Pharmacokinetics and Pharmacodynamics of Eltrombopag in Healthy Japanese Males

Yuri SHIDA, Naoki TAKAHASHI, Shigeru NOHDA and Toshiyasu HIRAMA
Clinical Pharmacology Department, GlaxoSmithKline K.K., Tokyo, Japan

The pharmacokinetics and pharmacodynamics of eltrombopag, a thrombopoietin receptor agonist developed for idiopathic thrombocytopenic purpura, were investigated in healthy Japanese adult males after single and repeat doses of eltrombopag in two clinical studies.

In the first study, subjects received a single oral dose of eltrombopag tablets at 30, 50, 75 and 100 mg and placebo in the fasted state. In the second study, each subject received single and once daily for 10 days repeat doses of eltrombopag (25, 50 or 75 mg) or placebo tablets. Plasma eltrombopag concentrations and platelet counts were measured in both studies. AUC and C_{max} were proportional to dose within the range of 30–100 mg. The AUC_{0–24} values after repeat doses of eltrombopag 25, 50 and 75 mg were 56, 130 and 161 μg•hr/mL, respectively, increasing nearly proportionally to the dose increase. The plasma concentration reached steady state in approximately 7 days after starting the repeat dose, and the change in pharmacokinetics caused by repeat dose was small. The AUC values obtained after single and repeat dose in Japanese subjects were nearly two-fold higher than those previously reported in non-Japanese subjects (predominantly white).

No significant changes in platelet count were observed after single oral doses up to 100 mg of eltrombopag. When 25, 50 and 75 mg were administered once daily for 10 days, the maximum increase in platelet count from the baseline was 54%, 72% and 90%, respectively, showing a dose-dependent increase. These increases were higher as compared with the previously reported increases in platelet count observed after 30, 50 and 75 mg were administered once daily for 10 days to non-Japanese healthy adults. The increase in platelet count from baseline became higher with increasing AUC in Japanese healthy adults.

These results suggest that the difference in platelet count increase between Japanese and non-Japanese is probably associated with the observed inter-ethnic difference in AUC. Eltrombopag might be used at a lower dosage in Japanese than in non-Japanese to attain similar degrees of platelet count increase.

Key words: eltrombopag, pharmacokinetics, pharmacodynamics, healthy male, ITP

Introduction

Eltrombopag olamine is a bis-monoethanolamine salt of eltrombopag, which is a thrombopoietin (TPO) receptor agonist developed by GlaxoSmithKline (Fig. 1). It is a low molecular weight compound available for oral administration. Eltrombopag induces proliferation and differentiation of the megakaryocytic lineage cells by activating a part of the TPO signaling pathway through a specific interaction with human TPO receptor and increases in platelet count result\(^1\). The thrombopoietic effect of eltrombopag is species-specific and seen only in humans and chimpanzees\(^1,2\). From these results, eltrombopag is expected to increase platelet count in various diseases causing thrombocytopenia including idiopathic thrombocytopenic purpura (ITP). Clinical development of eltrombopag targeting chronic ITP, an autoimmune disease with enhanced platelet destruction and suppression of megakaryopoiesis/thrombopoiesis by an immune reaction with autoantibody against platelets\(^3,4\), has been performed.

In healthy non-Japanese adults, repeat doses of eltrombopag \(\geq 30\) mg were reported to increase platelet count\(^5\). Also in non-Japanese ITP patients, a dose-response study was conducted at the doses of 30, 50 and 75 mg once daily, and significant efficacy was seen with 50 mg and 75 mg doses compared with placebo\(^5\).

According to the Japanese guideline\(^6\), for the treatment of ITP, eradication of Helicobacter pylori (\(H.\) pylori) is performed first in \(H.\) pylori-positive patients.
Patients showing no response to eradication of *H. pylori* or *H. pylori*-negative patients are treated with a corticosteroid followed by splenectomy (first-line therapy). However, there are cases where these first-line therapies cannot be adopted or intractable cases where the first-line therapies are not sufficiently effective. In such cases, an adequate platelet count cannot be maintained and the risk of hemorrhage and death increases. Immunosuppressive therapy or high-dose steroid therapy is used as a second-line therapy, although such therapies are not considered to be based on sufficient evidence and are accompanied by specific adverse reactions. As drugs which potentially increase platelet count in intractable ITP patients, TPO receptor agonists including eltrombopag are anticipated to be a new therapeutic option. As a TPO receptor agonist, romiplostim, once weekly injection, has recently been approved for ITP in countries including the United States. Eltrombopag to be administered orally once daily is expected to contribute to the treatment of the disease.

In the studies described in the present report, eltrombopag was orally administered as single doses of 30–100 mg and as single and repeat doses of 25–75 mg to healthy Japanese adult males to investigate the pharmacokinetics, safety and effect on platelet count. The present paper reports the results and discusses the relationships between dose and exposure and between dose and changes in platelet count in healthy Japanese adults that are different from those previously reported in healthy non-Japanese subjects.

### Study Methods

The studies were conducted at Osaki Clinic (Medical Co., LTA., Tokyo, Japan) in compliance with the Declaration of Helsinki (South Africa, 1996), the Good Clinical Practice (GCP) and the relevant provisions of the Pharmaceutical Affairs Law of Japan after obtaining approval from the IRB of Medical Co., LTA. Written informed consent was obtained from each subject.

1. **Study drug**

   Film-coated tablets containing 5 mg and 25 mg of eltrombopag as eltrombopag olamine, and corresponding placebo tablets were used in Study A. Film-coated tablets containing 25 mg eltrombopag as eltrombopag olamine and corresponding placebo tablets were used in Study B.

2. **Study design**

   **Study A**

   Study A was conducted in 16 healthy Japanese adult males as a placebo-controlled, double-blind, dose-escalating, 4-period incomplete crossover, single-dose study to investigate the pharmacokinetics, safety and pharmacodynamics of single dose of eltrombopag. Subjects were randomized into 4 groups (a) : placebo, 50 mg, 75 mg, 100 mg, b) : 30 mg, placebo, 75 mg, 100 mg, c) : 30 mg, 50 mg, placebo, 100 mg, d) : 30 mg, 50 mg, 75 mg, placebo) and administered single oral doses of eltrombopag tablets at 3 out of 4 active doses (30, 50, 75 and 100 mg) plus placebo tablets in the fasted state with 150 mL of water. Each period was separated by 12 days. For determination of eltrombopag concentrations in plasma and urine, blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours post-dose for each treatment, and urine samples were collected pre-dose and over 0-6, 6-12, 12-24, 24-48 and 48-72 hours post-dose for each treatment. For pharmacodynamic evaluation, platelet count was determined pre-dose and at 24, 72, 144 and 288 hours (12 days) after each single dose.

   **Study B**

   Study B was conducted in 42 healthy Japanese
adult males (14 subjects in each of 3 groups: 10 subjects administered eltrombopag and 4 subjects administered placebo per group) as a placebo-controlled, single-blind, parallel-group, single and repeat dose study to investigate the pharmacokinetics, safety and pharmacodynamics of single and repeat doses of eltrombopag. Each subject received a single dose of eltrombopag (25, 50 or 75 mg) or placebo tablets, and after 5 days washout, received once-daily administration of the same dose for 10 days. All the doses were orally administered in the fasted state with 150 mL of water. On the day of the single dose and on Day 10 of the repeat dose phase, blood samples were taken pre-dose and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose for the determination of plasma eltrombopag concentrations. In order to check whether a steady state was reached, plasma pre-dose (trough) eltrombopag concentrations were also determined during the repeat dose period. For pharmacodynamic evaluation, platelet count was determined pre-dose and at 24, 72 and 120 hours after each single dose, pre-dose on Days 1-3, Days 5-8 and Day 10 of repeat dosing and on Days 11, 12, 14, 16, 18, 22 and 26. Furthermore, platelet aggregation was evaluated pre-dose of single dose, pre-dose on Day 1 and Day 10 of repeat dosing and on Day 16.

For Study A, laboratory tests, vital sign determination and 12-lead electrocardiography were performed for safety evaluation up to 72 hours after each single dose and for Study B, these safety data were collected throughout the dosing period and up to 8 days after the last dose.

3. Determination method and data analysis

Pharmacokinetics

The eltrombopag concentrations in plasma and urine were determined using a validated liquid chromatography mass spectrometry (LC/MS-MS method). The lower limit of quantification (LLQ) was 10 ng/mL. Pharmacokinetic parameters (Cmax, tmax, t1/2, AUC0−24, AUC0−last, AUC0−∞, proportion AUC0−∞ extrapolated (% AUCex) and CL/F) were calculated from the plasma eltrombopag concentrations and actual sampling times with standard non-compartmental methods using WinNonlin Professional Ver. 3.1 (Pharsight Corp., Mountain View, CA, US) in both studies. AUC was calculated using the log-linear trapezoidal rule.

In Study B, in addition to the above, Rs (AUC0−24 on Day 10 of repeat dose/AUC0−∞ of single dose) and RCmax (Cmax on Day 10 of repeat dose/Cmax of single dose) were calculated as accumulation indices.

Statistical analysis of pharmacokinetics

In Study A, to investigate the linearity of exposure after single doses of 30-100 mg, the slope versus dose was calculated using a power model using Windows SAS Ver. 6.12 (SAS Institute, Cary, NC, USA).

In Study B, attainment of steady state was assessed by calculation of the slope of log transformed trough concentrations on Days 8, 9 and 10 versus study day using Solaris SAS Ver. 8.2 (SAS Institute, Cary, NC, USA).

Pharmacodynamics

Platelet count was determined with an automatic blood cell counter (direct current detection method).

In Study B, for evaluation of platelet count changes after starting repeat dosing, the following pharmacodynamic parameters were calculated using WinNonlin Professional Ver. 3.1: time of maximum platelet count (Platelet-Tmax), maximum platelet count (Platelet-max) and area under the platelet count-time curve (Platelet-AUC). Additionally, the absolute change (Δ) and percent change (%) after starting repeat dosing were calculated for each time point using the pre-dose platelet count (P0) as baseline value.

In order to investigate the change in platelet aggregation after repeat dosing, adenosine diphosphate (ADP) as an aggregation-inducing substance was added to platelet-rich plasma obtained by centrifugation of whole blood, and the light transmission determined with a laser light-scattering platelet aggregometer (PA-200, Kowa company, Ltd., Nagoya, Japan).

Results

1. Pharmacokinetics after single and repeat doses

Study A

The pharmacokinetic parameters after administration of single oral doses of eltrombopag in the fasted state in Study A are given in Table 1.

In Study A, the pharmacokinetics after single doses of 30, 50, 75 and 100 mg was investigated in 16 healthy Japanese adult males aged 20-33 years (25.9 years on average) and weighing 55.5-69.6 kg (61.3 kg on average). Plasma eltrombopag concentrations
reached a maximum at 3–4 hours (median value) after dosing for all doses. Overall the results are considered generally consistent with a proportional increase in exposure with dose (10). In addition, an analysis using the power model showed the slope for AUC$_{0-\infty}$ was 1.11 (1.03, 1.20) where the lower limit of the 90% confidence interval (CI) was slightly greater than 1, but the slope (90% CI) was 1.02 (0.93, 1.11) for C$_{\text{max}}$ and 1.07 (0.99, 1.15) for AUC$_{0-\text{last}}$, indicating a proportional increase in exposure with dose.

The mean elimination half life calculated from plasma eltrombopag concentration determined up to 72 hours after dosing was in the range of 23–28 hours for all doses. By sampling up to 72 hours after administration, the proportion of AUC$_{0-\infty}$ extrapolated following doses of 50 mg or greater was 13–14% on average, and exceeded 20% in 1 subject at each of 50 and 75 mg and in 2 subjects at 100 mg.

Urinary eltrombopag concentrations were also determined. The greatest individual proportion of the dose excreted in urine was 0.032% and in other subjects all concentrations were below the level of quantitation.

**Study B**

In Study B, based on the results of Study A, blood samples were taken up to 120 hours after both the single dose and the last dose in the repeat dose phase for calculation of pharmacokinetic parameters. The pharmacokinetics after single and 10 days repeat doses of 25, 50 and 75 mg of eltrombopag (n=10) were administered in Study B (open circle).
Table 2  Summary of eltrombopag pharmacokinetic parameters after single and repeat oral doses in healthy Japanese males (Study B)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Treatment</th>
<th>n</th>
<th>C_{max} (µg/mL)</th>
<th>t_{max} (hr)</th>
<th>AUC (µg·hr/mL)</th>
<th>t_{1/2} (hr)</th>
<th>CL/F (L/hr)</th>
<th>Rs</th>
<th>RC_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Single</td>
<td>10</td>
<td>3.4</td>
<td>3.0</td>
<td>51(^{1})</td>
<td>29.2</td>
<td>0.49</td>
<td>1.09</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
<td>(2.7, 4.3)</td>
<td>(20–5.0)</td>
<td>(38, 70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>repeat</td>
<td>10</td>
<td>4.7</td>
<td>3.0</td>
<td>56(^{b})</td>
<td>39.6</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3.9, 5.7)</td>
<td></td>
<td>(43, 72)</td>
<td>(37.4, 41.9)</td>
<td></td>
<td>(0.35, 0.58)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Single</td>
<td>10</td>
<td>6.0</td>
<td>3.0</td>
<td>101(^{1})</td>
<td>30.5</td>
<td>0.49</td>
<td>1.18</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
<td>(4.5, 8.1)</td>
<td>(1.5–5.0)</td>
<td>(79, 130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>repeat</td>
<td>9</td>
<td>10.4</td>
<td>4.0</td>
<td>130(^{2})</td>
<td>50.2</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(8.7, 12.4)</td>
<td></td>
<td>(107, 158)</td>
<td>(42.7, 59.1)</td>
<td></td>
<td>(0.32, 0.47)</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Single</td>
<td>10</td>
<td>7.9</td>
<td>3.0</td>
<td>130(^{2})</td>
<td>31.6</td>
<td>0.58</td>
<td>1.24</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
<td>(6.0, 10.4)</td>
<td>(2.0–6.0)</td>
<td>(105, 161)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>repeat</td>
<td>10</td>
<td>12.5</td>
<td>4.0</td>
<td>161(^{2})</td>
<td>46.6</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(10.4, 14.9)</td>
<td></td>
<td>(138, 188)</td>
<td>(39.1, 55.5)</td>
<td></td>
<td>(0.40, 0.54)</td>
<td></td>
</tr>
</tbody>
</table>

C_{max}, AUC, t_{1/2}, and CL/F are given as geometric mean (95% CI). T_{max} is given as median (range) Accumulation ratios : Rs and RC_{max} are given as point estimate of geometric mean (90% CI)

a : AUC_{0–24}  b : AUC_{0–24}

Fig. 3  Mean plasma eltrombopag concentration-time profile following single and 10 days of repeat oral doses in healthy Japanese males (Study B)

Plasma concentration profiles up to 5 days after single dose, trough concentration during repeat dosing, and plasma concentration up to 5 days after completion of repeat dosing are presented. Day 6 of single dose phase corresponds with Day 1 of repeat dose phase. Downward arrows (↓) denotes study drug administration.

B are given in Table 2, and the mean plasma eltrombopag concentration time profiles are shown in Figure 3.

After single and repeat doses of 25–75 mg in the fasted state, maximum plasma eltrombopag concentrations were reached at 3–4 hours (median value) after dosing for all doses, as in Study A. C_{max} and AUC_{0–∞} values after single doses were slightly lower than those observed in Study A (Table 2). The exposure (C_{max} and AUC) after single and repeat doses increased approximately in proportion to dose (Fig. 2). The elimination half life after single doses and repeat doses were 30–32 hours and 40–50 hours, respectively. The elimination half life after single
doses was slightly longer as compared with Study A. The proportion of AUC\(_{0-\infty}\) extrapolated after single doses was less than 10% in all subjects.

The steady state ratio after 10 days repeat doses of eltrombopag 25-75mg, i.e., Rs (AUC\(_{0-24}\) on Day 10 of repeat dose/AUC\(_{0-\infty}\) after single dose), was in the range of 1.1-1.2. The 90% CI for the mean Rs values included unity for the 25 and 50 mg doses and marginally excluded unity for the 75 mg dose, suggesting that the pharmacokinetics of eltrombopag is generally linear and time-invariant (Table 2).

Visual check indicated that steady state was reached within 7 days after starting dosing (Day 8) (Fig.3). The slope (90% CI) of log trough concentration on Days 8, 9 and 10 versus study day was 0.96 (0.78, 1.18) for the 25-mg group, 1.06 (0.95, 1.19) for the 50-mg group and 1.00 (0.91, 1.10) for the 75-mg group. The 90% CI included 1, which also indicated that the slope was zero and that steady state had been attained.

### 2. Pharmacodynamics after single and repeat doses

No significant changes in platelet count were observed after single oral doses of eltrombopag 30–100 mg in Study A. In Study B, no significant changes in platelet count were observed after single oral doses of eltrombopag 25-75 mg. However, after 10-days repeat doses of eltrombopag 25, 50 or 75 mg, increases in platelet count were seen at all dose levels. The increases in platelet count from baseline (% change of Platelet-max) after 10-days repeat dosing were 54% in the 25-mg group, 72% in the 50-mg group and 90% in the 75-mg group, indicating a dose-dependent increase. The baseline platelet counts in the healthy Japanese were similar across all groups and consistent with expectations in this population (Table 3).

The platelet count after 10-days repeat dosing reached the maximum 4-6 days after the last dose and returned to the reference range (13.1–36.2 × 10\(^4\)/mL) within 16 days after the last dose in almost all the subjects (Fig.4, Table 3). However, in 1 subject administered 25 mg, it took 64 days for the platelet count to return to the reference range. In this subject, the platelet count increased from the baseline level of 32.3 × 10\(^4\)/mL to the maximum of 59.8 × 10\(^4\)/mL 4 days after the last dose.

Platelet function as measured by platelet aggregation was not notably affected by the administration of either eltrombopag or placebo.

The relationship between the increase in platelet count and the exposure (AUC\(_{0-24}\)) after 10-days repeat dosing with eltrombopag 25–75 mg was investigated graphically (Fig.5). There appears to be a positive correlation between AUC and increase in platelet count from baseline.

### 3. Safety

Eltrombopag was safe and well tolerated when administered as single doses up to 100 mg and repeat doses over 10 days up to 75 mg in healthy Japanese males.

There were 5 kinds of adverse events (6 episodes) reported in 5 of the 16 subjects in Study A. In Study B, there were 5 kinds of adverse events (6 episodes) reported in 6 of the 30 subjects who received eltrombopag. No events after administration of placebo were reported in the 12 subjects in Study B (Table 4).

All of these events except for acute pharyngitis after a single dose of placebo were mild and recovered without any treatment. There was no apparent relationship between the dose level of eltrombopag
and adverse event incidence.

**Discussion**

Although absolute bioavailability data for eltrombopag are not available, following a single oral administration of eltrombopag 75 mg as a solution to healthy non-Japanese, absorption of drug related material is estimated to be at least 52% based on urinary excretion and metabolites elimination in faeces. Eltrombopag is extensively metabolised via a number of pathways that include cleavage, oxidation and conjugation with glucuronic acid, glutathione or cysteine. Based on *in vitro* data, CYP1A2 and CYP2C8 are responsible for the oxidative metabolism and UGT1A1 and UGT1A3 are responsible for the glucuronidation. In addition, *in vitro* studies have identified eltrombopag as a substrate of the BCRP transporter, but not a substrate of OATP1B1 nor Pgp.
The pharmacokinetics of eltrombopag in healthy Japanese males was investigated with single doses of eltrombopag 30-100 mg in Study A, where dose proportionality of exposure (Cmax and AUC) was confirmed over this dose range. Evaluation of the proportion of AUC extrapolated suggested it was necessary to extend the blood-sampling time beyond 72 hours after dosing to adequately evaluate the terminal elimination phase of eltrombopag in plasma. Based on these results, in Study B a 5 day washout period was set between the single dose and the start of the repeat dose phase, and plasma eltrombopag concentrations were determined for up to 120 hours after both the single dose and last dose in the repeat dose phase.

Confirmation that steady state was reached within 7 days of starting the repeat dose phase was obtained by analysis of the slope of trough concentrations over time. The elimination half life after single dose was calculated to be 30-32 hours and is consistent with attaining the steady state within 7 days of starting dosing (i.e. within 5 half-lives). The Rs value after 10-days repeat dosing of eltrombopag 25-75 mg was 1.1-1.2, showing that eltrombopag has predictable and time-invariant pharmacokinetics on repeat dosing.

In Study A, the AUC values after single oral doses of 50 mg and 75 mg administered in the fasted state were 2.0 and 2.3 times higher than previously reported results in the fasted state in non-Japanese subjects\textsuperscript{13}. Though AUC\textsubscript{0−∞} in Study B was calculated from longer sampling duration than in Study A and the non-Japanese study, the exposures after single doses of 50 mg and 75 mg obtained in Study B were slightly lower than those obtained in Study A but were still 1.5-1.7 times higher than the AUC values obtained in the comparable study in non-Japanese under the same determination method\textsuperscript{13}. The AUC at steady state after repeat doses of 75 mg obtained in Study B was 2.0 times higher than that obtained in a study in non-Japanese using a capsule formulation of eltrombopag\textsuperscript{2}. Of note, relative bioavailability of capsule formulation was 15% higher than that of tablet\textsuperscript{13}.

In a population pharmacokinetic analysis using the results of a clinical study conducted in non-Japanese chronic ITP patients, an ethnic difference in exposure was observed between Asians who were principally of East Asian ancestry and non-Asians who were principally of European ancestry. The AUC in Asian was 1.87 fold higher than that of non-Asian ITP patients, consistent with the finding in the present study. Based on the population PK analysis, Asian

### Table 4

<table>
<thead>
<tr>
<th>Adverse Event (n, %)</th>
<th>Study A : Single dose study</th>
<th>Study B : Single and 10 days of repeat dose study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg (n=12)</td>
<td>50 mg (n=12)</td>
</tr>
<tr>
<td>Number of subjects with any AE(s)</td>
<td>1 (8.33%)</td>
<td>1 (8.33%)</td>
</tr>
<tr>
<td>Total bilirubin increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total bile acids increased</td>
<td>0</td>
<td>1 (8.33%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (8.33%)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute pharyngitis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\*AE related to the investigational product
a ) : Moderate event
b ) : One subject was withdrawn from the study 72 hours after single dosing (before the start of repeat dosing) for personal reason.
ancestry was associated with a 33.5% lower plasma eltrombopag CL/F, which translates to a 50% higher plasma eltrombopag exposure\textsuperscript{10}.

With respect to the ethnic difference between Asians and non-Asians noted in the population PK, a difference in body weight is one of the significant covariates for eltrombopag pharmacokinetic parameters. The AUC values, calculated using the same method as in the present study following 50 mg and 75 mg eltrombopag administration in the fasted state in the non-Japanese subjects were 65.2 and 76.9 \( \mu g \cdot hr/mL \) respectively, compared with 101 and 130 \( \mu g \cdot hr/mL \) at the same doses in Japanese subjects. The mean body weights of the non-Japanese subjects at the two dose levels were 70.3 kg and 76.0 kg compared with 63.4 and 65.3 kg for the Japanese subjects\textsuperscript{13}. While this may have contributed, it did not fully explain the ethnic difference in exposure. The results of population PK analysis in Japanese and non-Japanese healthy volunteers and ITP patients clearly show that bodyweight is one of the significant covariates for eltrombopag CL/F. However other factors (East Asian or other races, concomitantly administered corticosteroid or not, male or female, healthy or ITP patients) are also significant covariates for CL/F even when body weight is already included in the CL/F estimation model\textsuperscript{14}. As eltrombopag is a substrate of BCRP as well as several drug metabolizing enzymes such as CYP1A2, CYP2C8, UGT1A1 and UGT1A3\textsuperscript{11,12}, the activities of which can differ between East Asian and Western populations, it is unlikely that any one factor will be solely responsible for the inter-ethnic differences observed in eltrombopag pharmacokinetics. In practice, the factors responsible for the observed inter-ethnic difference in eltrombopag pharmacokinetics have not yet been defined.

In Study A, the urinary eltrombopag concentrations were analysed but were below the detection limit in most subjects. This result is consistent with the finding in a study in non-Japanese subjects that following a single oral dose of \(^{14}\)C-eltrombopag (75 mg), 59% of the dose was excreted via the feces and 31% via the urine, but of the drug related material in the urine none was detected as unchanged eltrombopag\textsuperscript{10}.

The mean maximum platelet count increase observed in Study B (54% in the 25-mg group, 72% in the 50-mg group and 90% in the 75-mg group) were greater than the mean maximum increases observed after 10-days repeat dose of eltrombopag 30 mg, 50 mg and 75 mg to healthy non-Japanese adults, in whom the increases were 24.1%, 42.9% and 50.4%, respectively\textsuperscript{2}. Figure 5 shows the relationship between platelet count increase and AUC is comparable among Japanese and non-Japanese subjects. The higher increases in platelet count in Japanese than in non-Japanese subjects is consistent with the inter-ethnic difference observed in systemic eltrombopag exposure. It was thus suggested that a similar platelet count-increasing effect of eltrombopag might be obtained at lower doses in Japanese than in non-Japanese subjects. Based on these results, the initial dose of eltrombopag recommended for East Asians is half of that recommended for non-Asians\textsuperscript{1,12}.

The adverse events reported after administration of eltrombopag in the 2 studies conducted in healthy Japanese adults were all mild and the subjects recovered without any treatment. Although the eltrombopag exposure in Japanese was significantly higher than in non-Japanese, the incidence of adverse events in Japanese was not higher than was observed in healthy non-Japanese subjects\textsuperscript{2,13}.

In 1 subject, the maximum platelet count after repeat doses of 25 mg was \( 59.8 \times 10^4/\mu L \), and platelet count took 64 days after the last dose to return to the reference range. The AUC value (31.4 \( \mu g \cdot hr/mL \)) after repeat dose in this subject was not particularly high compared with the other subjects. As platelet life is approximately 7-10 days\textsuperscript{15} and the peak platelet count in this subject was less than twice the upper limit of the normal range, the reason why platelet count did not return more rapidly to the normal range is unclear. There were no abnormal subjective/objective findings in this subject. The safety of eltrombopag was confirmed in single dose up to 100 mg and following 10-days repeat doses up to 75 mg.

The present study evaluated the safety, pharmacokinetics and pharmacodynamics of eltrombopag in healthy Japanese males for the first time. The pharmacokinetics and pharmacodynamics data show exposure and increase in platelet count that are higher compared to previously reported results in non-Japanese. The finding led to a lower starting dose of eltrombopag in Japanese.
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