

Study No: TPL111913
Title: TPL111913, a Multi-center, Open-label, Dose-ranging Phase II Study to Assess Efficacy, Safety and Pharmacokinetics of Eltrombopag in Japanese Thrombocytopenic Subjects with Chronic Liver Disease
Rationale: This was a study to assess the efficacy, safety and pharmacokinetics (PK) of eltrombopag in Japanese thrombocytopenic subjects with chronic liver disease (CLD).
Phase: II
Study Period: 06 Jan 2009 – 21 Aug 2009
Study Design: This was a multi-center, open-label, dose-ranging study to assess the efficacy, safety and pharmacokinetics of eltrombopag in Japanese thrombocytopenic subjects with CLD. This study consisted of Part A and Part B. Part B commenced after the safety and PK data of Part A were reviewed by the Safety Review Committee.
Centers: Ten centers in Japan
Indication: Thrombocytopenic subjects with chronic liver disease (CLD).
Treatment: This study consisted of Part A and Part B. Part A: Subjects were assigned to receive 12.5 mg eltrombopag once daily for 14 days. Part B: Subjects were randomly assigned either to receive 25 mg or 37.5 mg eltrombopag once daily for 14 or 21 days. Subjects with a platelet count <80 Gi/L on Day 15 received eltrombopag for an additional week (from Day 15 to Day 21 inclusive) if the subject agreed to it and the investigator considered it appropriate.
Objectives: To assess efficacy, safety and pharmacokinetics of eltrombopag in Japanese thrombocytopenic subjects with CLD. <u>Primary Objective:</u> To compare the effects of eltrombopag 12.5 mg, 25 mg and 37.5 mg on the change in platelet count from baseline (Visit 2), when administered once daily for 2 weeks to thrombocytopenic subjects with CLD (platelet count of <50 Gi/L).
Primary Outcome/Efficacy Variable: Change from baseline in platelet count on Day 15.
Secondary Outcome/Efficacy Variables: <i>Efficacy Variables:</i> Dose response, percent change from baseline in platelet count on Day 15, platelet counts by visit, change from baseline in platelet counts by visit and proportion of subjects with a shift from baseline in platelet count <50 Gi/L to ≥80 Gi/L on Day 15, and proportion of subjects with a shift from Day 15 in platelet count <80 Gi/L to ≥80 Gi/L on Day 22 when eltrombopag was administered for an additional week. <i>Safety and tolerability parameters:</i> Physical examination findings, blood pressure, heart rate, 12-lead electrocardiogram, ocular assessments, clinical laboratory tests, clinical monitoring/observation and adverse events (AEs) reporting. <i>PK variables:</i>

PK parameters of eltrombopag.

Statistical Methods:

Sample size:

The targeted number of subjects was 12 subjects in each cohort and 36 subjects in total. This study had not constructed statistical hypotheses, but had conducted an exploratory analysis of the dose-response. Based on the Monte-Carlo dose-response simulations of 12.5 mg, 25 mg and 37.5 mg, 12 subjects per group provide 90% power to detect a linear dose trend and saturation at a medium dose trend.

Analysis populations:

There were 5 analysis populations defined in this study:

The Full Analysis Set (FAS) was used as the primary population for analysis of efficacy and was defined as all enrolled subjects with the exception of: 1) those who received no doses of the study medication during the treatment period; 2) those without a baseline platelet assessment; and 3) those without at least one on-therapy (scheduled or unscheduled) platelet assessment.

The Per Protocol Set (PPS) consisted of FAS subjects who did not violate any inclusion or exclusion criteria, and who incurred no major protocol deviations pertaining to the assessment of treatment efficacy. The PPS was only used for supportive analyses of the primary and important secondary comparisons. The Safety Population consisted of all subjects who received at least one dose of the study medication. The PK Concentration Population was defined as all subjects from whom a PK sample was obtained and analyzed. The PK Parameter Population was defined as all subjects in the PK Concentration Population whose PK parameter data were evaluated

Efficacy analysis:

Primary Endpoint: Change from baseline in platelet count on Day15 was summarized by cohort. Point estimates were reported with associated two-sided 95% confidence intervals (CIs).

Secondary Endpoints:

Dose-response: As for the dose-response with the change in platelet count (12.5 mg, 25 mg and 37.5 mg), exploratory analyses were conducted using contrast methods. The data were analyzed using analysis of covariance (ANCOVA) with the platelet count at baseline as covariate. The data were also analyzed using ANCOVA with the platelet count at baseline and Child-Pugh class as covariate. The percent change from baseline in platelet count on Day 15 was summarized by cohort. Point estimates were reported with associated two-sided 95% CIs. The median platelet counts and the change from baseline in platelet counts at each assessment were summarized by cohort. The proportion of subjects with a shift from baseline in platelet count <50 Gi/L to ≥ 80 Gi/L on Day 15 was summarized by cohort. Point estimates were reported with exact two-sided 95% CIs. The proportion of subjects with a shift from Day 15 in platelet count <80 Gi/L to ≥ 80 Gi/L on

Day 22 was summarized when eltrombopag was administered for an additional week. Point estimates were reported with exact two-sided 95% CIs, if appropriate. PK analyses were performed in the 12.5 mg cohort.

Study Population: Male or female subjects ≥ 20 years of age with CLD, Child-Pugh score of ≤ 9 , baseline platelet count < 50 Gi/L, baseline serum sodium level > 130 mEq/L, hemoglobin concentration > 8 g/dL (stable for at least 4 weeks) at screening (Visit 1) and at the start of treatment (Visit 2) were eligible for inclusion in this study.

Number of Subjects:	Eltrombopag		
	12.5 mg	25 mg	37.5 mg
Planned, N	12	12	12
Randomised, N	12	14	12
Completed, n (%)	12 (100)	14 (100)	12 (100)
Total Number Subjects Withdrawn, N (%)	0	0	0
Demographics			
N (Safety Population/FAS)	12 (100)	14 (100)	12 (100)
Females: Males	4:8	4:10	4:8
Mean Age, years (SD)	62.2 (10.51)	57.7 (8.69)	66.3 (8.84)
Asian-Japanese heritage, n (%)	12 (100)	14 (100)	12 (100)

Primary Efficacy Results (FAS Population):

A summary of change from baseline in platelet count (Gi/L) on Day 15 is presented in the table below.

Visit	Statistic	Eltrombopag		
		12.5 mg	25 mg	37.5 mg
		N=12	N=14	N=12
Day 15	Mean	24.8	54.0	60.0
	95% CI	8.2, 41.4	28.2, 79.8	29.3, 90.7
	SD	26.13	44.70	48.36
	Median	22.0	38.5	48.0
	Min, Max	-9, 83	12, 187	8, 193

Secondary Outcome Variables:

Dose response (FAS Population):

Baseline platelet counts as covariate: The linearity and saturation at the medium dose was statistically significant, indicating that the effect of the treatment dose on platelet count was linear or saturate at the medium dose.

Baseline platelet counts and Child-Pugh class as covariate: The linearity and saturation at the medium dose was statistically significant, indicating that the effect of the treatment dose on platelet count was linear or saturate at the medium dose.

A summary of percent change from baseline in platelet count (Gi/L) on Day 15 (FAS Population) is presented in the table below:

Visit	Statistic	Eltrombopag		
		12.5 mg	25 mg	37.5 mg
		N=12	N=14	N=12
Day 15	Mean	57.86	134.57	158.45
	95% CI	18.77, 96.94	81.36, 187.78	92.32, 224.59
	SD	61.515	92.159	104.089
	Median	48.91	115.26	164.49
	Min, Max	-19.1, 193.0	41.3, 415.6	17.8, 393.9

A summary of platelet counts (Gi/L) by visit (FAS Population) is presented in the table below.

Visit	Statistic	Eltrombopag		
		12.5 mg	25 mg	37.5 mg
		N=12	N=14	N=12
Day 1	n	12	14	12
	Median	42.5	38.0	40.0
	Min, Max	36, 49	19, 48	23, 49
Day 8	n	12	14	12
	Median	50.5	49.5	52.0
	Min, Max	37, 73	27, 88	32, 87
Day 15	n	12	14	12
	Median	66.0	73.0	81.5
	Min, Max	37, 126	31, 232	53, 242
Day 22	n	NA	6	2
	Median	NA	82.5	72.5
	Min, Max	NA	35, 126	57, 88
Final Assessment Point ¹	n	12	14	12
	Median	66.0	95.5	85.5
	Min, Max	37, 126	35, 232	57, 242
Follow-Up 1 (Day 25)	n	12	13	11
	Median	63.5	100.0	109.0
	Min, Max	41, 173	38, 271	59, 372
Follow-Up 2 (Day 29)	n	12	13	12
	Median	67.5	119.0	120.0
	Min, Max	46, 178	40, 387	66, 376
Follow-Up 3 (Day 36)	n	11	13	11
	Median	65.0	87.0	97.0
	Min, Max	36, 157	29, 382	59, 295

1. Final Assessment Point is the last visit during treatment period, Day 15 or Day 22

A summary of change from baseline in platelet counts (Gi/L) by visit (FAS Population) is presented in the table below.

Visit	Statistic	Eltrombopag		
		12.5 mg	25 mg	37.5 mg
		N=12	N=14	N=12
Day 8	n	12	14	12
	Mean	6.9	14.6	15.4
	SD	9.43	11.80	8.96
	Median	4.5	12.0	14.0
	Min, Max	-3, 30	2, 42	7, 38

Day 15	n	12	14	12
	Mean	24.8	54.0	60.0
	SD	26.13	44.70	48.36
	Median	22.0	38.5	48.0
	Min, Max	-9, 83	12, 187	8, 193
Final Assessment Point ¹	n	12	14	12
	Mean	24.8	64.0	61.9
	SD	26.13	42.51	47.77
	Median	22.0	58.0	55.0
	Min, Max	-9, 83	16, 187	12, 193
Follow-Up 1 (Day 25)	n	12	13	11
	Mean	33.0	73.8	97.6
	SD	36.36	50.14	83.38
	Median	22.0	59.0	74.0
	Min, Max	-6, 130	19, 226	14, 323
Follow-Up 2 (Day 29)	n	12	13	12
	Mean	41.5	100.9	108.3
	SD	40.50	81.96	81.26
	Median	26.0	88.0	89.0
	Min, Max	0, 135	21, 342	21, 327
Follow-Up 3 (Day 36)	n	11	13	11
	Mean	35.7	82.2	83.0
	SD	36.58	83.13	68.31
	Median	26.0	52.0	67.0
	Min, Max	0, 114	10, 337	14, 246

1. Final Assessment Point is the last visit during treatment period, Day 15 or Day 22.

The number and proportion of responders¹ on Day15 (FAS Population) is presented in the table below.

Visit	Statistic	Eltrombopag		
		12.5 mg	25 mg	37.5 mg
		N=12	N=14	N=12
Day 15	n	12	14	12
	Number of responders ¹ (%)	3 (25)	6 (42.9)	7 (58.3)
	95% CI	5.5, 57.2	17.7, 71.1	27.7, 84.8

1. Responders: subject with a shift from baseline in platelet count <50 Gi/L to ≥80 Gi/L on Day 15.

The number and proportion of responders¹ on Day 22 (FAS Population) is presented in the table below.

Visit	Statistic	Eltrombopag	
		25 mg	37.5 mg
		N=14	N=12
Day 22	n	6	2
	Number of responders ¹ (%)	3 (50)	1 (50)
	95% CI	11.8, 88.2	1.3, 98.7

1. Responders: subjects with a shift from Day 15 in platelet count <80 Gi/L to ≥80 Gi/L on Day 22.

Safety Results: On-therapy AEs were defined as any events that occurred after subjects started

treatment and up to the stop date of eltrombopag. Off-therapy AEs were defined as events that occurred after the stop date of eltrombopag. On- and off-therapy AEs were defined as any events that occurred during this study. Occurrence of AEs was more in the off-therapy period compared to on-therapy period and there were no on-therapy AEs experienced by 2 or more subjects in any cohort. One SAE of ascites occurred during the on-therapy period and 2 SAEs including pleural effusion and portal vein thrombosis (in the same subject) occurred post study visit. This subject had a partial splenic embolization during the off-therapy period and the portal vein thrombosis occurred 21 days after the end of the treatment. The subject had a medical history of hepatocellular carcinoma, esophageal varices and liver cirrhosis. All the SAEs were reported in the 37.5 mg cohort and considered to be drug-related by the investigator.

A summary of on- and off-therapy AEs and SAEs on-therapy are presented in the table below.

Most Frequent Adverse Events – On- and off-Therapy	Eltrombopag						
	12.5 mg	25 mg	37.5 mg				
	N=12	N=14	N=12				
Subjects with any AE(s), n (%)	6 (50)	7 (50)	9 (75)				
Back pain	1 (8)	0	4 (33)				
Pyrexia	0	3 (21)	2 (17)				
Postoperative fever	3 (25)	0	2 (17)				
Pleural effusion	2 (17)	0	2 (17)				
Abdominal distension	1 (8)	0	2 (17)				
Ascites	1 (8)	0	2 (17)				
Procedural pain	2 (17)	0	1 (8)				
Alanine aminotransferase increased	2 (17)	1 (7)	0				
Aspartate aminotransferase increased	2 (17)	1 (7)	0				
Serious Adverse Events – On-Therapy							
n (%) [n considered by the investigator to be related to study medication]							
	Eltrombopag						
	12.5 mg	25 mg	37.5 mg				
	N=12	N=14	N=12				
Subjects with any SAE(s), n (%) [related]	0	0	1 (8)[1]				
Ascites	0	0	1 (8)[1]				
Subjects with fatal SAE(s), n (%) [related]	0	0	0				
Pharmacokinetics: A summary of log transformed PK parameters (Part A: 12.5 mg) is presented in the table below.							
Parameter	N	n	Geo. Mean ¹	95%CI of Geo. Mean		SD logs	%CVb ²
				Lower	Upper		
C _{max} (ng/ml)	12	11	3412.999	2549.0060	4569.8448	0.4345	45.6
T _{max} (h)	12	11	3.444	2.4593	4.8226	0.5012	53.4
AUC _(0-t) (h*ng/mL)	12	11	65244.180	46617.4188	91313.5730	0.5004	53.3
AUC ₍₀₋₂₄₎ (h*ng/mL)	12	11	65235.699	46748.123	91034.594	0.4960	52.8
1. Geometric mean							

2. CVb= Between subject variability

Conclusions:

Efficacy:

- Eltrombopag increases platelet counts in thrombocytopenic subjects with CLD (platelet counts <50 Gi/L) in a dose dependent manner.
- The effect of the eltrombopag treatment on platelet count was linear or saturate at the medium dose.
- The median platelet counts in all the cohorts increased towards the follow-up 2 (Day 29) and remained higher in follow-up 3 (Day 36) than baseline.
- The number of subjects with a shift from baseline in platelet count <50 Gi/L to ≥ 80 Gi/L on Day 15 was 3 (25%) in the 12.5 mg cohort, was 6 (42.9%) in the 25 mg cohort and was 7 (58.3%) in the 37.5 mg cohort.
- The number of subjects with a shift from Day 15 in platelet count <80 Gi/L to ≥ 80 Gi/L on Day 22 was 3 (50%) in the 25 mg cohort and was 1 (50%) in the 37.5 mg cohort.

Safety:

- The most common AEs noted during the study were back pain, pyrexia, postoperative fever and pleura effusion; these events occurred during off-therapy and were considered to be associated with invasive procedure. None of these events increased in incidence in a dose-dependent manner.
- Majority of the AEs were reported during off-therapy and were of mild to moderate intensity.
- A total of 2 subjects experienced the SAEs in this study and 3 SAEs were reported. All the SAEs were reported in the 37.5 mg cohort. One SAE of ascites occurred in on-therapy period and 2 SAEs including pleural effusion and portal vein thrombosis occurred post study visit.
- No subject was withdrawn from the study due to AEs.

Pharmacokinetics:

- C_{max} and $AUC_{(0-24)}$ (Geometric mean [95%CI]) of the 12.5 mg cohort were 3413.0 (2549.0, 4569.8) ng/mL and 65235.7 (46748.1, 91034.6) h*ng/mL, respectively.