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| <b>Study No.:</b> TRA104412   |
| <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 Subjects with Mild, Moderate or Severe Renal Impairment  |
| <b>Rationale:</b> This study was to evaluate the pharmacokinetics (PK) of a single oral 50 mg dose of eltrombopag in subjects with mild, moderate or severe renal impairment and a group of healthy subjects matched to the moderate group.   |
| <b>Phase:</b> I   |
| <b>Study Period:</b> 26 Sep 2006 – 03 Jan 2008  |
| <b>Study Design:</b> Open-label, non-randomized single-dose, pharmacokinetic study.   |
| <b>Centres:</b> 2 centers located in the U.S  |
| <b>Indication:</b> Thrombocytopenia   |
| <b>Treatment:</b> Eltrombopag was administered orally once at a dose of 50 mg (one 50 mg tablet). The 50 mg dose of eltrombopag was selected because it was anticipated that exposures in subjects with renal impairment would not increase to values greater than those observed in previous clinical studies where eltrombopag was safely administered as single doses up to 75 mg. Subjects fasted for 2 hours prior to administration of study medication and for 2 hours post-dosing of study medication. No further dosing was administered.  |
| <b>Objectives:</b><br><b>Primary:</b> To compare the PK of eltrombopag (50 mg) following a single dose in subjects with renal impairment (mild, moderate or severe) with healthy subjects matched to the moderate group.<br><b>Secondary:</b> To describe the safety profile of a single 50 mg oral dose of eltrombopag in healthy subjects and those with renal impairment. To assess the effect of renal impairment on the plasma protein binding of eltrombopag.   |
| <b>Primary Outcome Variable:</b> AUC(0-∞) and Cmax of eltrombopag   |
| <b>Secondary Outcome Variable(s):</b> Incidence of AEs and changes in vital signs and laboratory values from baseline. AUC(0-t), tmax and half-life (t1/2); free fraction (% unbound of eltrombopag); and apparent clearance (CL/F) of eltrombopag. (Note: Plasma unbound eltrombopag concentrations could not be measured due to high variability in the quality control samples.)   |
| <b>Statistical Methods:</b> Following log <sub>e</sub> -transformation, AUC(0-∞), AUC(0-t), Cmax, CL/F and t1/2 were separately analyzed by analysis of variance (ANOVA). The model included group and day as fixed-effects. 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.<br>Safety data included extent of exposure, AEs, clinical laboratory evaluations, vital signs, ECGs, physical examination and ophthalmic examination. No formal statistical comparisons were made for the safety data. Safety data were listed and summarized, where appropriate.<br>Safety data were listed and summarized.   |
| <b>Study Population:</b> Male and female subjects, 18 to 75 years of age (inclusive), of any ethnic origin, with a body mass index (BMI) of 19 to 38 kg/m <sup>2</sup> , and considered to be either healthy or with a degree of renal impairment (mild, moderate or severe) were eligible. Healthy subjects were matched to the moderate renal impairment group for sex, age and BMI. The degree of renal impairment was based on clinical history and 24-hour urine creatinine clearance levels and assessed using the criteria outlined in the FDA Guidance document, "Guidance for Industry: Pharmacokinetics in Patients with Limited Renal Function – Study Design, Data Analysis and Impact on Dosing and Labelling (May 1998)." Subjects with mild, moderate or severe renal impairment were defined by a creatinine clearance of 50 to 80 mL/min, 30 to 49 mL/min or <30 mL/min, respectively. |

|  | Healthy Subjects       | Renal Impaired Subjects   |                        |                         | Total                   |
|--|------------------------|---------------------------|------------------------|-------------------------|-------------------------|
|  |                        | Mild                      | Moderate               | Severe                  |                         |
| Number of Subjects Planned, N:                         | 8                      | 8                         | 8                      | 2 - 8                   | 26 - 32                 |
| Number of Subjects Entered, N:                         | 8                      | 8                         | 8                      | 5                       | 29                      |
| Number of Subjects included in Safety analysis, n (%): | 8<br>(100%)            | 8<br>(100%)               | 8<br>(100%)            | 5<br>(100%)             | 29<br>(100%)            |
| Number of Subjects included in PK analysis, n (%):     | 8<br>(100%)            | 8<br>(100%)               | 8<br>(100%)            | 5<br>(100%)             | 29<br>(100%)            |
| Number of Subjects Completed, n (%):                   | 8<br>(100%)            | 8<br>(100%)               | 8<br>(100%)            | 5<br>(100%)             | 29<br>(100%)            |
| Number of Subjects Withdrawn (any reason), n (%):      | 0                      | 0                         | 0                      | 0                       | 0                       |
| <b>Demographics</b>                                    |                        |                           |                        |                         |                         |
| Number of Subjects                                     | Healthy Subjects       | Renal Impairment Subjects |                        |                         | Total                   |
|  |                        | Mild                      | Moderate               | Severe                  |                         |
| Age, (in Yrs), Mean (Range)                            | 61.1<br>(45 - 70)      | 64.0<br>(39 - 74)         | 63.0<br>(48 - 73)      | 53.4<br>(41 - 66)       | 61.1<br>(39 - 74)       |
| <b>Sex, n (%)</b>                                      |                        |                           |                        |                         |                         |
| Female:  | 4 (50%)                | 4 (50%)                   | 4 (50%)                | 2 (40%)                 | 14 (48%)                |
| Male:  | 4 (50%)                | 4 (50%)                   | 4 (50%)                | 3 (60%)                 | 15 (52%)                |
| BMI, (kg/m <sup>2</sup> ), Mean (Range)                | 27.42<br>(20.2 - 30.6) | 28.97<br>(22.3 - 36.8)    | 27.69<br>(22.7 - 35.8) | 24.85<br>(19.7 - 28.9)  | 27.48<br>(19.7 - 36.8)  |
| Height, (cm), Mean (Range)                             | 169.6<br>(152 - 181)   | 164.9<br>(157 - 177)      | 166.4<br>(160 - 180)   | 172.6<br>(164 - 186)    | 167.9<br>(152 - 186)    |
| Weight, (kg), Mean (Range)                             | 79.53<br>(46.7 - 96.0) | 78.81<br>(57.7 - 108.5)   | 76.88<br>(58.2 - 97.5) | 75.04<br>(54.4 - 100.0) | 77.82<br>(46.7 - 108.5) |
| <b>Ethnicity, n (%)</b>                                |                        |                           |                        |                         |                         |
| Hispanic or Latino:                                    | 0                      | 0                         | 1 (13%)                | 0                       | 1 (3%)                  |
| Not Hispanic or Latino:                                | 8 (100%)               | 8 (100%)                  | 7 (88%)                | 5 (100%)                | 28 (97%)                |
| <b>Race, n (%)</b>                                     |                        |                           |                        |                         |                         |
| African American/African Heritage                      | 0                      | 0                         | 2<br>(25%)             | 1<br>(20%)              | 3<br>(10%)              |
| Asian - Central/South Asian Heritage                   | 0                      | 1<br>(13%)                | 0                      | 0                       | 1<br>(3%)               |
| White -White/<br>Caucasian/European Heritage           | 8<br>(100%)            | 7<br>(88%)                | 6<br>(75%)             | 4<br>(80%)              | 25<br>(86%)             |

| <b>Primary PK Results:</b>   |                                    |                                    |  |                                      |
|--|------------------------------------|------------------------------------|--|--------------------------------------|
| <b>Summary of Derived Plasma Eltrombopag PK Parameters Following Administration of a Single 50 mg Dose</b>       |                                    |                                    |  |                                      |
| <b>Plasma Eltrombopag PK Parameter</b>   | <b>Healthy (N=8)</b>               | <b>Renal Impaired – Mild (N=8)</b> | <b>Renal Impaired – Moderate (N=8)</b> | <b>Renal Impaired – Severe (N=5)</b> |
| AUC(0-t) <sup>1</sup><br>(µg.h/mL)   | 59.4<br>(41.8, 84.4)<br>[44]       | 39.8<br>(24.5, 64.5)<br>[63]       | 37.5<br>(22.1, 63.5)<br>[70]           | 22.7<br>(3.76, 137)<br>[267]         |
| AUC(0-∞) <sup>1</sup><br>(µg.h/mL)   | 64.2<br>(46.1, 89.3)<br>[41]       | 43.6<br>(27.4, 69.3)<br>[60]       | 41.0<br>(24.9, 67.6)<br>[65]           | 25.9<br>(4.76, 141)<br>[233]         |
| C <sub>max</sub> <sup>1</sup><br>(µg/mL)   | 6.14<br>(4.60, 8.21)<br>[36]       | 4.29<br>(3.00, 6.11)<br>[44]       | 5.01<br>(3.03, 8.29)<br>[66]           | 2.81<br>(0.62, 12.79)<br>[186]       |
| t <sub>1/2</sub> <sup>1</sup><br>(h)   | 25.8<br>(22.2, 29.9)<br>[18]       | 19.6<br>(14.0, 27.4)<br>[42]       | 15.6<br>(10.6, 22.9)<br>[49]           | 14.0<br>(4.73, 41.3)<br>[107]        |
| CL/F <sup>1</sup><br>(L/h)   | 0.78<br>(0.56, 1.08)<br>[41]       | 1.15<br>(0.72, 1.82)<br>[60]       | 1.22<br>(0.74, 2.01)<br>[65]           | 1.93<br>(0.35, 10.51)<br>[233]       |
| T <sub>max</sub> <sup>2</sup><br>(h)   | 2.54<br>(2.50, 3.00)               | 3.00<br>(2.50, 4.00)               | 2.74<br>(1.00, 4.00)                   | 2.50<br>(2.50, 6.00)                 |
| 1. Data presented as geometric mean (95% CI) [CVb%]  |                                    |                                    |  |                                      |
| 2. Data presented as median (minimum, maximum)   |                                    |                                    |  |                                      |
| <b>Comparison of Plasma Eltrombopag PK Parameters for Subjects with Renal Impairment versus Healthy Subjects</b> |                                    |                                    |  |                                      |
| <b>Plasma Eltrombopag PK Parameter</b>   | <b>Comparison (Test/Reference)</b> | <b>GLS Mean Ratio</b>              | <b>90% CI</b>                          |                                      |
| AUC(0-t)   | Mild/Healthy                       | 0.67                               | (0.35, 1.29)                           |                                      |
|  | Moderate/Healthy                   | 0.63                               | (0.33, 1.21)                           |                                      |
|  | Severe/Healthy                     | 0.38                               | (0.18, 0.81)                           |                                      |
| AUC(0-∞)   | Mild/Healthy                       | 0.68                               | (0.37, 1.26)                           |                                      |
|  | Moderate/Healthy                   | 0.64                               | (0.34, 1.19)                           |                                      |
|  | Severe/Healthy                     | 0.40                               | (0.20, 0.82)                           |                                      |
| C <sub>max</sub>   | Mild/Healthy                       | 0.70                               | (0.40, 1.22)                           |                                      |
|  | Moderate/Healthy                   | 0.81                               | (0.47, 1.42)                           |                                      |
|  | Severe/Healthy                     | 0.46                               | (0.24, 0.86)                           |                                      |
| t <sub>1/2</sub>   | Mild/Healthy                       | 0.76                               | (0.50, 1.15)                           |                                      |
|  | Moderate/Healthy                   | 0.60                               | (0.40, 0.91)                           |                                      |
|  | Severe/Healthy                     | 0.54                               | (0.34, 0.87)                           |                                      |
| CL/F   | Mild/Healthy                       | 1.47                               | (0.79, 2.74)                           |                                      |
|  | Moderate/Healthy                   | 1.56                               | (0.84, 2.91)                           |                                      |
|  | Severe/Healthy                     | 2.48                               | (1.22, 5.03)                           |                                      |

| <b>Most Frequent AEs – On-Therapy (Preferred Term)</b> | <b>Healthy (N = 8)</b> | <b>Renal Impaired Subjects</b> |                         |                       | <b>Total (N = 29)</b> |
|--|------------------------|--------------------------------|-------------------------|-----------------------|-----------------------|
|  |                        | <b>Mild (N = 8)</b>            | <b>Moderate (N = 8)</b> | <b>Severe (N = 5)</b> |                       |
| Any event  | 3 (38%)                | 4 (50%)                        | 5 (63%)                 | 4 (80%)               | 16 (55%)              |
| Headache   | 0                      | 3 (38%)                        | 0                       | 2 (40%)               | 5 (17%)               |
| Dyspepsia  | 0                      | 1 (13%)                        | 2 (25%)                 | 0                     | 3 (10%)               |
| Nausea   | 0                      | 0                              | 0                       | 2 (40%)               | 2 (7%)                |
| Hypoglycemia   | 0                      | 1 (13%)                        | 0                       | 1 (20%)               | 2 (7%)                |

| Nasopharyngitis   | 1 (13%)            | 0                       | 0                   | 1 (20%)           | 2 (7%)            |
|---|--------------------|-------------------------|---------------------|-------------------|-------------------|
| <b>Drug-Related Adverse Events</b>  |                    |                         |                     |                   |                   |
| Adverse Event<br>(Preferred Term)   | Healthy<br>(N = 8) | Renal Impaired Subjects |                     |                   | Total<br>(N = 29) |
|   |                    | Mild<br>(N = 8)         | Moderate<br>(N = 8) | Severe<br>(N = 5) |                   |
| Headache  | 0                  | 1 (13%)                 | 0                   | 1 (20%)           | 2 (7%)            |
| Nausea  | 0                  | 0                       | 0                   | 2 (40%)           | 2 (7%)            |
| Dizziness   | 0                  | 0                       | 0                   | 1 (20%)           | 1 (3%)            |
| Paresthesia   | 1 (13%)            | 0                       | 0                   | 0                 | 1 (3%)            |
| Dyspepsia   | 0                  | 1 (13%)                 | 0                   | 0                 | 1 (3%)            |
| <b>Serious Adverse Events - On-Therapy:</b> No non-fatal or fatal SAEs were reported during this study. |                    |                         |                     |                   |                   |
| <b>Publications:</b> None at the time of this report.   |                    |                         |                     |                   |                   |