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<b>Study No:</b> TRA103452
<b>Title :</b> An Open-Label, Non-Randomized Pharmacokinetic and Safety Study of a Single Oral Dose of 50 mg Eltrombopag in Healthy Subjects and in Volunteers with Mild, Moderate or Severe Hepatic Impairment
<b>Rationale:</b> The pharmacokinetics (PK) of a single oral dose of 50 mg eltrombopag in subjects with hepatic impairment and a group of healthy subjects matched to the moderate group will be evaluated in order to determine dosing recommendations for patients with liver disease.
<b>Phase:</b> I
<b>Study Period:</b> 18Apr2006 – 07Mar2007
<b>Study Design:</b> A Phase I, open-label, parallel-group study in which each subject received a single 50 mg oral dose of eltrombopag.
<b>Centres:</b> Two centers in Australia, one center in New Zealand and two centers in US.
<b>Indication:</b> Thrombocytopenia
<b>Treatment:</b> Subjects were to be administered a single 50 mg oral dose of eltrombopag. No further dosing was required.
<b>Objectives:</b> <b>Primary Objective:</b> <ul style="list-style-type: none"> <li>To compare the PK of a single 50 mg oral dose of eltrombopag in subjects with hepatic impairment (mild, moderate or severe) versus healthy control subjects.</li> </ul> <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>To describe the tolerability of a single 50 mg oral dose of eltrombopag in normal subjects and those with hepatic impairment.</li> <li>To assess the effect of hepatic impairment on the plasma protein binding of eltrombopag.</li> </ul> <b>Primary Endpoint:</b> <ul style="list-style-type: none"> <li>AUC(0-inf) and Cmax of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.</li> </ul> <b>Secondary Endpoints:</b> <ul style="list-style-type: none"> <li>AUC(0-t) of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.</li> <li>tmax of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.</li> <li>t<sub>1/2</sub> of eltrombopag following a single 50 mg oral dose in subjects with mild, moderate or severe hepatic impairment and healthy control subjects.</li> <li>Free fraction (% unbound) of eltrombopag.</li> <li>Evaluation of AEs and changes in vital signs and laboratory values from baseline.</li> </ul>
<b>Statistical Methods:</b> Following log <sub>e</sub> - transformation, AUC and Cmax were separately analyzed by analysis of variance (ANOVA), fitting terms for group. The endpoints were compared between healthy subjects and subjects with each level (mild, moderate or severe) of hepatic impairment. The comparisons were evaluated by the differences in least squares means between groups, respectively and the corresponding 90% confidence intervals (CI). Point and interval estimates of the differences in means were exponentiated to give corresponding point and 90% CI estimates of the ratios of geometric means of the PK parameters.
<b>Safety Analyses</b> Safety data are listed and summarized.
<b>Study Population:</b> Subjects were male or female, 18 to 65 years of age (inclusive), of any ethnic origin, BMI of 19 – 37 kg/m <sup>2</sup> , and considered to be either healthy or with a degree of hepatic impairment (mild, moderate or severe). The degree of hepatic impairment was based on clinical history and assessed using the criteria in the Child-Pugh classification of liver disease. Subjects with mild hepatic impairment were defined by a Child-Pugh score of 5 to 6. Subjects with moderate hepatic impairment were defined by a Child-Pugh score of 7 to 9. Subjects with severe hepatic impairment were defined by a Child-Pugh score of > 9.

Number of Subjects (n, %)	Healthy Subjects	Hepatic Impairment Subjects			Total
		Mild	Moderate	Severe	
Number of Subjects Planned, N:	8	8	8	8	32
Number of Subjects Enrolled, N:	8	8	8	9	33
Number of Subjects included in Safety analysis:	8 (100%)	8 (100%)	8 (100%)	9 (100%)	33 (100%)
Number of Subjects included in PK analysis:	8 (100%)	8 (100%)	8 (100%)	8 (89%)	32 (97%)
Number of Subjects Completed:	8 (100%)	8 (100%)	8 (100%)	9 (100%)	33 (100%)
Number of Subjects Withdrawn (any reason):	0	0	0	0	0
Demographics	Healthy Subjects	Hepatic Impairment Subjects			Total
		Mild	Moderate	Severe	
<b>Age: Median (range)</b>					
Adults (18 to 65 yrs, inclusive),:	53.0 (38–59)	55.5 (43-59)	51.5 (41-64)	50.0 (43-60)	51.0 (38–64)
<b>Sex</b>					
Female, n (%):	1 (12%)	0	1 (12%)	1 (11%)	3 (9%)
Male, n (%):	7 (88%)	8 (100%)	7 (88%)	8 (89%)	30 (91%)
<b>Ethnicity</b>					
Hispanic or Latino:	1 (12%)	0	2 (25%)	0	3 (9%)
Not Hispanic or Latino:	7 (88%)	8 (100%)	6 (75%)	9 (100%)	30 (91%)
<b>Race</b>					
African American/African Heritage:	1 (13%)	0	0	0	1 (3%)
American Indian or Alaskan Native	1 (13%)	0	0	0	1 (3%)
Asian – Central/South Asian Heritage	0	1 (13%)	0	0	1 (3%)
Native Hawaiian or Other Pacific Islander	0	1 (13%)	0	0	1 (3%)
White – White/Caucasian/European Heritage:	6 (75%)	6 (75%)	8 (100%)	9 (100%)	29 (88%)

**Pharmacokinetics (PK):**

Following a single, oral 50 mg dose of eltrombopag, moderate to high-between-subject variability was observed in the PK parameters and variability in AUC(0-inf) and Cmax appeared to increase and tmax was delayed with increasing severity of hepatic impairment.

Parameter	Healthy Subjects (N=8)	Hepatic-Impaired Subjects		
		Mild (N=8)	Moderate (N=8)	Severe (N=8)
AUC(0-t) <sup>a</sup> (ng.h/mL)	61,377 (59.2)	82,661 (41.6)	107,835 (54.3)	99,331 (83.3)
AUC(0-∞) <sup>a</sup> (ng.h/mL)	66,026 (57.9)	92,814 (42.9)	127,211 (60.9)	118,752 (83.0)
Cmax <sup>a</sup> (ng/mL)	5,427 (47.0)	4,677 (49.5)	3,843 (63.3)	2,754 (86.9)
t1/2 <sup>a</sup> (h)	21.3 (39.9)	36.4 (56.7)	44.4 (34.4)	45.6 (12.3)
Tmax <sup>b</sup> (h)	3.00 (2.5, 6.0)	3.46 (2.5, 4.0)	4.90 (2.0, 7.0)	4.00 (3.0, 8.0)

a. Geometric mean (Coefficient of variation as a percentage [CVb%])

b. Presented as median and (minimum, maximum).

Plasma eltrombopag AUC(0-∞) and t1/2 values were higher in subjects with mild, moderate or severe hepatic impairment than healthy subjects, with moderate and severe hepatic impaired subjects having the highest values. However, there was significant overlap in the data, particularly for AUC(0-∞), between the groups. In contrast, Cmax values appeared to decrease with increasing severity of hepatic impairment.

Parameter	Comparison (Test/Reference)	Ratio	90% CI
AUC(0-∞) (ng·h/mL)	Severe/Healthy <sup>a</sup>	1.80	(1.11, 2.92)
	Moderate/Healthy <sup>a</sup>	1.93	(1.19, 3.13)
	Mild/Healthy	1.41	(0.87, 2.28)
Cmax (ng/mL)	Severe/Healthy <sup>a</sup>	0.51	(0.31, 0.83)
	Moderate/Healthy	0.71	(0.43, 1.15)
	Mild/Healthy	0.86	(0.53, 1.40)
t1/2 (h)	Severe/Healthy <sup>a</sup>	2.14	(1.56, 2.93)
	Moderate/Healthy <sup>a</sup>	2.08	(1.52, 2.86)
	Mild/Healthy <sup>a</sup>	1.71	(1.24, 2.34)

a. Considered statistically significant based on CIs that do not include 1.0.

Safety results:				
An on-therapy adverse event (AE) or serious adverse event (SAE) was defined as an AE or SAE occurring from the time a subject provides consent to the study and continuing through the 14-day follow-up visit.				
Adverse Events (AEs):				
Most Frequent AEs	Healthy (N = 8)	Hepatic Impaired – Mild (N = 8)	Hepatic Impaired – Moderate (N = 8)	Hepatic Impaired – Severe (N = 9)
Back Pain	1 (13%)	1 (13%)	2 (25%)	0
Mylagia	2 (25%)	0	0	0
Headache	2 (25%)	1 (13%)	1 (13%)	3 (33%)
Nausea	2 (25%)	0	1 (13%)	0
Diarrhea	1 (13%)	0	1 (13%)	0
Drug-Related AEs	Healthy (N = 8)	Hepatic Impaired – Mild (N = 8)	Hepatic Impaired – Moderate (N = 8)	Hepatic Impaired – Severe (N = 9)
Back Pain	1 (13%)	0	0	0
Mylagia	1 (13%)	0	0	0
Pain in Extremity	1 (13%)	0	0	0
Nausea	2 (25%)	0	0	0
Diarrhea	1 (13%)	0	0	0
Asthenia	0	0	1 (13%)	0
Chills	0	1 (13%)	0	0
Hypoglycemia	0	0	1 (13%)	0
Serious Adverse Events:				
There were no serious adverse events or deaths reported during this study.				

Publications: None at the time of this report.