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Study No: TRA102860
Title : A Two-Part, Randomized, Placebo-Controlled Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of Single, Oral Doses of the Thrombopoietin Receptor Agonist, Eltrombopag; and the Effect of Eltrombopag on Cardiac Repolarization as Compared to Placebo and Single Oral Doses of Moxifloxacin in Healthy Adult Subjects
Rationale: This study was performed in two parts in healthy volunteers. Part 1 evaluated the safety, PK and PD of escalating doses of eltrombopag. Part 2 evaluated the potential effects of eltrombopag on the QTc interval, a thorough QTc study performed in consideration of the ICH E14 guideline
Phase: I
Study Period: Part 1: 13 March 2006 – 07 August 2006; Part 2: 09 March 2007 – 02 August 2007
Study Design: Part 1: double-blind, placebo-controlled, randomized, parallel, repeat dose escalation study conducted in healthy adult subjects. Part 2: double-blind, placebo and active (moxifloxacin) controlled, randomized, balanced cross-over study conducted in healthy adult subjects.
Centres: Part 1: two centers in the US; Part 2: three centers in the US.
Indication: Thrombocytopenia
Treatment: Part 1: subjects received a single dose of placebo or either 100 mg, 150 mg or 200 mg of eltrombopag as five daily oral doses. Part 2: each subject received each of following four regimens in a randomized, crossover fashion: <ul style="list-style-type: none"> • Treatment A: eltrombopag 50 mg QD for five days + placebo for moxifloxacin on Day 5. • Treatment B: eltrombopag 150 mg QD for five days + placebo for moxifloxacin on Day 5. • Treatment C: placebo for eltrombopag QD for five days + placebo for moxifloxacin on Day 5. • Treatment D: placebo for eltrombopag QD for five days + moxifloxacin 400 mg (single dose) on Day 5.
Objectives: Part 1: The primary objective was to assess the safety and tolerability of eltrombopag in healthy adult subjects after five daily oral doses of 100 mg, 150 mg and 200 mg. Part 2: The primary objective was to determine the effect of repeat daily doses of 50 mg and 150 mg eltrombopag (therapeutic and supratherapeutic doses respectively) on QTcF as compared to placebo and an active comparator.
Statistical Methods: Part 1: Following loge-transformation, AUC(0- τ) (for the purpose of estimating Ro) and Cmax (for the purpose of estimating R[Cmax]), for each treatment, were analyzed using a mixed effect model, fitting fixed effect terms for day and fitting subject as random effect. Point estimates and corresponding 90% CIs for the difference between Day 5 and Day 1 for each treatment were separately constructed using the residual variance. The point estimates and corresponding 90% CIs were then back-transformed to provide 90% CIs for the ratios of the geometric means for the comparisons of interest (e.g., Ro and R[Cmax]). Dose proportionality was assessed by fitting the Power Model, relating log-transformed plasma eltrombopag repeat dose AUC(0- τ) and Cmax to log-transformed dose (log-transformed pharmacokinetic parameter = $\alpha + \beta * \log$ -transformed dose), by restricted maximum likelihood using SAS Version 8.2 MIXED procedure. The common slope was estimated and the associated 90% CI was constructed to examine dose proportionality. Platelet count, peripheral blood smear, and platelet aggregation were descriptively summarized by treatment and time point. Maximum platelet counts from active dose group were compared to those from placebo using analysis of covariance. No formal statistical analyses were performed for platelet aggregation and peripheral blood smear. Safety parameters including AEs, clinical laboratory evaluations, physical examination findings, vital sign measurements, and 12-lead ECG results were listed and summarized by treatment. Part 2: The primary endpoint changes from baseline QTcF were analyzed by mixed effect analysis of covariance (ANCOVA) fitting terms appropriate to the study design, including sequence, period, regimen, time and time-by-regimen interaction as fixed effects and subject as a random effect. Baseline QTcF was included in the model as a covariate. Point estimates and 90% CIs were constructed for the difference, active-placebo, for 50 mg eltrombopag and 150 mg eltrombopag at each time point using the residual variance. A lack of effect on the QTcF interval was pre-specified as the upper 90% CI value less than 10 msec for all timepoints and assay sensitivity was pre-specified as the lower 90% CI values, from the comparison moxifloxacin-placebo, greater than 5 msec for at least one timepoint.

Replicates at each time point were averaged first prior to the analysis.
 An outlier analysis to determine the number and percentage of subjects in which an increase from baseline in QTc greater than 30 msec and 60 msec occurred for each regimen was performed when appropriate. Individual subjects who had a QTc value greater than or equal to 450, 480, and 500 msec were summarized for each regimen. All above calculations were done for replicated ECGs also.
 Secondary endpoints (including change from baseline QTcB and QTci) were similarly analyzed.
 Maximum platelet counts from active dose group were compared to those from placebo using mixed effect analysis of covariance.

Study Population

Number of Subjects: - Part 1	Placebo N=6	Eltrombopag			Total (N=33)
		100 mg N=10	150 mg N=9	200 mg N=8	
Planned, N ¹	6	8	8	8	30
Enrolled, N	6	10	9	8	33
Completed, n (%)	6 (100)	8 (80)	8 (89)	7 (88)	29 (88)
Total Number Subjects Withdrawn, n (%)	0	2 (20)	1 (11)	1 (13)	4 (12)
Withdrawn Due to Adverse Events, n (%)	0	1 (10)	1 (11)	0	2 (6)
Withdrawn Due to Lack of Efficacy, n (%)	0	0	0	0	0
Withdrawn for Other Reasons, n (%)	0	1 (10)	0	1 (13)	2 (6)
Demographics					
N (Safety)	6	10	9	8	33
Females: Males	1:5	5:5	4:5	5:3	15:18
Mean Age in Years (SD)	26.3 (7.91)	24.9 (6.19)	36.8 (12.5)	29.4 (8.48)	29.5 (9.96)
Mean Weight in Kg (SD)	70.9 (11.5)	72.0 (12.2)	73.9 (13.8)	73.3 (8.75)	72.6 (11.3)
White n (%)	4 (67)	6 (60)	6 (67)	6 (75)	22 (67)

1. A sufficient number of subjects were to be enrolled to ensure at least 8 subjects completed each eltrombopag dose level in Part 1 of the study.

Number of Subjects - Part 2:	Treatment Sequence ¹				Total
	DCAB	ADBC	BACD	CBDA	
Dosed, N	21	20	23	23	87
Completed, n (%)	14 (67)	11 (55)	11 (48)	12 (52)	48 (55)
Total Number Subjects Withdrawn, n (%)	7 (33)	9 (45)	12 (52)	11 (48)	39 (45)
Withdrawn Due to Adverse Events, n (%)	2 (10)	3 (15)	1 (4)	0	6 (7)
Withdrawn Due to Lack of Efficacy, n (%)	0	0	0	0	0
Withdrawn for Other Reasons, n (%)	5 (24)	6 (30)	11 (48)	11 (48)	33 (38)

1. Treatment Sequence:

A: 50mg eltrombopag QD for five days + Placebo for moxifloxacin on Day 5

B: 150mg eltrombopag QD for five days + Placebo for moxifloxacin on Day 5

C: placebo for eltrombopag QD for five days + Placebo for moxifloxacin on Day 5

D: placebo for eltrombopag QD for five days + 400 mg moxifloxacin on Day 5

Demographics	Total N=87
N (Total)	87
Females: Males	25:62
Mean Age in Years (SD)	29.9 (9.17)
Mean Weight in Kg (SD)	76.4 (11.5)
White n (%)	62 (71)

Pharmacokinetics (PK) Endpoints:**Summary of Plasma Eltrombopag PK Parameters in Study TRA102860 Part 1**

Day	Dose (mg)	N	AUC (0- τ) ($\mu\text{g hr/mL}$)	C _{max} ($\mu\text{g/mL}$)	t _{max} (h)
1	100	8	96.6 (78.7, 119) [25.0]	10.3 (8.31, 12.8) [26.2]	3.50 (2.00, 6.00)
	150	8	142 (104, 193)	17.3 (12.4, 24.1)	

2.28
(1.50, 6.00)

			[38.6]	[41.5]	
	200	7	167 (121, 231) [36.2]	18.3 (11.6, 28.8) [52.3]	4.00 (2.50, 4.00)
5	100	8	161 (116, 222) [40.0]	14.9 (10.9, 20.4) [38.7]	3.01 (2.50, 4.00)
	150	8	239 (187, 304) [29.6]	22.8 (18.2, 28.5) [27.3]	2.75 (1.50, 4.00)
	200	7	302 (198, 463) [48.5]	24.8 (16.2, 37.7) [48.1]	2.50 (2.50, 3.00)

Data presented as geometric mean (95% CI) [CVb%], except tmax presented as median (minimum, maximum)

Summary of Plasma Eltrombopag PK Parameters in Study TRA102860 Part 2

Day	Dose (mg)	N	AUC(0- τ) ($\mu\text{g hr/mL}$)	Cmax ($\mu\text{g/mL}$)	C τ ($\mu\text{g/mL}$)	tmax (h)
5	50	60	65.4 (59.7, 71.6) [36.4]	6.40 (5.87, 6.97) [34.2]	1.19 (1.05, 1.34) [51.2]	3.19 (2.17, 6.22)
	150	73	204 (186, 223) [39.3]	19.0 (17.4, 20.6) [37.5]	4.07 (3.64, 4.55) [50.3]	2.67 (1.67, 6.20)

Data presented as geometric mean (95% CI) [CVb%], except tmax presented as median (minimum, maximum)

Summary of Plasma Moxifloxacin PK Parameters in Study TRA102860 Part 2

Dose (mg)	N	AUC(0-t) ($\mu\text{g hr/mL}$)	Cmax ($\mu\text{g/mL}$)	tmax (h)
400	60	22.6 (21.4, 23.9) [21.1]	2.05 (1.93, 2.18) [23.7]	2.17 (0.63, 6.17)

Data presented as geometric mean (95% CI) [CVb%], except tmax presented as median (minimum, maximum)

Pharmacodynamics (PD) Endpoints:

Summary of Statistical Analysis of QTc Time-Matched Change from Baseline Treatment Comparisons, Mean Difference (90% CI), for eltrombopag

Treatment Difference from Placebo and 90% CI (msec)

Time	QTcF		QTcB		Qtci	
Time (hr)	50 mg eltrombopag	150 mg eltrombopag	50 mg eltrombopag	150 mg eltrombopag	50 mg eltrombopag	150 mg Eltrombopag
-0.5	0.24 (-1.83, 2.32)	-1.64 (-3.66, 0.38)	0.48 (-2.23, 3.20)	-2.52 (-5.16, 0.13)	0.88 (-1.16, 2.91)	-1.70 (-3.68, 0.29)
0.5	-0.63 (-2.65, 1.40)	-1.02 (-2.99, 0.94)	-1.35 (-3.99, 1.30)	-1.05 (-3.63, 1.52)	-0.46 (-2.45, 1.53)	-1.07 (-3.00, 0.86)
1	-0.03 (-2.04, 1.98)	2.29 (0.34, 4.24)	-1.03 (-3.64, 1.61)	2.36 (-0.19, 4.90)	-0.43 (-2.40, 1.55)	2.16 (0.24, 4.07)
2	1.54 (-0.47, 3.55)	1.86 (-0.09, 3.81)	1.23 (-1.40, 3.86)	2.32 (-0.23, 4.86)	1.59 (-0.38, 3.57)	1.80 (-0.11, 3.71)
3	1.52 (-0.49, 3.53)	0.79 (-1.16, 2.75)	1.87 (-0.76, 4.50)	0.98 (-1.58, 3.53)	0.89 (-1.08, 2.87)	0.36 (-1.56, 2.28)
4	0.23 (-1.79, 2.25)	0.10 (-1.83, 2.04)	-1.10 (-3.74, 1.54)	-0.43 (-2.96, 2.11)	-0.01 (-2.00, 1.97)	-0.23 (-2.13, 1.68)
6	1.36 (-0.69, 3.41)	1.95 (-0.02, 3.93)	2.78 (0.10, 5.46)	1.68 (-0.90, 4.26)	1.17 (-0.84, 3.18)	2.05 (0.11, 3.99)
12	1.06 (-0.97, 3.08)	0.17 (-1.76, 2.10)	1.43 (-1.23, 4.06)	0.07 (-2.45, 2.59)	1.44 (-0.55, 3.42)	0.80 (-1.10, 2.69)
23.25	-0.53 (-2.55, 1.49)	0.03 (-1.92, 1.99)	-1.42 (-4.06, 1.22)	0.61 (-3.16, 1.95)	-0.10 (-2.08, 1.88)	-0.21 (-2.13, 1.71)

Summary of Statistical Analysis of QTc Time-Matched Change from Baseline Treatment Comparisons, Mean Difference (90% CI), for 400 mg Moxifloxacin				
Treatment Difference from Placebo and 90% CI (msec)				
Time (hr)	QTcF	QTcB	QtcI	
-0.5	0.69 (-1.34, 2.72)	-0.08 (-2.73, 2.58)	0.80 (-1.19, 2.80)	
0.5	5.05 (3.06, 7.04)	6.12 (3.52, 8.72)	4.96 (3.00, 6.91)	
1	9.85 (7.87, 11.8)	11.59 (8.99, 14.19)	9.52 (7.56, 11.47)	
2	10.6 (8.64, 12.6)	10.98 (8.39, 13.56)	10.43 (8.49, 12.38)	
3	11.2 (9.17, 13.2)	11.05 (8.45, 13.65)	10.68 (8.73, 12.64)	
4	11.6 (9.64, 13.6)	10.95 (8.34, 13.56)	10.98 (9.02, 12.94)	
6	8.07 (6.06, 10.1)	8.09 (5.47, 10.71)	8.11 (6.14, 10.08)	
12	6.71 (4.71, 8.71)	7.11 (4.49, 9.72)	6.76 (4.79, 8.72)	
23.25	5.25 (3.23, 7.26)	3.09 (0.45, 5.73)	5.41 (3.43, 7.39)	
Summary of Statistical Analysis of Maximum Platelet Count				
Treatment Comparison	Ratio (95% CI)	p-value	%CVw	
50 mg vs Placebo	1.10 (1.04, 1.16)	0.0014	14.97	
150 mg vs Placebo	1.31 (1.24, 1.38)	<0.0001	--	
Summary of Maximum Increase from Baseline Platelet Count (X10 ⁹ /L)				
Parameter	Placebo N=64	Eltrombopag		Moxifloxacin 400 mg N=63
		50 mg N=62	150 mg N=77	
Mean (SD)	16.3 (32.7)	47.5 (44.2)	110 (79.9)	13.0 (32.0)
Median (Range)	8.0 (-58, 96)	46.0 (-39, 182)	116 (-69, 256)	5.5 (-63, 123)
PK/PD Endpoints:				
Final Parameters Estimates from Plasma Eltrombopag Concentration-ddQTcF NONMEM Analysis				
Parameter	Description	Estimate (RSE%) ¹	Bootstrap median (90% CI) ²	Unit
Θ_1	pre-dose ddQTcF (intercept)	-0.792 (138)	-0.860 (-2.49, 1.05)	msec
ω_1	Inter-individual variability for intercept	32.6 (24)	30.9 (18.3, 43.2)	msec
ω_{3-4}	Inter-occasion variability for intercept	12.1 (52)	12.2 (3.50, 22.0)	msec
Θ_2	slope relating plasma eltrombopag concentration to ddQTcF	0.120 (63)	0.115 (-0.014, 0.245)	msec/ μ g/mL
ω_2	Inter-individual variability for slope	0.00652 (1718)	1.30×10^{-8} (8.47×10^{-12} , 0.0897)	msec/ μ g/mL
ω_{5-6}	Inter-occasion variability for slope	0.0392 (263)	0.0120 (8.32×10^{-11} , 0.0837)	msec/ μ g/mL
σ	random residual error	96.7 (8)	96.8 (84.6, 109)	
1. All estimates of random-effect parameters are variances, and the units represent the unit of the η and ε estimate from that distribution. RSE = relative standard error (standard error/estimate x 100%)				
2. 500 bootstrap runs.				
Summary of Simulated ddQTcF at C _{max} for Therapeutic and Supratherapeutic Eltrombopag Doses				
Dose (mg) QD	Plasma eltrombopag C _{max} (μ g/mL)	Predicted ddQTcF (msec)		

	mean (95% CI)	mean (90% CI) ¹
50	6.72 (6.35, 7.10)	0.02 (-1.92, 2.42)
150	20.2 (19.0, 21.3)	1.60 (-0.50, 4.03)
300 ²	40.3 (38.1, 42.6)	4.03 (1.55, 6.79)

- Based on 1000 study simulations per dose level
(n=60 subjects for 50 mg, n=73 subjects for 150 mg, n=81 subjects for 300 mg per simulation)
- Simulations extrapolated beyond range of observed data ; dose proportionality and constant coefficient of variation assumed

Safety results:

	Placebo N=6	Eltrombopag			Total N=33
		100 mg N=10	150 mg N=9	200 mg N=8	
Adverse Events – Part 1:	n (%)	n (%)	n (%)	n (%)	n (%)
No. subjects with Any AE	3 (50)	7 (70)	8 (89)	6 (75)	24 (73)
Headache	2 (33)	1 (10)	2 (22)	4 (50)	9 (27)
Dermatitis contact	0	1 (10)	4 (44)	1 (13)	6 (18)
Vessel puncture site hemorrhage	3 (50)	1 (10)	1 (11)	0	5 (15)
Ecchymosis	1 (17)	1 (10)	1 (11)	0	3 (9)
Vessel puncture site hematoma	0	0	3 (33)	0	3 (9)
Nausea	1 (17)	1 (10)	0	1 (13)	3 (9)
Conjunctivitis	0	1 (10)	1 (11)	0	2 (6)
Vomiting	1 (17)	1 (10)	0	0	2 (6)
Urinary tract infection	0	1 (10)	1 (11)	0	2 (6)
Excoriation	0	0	1 (11)	1 (13)	2 (6)

	Placebo N=64	Eltrombopag		Moxifloxacin 400 mg N=63
		50 mg N=62	150 mg N=77	
Adverse Events – Part 2	n (%)	n (%)	n (%)	n (%)
No. subjects with Any AE	37 (58)	41 (66)	45 (58)	33 (52)
Application site dermatitis ¹	6 (9)	9 (15)	11 (14)	9 (14)
Ecchymosis ¹	8 (13)	10 (16)	9 (12)	5 (8)
Headache	7 (11)	7 (11)	10 (13)	8 (13)
Contusion	6 (9)	2 (3)	4 (5)	1 (2)
Vessel puncture site hemorrhage	4 (6)	4 (6)	4 (5)	4 (6)
Blood creatine phosphokinase increased	3 (5)	1 (2)	4 (5)	4 (6)
Excoriation	3 (5)	4 (6)	1 (1)	2 (3)
Application site erythema ¹	2 (3)	2 (3)	0	2 (3)
Application site pruritus ¹	2 (3)	1 (2)	1 (1)	1 (2)
Pain in extremity	2 (3)	1 (2)	0	1 (2)
Vision blurred	2 (3)	1 (2)	0	1 (2)
Dermatitis contact	1 (2)	0	0	3 (5)
Nausea	1 (2)	2 (3)	3 (4)	4 (6)
Diarrhea	1 (2)	2 (3)	4 (5)	0
Hematuria	1 (2)	0	3 (4)	0
Dizziness	0	2 (3)	1 (1)	5 (8)
Atrioventricular block second degree	0	4 (6)	1 (1)	2 (3)
Abdominal pain	0	1 (2)	4 (5)	1 (2)
Pharyngolaryngeal pain	0	2 (3)	2 (3)	0
Fatigue	0	1 (2)	1 (1)	2 (3)
Rhinorrhea	0	0	2 (3)	2 (3)
Dermatitis	0	3 (5)	0	0
Musculoskeletal chest pain	0	1 (2)	0	2 (3)
Ventricular extrasystoles	0	1 (2)	0	2 (3)

1. These AEs were related to ECG electrode placements					
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:					
Serious Adverse Events – Part 1:	Placebo N=6	Eltrombopag			Total N=33
		100 mg N=10	150 mg N=9	200 mg N=8	
	n (%)	n (%)	n (%)	n (%)	n (%)
No. subjects with Any SAE	0	0	0	0	0
Serious Adverse Events – Part 2	Placebo N=64	Eltrombopag		Moxifloxacin 400 mg N=63	
		50 mg N=62	150 mg N=77		
	n (%)	n (%)	n (%)	n (%)	
No. subjects with Any SAE	0	0	0	0	

Publications: None at the time of this report
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