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<b>Study No:</b> TRA106914
<b>Title :</b> A Double Blind Placebo Controlled Study to Investigate the Phototoxic Potential of Eltrombopag in Healthy Subjects
<b>Rationale:</b> An in vitro phototoxicity test using BALB/C 3T3 fibroblast neutral red uptake revealed that eltrombopag induced a concentration dependent phototoxicity. These results indicate a potential for eltrombopag-induced photoirritation in the presence of ultraviolet A (UVA, 315 to 400nm) light. This study was, therefore, conducted to assess the phototoxic potential of eltrombopag in humans.
<b>Phase:</b> 1
<b>Study Period:</b> 07 Mar 2008 – 24 Sep 2008
<b>Study Design:</b> A double blind for eltrombopag and observer blind for ciprofloxacin, placebo and positively controlled, randomized, parallel group study
<b>Centres:</b> One center in the United Kingdom
<b>Indication:</b> Thrombocytopenia
<b>Treatment:</b> Subjects received one of the following study medications in multiple oral doses over 6 days: <ul style="list-style-type: none"> <li>• Eltrombopag 75 mg QD</li> <li>• Placebo to match eltrombopag</li> <li>• Ciprofloxacin 500 mg BID</li> </ul>
<b>Objectives:</b> Primary Objective: <ul style="list-style-type: none"> <li>• Evaluate the photosensitising potential of eltrombopag as measured by phototoxic index (PI) and change from baseline in minimum erythema dose (MED) when dosed orally at 75 mg once daily (QD) as compared to placebo and a positive control, ciprofloxacin 500 mg twice daily (BID)</li> </ul>
<b>Statistical Methods:</b> Non-parametric methods were used to describe and to analyze the data for the following reasons: <ul style="list-style-type: none"> <li>• there was evidence of non-normality in most treatment groups across the wavebands for MED and PI due to the fact that nominal erythema doses were tested</li> <li>• some of subjects provided censored MED values if no skin response was observed through all tested erythema doses.</li> </ul> <p>Descriptive statistics did not include mean and 95% CIs, but included lower and upper quartiles. For wavelengths where greater than 75% of the data were censored (imputed with next incremental dose) or less than three subjects provided non-censored data values, summary statistics were not displayed. Hodges-Lehman estimate was calculated to provide the median difference and corresponding distribution free confidence interval (CI) were calculated based on Wilcoxon's Rank Sum Test.</p>
<b>Study Population:</b> Healthy adult male and female subjects.

Number of Subjects	Eltrombopag	Placebo	Ciprofloxacin
Number of subjects planned, N:	12	12	12
Number of subjects randomized, N:	12	12	12
Number of subjects included in All subjects (safety) population, n (%):	12	12	12
Number of subjects completed as planned, n (%):	12	12	12
Number of subjects withdrawn (any reason), n (%):	0	0	0
Number of subjects withdrawn for SAE, n (%):	0	0	0
Number of subjects withdrawn for AE, n (%):	0	0	0
<b>Demographics</b>			
Age in Years, Mean (Min-Max)	41.2 (19-56)	37.7 (19-54)	30.3 (21-50)
Sex, n (%)			
Female:	1 (8)	3 (25)	4 (33)
Male:	11 (92)	9 (75)	8 (67)
BMI, Mean (Min-Max)	24.6 (20.6-27.1)	24.3 (21.9-28.7)	24.5 (20.4-29.0)
Height, Mean (Min-Max)	174.4 (161-183)	170.9 (163-181)	172.3 (154-203)
Weight, Mean (Min-Max)	75.0 (61.0-90.6)	71.1 (60.3-81.2)	73.2 (52.1-91.1)
Ethnicity, n (%)			
Hispanic or Latino:	0	0	0
Not Hispanic or Latino:	12 (100)	12 (100)	12 (100)
Race, n (%)			
White – White/Caucasian/European Heritage	12 (100)	12 (100)	12 (100)

**Photosensitivity Results:**

The primary endpoint for this study was the PI following repeat dosing for each wavelength tested at 24 h post-irradiation (delayed erythema). The delayed phototoxic factor at wavelength of  $400 \pm 30$  nm and  $430 \pm 30$  nm was not formally analysed as less than three subjects had provided non censored MED. Furthermore MEDs at wavelength of  $430 \pm 30$  nm were greater than  $82000 \text{ mJ/cm}^2$  for all subjects.

At wavebands  $295 \pm 5$  nm,  $300 \pm 5$  nm,  $305 \pm 30$  nm, and SS WS nm there was no notable differences in medians for the comparisons of interest after administration of any of the three treatments. At wavebands  $335 \pm 30$  nm and  $365 \pm 30$  nm there was no notable difference between median delayed PI following administration of repeat dose eltrombopag 75 mg as compared with placebo. However delayed PI at  $335 \pm 30$  nm and  $365 \pm 30$  nm was increased in terms of the estimated median difference (95% CI) of 0.75 (0.222, 2.037) and 1.20 (0.404, 1.720), respectively, following administration of ciprofloxacin relative to placebo. Comparing eltrombopag 75 mg with ciprofloxacin 500 mg, the delayed PI was decreased for waveband  $335 \pm 30$  nm and  $365 \pm 30$  nm in terms of the estimated median difference (95% CI) of -0.94 (-2.037, -0.289) and -1.38 (-1.882, -0.432).

This implies that, as expected ciprofloxacin at 500 mg BID for six days increased the photosensitivity of the skin compared to administration of placebo, resulting in mild phototoxicity, while eltrombopag did not increase the photosensitivity of the skin when administered for six days at 75 mg QD.

The other primary endpoint was the change from baseline MED at 24 h post-irradiation and the results were similar to those for the delayed PI.

Another pharmacodynamic endpoint was the concentration of porphyrins, ANF, anti-Ro, and anti-La (tests for lupus erythematosus) which showed no notable change following exposure to any of the three treatments.

In conclusion, eltrombopag 75 mg dosed for six days had no effect on skin photosensitivity and the study was valid as the positive control (ciprofloxacin) resulted in the expected mild increase in photosensitivity. Placebo treatment group did not show positive increase in photosensitivity as expected.

**Safety results:**

Ten (28%) subjects reported 30 AE episodes. One subject had a severe AE of eosinophilia with a duration of 15 days. The AE did not require the subject to withdraw from the study. The intensity of the remaining AEs was mild to

moderate. No AEs caused the subject to withdraw from the study. Table 1 shows the number of subjects reporting AEs in the study.

**Table 1 Summary of AEs Occurring in  $\geq$  2% of Subjects in Any Treatment Group**

Preferred Term	Placebo N=12	Eltrombopag N=12	Ciprofloxacin N=12
	n (%)	n (%)	n (%)
Subjects with Any AE	3 (25)	2 (17)	5 (42)
<b>Nervous system disorders</b>			
Any event	0	1(8)	3(25)
Dizziness	0	0	2(17)
Headache	0	0	1*(8)
Migraine	0	1(8)	0
<b>Blood and lymphatic system disorders</b>			
Any event	0	1(8)	1(8)
Eosinophilia	0	0	1*(8)
Thrombocythaemia	0	1*(8)	0
<b>General disorders and administration site conditions</b>			
Any event	1(8)	0	1(8)
Oedema peripheral	0	0	1(8)
Vessel puncture site haematoma	1(8)	0	0
<b>Cardiac disorders</b>			
Any event	0	0	1(8)
Tachycardia	0	0	1*(8)
<b>Gastrointestinal disorders</b>			
Any event	0	1(8)	0
Dyspepsia	0	1(8)	0
<b>Immune system disorders</b>			
Any event	1(8)	0	0
Seasonal allergy	1(8)	0	0
<b>Infections and infestations</b>			
Any event	0	1(8)	0
Nasopharyngitis	0	1(8)	0
<b>Investigations</b>			
Any event	1(8)	0	0
Blood creatine phosphokinase increased	1(8)	0	0
<b>Musculoskeletal and connective tissue disorders</b>			
Any event	0	0	1(8)
Back pain	0	0	1(8)
<b>Psychiatric disorders</b>			
Any event	1(8)	0	0
Nightmare	1(8)	0	0

\* Drug related adverse events.

**Serious Adverse Events: None**

**Publications: None at this time**