italy (14 centres), Spain (9 centres), France (7 centres), Poland (5 centres), Argentina (4 centres), Korea (4 centres), Pakistan (4 centres), Russia (3 centres), Canada (2 centres), Taiwan (2 centres), Belgium (1 centre) and India (1 centre)
Indication: Chronic Liver Disease
Treatment: Subjects were randomised to either 75 mg oral eltrombopag or matched placebo in a 1:1 ratio in accordance with the randomisation schedule. Subjects were stratified at randomisation according to the type of invasive procedure that was planned.
Objectives: The primary objective of the study was to demonstrate the ability of eltrombopag, compared to placebo to reduce the proportion of subjects with chronic liver disease and thrombocytopenia (platelets <50 Gi/L) who received platelet transfusions administered prior to, during and up to 7 days following elective invasive procedures.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the proportion of subjects with chronic liver disease and thrombocytopenia (platelets <50 Gi/L) who do not require a platelet transfusions prior to, during and up to 7 days following elective invasive procedures.
Secondary Outcome/Efficacy Variable(s): Secondary endpoints were: Proportion of subjects with WHO bleeding Score ≥ 2 prior to, during and up to seven days following elective invasive procedures; Number of platelet transfusions administered prior to, during and up to 4 weeks (30 days) following elective invasive procedures; Assessment of platelet counts throughout the study.
Statistical Methods: The study was powered to demonstrate a clinically meaningful difference between eltrombopag and placebo with respect to the primary endpoint for the ITT population. In addition, the study was powered to ensure sufficient sample size for the following important secondary objective: To compare eltrombopag and placebo with respect to the occurrence of bleeding (defined by World Health Organisation (WHO) bleeding grade ≥ 2) for the ITT population. The proportion of subjects with bleeding was assumed to be 20%. An absolute eltrombopag minus placebo difference of no more than 10% was desired. A total of 500 subjects (250 randomised to eltrombopag and 250 randomised to placebo) would provide 80% power to rule out this absolute difference of 10% at $\alpha=0.025$; this is a one-sided test for non-inferiority. Assuming that the proportions of subjects avoiding platelet transfusion prior to, during, and over the 7 days following an elective invasive procedure would be 20% with placebo and 50% with eltrombopag, a total of 120 subjects (60 subjects pre group) would provide 90% power to detect a statistically significant treatment effect at two-sided $\alpha=0.05$ in the Intent to Treat (ITT) population. The primary analysis compared eltrombopag with placebo for the avoidance of platelet transfusion prior to and up to 7 days following an elective invasive procedure. The Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for the four randomisation strata, was used to compare treatments. Model adjusted differences and associated 95% confidence intervals (CIs) were derived. The proportion of subjects having a bleeding episode of WHO Grade ≥ 2 prior to and up to 7 days following an elective invasive procedure were summarised by treatment group. A model-adjusted difference in proportions and associated CIs were derived. Non-inferiority with respect to the occurrence of bleeding was inferred by ensuring that the upper 97.5% confidence limit for the eltrombopag minus placebo difference did not

exceed 10%. The proportion of subjects with an increase in platelet count to >80 Gi/L within 14 days after randomisation was compared between treatments using the stratified CMH chi-square test. The maximum bleeding severity grade observed post-randomisation and the total number of platelet transfusions during the study were compared between treatments using the Wilcoxon rank sum test adjusting for the randomisation strata using the van Elteren procedure. The primary endpoint was analysed separately for the four randomisation strata, and other important subgroups (geographic region, gender, age, race, weight, MELD score and Child-Pugh Class. The Breslow-Day test for homogeneity of treatment effect was used to evaluate treatment-by-strata and treatment-by-subgroup interactions. In addition, randomisation-based non-parametric analysis of covariance was used to evaluate the effect of treatment on the primary endpoint while simultaneously adjusting for the randomisation strata and controlling for important subgroups. Sensitivity analyses were performed to assess the impact of subjects with pre-procedural platelet counts between 50 Gi/L and 80 Gi/L being transfused or not transfused according to local guidelines. Following the suspension of the study for safety reasons, univariate and multivariate analyses were performed to explore the possible predictors of thromboembolic events (TEE). The ITT Population was the primary population for reporting efficacy and was defined as all subjects who were randomised to treatment. The Safety population was used for the assessment of safety and was defined as all randomised subjects who received at least one dose of study medication.

Study Population: Male or female subjects aged ≥ 18 years with chronic liver disease and a platelet count <50 Gi/L, who were scheduled to undergo an elective invasive procedure and required a platelet transfusion to manage the risk of bleeding associated with the procedure.

	Placebo	Eltrombopag
Number of Subjects:		
Planned, N	250	250
Randomised, N	147	145
Completed, n (%)	127 (86)	127 (88)
Total Number Subjects Withdrawn, N (%)	20 (14)	18 (12)
Withdrawn due to Adverse Events n (%)	3 (2)	3 (2)
Withdrawn due to Lack of Efficacy n (%)	1 (<1)	0
Withdrawn for other reasons n (%)	16	15
Demographics	Placebo	Eltrombopag
N (ITT)	147	145
Females: Males	55:92	49:96
Mean Age, years (SD)	53.5 (11.78)	51.6 (11.04)
White, n (%)	93 (63)	85 (59)
Baseline Child-Pugh Classification, n (%)		
A (5-6)	59 (41)	68 (48)
B (7-9)	64 (44)	57 (40)
C (>9)	17 (12)	10 (7)
Median MELD Score (min, max)	12 (6, 25)	12 (6, 24)
Primary Efficacy Results:	Placebo	Eltrombopag
N (ITT)	145	147
Avoidance of Platelet Transfusion; n (%)	28 (19)	104 (72)
Difference between treatments (%)	52.8	
95% Confidence Interval	43.2, 62.4	
p-value	<0.0001	
Secondary Outcome Variable(s):	Placebo	Eltrombopag
N(ITT)	145	147
WHO Bleeding Score ≥ 2 ; n(%)	34 (23)	25 (17)
Difference between treatments (%)	-5.9	
95% CI	-15.1, 3.3	

Number of platelet transfusion episodes, n (%)		
0	30 (20)	106 (73)
1	93 (63)	24 (17)
2	3 (2)	1 (<1)
3	2 (1)	0
4	3 (2)	0
6	1 (<1)	0
Died or withdrew from study prior to having any platelet transfusions	15 (10)	14 (10)
Platelet Count Categories throughout the Study; n(%)		
Screening	n=147	n=145
<50 Gi/L	133 (90)	136 (94)
≥50 to ≤80 Gi/L	14 (10)	8 (6)
>80 to ≤200 Gi/L	0	0
>200 to ≤400 Gi/L	0	0
>400 Gi/L	0	0
Day 8	n=139	n=135
<50 Gi/L	98 (67)	48 (33)
≥50 to ≤80 Gi/L	34 (23)	50 (34)
>80 to ≤200 Gi/L	7 (5)	33 (23)
>200 to ≤400 Gi/L	0	3 (2)
>400 Gi/L	0	0
Day 15	n=132	n=131
<50 Gi/L	98 (67)	14 (10)
≥50 to ≤80 Gi/L	26 (18)	31 (21)
> 80 to ≤200 Gi/L	8 (5)	67 (46)
> 200 to ≤400 Gi/L	0	19 (13)
> 400 Gi/L	0	0
Procedure +7 Day Follow-up	n=128	n=126
< 50 Gi/L	78 (53)	11 (8)
≥50 to≤80 Gi/L	38 (26)	20 (14)
>80 to ≤200 Gi/L	12 (8)	60 (41)
>200 to ≤400 Gi/L	0	30 (21)
>400 Gi/L	0	4 (3)
Procedure + 14 Day Follow-up	n=117	n=125
<50 Gi/L	63 (43)	22 (15)
≥50 to ≤80 Gi/L	40 (27)	21 (14)
>80 to ≤200 Gi/L	11 (7)	62 (43)
>200 to ≤400 Gi/L	2 (1)	17 (12)
>400 Gi/L	0	3 (2)
Procedure + 21 Day Follow-up	n=121	n=117
< 50 Gi/L	80 (54)	38 (26)
≥50 to ≤80 Gi/L	30 (20)	33 (23)
> 80 to ≤200 Gi/L	10 (7)	38 (26)
> 200 to ≤400 Gi/L	0	7 (5)
> 400 Gi/L	0	1 (<1)
Maximum post-baseline	n=144	n=140
<50 Gi/L	60 (41)	11 (8)
≥50 to ≤80 Gi/L	53 (36)	23 (16)
> 80 to ≤200 Gi/L	28 (19)	62 (43)
> 200 to ≤400 Gi/L	3 (2)	37 (26)
> 400 Gi/L	0	7 (5)
Adverse events (AEs) and serious adverse events (SAEs) with onset on or after the start date of study medication and up to 30 days after the last dose of study medication.		

Most Frequent Adverse Events – On-Therapy	Placebo	Eltrombopag
N (Safety)	145	143
Subjects with any adverse event; n(%)	85 (59)	79 (55)
Headache	6 (4)	11 (8)
Pyrexia	10 (7)	8 (6)
Abdominal pain	7 (5)	7 (5)
Diarrhoea	5 (3)	7 (5)
Nausea	7 (5)	7 (5)
International normalised ratio increased	3 (2)	6 (4)
Anaemia	1 (<1)	5 (3)
Epistaxis	3 (2)	5 (3)
Oedema peripheral	2 (1)	5 (3)
Pyuria	1 (<1)	5 (3)
Ascites	4 (3)	4 (3)
Portal vein thrombosis	1 (<1)	4 (3)
Vomiting	3 (2)	4 (3)
Activated partial thromboplastin time prolonged	0	3 (2)
Blood bilirubin increased	3 (2)	3 (2)
Cataract	5 (3)	3 (2)
Haemoglobin decreased	2 (1)	3 (2)
Hepatic encephalopathy	7 (5)	4 (3)
Hypertension	0	3 (2)
Mesenteric vein thrombosis	1 (<1)	3 (2)
Toothache	1 (<1)	3 (2)
Abdominal pain upper	5 (3)	2 (1)
Insomnia	3 (2)	2 (1)
Leukopenia	3 (2)	2 (1)
Urinary tract infection	5 (3)	2 (1)
Visual acuity reduced	1 (<1)	2 (1)
Sepsis	0	2 (1)
Proteinuria	1 (<1)	2 (1)
Hypoaesthesia	1 (<1)	2 (1)
Hyperbiliruinaemia	1 (<1)	2 (1)
Helicobacter infection	0	2 (1)
Gastroenteritis	1 (<1)	2 (1)
Dyspnoea	1 (<1)	2 (1)
Asthenia	2 (1)	2 (1)
Alanin aminotransferase increased	0	2 (1)
Haematoma	3 (2)	1 (<1)
Haematuria	4 (3)	1 (<1)
Dizziness	4 (3)	0
Myalgia	3 (2)	0
Rectal haemorrhage	3 (2)	0
Pruritis	3 (2)	0
Back pain	2 (1)	1 (<1)
Constipation	2 (1)	1 (<1)
Contusion	2 (1)	1 (<1)
Cough	2 (1)	1 (<1)
Dysuria	2 (1)	1 (<1)
Fatigue	2 (1)	1 (<1)
Serious Adverse Events - On-Therapy; n (%) [n considered by the investigator to be related to study medication]		
	Placebo	Eltrombopag
	n (%) [related]	n (%) [related]
N (Safety)	145	143
Subjects with any SAEs-Includes both fatal and non-fatal events	17 (12)	19 (13)

Portal vein thrombosis	1 (<1) [1]	4 (3) [4]
Mesenteric vein thrombosis	1 (<1) [1]	3 (2) [3]
Hepatic encephalopathy	3 (2)	2 (1)
Sepsis	0	2 (1) [1]
Gastroenteritis	1 (<1)	1 (<1)
Rectal haemorrhage	2 (1)	0
Cataract	3 (2) [3]	1 (<1) [1]
Encephalopathy	1 (<1)	1 (<1)
Gastric ulcer haemorrhage	1 (<1)	0
impaired gastric emptying	1 (<1)	0
nausea	1 (<1)	0
oesophageal varices	1 (<1)	0
peritonitis bacterial	1 (<1)	0
tuberculosis	1 (<1)	0
hepatorenal syndrome	1 (<1)	0
pneumothorax	1 (<1)	0
thrombocytopenia	1 (<1)	0
acute MI	1 (<1)	0
multi-organ failure	1 (<1)	0
orthostatic hypotension	1 (<1)	0
shock	1 (<1)	0
wound dehiscence	1 (<1)	0
renal failure acute	1 (<1)	0
abdominal pain	0	1 (<1)
appendix disorder	0	1 (<1)
ascites	0	1 (<1)
colitis ischaemic	0	1 (<1)
ileus paralytic	0	1 (<1)
intestinal perforation	0	1 (<1) [1]
oesophageal haemorrhage	0	1 (<1)
pancreatic acute	0	1 (<1)
peritonitis	0	1 (<1) [1]
upper GI haemorrhage	0	1 (<1)
appendicitis	0	1 (<1)
pneumonia	0	1 (<1)
pyelonephritis acute	0	1 (<1)
macular degeneration	0	1 (<1) [1]
visual acuity reduced	0	1 (<1) [1]
chronic hepatic failure	0	1 (<1) [1]
acute respiratory failure	0	1 (<1)
hepatic hydrothorax	0	1 (<1)
pneumonia aspiration	0	1 (<1)
thrombocytosis	0	1 (<1) [1]
atrial fibrillation	0	1 (<1)
pyrexia	0	1 (<1)
fluid retention	0	1 (<1)
B-cell lymphoma	0	1 (<1)
Subjects with fatal SAEs	2 (1)	3 (2)
Gastroenteritis	1 (<1)	0
Shock	1 (<1)	0
Multi-organ failure	1 (<1)	0
Sepsis	0	2 (1) [1]
Appendix disorder	0	1 (<1)
Upper gastrointestinal haemorrhage	0	1 (<1)
B-cell lymphoma	0	1 (<1)

Conclusion:
publication pending