# Pharmacokinetic/Pharmacodynamic Analyses of Avatrombopag in Healthy Subjects and Patients with Chronic Liver Disease

健康成人及び慢性肝疾患患者における

アバトロンボパグの薬物動態／薬力学解析

２０１９年

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# Abbreviation

| | |
|---|---|
| ALB | albumin |
| AUC | area under the plasma concentration-time curve |
| $AUC_{(0\text{-}inf)}$ | area under the plasma concentration-time curve from 0 time extrapolated to infinity |
| AUCR | the ratios of the area under the curve of avatrombopag in the presence and absence of the inhibitor or inducer |
| $AUEC_{(0\text{-}28d)}$ | area under the effect curve for platelet count following avatrombopag dosing through 28 days after dosing |
| BID | twice a day |
| BMI | body mass index |
| BM1 | precursor production compartment |
| BM2 | transit compartment |
| BM3 | maturation compartment |
| CIs | confidence intervals |
| CL/F | apparent clearance |
| $C_{max}$ | maximum observed plasma concentration |
| CLD | chronic liver disease |
| CYP | cytochrome P450 |
| CV% | coefficient of variation |
| D1 | duration for zero-order absorption |
| DDI | drug-drug interaction(s) |
| $E_{max}$ | maximum increase in platelet counts |
| F1 | relative bioavailability |
| GM | geometric mean |
| IIV | interindividual variability |
| IOV | interoccasion variability |
| IRB | Institutional Review Board |
| IS | internal standard |
| Ka | absorption rate constant |
| $K_{in}$ | zero-order production rate of platelet precursors |
| $K_{out}$ | first-order maturation rate of platelet precursors |
| LC-MS/MS | liquid chromatography followed by tandem mass spectrometry |
| LS | least square |
| ND | not determined |
| NONMEM | nonlinear mixed-effects modeling software |
| %CV or CV% | percent coefficient of variation |
| PBPK | physiologically based pharmacokinetic |
| PD | Pharmacodynamics(s) |
| PI(s) | prediction interval(s) |

| | |
|---|---|
| PK | Pharmacokinetic(s) |
| PK/PD | pharmacokinetic/pharmacodynamics |
| QD | once a day |
| QF | four times a day |
| SD | standard deviation |
| SE | standard error |
| TPO | thrombopoietin |
| $t_{½}$ | terminal elimination phase plasma half-life |
| $TE_{max}$ | time of maximum increase in platelet count |
| $t_{max}$ | time at which the highest drug concentration occurs |
| V/F | apparent central volume |
| 1G tablet | first-generation tablet |
| 2G tablet | final to-be-marketed second-generation tablet |

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# Preface

Assessment of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of new drug candidates is critical for their successful clinical development. Multidisciplinary analyses are used to guide safe and effective dosing such as in vitro metabolism data, drug-drug interactions (DDI), ethnic differences, modeling and simulation, and clinical outcomes[1]. The occurrence of DDI has the potential to significantly affect not only the safety and efficacy but also dosage regimen. In the past several decades, we have typically evaluated the potential of DDI risk using in vitro and in vivo methods. In this study, the author evaluated the PK/PD and DDI risk of avatrombopag maleate (E5501, DOPTELET®), thereafter avatrombopag, using physiologically based PK (PBPK) modeling and PK/PD simulation methods to optimize the dosage regimen in target patients.

Thrombocytopenia is observed in patients with chronic liver disease (CLD), where it is associated with increased risk of bleeding with invasive procedures. The current treatment options for thrombocytopenia are limited to platelet transfusions, which is the standard care, and a few surgical treatments such as splenectomy, splenic artery embolization, and transjugular intrahepatic portosystemic stent shunting. In addition to the potential risks of transfusion reactions and infections, which can be fatal, repeated platelet transfusions are also associated with the development of platelet refractoriness, which is a serious concern for this patient population, who are at a higher risk of spontaneous bleeding, including gastrointestinal bleeding secondary to varices and coagulopathies, common comorbidities of CLD[2].

Avatrombopag, is an orally administered, small-molecule, thrombopoietin (TPO) receptor agonist that is believed to act on the TPO receptor c-Mpl, promotes megakaryocyte production, maturation, and the formation of platelets[3,4]. Avatrombopag is indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. The recommended daily dose of avatrombopag is based on a patient's baseline platelet count prior to a scheduled procedure. Patients with a platelet count less than $40\times10^9$/L will receive avatrombopag 60 mg orally once daily for 5 consecutive days 10-13 days prior to a scheduled procedure whereas those with a platelet count of $40\times10^9$/L to less than

$50 \times 10^9$/L will receive avatrombopag 40 mg orally once daily for 5 consecutive days 10-13 days prior to a scheduled procedure[5]. Drugs with TPO receptor agonist activity such as avatrombopag are expected to raise platelet count before invasive procedures, resulting in a reduction in platelet transfusion, and also enable more patients to undergo the procedure[6].

This thesis consists of 4 Chapters. The first chapter is to characterize and compare the PK, PD, and the safety and tolerability following a single dose of avatrombopag between healthy Japanese and White subjects. The second chapter summarizes drug-drug interactions of avatrombopag as a victim with dual or selective cytochrome P450 (CYP) 2C9 and CYP3A inhibitors and inducers in healthy subjects. The third chapter provides and overview of the population PK/PD relationship between plasma avatrombopag concentrations and platelet count developed using modeling methods. In Chapter 4, platelet count following avatrombopag administration with and without concomitant medication was simulated using the final population PK/PD model to explore potential dose adjustments. The results of this simulation are referenced in the approved label in the United States[5], and in the proposed labelling of the avatrombopag submission in the European Union.

# Chapter 1 Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Avatrombopag in Healthy Japanese and White Subjects

## Introduction

Avatrombopag is an orally administered small-molecule thrombopoietin (TPO) receptor agonist that acts on the TPO receptor c-Mpl, activate the intracellular signaling system, and promote production of platelets and megakaryocytes from hemopoietic precursor cells, in the same way as TPO[3,4].

Avatrombopag is freely soluble in formic acid, slightly soluble in methanol, dehydrated ethanol, and acetic acid, and sparing soluble in water at pH 13. However, it is practically insoluble in water below pH 12 and 0.1N hydrochloride. In addition, studies with LLC-PK cells have shown that avatrombopag has low to moderate in vitro permeability. In spite of the low permeability and solubility, avatrombopag is believed to have good oral bioavailability. Preclinical studies have shown that, overall, avatrombopag was well absorbed ranged from approximately 50% to 90% in mouse, rat, dog and cynomolgus monkey. The absolute bioavailability was unknown in human.

Plasma protein binding of avatrombopag is greater than 96% in human plasma[5] and it binds mainly to albumin. The concentration in erythrocyte is approximately 50% of that in plasma.

In a human mass balance study with a single oral administration of 20 mg $^{14}$C-labeled avatrombopag suspension, a major route of excretion of avatrombopag and its metabolites is by the fecal route, accounting for approximately 88% of the administered dose in healthy male subjects. The excretion in urine is approximately 6% of the dose. The majority of total radioactivity was excreted by 72 hours in urine and by 168 hours in feces. Approximately 34% and 44% of the dose is unchanged drug and 4-hydroxy derivative (the primary metabolite of avatrombopag) in feces, respectively. No metabolites were detectable in plasma.

In vitro study data using human hepatocytes and recombinant human cytochrome P450 (CYP) suggests that avatrombopag is metabolized by CYP3A4 and CYP2C9. The metabolic and elimination pathways of avatrombopag in humans were shown in Figure1-1[7].

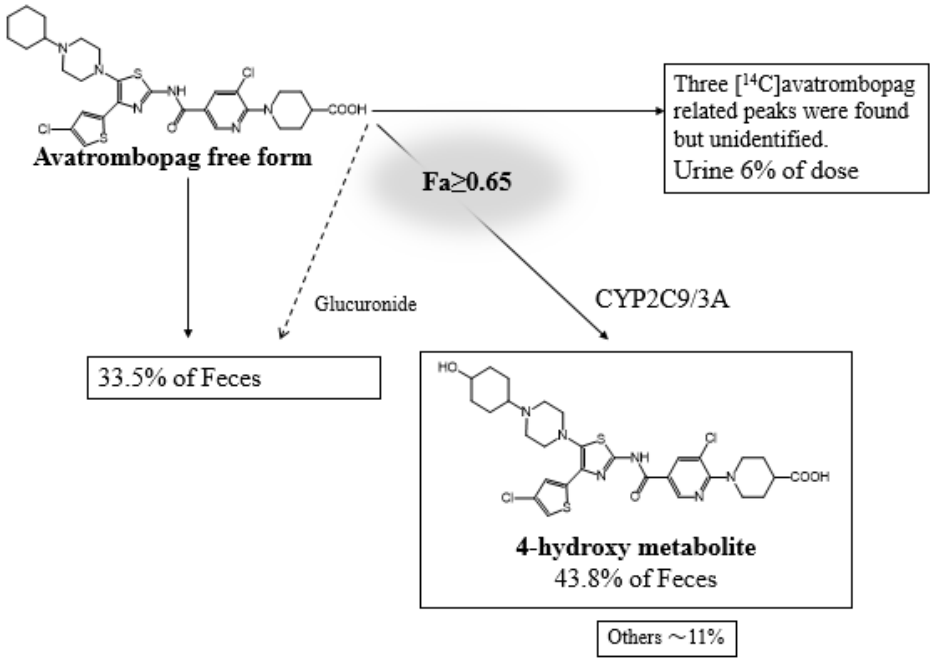


**Figure 1-1 Metabolic and Elimination Pathway of Avatrombopag in Humans**
Fa is assumed to be more than 0.65 from the human mass balance study. The dotted line represents an uncertain pathway. CYP, cytochrome P450; Fa, fraction of administered dose that is absorbed.

The nonclinical pharmacology and toxicology data supported proceeding to clinical testing, therefore, a single-dose study was conducted to characterize and compare the PK (including the food effect), PD (platelet count), and the safety and tolerability between healthy Japanese and White subjects.

## Method

*Study Design*

A randomized, open-label, 5-treatment period, single-dose study was conducted to assess the PK and PD of avatrombopag and to explore the effects of ethnicity. The dose-proportionality of PK, the effect of food on exposure, and the safety and tolerability were compared between Japanese and White subjects. Subjects were

randomly assigned 1:1:1:1 stratified by race to 1 of 4 treatment periods (sequences A to D) as shown in Table 1-1. Each subject received a single oral dose of 40 or 60 mg under fasted and fed (high-fat meal) conditions or 20 mg under fed conditions. The washout period of 28 days or longer was set between the administration of avatrombopag in each period.

**Table 1-1 Study Design and Dosing Paradigm**

| Treatment Period<br>Food condition | 1<br>Fed | 2<br>Fed | 3<br>Fasted | 4<br>Fasted | 5<br>Fed |
|---|---|---|---|---|---|
| Sequence A | 40 mg | 60 mg | 40 mg | 60 mg | 20 mg |
| Sequence B | 60 mg | 40 mg | 40 mg | 60 mg | 20 mg |
| Sequence C | 40 mg | 60 mg | 60 mg | 40 mg | 20 mg |
| Sequence D | 60 mg | 40 mg | 60 mg | 40 mg | 20 mg |

The washout period of 28 days or longer was set between the administration of avatrombopag in each period.

This study was conducted in a total of 24 healthy Japanese and 24 healthy White male and female subjects at a single center (California Clinical Trials Medical Group) in the United States, according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the Institutional Review Board (IRB), and informed consent for all participants was obtained prior to screening.

*Subjects*

Healthy male and female 24 Japanese or 24 white subjects aged 20 to 55 years with body mass index (BMI) from 18 to 28 $kg/m^2$ were included. Japanese subjects were defined as having been born in Japan or Japanese parents and grandparents, living outside of Japan for <5 years, and keeping their Japanese lifestyle, habits, and diet. Subjects were excluded from this study if their platelet counts were less than the limit of normal or more than $350\times10^9/L$ at the time of screening and at each baseline assessment.

*Study Drug Formulation and Administration*

The study drug was provided as a tablet containing 20 mg of avatrombopag (1-(3-chloro-5-{[4-(4-chloro-2-thienyl)-5-(4-cyclohexylpiperazin-l-yl)-1,3-thiazol-2-yl] carbamoyl}-2-pyridyl) piperidine-4-caboxylic acid monomaleate) by Eisai Co., Ltd. Under fasted conditions, subjects were administered study drug following an overnight fast of at least 10 hours with 240 m of water. Subjects were not allowed any food for at least 4 hours after dosing. Under fed conditions, subjects started taking a high-fat meal (approximately 800 to 1000 kcal, with at least 50% calories derived from fat) 30 minutes before the time to receive the study drug[8,9]. Subjects were administered study drug with 240 mL of water at 30 minutes after the start of the meal. Subjects were not allowed any additional food for a period of 4 hours after dosing.

*Bioanalytical Methods*

Plasma was separated by centrifugation at 1500×g for 10 min at 4°C. The plasma samples were stored in polypropylene tubes at approximately –20°C until analysis. The plasma concentrations of avatrombopag were quantified by using a validated liquid chromatography followed by tandem mass spectrometry (LC–MS/MS) in human plasma with sodium heparin as anticoagulant. The method utilized a protein precipitation procedure to extract avatrombopag and deuterated-internal standard (IS, YM-385029; avatrombopag-$d_{10}$) from 100 μL of human plasma, a reversed-phase high-performance liquid chromatography C8 column, 5 μm, 50×2.0 mm column, with a mobile phase gradient using 10 mmol/L ammonium formate in water, pH4 and methanol:acetonitrile (1:1) to separate the analyte from the matrix and an LC–MS/MS instrument with positive

electrospray ionization multiple reaction monitoring mode to quantify the analyte. The mass spectrometer was operated in positive electrospray ionization mode and the resolution setting used was unit for both Q1 and Q3. The multiple reaction monitoring transition was m/z 649.2→267.1 for avatrombopag and m/z 659.4→267.1 for the IS. The interrun accuracy was <4.50%; interrun precision was <10.2% and intrarun accuracy was <6.50%; intrarun precision was <12.3% with all met the acceptance criteria within ±15%. At the lower limit of quantitation of 1.00 μg/L, the interrun accuracy was <-7.20%; interrun precision was <15.1%; intrarun accuracy was <–13.1%;

intrarun precision was <14.8% with all met the acceptance criteria within ±20%. The calibration curve ranged from 1.00 μg/L to 500 μg/L for avatrombopag. Platelet count was determined at study site through a local clinical laboratory.

*PK Assessment*

Serial blood samples for measuring plasma avatrombopag concentration were collected predose and 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, and 96 hours after dosing. Noncompartmental PK analysis was performed to derive PK parameters of avatrombopag in plasma using Phoenix WinNonlin software (Pharsight, Mountain View, California). PK parameters included the maximum observed plasma concentration ($C_{max}$), time at which the highest drug concentration occurs ($t_{max}$), the area under the plasma concentration-time curve from 0 time to time extrapolated to infinity ($AUC_{(0\text{-}inf)}$), and the terminal elimination phase plasma half-life ($t_{½}$).

*PD Assessment*

Blood samples for determination of platelet count (normal range: apparently 150 to $400\times10^9$/L) were collected predose and on days 5, 6, 11, 14, 21, 24, and 28 after avatrombopag administration. The change from baseline in platelet count for each time point after avatrombopag dosing was estimated. Noncompartmental analysis for drug effect was performed to derive PD parameters of avatrombopag in plasma using PhoenixWinNonlin software. PD parameters included the observed time of maximum increase in platelet count following avatrombopag dosing in each treatment ($TE_{max}$), the maximum increase in platelet counts following avatrombopag dosing observed in each treatment ($E_{max}$), and the area under the effect curve for platelet count following avatrombopag dosing (day 1 in each treatment) through 28 days after dosing (Day 28 in each treatment) ($AUEC_{(0–28d)}$).

*Statistical Analysis*

All statistical programming and analyses were performed using Phoenix WinNonlin and SAS software, version 9.2 or later (SAS Institute, Inc, Cary, North Carolina).

1) Comparison of ethnicity

Comparison between Japanese subjects (test) and white subjects (reference) at doses of 40 and 60 mg was made by estimating the percentage of geometric least-squares mean (Japanese/white) and 90% confidence intervals (CIs). Considering PK variability, it was determined that we may conclude that PK was similar between Japanese and white subjects if the percentage of geometric least squares mean was within 0.77 and 1.3.

2) Food effect

Food effect was assessed using ratios of PK parameters (fed/fasted) of the geometric least-squares mean and 90%CIs for PK parameters using a mixed-effect model.

3) Dose proportionality

Dose proportionality was evaluated using a power model to assess the slope parameter and 95%CIs using the equation $\log(Y) = \alpha + \beta\log(X)$, where X is dose and Y is $C_{max}$ or AUC. Dose proportionality was concluded if the slope was contained within the interval of 0.7 to 1.3[10].

## Results

## 1) Demographic and Disposition

Forty-eight healthy subjects were enrolled and randomized, 36 of whom (18 subjects in each race group) completed all planned study procedures. The baseline demographics of the study participants are summarized in Table 1-2. The mean weight and height of the Japanese subjects were slightly lower than those of the white subjects, but there were no other notable differences between Japanese and white subjects in demographic characteristics. Among the 12 subjects who discontinued the study, 3 subjects were discontinued due to noncompliance, 7 subjects withdrew consent, 1 subject was discontinued due to an adverse event of influenza-like illness, and 1 subject was discontinued due to a decrease in pulse rate (60 mg fed conditions).

Table 1-2 The Baseline Demographic Characteristic of Subjects

| Race | N | Sex, n Male/female | Age, y | Weight, kg | Height, cm | BMI, kg/m$^2$ |
|---|---|---|---|---|---|---|
| Japanese | 24 | 12/12 | 35 (22-54) | 62 (42-87) | 165 (148-180) | 23 (19-28) |
| White | 24 | 12/12 | 35 (23-51) | 70 (50-91) | 170 (152-187) | 24 (20-28) |

The values were shown as Mean (Min-Max). BMI = body mass index.

## 2) PK Results

Mean (+ standard error) plasma avatrombopag concentration-time profiles under fed conditions by race group are presented in Figure 1-2. Corresponding PK parameters are summarized in Table 1-3.

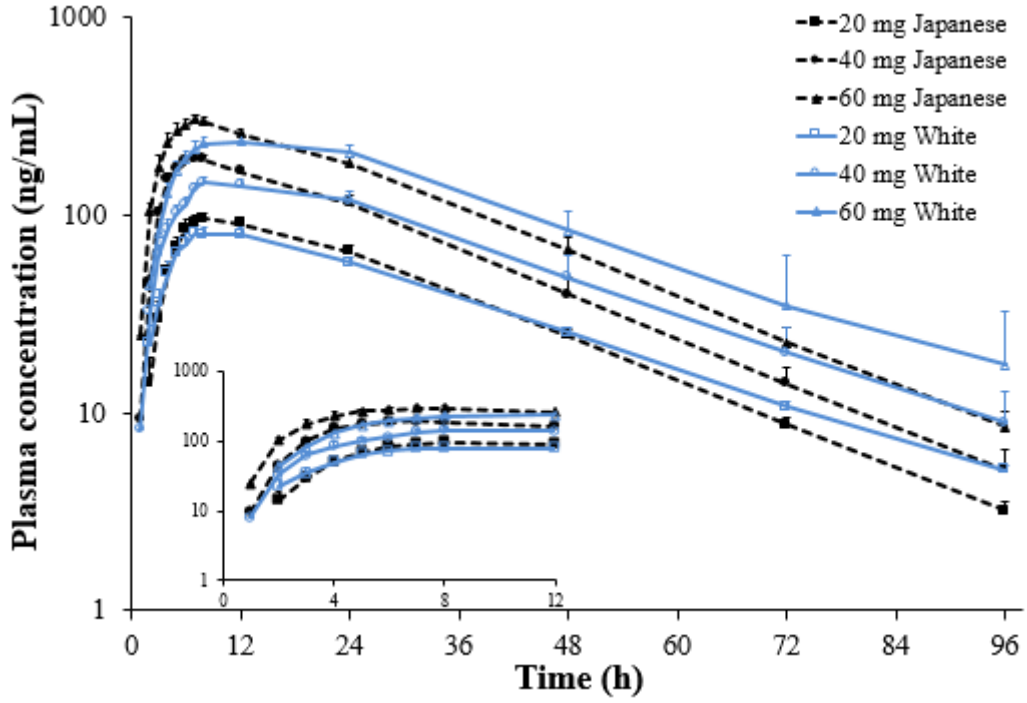


**Figure 1-2 Mean (+SE) plasma avatrombopag concentration-time profiles following single oral doses of 20, 40, and 60 mg under fed conditions in Japanese (dot black line) and White (solid blue line) subjects.**
Semi-log scale. SE, standard error.

**Table 1-3 Pharmacokinetic parameters of avatrombopag and ethnic comparison following single oral dose administration in Japanese and White subjects**

| | | | | Mean (SD) | | | |
|---|---|---|---|---|---|---|---|
| Race | Food condition | Dose (mg) | N | $C_{max}$ (ng/mL) | $t_{max}$[a] (h) | $t_{½}$ (h) | $AUC_{(0\text{-inf})}$ (ng•h/mL) |
| Japanese | Fed | 20 | 18 | 109 (26.9) | 7 (3-12) | 16.4 (2.09) | 3220 (831) |
| | Fed | 40 | 23 | 208 (54.1) | 6 (3-12) | 16.1 (1.96) | 5870 (1790) |
| | Fed | 60 | 23 | 332 (93.3) | 7 (3-24) | 16.0 (1.54) | 9400 (2240) |
| White | Fed | 20 | 18 | 95.4 (49.1) | 7 (3-24) | 18.6 (3.90) | 3160 (2350) |
| | Fed | 40 | 24 | 164 (62.8) | 8 (3-24) | 18.0 (4.13) | 5900 (3560) |
| | Fed | 60 | 24 | 284 (122) | 7.5 (3-24) | 18.2 (3.95)[b] | 10000 (7130)[b] |
| Japanese/White | %GM ratio [90% CIs] | 40 | | 129 [110, 151] | | | 108 [89.1, 131] |
| | %GM ratio [90% CIs] | 60 | | 121 [103, 142] | | | 104 [85.7, 127] |

a: Median (range); b: n=23; $AUC_{(0\text{-inf})}$ = area under the concentration-time curve from zero to infinity; CI = confidence intervals; $C_{max}$ = maximum plasma concentration; %GM ratio = geometric mean of Japanese/ White × 100; $t_{max}$ = time to maximum plasma concentration; $t_{½}$ = terminal half-life.

Following single-dose administration of 20, 40, and 60 mg, avatrombopag under fed conditions attained $C_{max}$ at approximately 6 to 8 hours after dosing in both Japanese and White subjects. Mean $t_{½}$ values were similar in Japanese and Whites, ranging from 16 to 17 hours in Japanese and from 18 to 19 hours in White subjects. Avatrombopag $C_{max}$ at 40- and 60-mg doses in Japanese subjects were slightly higher than those in White subjects. The relative differences expressed as percentages of geometric least-squares means (Japanese/White) for $C_{max}$ indicate that Japanese $C_{max}$ values were 29% higher than those of Whites. In contrast, $AUC_{(0\text{-inf})}$ values were similar in both race groups for the 40- and 60-mg doses. Mean avatrombopag $C_{max}$ and AUC values each increased in a dose-proportional manner following single dose administration of 20, 40, and 60 mg for both race groups under fed conditions.

Overall, consumption of a high-fat meal did not have clinically important effects on the rate or extent of avatrombopag absorption. However, a clinically important outcome of this study was the observation that consumption of a high-fat meal was associated with substantially reduced intersubject variability of avatrombopag PK (Table 1-4) compared to dosing under fasted conditions; 23.7% to 30.0% for under fed conditions vs. 46.1% to 53.0% under fasted conditions in Japanese, 38.2% to 62.3% for under fed conditions vs. 51.9% to 60.8% under fasted conditions in White. This finding led to the recommendation in further clinical testing to administer avatrombopag with food.

**Table 1-4 The Food Effect on Avatrombopag PK parameters**

| Race | PK Parameters | Dose (mg) | N | | Geometric LS Mean (%CV) | | %Ratio | 90% Confidence Interval of %Ratio |
|---|---|---|---|---|---|---|---|---|
| | | | Fed | Fasted | Fed | Fasted | | |
| Japanese | $C_{max}$ | 40 | 23 | 18 | 199 (26.0) | 238 (46.1) | 83.9 | 68.6, 103 |
| | (ng/mL) | 60 | 23 | 18 | 320 (28.1) | 333 (53.0) | 96.2 | 78.6, 118 |
| | $t_{max}$ | 40 | 23 | 18 | 6 (3-12) | 5 (3-12) | | |
| | (h) | 60 | 23 | 18 | 7 (3-24) | 5 (4-7) | | |
| | $AUC_{(0\text{-inf})}$ | 40 | 23 | 18 | 5640 (30.0) | 6130 (47.9) | 91.9 | 75.6, 112 |
| | (ng•h/mL) | 60 | 23 | 18 | 9130 (23.7) | 8430(51.7) | 108 | 89.2, 132 |
| White | $C_{max}$ | 40 | 24 | 21 | 155 (38.2) | 117 (59.5) | 132 | 108, 164 |
| | (ng/mL) | 60 | 24 | 20 | 263 (42.8) | 183 (60.1) | 144 | 116, 179 |
| | $t_{max}$ | 40 | 24 | 21 | 8 (3-24) | 6 (4-24) | | |
| | (h) | 60 | 24 | 20 | 7.5 (3-24) | 5 (4-24) | | |
| | $AUC_{(0\text{-inf})}$ | 40 | 24 | 21 | 5210 (53.3) | 3340 (51.9) | 156 | 126, 194 |
| | (ng•h/mL) | 60 | 23 | 20 | 8690 (62.3) | 4840 (60.8) | 180 | 144, 224 |

%Ratio = Fed/ Fasted × 100. a: Median (range); $AUC_{(0\text{-inf})}$ = area under the concentration-time curve from time 0 to infinity; $C_{max}$ = maximum drug concentration; $t_{max}$ = time to reach maximum concentration after drug administration.

Geometric least-squares mean values at 40- and 60-mg doses comparing the fed and fasted administrations were 83.9% and 96.2% for $C_{max}$, 91.9% and 108% for $AUC_{(0\text{-inf})}$ in Japanese subjects. Geometric least-squares mean values at 40- and 60-mg doses comparing the fed and fasted administrations were 132% and 144% for $C_{max}$, 156% and 180% for $AUC_{(0\text{-inf})}$ in White subjects. The 90% CIs of neither percentage ratio met the bioequivalence criteria due to large variability of PK parameters, especially under fasted conditions. Coadministration with a high-fat meal did not affect $t_{max}$ of avatrombopag in either race group administered single 40- or 60-mg doses.

## 3) PD Results

Increases in platelet count following single doses of avatrombopag were observed at 20- to 60-mg doses. Platelet counts generally increased to a maximum mean change from baseline of approximately 50 to $110\times10^9$/L on days 8 to 11, then decreased to approximate baseline levels by the end of the treatment period (day 28) as illustrated in Figure 1-3. Although characterized by relatively high variability, the response of platelet count was similar between race groups.

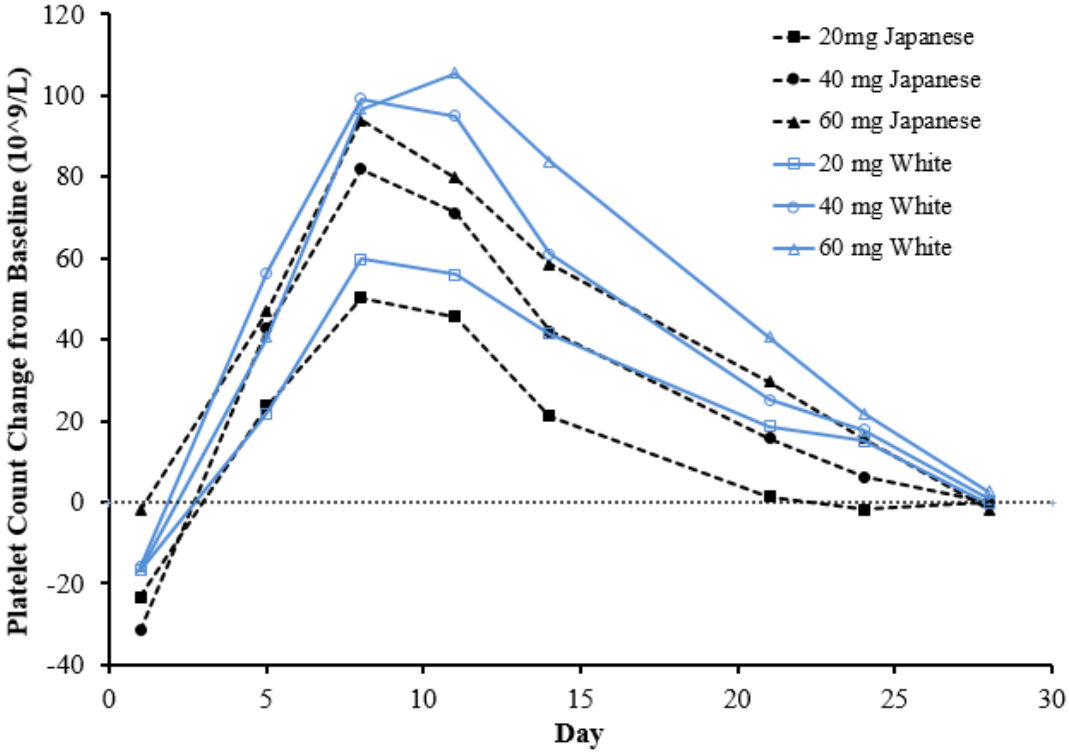


**Figure 1-3 Mean platelet count vs time profile following single dose under fed conditions.**

The PD parameters were comparable between Japanese and White subjects under fed conditions (Table 1-5). Across all treatments and race groups, the median observed time of maximum increase in platelet count was 8 to 11 hours. Only 1 White subject in each cohort administered 40 and 60 mg fed had a maximum increase in platelet counts >500×$10^9$/L. The systemic exposure to avatrombopag appeared to be correlated with area under the effect curve for platelet count over 28 days of treatment.

**Table 1-5 Pharmacodynamic parameters of avatrombopag following single oral dose administration in Japanese and White subjects under fed condition.**

| | | | | Mean (SD) | | |
|---|---|---|---|---|---|---|
| Race | Food condition | Dose (mg) | N | $E_{max}$ ($10^9$/L) | $TE_{max}$[a] (day) | $AUC_{(0-28d)}$ (day•$10^9$/L) |
| Japanese | Fed | 20 | 18 | 300 (55.3) | 8 (5-11) | 432 (1020) |
| | Fed | 40 | 23 | 323 (66.6) | 8 (5-11) | 887 (988) |
| | Fed | 60 | 23 | 333 (61.9) | 8 (8-28) | 1160 (671) |
| White | Fed | 20 | 18 | 302 (79.8) | 11 (8-21) | 743 (779) |
| | Fed | 40 | 24 | 329 (69.4) | 8 (8-28) | 1260 (602) |
| | Fed | 60 | 23 | 340 (80.9) | 11 (8-21) | 1430 (772) |

a: Median (range); $AUEC_{(0-28d)}$ = area under the effect curve for platelet count following avatrombopag dosing (Day 1 in each treatment) through 28 days after dosing (Day 28 in each treatment); $E_{max}$ = maximum increase in platelet counts following avatrombopag dosing observed in each treatment; SD = standard deviation; $TE_{max}$ = observed time of maximum increase in platelet count following avatrombopag dosing in each treatment.

## Discussion

The high PK variability seen in the fasted state may mask potential PK difference between Japanese and White subjects and assessment of dose-proportionality, therefore these evaluations were conducted using the PK and PD data under fed condition.

Following the oral single-dose administration under fed condition, avatrombopag showed linear PK across a range of 20 to 60 mg dose. The absorption of avatrombopag is relatively slow, with peak plasma avatrombopag concentrations observed at approximately 5 to 8 hours postdose. Avatrombopag is characterized by poor aqueous solubility, and the slow absorption rate may reflect solubility-rate–limited absorption. Importantly, poor solubility did not impact the rate or extent of drug absorption across the range of doses tested, as evidenced by confirmation of dose proportionality in $C_{max}$ and AUC for doses ranging from 20 to 60 mg. Values of $t_{max}$ and $t_{½}$ are constant and independent of dose.

Administration of avatrombopag with a high-fat meal did not have an impact on the rate or extent of absorption in Japanese subjects. However, exposure was increased in white subjects when avatrombopag was administered with a high-fat meal. The apparent effects of a high-fat meal on the exposure in White subjects is most likely a reflection of high variability and lower than expected PK exposures under fasted conditions rather than a true food effect in the White subjects only. An observation of avatrombopag PK was that the avatrombopag plasma exposures after single dosing under fasted condition were characterized by high intersubject variability, with coefficient of variation (CV%) of approximately 46.1% to 60.8%. Importantly, the intersubject variability was substantially reduced under fed conditions, which ranged from approximately 23.7% to 30% CV% in Japanese or approximately 38.2% to 62.3% CV% in Whites. In previous study, a low-fat (500 kcal, containing fat content of approximately 5% of total caloric content of the meal) or high-fat meal did not affect avatrombopag AUC and $C_{max}$, but reduced the intra-subject variability by 50 to 70% and inter-subject variability by 40 to 49%[11]. Interestingly, food affected only the variability in the derived PK parameters without influencing the rate or extent of absorption, as shown by the lack of an effect of food on mean values of $C_{max,}$ AUC, and

$t_{max}$. These results could be explained by food potentially prolonging gastrointestinal transit and thus allowing greater uniformity of solubility of avatrombopag, thereby reducing variability in absorption. Based on this result, avatrombopag is administered under fed conditions for clinical use.

While substantially delayed relative to PK, avatrombopag increased platelet count in a dose-dependent manner. After single doses, platelet count reached a maximum by 11 days postdose and then returned to baseline level by 27 days postdose. This delayed response of platelet count is predicted from the hypothesized mechanism of action for avatrombopag, which acts on the TPO receptor concurrently with endogenous TPO and differentiation into megakaryocytes, and thereby increases the number of circulating platelets. Given this delay in PD response and the known natural fluctuation of platelet count during the day, small variations in PK generally have no significant influence on platelet response.

The PK and PD of avatrombopag were similar between Japanese and White subjects, thus enabling the possibility of the same dosage regimen and simultaneous global clinical development, which may lead to faster access for the patients who need these new products.

# Chapter 2 Pharmacokinetic/Pharmacodynamic Drug-drug Interactions of Avatrombopag when Co-administered with Dual or Selective CYP2C9 and CYP3A Interacting Drugs

## Introduction

Avatrombopag metabolism is mediated by CYP2C9 and CYP3A to form 4-hydroxy metabolite. The relative percentage contribution of the two major CYP enzymes toward the CYP dependent metabolism of avatrombopag was assessed using the relative activity factor in human liver microsomes and recombinant CYP enzyme[12]. Among the two drug-metabolizing CYP isoforms evaluated, the contributions of CYP2C9 in 4-hydroxy cis and trans metabolites were 76.2% and 17.1%, respectively. The contribution of CYP3A4 on avatrombopag 4-hydroxy cis and trans metabolites were 23.8% and 82.9% (Table 2-1). Overall, the data suggested that avatrombopag metabolism is mediated by CYP2C9 and CYP3A equally to form 4-hydroxy metabolite. These CYP enzymes seemed likely to contribute ≥25% of total clearance each based on in vitro data.

**Table 2-1 Percent Contributions of CYP2C9 and CYP3A4 to the Formation of 4-Hydroxyl Metabolite of Avatrombopag**

| Metabolite | CYP Isoform Tested | Relative Contribution (%) |
|---|---|---|
| 4-hydroxy *cis* | CYP2C9 | 76.2 |
| | CYP3A4 | 23.8 |
| 4-hydroxy *trans* | CYP2C9 | 17.1 |
| | CYP3A4 | 82.9 |

Relative Contribution = % Contribution of each CYP / Total % Contribution from each metabolite.
% Contribution = $[(V_{max}/K_m \text{ in rCYP})/(V_{max}/K_m \text{ in HLM})] \cdot RAF \cdot 100$.
$RAF = (V_{max}/K_m \text{ of CYP in HLM})/(V_{max}/K_m \text{ of rCYP})$.

Physiologically based pharmacokinetic (PBPK) modeling and simulation can be used to predict the PK behavior of drug using compound-specific parameters from nonclinical and clinical data[13]. PBPK models were developed for avatrombopag using SimCYP (version 14.1) software (www.simcyp.com) and drug-drug interaction (DDI) simulations of avatrombopag were performed with the CYP inhibitors itraconazole, ketoconazole, fluconazole, verapamil, sulphaphenazole, and with the CYP inducer rifampin. The predicted DDI risks were calculated from the ratios of the area under

the curve of avatrombopag in the presence and absence of the inhibitor or inducer (AUCR) in Table 2-2.

**Table 2-2 Predicted AUC Ratios (AUCR) and DDI risk for Avatrombopag 20 mg oral tablet.**

| Concomitant drug | AUCR[a] | Predicted DDI risk[b] |
|---|---|---|
| Itraconazole 200 mg QF (strong CYP3A inhibitor) | 1.29-1.78 | Small |
| Fluconazole 400 mg QD (moderate CYP2C9 and CYP3A inhibitor) | 2.11-3.59 | Moderate |
| Ketoconazole 200 mg BID (strong CYP3A inhibitor) | 1.44-2.27 | Small-Moderate |
| Sulphaphenazole 2 g QD (CYP2C9 inhibitor) | 1.48-2.30 | Small-Moderate |
| Verapamil 240 mg QD (moderate CYP3A) | 1.17-1.47 | Negligible-Small |
| Rifampin 600 mg QD (strong CYP3A and moderate CYP2C9 inducer) | 0.22-0.43 | Moderate |

a: the range of AUCR which was derived from 2 different absorption models and 3 different clearance models.
b: Impact qualified according to "FDA Guidance" for Industry. Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.
AUCR, the ratios of the area under the curve of avatrombopag in the presence and absence of the inhibitor or inducer; BID, twice a day; QD, once a day; QF, four times a day

CYP2C9 and CYP3A-mediated interactions were considered as the highest-risk metabolism-based interactions that might affect the exposure of avatrombopag according to in vitro metabolism data and PBPK simulations. To evaluate the maximum potential effect of metabolism-based inhibition, fluconazole was selected as a moderate dual inhibitor of CYP2C9 and CYP3A. Fluconazole is the only reference CYP2C9 inhibitor recommended in the European Medicines Agency guideline[14], and among those noted in the Food and Drug Administration[15-17], and Ministry of Health, Labour and Welfare draft guidance[18]. Itraconazole was selected as a strong CYP3A inhibitor to evaluate the impact of strong CYP3A inhibition, and has been shown not to impact the CYP2C9 activity[19,20]. Although the inhibition potential of itraconazole is considered to be less than that of ketoconazole[21], itraconazole has been used in clinical drug–drug interaction studies as a typical inhibitor of CYP3A since ketoconazole was reported to cause serious safety concerns related to liver toxicities[22]. To evaluate the maximum effect of metabolism-based induction, rifampin was selected as a strong CYP3A inducer with moderate CYP2C9 inducing potency[14,17,18].

A clinical drug interaction study was therefore conducted with the above-mentioned three drugs to evaluate the impact of those drugs on PK and PD and safety of avatrombopag and provide appropriate guidance to the prescribing physicians on

concomitant administrations of avatrombopag with drugs that are known CYP2C9- and/or CYP3A-interacting drugs.

## Method

*Study Design*

This study was an open-label, drug-drug interaction study at a single center (Worldwide Clinical Trials Early Phase Services, LLC) in the United State. The study was divided into three Parts. In Part A, the effects of steady-state dosing of a moderate inhibitor of CYP2C9 and CYP3A (i.e. fluconazole) on single dose PK of avatrombopag were assessed. In Part B, the effects of steady-state dosing of a strong CYP3A inhibitor (itraconazole) on the single dose PK of avatrombopag were assessed. In Part C, the effects of steady-state dosing of a strong CYP3A and moderate CYP2C9 inducer (rifampin) on the single dose PK of avatrombopag were assessed. There were 16 subjects enrolled in each study part, and each part was conducted in parallel. Each part of the study consisted of two treatment periods: Period 1 (administration of a single oral dose of avatrombopag 20-mg alone) and Period 2 (administration of oral doses of each inhibitor or inducer alone and concomitant administration of a single oral dose of avatrombopag 20-mg with each inhibitor or inducer [fluconazole in Part A, itraconazole in Part B, or rifampin in Part C]). Each period was separated by a washout interval of at least 28 days. Subjects whose platelet count exceeded $600 \times 10^9$/L during the study were to be discontinued. Subjects whose platelet count exceeded $400 \times 10^9$/L were to be administered low-dose aspirin at the discretion of the investigator. This study was approved by the IRB of the site, and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants were given the explanation of the study, and written informed consent was obtained prior to screening.

*Subjects*

A total of 48 healthy, nonsmoking subjects, male and female aged 18–55 years with BMI 18–28 kg/m$^2$ were enrolled. There were 16 healthy male and female subjects in each Part. Subjects were excluded if: their platelet count was not between the lower limit of normal and $300 \times 10^9$/L at the time of screening and at baseline of each period;

they used any prescription drugs or St. John's Wort within 4 weeks before first dosing of avatrombopag; they took over-the-counter medications within 2 weeks before; or they took any food or beverages (e.g. alcohol, grapefruit juice) that might have affected the various drug metabolizing enzymes and transporters within 1 week before first dosing of avatrombopag. Subjects whose platelet count exceeded $600\times10^9$/L during the study were to be discontinued.

*Study Drug Formulation and Administration*

Avatrombopag 20-mg tablet was administrated under fed conditions (approximately 800–1000 calories, containing fat content of approximately 50% of total caloric content of the meal).

Part A: Subjects were administered a single oral dose of avatrombopag 20 mg on Day 1 of Period 1. Subjects were administered fluconazole (Diflucan 200-mg tablet; Pfizer, NY, USA) 400 mg once daily on Days 1 to 16 and a single dose of avatrombopag 20 mg on Day 7 in Period 2. Each dose of avatrombopag was administered 30 min after the start of the meal.

Part B: Subjects were administered a single oral dose of avatrombopag 20 mg on Day 1 of Period 1. Subjects were administered itraconazole (Sporanox 100-mg capsule; Janssen Pharma, NJ, USA) 200 mg twice daily on Day 1 and 200 mg once daily on Days 2 to 16 of Period 2. A single dose of avatrombopag 20 mg was administered on Day 7 of Period 2. Each dose of avatrombopag was administered 30 min after the start of the meal.

Part C: Subjects were administered a single oral dose of avatrombopag 20 mg on Day 1 of Period 1. In Treatment Period 2, rifampin (Rifadin 200-mg capsule; Sanofi-aventis U.S. LLC, Bridgewater NJ, USA) 600 mg was administered once daily on Days 1 to 16. To avoid a food effect on rifampin absorption[23], each dose was administered 1 h before subjects consumed a meal. On Day 7 of Period 2, rifampin 600 mg and avatrombopag 20 mg were administered 1 h before starting meal consumption and 30 min after starting meal consumption, respectively.

*Bioanalytical Methods*

The Bioanalytical Methods refer to the Method in Chapter 1. In addition, lack of bioanalytical interference between avatrombopag and the inhibitor or inducer (fluconazole, itraconazole and rifampin) were documented prior to plasma sample analysis.

*PK Assessments*

Serial blood samples for measuring plasma avatrombopag concentration were collected predose and 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 144, and 216 hours after avatrombopag administration. Noncompartmental PK analysis method refers to Chapter 1.

*PD Assessments*

Blood samples for determination of platelet count (normal range: apparently 150 to $400\times10^9$/L) were collected predose and on days 3, 4, 5, 6, 7, 8, 12, 14, 21, and 28 after avatrombopag administration. PD analysis method refers to Chapter 1.

*Statistical Analysis*

Statistical analyses were performed using Phoenix WinNonlin and SAS (Version 9.3, SAS institute Inc., Cary, NC, USA) software. PK data were summarized using descriptive statistics. Log transformed $C_{max}$ and $AUC_{(0\text{-inf})}$ and untransformed $t_{½}$ were analyzed using mixed effect models to yield the ratios (test/reference) of geometric least square means and 90% CIs, and the difference between test and reference and 90% CIs, respectively. The mixed model included period as a fixed effects and subjects as a random effect. A nonparametric (Hodges–Lehmann) method was used to estimate the median difference between test and reference for $t_{max}$.

The statistical analysis for PD parameters was performed on untransformed data due to the presence of negative values using a mixed effect model with period as a fixed effect and subject as a random effect. Treatment means, difference of treatment means and 90% CIs were presented on the untransformed data.

## Results

## 1) Part A; Fluconazole, a dual moderate inhibitor of CYP2C9 and CYP3A

Avatrombopag plasma concentrations were elevated when avatrombopag was coadministered with fluconazole compared to avatrombopag alone (Figure 2-1). Coadministration of avatrombopag and fluconazole increased $C_{max}$ and AUC of avatrombopag by 1.17-fold and 2.16-fold, respectively. Coadministration of fluconazole extended $t_{½}$ of avatrombopag by approximately 2.0-fold (19.7 h in avatrombopag alone vs. 39.8 h in avatrombopag+fluconazole) but $t_{max}$ was unaffected by fluconazole coadministration (Table 2-3). Consistent with the PK effect of fluconazole, the mean profile of platelet count over time was greater during coadministration with fluconazole compared with avatrombopag alone. Coadministration of avatrombopag and fluconazole increased $E_{max}$ by 1.66-fold (calculated as a ratio of mean value for coadministration of fluconazole and avatrombopag to mean for avatrombopag alone) and the mean difference in $E_{max}$ between two treatments was $21.19\times10^9$/L. There was approximately a 1.47-fold increase in $AUEC_{(0\text{-}28d)}$ with coadministration of avatrombopag and fluconazole (Table 2-4). Relative to the magnitude of PK interaction, coadministration with fluconazole resulted in a PD interaction to a lesser degree; however, the $>20\times10^9$/L mean difference in $E_{max}$ with fluconazole coadministration is considered a clinically significant effect.

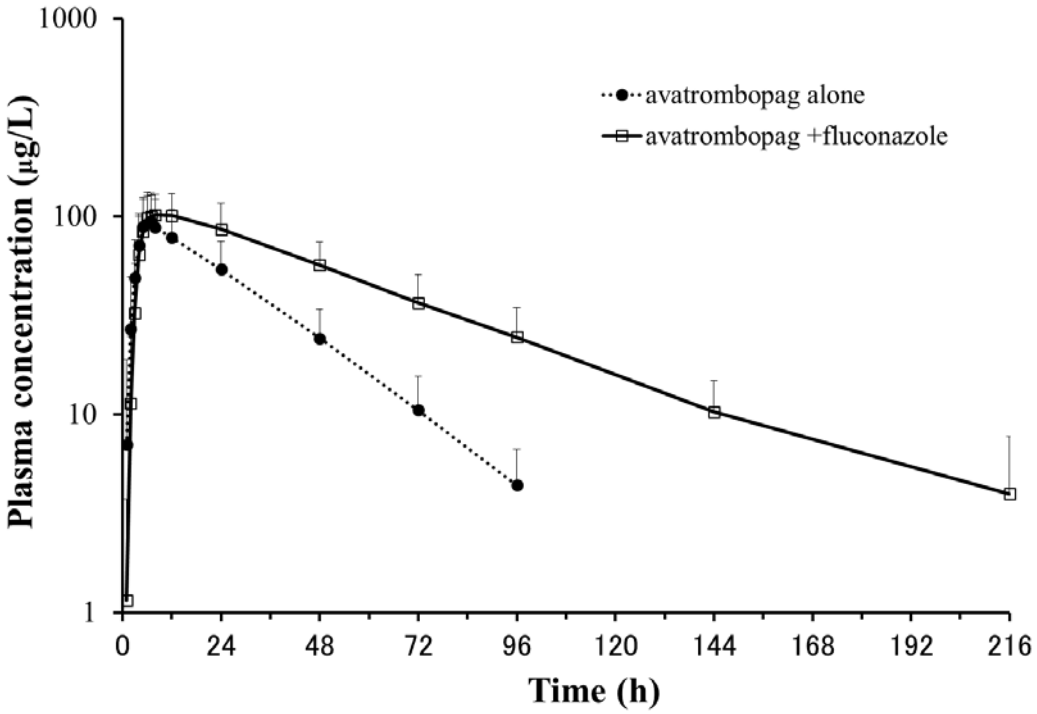


**Figure 2-1 Mean (+ SD) plasma concentration–time profiles of avatrombopag following administration of avatrombopag alone and concomitantly with fluconazole.**

n = 16

**Table 2-3. Summary of pharmacokinetic parameters of avatrombopag and statistical comparisons following administration of avatrombopag 20 mg with or without fluconazole, itraconazole and rifampin**.

| Treatment (Test:Reference) | Parameter | n | | Arithmetic mean (Standard deviation) | | LS Mean Ratio | 90% confidence interval |
|---|---|---|---|---|---|---|---|
| | | Test | Reference | Test | Reference | | |
| Avatrombopag+Fluconazole: avatrombopag | $C_{max}$ (µg/L) | 16 | 16 | 115 (34.5) | 101 (37.1) | 1.17 | 0.964, 1.42 |
| | $AUC_{(0\text{-}inf)}$ (µg·h/L) | 15 | 16 | 6800 (2340) | 3170 (1160) | 2.16 | 1.71, 2.72 |
| | $t_{½}$ (h) | 15 | 16 | 39.8 (5.12) | 19.7 (2.44) | 20.2[a] | 18.4, 22.1[a] |
| | $t_{max}$ (h) | 16 | 16 | 7 (5, 24) | 7 (4, 12) | ND | ND |
| Avatrombopag+Itraconazole: avatrombopag | $C_{max}$ (µg/L) | 13 | 16 | 123 (55.0) | 106 (31.2) | 1.07 | 0.855, 1.35 |
| | $AUC_{(0\text{-}inf)}$ (µg·h/L) | 13 | 16 | 4990 (3070) | 3380 (1530) | 1.37 | 1.10, 1.72 |
| | $t_{½}$ (h) | 13 | 16 | 28.0 (9.77) | 19.6 (3.25) | 8.47[a] | 5.25, 11.7[a] |
| | $t_{max}$ (h) | 13 | 16 | 6 (3, 12) | 6 (4, 12) | ND | ND |
| Avatrombopag+Rifampin: avatrombopag | $C_{max}$ (µg/L) | 14 | 16 | 108 (33.5) | 103 (37.9) | 1.04 | 0.882, 1.23 |
| | $AUC_{(0\text{-}inf)}$ (µg·h/L) | 13 | 16 | 1790 (776) | 3340 (1760) | 0.568 | 0.465, 0.623 |
| | $t_{½}$ (h) | 13 | 16 | 9.77 (1.49) | 20.3 (5.34) | -10.5[a] | -12.7, -8.21[a] |
| | $t_{max}$ (h) | 14 | 16 | 5 (2, 12) | 6 (3, 8) | ND | ND |

$C_{max}$, $AUC_{(0\text{-}inf)}$ and $t_{½}$ presented as Arithmetic means (Standard deviation), $t_{max}$ presented as Median (range). a: LS mean difference (90% confidence interval)

$AUC_{(0\text{-}inf)}$, area under the concentration-time curve from 0 time extrapolated to infinite time; $C_{max}$, maximum observed concentration; LS, least square; ND, not determined; $t_{½}$, terminal elimination phase half-life; $t_{max}$, time at which the highest drug concentration occurs.

**Table 2-4. Summary of pharmacodynamic parameters and statistical comparisons following administration of avatrombopag 20 mg with or without fluconazole, itraconazole and rifampin**.

| Treatment (Test:Reference) | Parameter | n | | Arithmetic mean (Standard deviation) | | LS Mean Difference | 90% confidence interval |
|---|---|---|---|---|---|---|---|
| | | Test | Reference | Test | Reference | | |
| Avatrombopag+Fluconazole: avatrombopag | $E_{max}$ ($10^9$/L) | 16 | 16 | 307 (64.5) | 285 (59.9) | 21.19 | 2.89, 39.49 |
| | $TE_{max}$ (day) | 16 | 16 | 10 (7, 12) | 10 (7, 12) | ND | ND |
| | $AUEC_{(0-28d)}$ (h·$10^9$/L) | 16 | 16 | 23300 (14100) | 15800 (7790) | 7480 | 2400, 12560 |
| Avatrombopag+Itraconazole: avatrombopag | $E_{max}$ ($10^9$/L) | 13 | 16 | 307 (84.1) | 314 (73.2) | -5.92 | -30.98, 19.14 |
| | $TE_{max}$ (day) | 13 | 16 | 10 (3, 21) | 10 (4, 28) | ND | ND |
| | $AUEC_{(0-28d)}$ (h·$10^9$/L) | 12 | 14 | 25100 (18100) | 18100 (11800) | 6658 | 1200, 12116 |
| Avatrombopag+Rifampin: avatrombopag | $E_{max}$ ($10^9$/L) | 14 | 16 | 307 (40.4) | 317 (42.1) | -9.73 | -19.50, 0.05 |
| | $TE_{max}$ (day) | 14 | 16 | 7 (5, 12) | 8.5 (5, 28) | ND | ND |
| | $AUEC_{(0-28d)}$ (h·$10^9$/L) | 14 | 15 | 3460 (10300) | 15300 (8600) | -12001 | -14905, -9096 |

$E_{max}$ and $AUEC_{(0-28d)}$ presented as Arithmetic means (Standard deviation), $TE_{max}$ presented as Median (range).
$AUEC_{(0-28d)}$, area under the effect curve for platelet count; $E_{max}$, maximum platelet counts; LS, least square; ND, not determined; $TE_{max}$, observed time of maximum increase in platelet counts

## 2) Part B; Itraconazole, a strong CYP3A inhibitor

Mean plasma concentrations of avatrombopag during coadministration of itraconazole were slightly higher than after avatrombopag alone (Figure 2-2). Following coadministration of itraconazole, $C_{max}$ and $t_{max}$ of avatrombopag did not show apparent difference whereas $AUC_{(0–inf)}$ increased by 1.37-fold and $t_{½}$ was prolonged 1.4-fold compared to avatrombopag alone (Table 2-3).

The mean profile of platelet count over time was similar between coadministration with itraconazole and avatrombopag alone. The mean difference in $E_{max}$ for avatrombopag alone and for coadministration with itraconazole was not statistically significant (Table 2-4), indicating that itraconazole has no impact on the PD effect of avatrombopag.

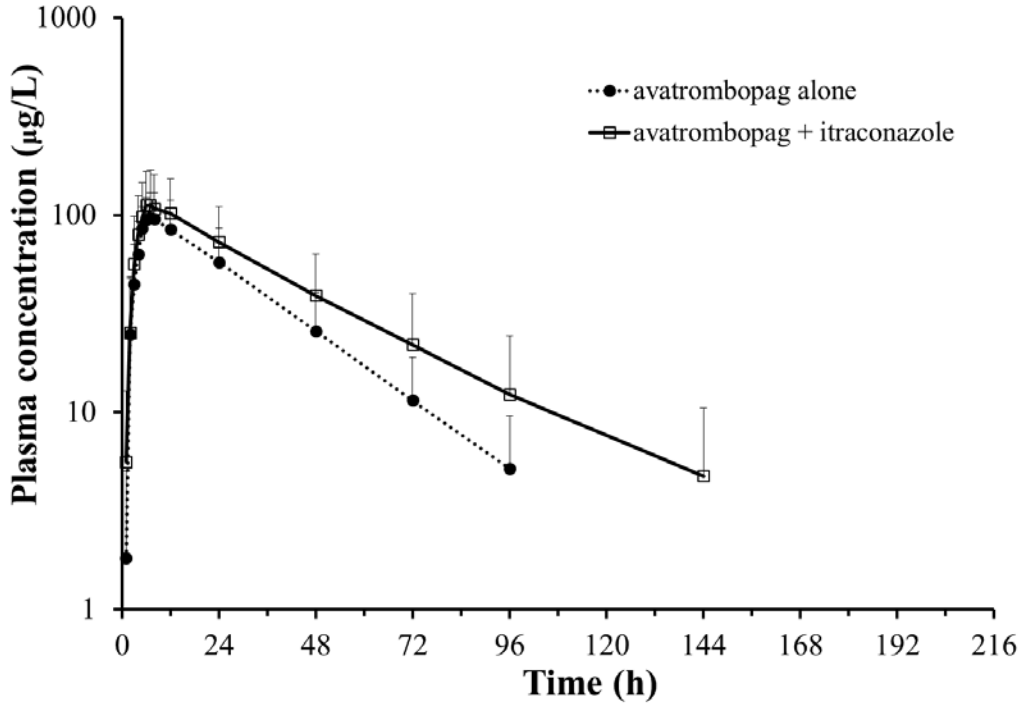


**Figure 2-2 Mean (+ SD) plasma concentration–time profiles of avatrombopag following administration of avatrombopag alone and concomitantly with itraconazole.**

avatrombopag alone: n=16, avatrombopag + itraconazole: n=13

## 3) Part C; Rifampin, a strong CYP3A and moderate CYP2C9 dual inducer

After $C_{max}$ was reached, mean plasma concentrations of avatrombopag during coadministration with rifampin declined more rapidly than those of avatrombopag administered alone (Figure 2-3). Coadministration of rifampin resulted in no apparent

difference in $C_{max}$ or $t_{max}$ but did lead to an approximately 0.5-fold decrease in AUC and a 0.5-fold shortening of $t_{½}$ (20.3 h for avatrombopag alone vs. 9.77 h for avatrombopag+rifampin) were observed (Table 2-3).

The platelet count on coadministration with rifampin returned to baseline level by approximately Day 14, i.e. 7 days after administration of avatrombopag with rifampin, while the platelet count on administration avatrombopag alone returned to baseline by 27 days after administration of avatrombopag. Further to this faster return to baseline platelet levels on coadministration with rifampin, there was approximately a 5-fold reduction in $AUEC_{(0\text{-}28d)}$ with coadministration of avatrombopag and rifampin compared to that of avatrombopag alone. However, the mean difference in $E_{max}$ for avatrombopag alone and coadministration with rifampin was not statistically significant (Table 2-4).

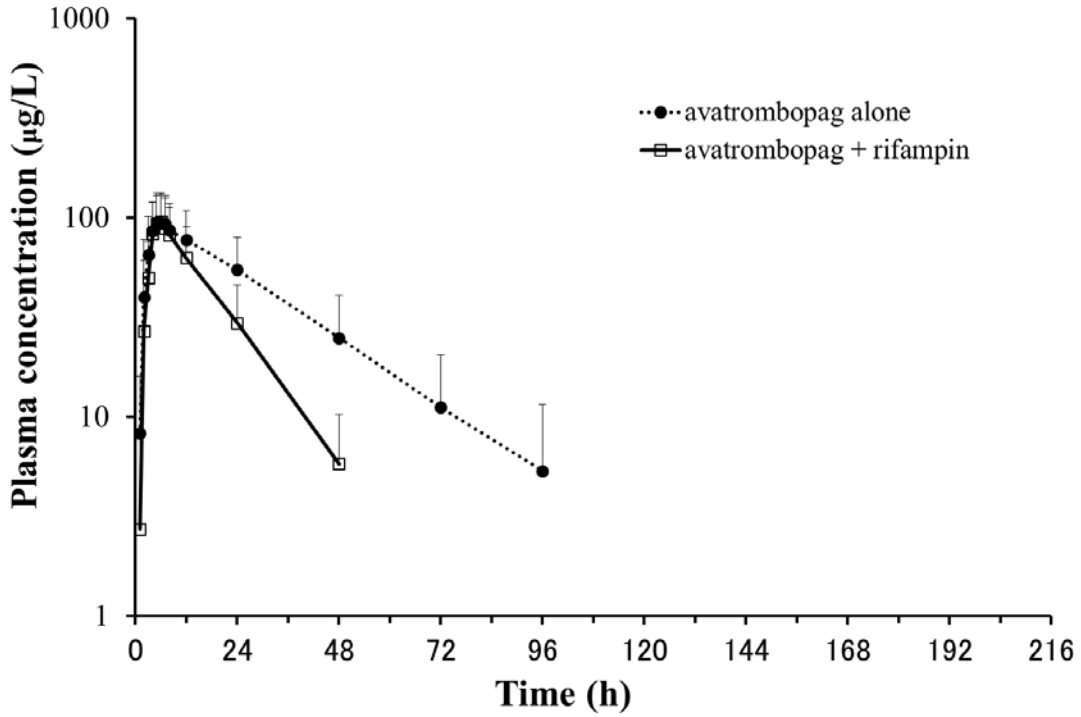


**Figure 2-3 Mean (+ SD) plasma concentration–time profiles of avatrombopag following administration of avatrombopag alone and concomitantly with rifampin.**
avatrombopag alone: n=16, avatrombopag + rifampin: n=14

## Discussion

The study used fluconazole, a dual moderate inhibitor of CYP2C9 and CYP3A; itraconazole, a strong CYP3A only inhibitor; and rifampin, a dual inducer having strong inducing potency of CYP3A and moderate potency of CYP2C9. In vitro data using

recombinant CYP enzyme indicated that CYP2C9 and CYP3A contributed equally to the metabolism of avatrombopag; no other major enzymes were identified. The evaluations of the interaction with the three different interacting drugs in this study were expected not only to provide insights into the relative role of either CYP2C9 or CYP3A in metabolic clearance of avatrombopag, but also to be helpful in providing dosing recommendations on concomitant use of such interacting drugs with avatrombopag.
The study designs proposed for each of these interactions were standard procedures intended to maximize the extent of inhibition/induction of the interacting drugs under steady-state dosing conditions[24-26] and assessing those effects on a single dose profile of avatrombopag.

Results demonstrated a significant increase in systemic exposure to avatrombopag (AUC: 2.16-fold) when coadministered with a dual inhibitor of CYP2C9 and CYP3A, fluconazole; a smaller effect (1.17-fold) was observed on $C_{max}$. Among PD parameters such as $E_{max}$ and $AUEC_{(0-28d)}$, for clinical practice, physicians refer to the maximum increase in platelet count; thus, $E_{max}$ is the determining factor for making decisions on whether the patients require platelet transfusion[27-29]. However, $AUEC_{(0-28d)}$ is also useful when considering clinical relevance. For example, a greater than $20\times10^9$/L increase in $E_{max}$ caused by fluconazole coadministration might become a trigger of the event of portal vein thrombosis and thrombophlebitis septic. Thus, the finding that $AUEC_{(0-28d)}$ was significantly increased by fluconazole co-administration is clinically important. Accordingly, dose adjustment of avatrombopag might be needed when coadministered with dual inhibitors of CYP3A and CY2C9.

In contrast, a strong CYP3A inhibitor, itraconazole, had milder effects on the avatrombopag PK and PD than those of fluconazole. Even though inhibition by itraconazole is known to be a less potent CYP inhibitor compared to ketoconazole[21], the PBPK simulation results predicted that ketoconazole would also have a milder effect on the avatrombopag than those of fluconazole. As itraconazole is known to have no impact on CYP2C9 activity[19,20], the substantial impact of fluconazole suggests that CYP2C9 may play a more dominant role in metabolic clearance of avatrombopag than CYP3A.

Coadministration with a dual inducer of CYP2C9 and CYP3A, rifampin, demonstrated an approximately 0.5-fold decrease in AUC without any effect on $C_{max}$. Avatrombopag $t_{½}$ was shortened by approximately 10 h when coadministered with rifampin. Taken together with drug interactions seen with inhibitors, the results of coadministration with rifampin is likely to be driven primarily by CYP2C9 induction. Regarding the impact of coadministration of rifampin on the platelet count profile, there was an approximate 5-fold reduction in $AUEC_{(0\text{-}28d)}$ without any impact on $E_{max}$. Even though $E_{max}$ is more relevant in influencing the decisions on need of platelet transfusions for a patient requiring a surgical procedure, a 5-fold reduction in $AUEC_{(0\text{-}28d)}$ has significant clinical impact.

# Chapter 3 Population PK/PD analyses of Avatrombopag in Patients with Chronic Liver Disease

## Introduction

The objectives of this analysis were to describe the PK characteristics of avatrombopag in healthy subjects and patients with chronic liver disease (CLD), to compare the PK in CLD patients to that in healthy subjects, and to identify covariates that explain interindividual variability (IIV) in PK. The PK/PD relationship between avatrombopag plasma concentration and platelet count and examined covariates that might affect the PK/PD relationship in CLD patients with thrombocytopenia were assessed.

## Method

For the population PK analysis, data from 787 healthy subjects and patients with CLD and thrombocytopenia were pooled from 10 phase 1 studies, 2 phase 2 studies, and 2 phase 3 studies in Table 3-1. The PK/PD analysis data set for platelet count consisted of pooled data from 396 patients with CLD from 2 phase 2 and 2 phase 3 studies. All protocols were approved by the local IRB for each of the study sites, and all subjects provided signed consent. All studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

The PK and PK/PD models were developed using nonlinear mixed-effects modeling software (NONMEM) version 7.3 interfaced with PDx-Pop version 5.2 (ICON Development Solutions, Ellicott City, Maryland).

**Table 3-1 Description of Studies included in Population PK and PK/PD**

| Study description | Subjects (M/F)[a] | Design | Samples[b] | Dose/ Formulation/ Food condition |
|---|---|---|---|---|
| Single dose escalation | HV (27/15) | DB | 18/0 | 1-100 mg, SUS, fasting |
| Multiple dose escalation | HV (13/6) | DB | 32/0 | 3-20 mg QD, SUS, fasting |
| Relative BA, SUS-1G | HV (15/2) | OL, XO | 51/0 | 10 mg, SUS-1G fasting and fed |
| TQTS | HV (15/31) | DB, XO | 12/0 | 100 mg, 1G, fasting[c] |
| Relative BA, 1G-2G | HV (13/3) | OL, XO | 39/0 | 40 mg, 1G-2G, fasting and fed[c] |
| Single, and multiple dose escalation in Japanese, Chinese and White | HV (29/12) | DB, XO | 64/0 | 10-80 mg, 10 mg QD, 2G,fasting |
| Relative BA, two-Lots, intra-subject variability | HV (35/7) | OL, XO | 60/0 | 40 mg, 2G, fasting |
| Effect of food, high-fat | HV (71/13) | OL | 30/0 | 40 mg, 2G, fasting and fed |
| Effect of food, low-fat | HV (17/19) | OL | 48/0 | 40 mg, 2G, fasting and fed |
| Single dose escalation in Japanese and White | HV (24/24) | OL | 70/0 | 20-60 mg, 2G, fasting and fed |
| Phase 2, dose-finding study | PTS (62/31) | DB, PG | 6/11 | 100 mg L+ 20-80 mg, 80 mg L + 10-20 mg, 1G[c]-2G, fasting |
| Phase 2, dose-finding study in Japanese | PTS (19/9) | DB, PG | 3/6 | 20-60 mg QD, 2G, fed |
| Phase 3 pivotal study | PTS (100/47) | DB, PG | 3/6 | 40, 60 mg QD, 2G, fed |
| Phase 3 pivotal study | PTS (83/45) | DB, PG | 3/6 | 40, 60 mg QD, 2G, fed |

BA, bioavailability; HV, healthy volunteer; Form, formulation; MD, multiple dose; OL, open-label; PG, parallel group; PTS, patients with thrombocytopenia with liver disease prior to elective procedure; QD, once daily; SUS, suspension; SD, single dose; TQTS, through QT study; XO, cross-over; 1G, 1st generation tablet; 2G, 2nd generation tablet.
a. number of subjects to be included in the analysis; b. median number of PK/ PD samples per subject used in analyses; c. Lot 56789-101 of 1G.

*PK Model for Avatrombopag*

The pooled PK data set included 15515 avatrombopag plasma concentrations from a total of 787 subjects, of which 1414 plasma concentrations were from 396 patients with CLD. A summary of the demographics and covariates included in the population PK analysis is presented in Table 3-2.

**Table 3-2 Characteristics for Population Pharmacokinetic Dataset (N=787)**

| Continuous characteristic | Median (range) | Discrete characteristics | Frequency |
|---|---|---|---|
| Age (y) | 47 (18-86) | Subjects (healthy/patients) | 391/396 |
| Body weight (kg) | 75 (39-175) | Sex (male/female) | 524/263 |
| ALP (U/L) | 81 (19-1589) | Race (Caucasian/Black/Asian/ Other) | 522/59/179/27 |
| AST (U/L) | 29 (9-377) | Formulation (suspension/1G[b]/2G)[c] | 77/130/612 |
| ALT (U/L) | 25 (6-304) | Food condition (fasted/fed/unknown) | 273/421/93 |
| CRCL (mL/min) | 115 (26-509) | Concomitant proton pomp inhibitor (Yes/No) | 173/614 |
| Bilirubin (mg/dL) | 16 (3-176) | Concomitant H2-blocker (Yes/No) | 18/769 |
| Albumin (g/dL) | 42 (18-53) | Concomitant CYP3A inhibitor (Yes/No) | 12/775 |
| INR | 1.1 (0.9-3.4) | Concomitant Antacids (Yes/No) | 10/777 |
| eGFR (mL/min)[a] | 96 (30-208) | Concomitant P-gp inhibitors (Yes/No) | 25/762 |
| | | Child Turcotte Pugh (5-6/7-9/10-15/healthy/Missing) | 212/151/31/391/2 |
| | | MELD score (≤9/>9/healthy/Missing) | 126/269/391/1 |
| | | Etiology of chronic liver disease (viral hepatitis/ Non-alcoholic steatohepatitis/ Alcoholic /Other) | 242/45/49/60 |

a: Upper limit was capped at 150 mL/min when tested as a covariate; b: Of 130, 113 is 1G Tablet of Lot 56789-101; c: a total number of subjects; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CRCL, creatinine clearance; eGFR, estimated glomerular filtration rate; MELD score, Model for end stage liver disease; P-gp, P-glycoprotein.

A total of 3 formulations were developed during the course of the clinical development: a suspension formulation for initial phase 1 studies, a designated first-generation (1G)

tablet formulation for subsequent phase 1 and phase 2 studies, and a final to-be-marketed second-generation (2G) tablet formulation for phase 1 multiple clinical pharmacology/biopharmaceutical studies, phase 2 studies, and phase 3 studies. One lot of the 1G tablet formulation (Lot 56789-101) was found to have manufacturing issues related to powder flow and content uniformity with reduced bioavailability relative to other 1G and 2G lots; therefore, this lot was distinguished for modeling purposes. Of 15515 avatrombopag plasma concentrations, 1461 from suspension formulation, 1491 from 1G tablet (including 987 samples associated with Lot 56789-101), and 12563 from 2G tablets were available for population PK analysis. None of the subjects in the PK data set received concomitant CYP3A4 inducers or CYP2C9 inducers or inhibitors. Based on a graphic analysis of avatrombopag concentration-time profiles, the process of model building initiated with fitting a 1-compartment model to the data and proceeding to more suitable effects added or deleted one at a time. One-compartment models with either first-order absorption (absorption rate constant [Ka]) or simultaneous zero (duration of absorption [D1]) and first-order absorption with lag time and first-order elimination from the central compartment were tested with the first-order conditional estimation with interaction. Relative bioavailability (F1) to the suspension for 1G tablet (Lot 56789-101) and other 1G and 2G tablets were tested. Based on model development both Ka and F1 for the other 1G tablet was similar to that for the 2G tablet, and hence common Ka and F1 parameters were used for other 1G and 2G tablets in all subsequent analyses. The effect of food on Ka, D1, and F1, and the effect of formulation on Ka and D1 were tested. Residual error was best described by a combined additive and proportional error for time after dose ≤4 hours and another for time after dose >4 hours. The IIV was estimated for all parameters except for lag time using an exponential error structure, which assumed log-normal distribution for PK parameters. Interoccasion variability (IOV) on F1 parameters was also assessed.

Model development was initially attempted using pooled full profile data from all studies; however the model was unstable and did not converge successfully despite a very large drop in the objective function when modeling IOV on F1 for the 1G and 2G tablets. Therefore, a PK base model was developed based on phase 1 study data only, followed by PK base model development for all data where population parameter

estimates for Ka, D1, F1, and IOV on F1, but not their IIV, obtained from PK base model development based on phase 1 were fixed. The residual variability was assessed by proportional and combined additive/proportional error structures, with all permutations of IIV and residual variability error structures tested systematically. The following criteria were considered to assess the model selection: (1) a P value of .01 for 1 additional parameter; (2) the successful convergence of the minimization procedure; (3) at least 3 significant digits; (4) termination of covariance step without any error message; and (5) relative standard errors of the estimates >50%. In addition, goodness-of-fit plots of the population and individual predicted concentration vs observed concentrations, plots of conditioned weighted residuals vs population predictions, and conditioned weighted residuals vs time were used to assess the PK model. The final population PK model for avatrombopag was validated using the visual predictive check[30] and bootstrap resampling technique[31]. Bootstrap estimates were used to compute CIs for all model parameters, including those for the covariate estimates. Two hundred bootstrap replicates of the actual data set were performed.

*PK/PD Model for Platelet Count*

The pooled population PK/PD data set included 1877 platelet count-time data from 394 patients with CLD. A summary of the demographics and covariates included in the PK/PD analysis is presented in Table 3-3.

**Table 3-3 Characteristics for Pharmacokinetic/Pharmacodynamic Analysis (N=394)**

| Continuous characteristic | Median (range) | Discrete characteristics | Frequency |
|---|---|---|---|
| Age (y) | 58 (19-86) | Subjects (healthy/patients) | 0/394 |
| Body weight (kg) | 79 (39-175) | Sex (male/female) | 264/130 |
| Albumin (g/dL) | 34 (18-49) | Race (Caucasian/Black/East Asian[a]/Asian/ Other) | 239/15/107/16/17 |
| Baseline platelet count ($10^9$/L) | 39 (10-107) | Baseline platelet count (< 30/≥30 to <40/40≤) ($10^9$/L) | 69/148/177 |
| Baseline TPO (U/L) | 100 (31-895) | Hepatocellular carcinoma (Yes/No) | 86/308 |
| | | Splenomegaly (Yes/No) | 190/204 |
| | | Presence of anti-platelet therapy (Yes/No) | 2/392 |
| | | Concomitant steroid therapy (Yes/No) | 13/381 |
| | | Child Turcotte Pugh (5-6/7-9/10-15) | 212/151/31 |
| | | MELD score (≤9/>9/Missing) | 126/267/1 |
| | | Etiology of chronic liver disease (viral hepatitis/ Non-alcoholic steatohepatitis/ Alcohoric /Other) | 241/44/49/60 |

a: Japanese, Chinese and Koreans; MELD score, Model for end stage liver disease; TPO, thrombopoietin.

A 6-compartment PK/PD life-span model with a linear relationship for drug effect, with 2 PK compartments (absorption and disposition) and 4 PD compartments, was applied to platelet count data, as depicted in Figure 3-1. Individual post hoc estimates from the final PK model were used as the PK exposure input for the PK/PD model, and the PK/PD model was constructed using the first-order conditional estimation with interaction method. In the PK/PD model, there was 1 precursor production compartment (BM1), 2 transit/maturation compartments (BM2 and BM3), and 1 platelet (blood) compartment (platelet) with a linear drug effect on platelet production (slope). The linear effect of avatrombopag on platelet count stimulation was as follows:

Stimulation = 1 + Slope × Plasma concentration

where stimulation defines the relationship between avatrombopag concentration and megakaryocyte production. The residual variability was assessed by proportional, additive, and combined error structures. The model was parameterized for observed baseline platelet count, slope for drug effect, first-order maturation rate of platelet precursors ($K_{out}$), and zero-order production rate of platelet precursors ($K_{in}$) with exponential IIV estimated for all parameters. The criteria for assessing the model selection were the same as for PK model development. Goodness-of-fit plots of the population and individual predicted platelet count vs observed platelet count, plots of weighted residuals vs population predicted platelet count, and weighted residuals vs time were used to assess the PK/PD model. The final PK/PD model for avatrombopag was validated using the visual predictive check and bootstrap resampling technique. Bootstrap estimates were used to compute CIs for all model parameters, including those for the covariate estimates. One hundred bootstrap replicates of the actual data set were performed.

*Covariate Model Development*

The association between subject covariates and PK or PK/PD parameters were performed in a stepwise fashion. Individual Bayes post hoc PK or PK/PD parameter estimates generated from the basic model as well as their difference from the corresponding population value were plotted vs the covariates to identify potential relationships. Eta shrinkage was calculated and reported for IIV parameter estimates.

Parameters with >30% of shrinkage were excluded from the covariate analysis. The associations between PK or PK/PD and covariates were evaluated by a univariate addition and ranked in descending order according to the change in objective function value. Variables were then tested by stepwise addition to the model. Covariates were included in the model at a significance level of 1%. When no further significant covariates could be included at the 1% significance level, multivariate and backward deletion were carried out at the 0.1% significance level, where the relative influence of each covariate on the model was reevaluated by deleting it from the full model on an individual basis. Continuous covariates were centered at the median of the observed values, and categorical covariates were tested and incorporated in the model as index variables.

## Results

### 1) PK Model

The PK of avatrombopag in healthy subjects and patients with CLD was best described by a 1-compartment model with simultaneous first- and zero-order absorption, with lag time, and elimination parameterized for apparent clearance (CL/F), apparent central volume (V/F), Ka with an effect of tablet formulation, D1, lag time, and bioavailability for the 1G (excluding lot no. 56789-101) and 2G tablets, and bioavailability for the 1G lot no. 56789-101 relative to the suspension formulation with IIV estimated for CL/F, V/F, Ka, D1, and both F1 parameters. In addition, IOV was included for F1 for the 1G and 2G tablets. The population PK parameter estimates and bootstrapped 95% confidence interval for the final PK model of avatrombopag are presented in Table 3-4.

**Table 3-4 Population PK Model Parameters for Avatrombopag**

| Parameter | Estimate (95% CI) | %RSE [(b)] | Shrinkage (%) | Bootstrap Median (95% CI) |
|---|---|---|---|---|
| CL/F (L/h) | 6.89 (6.64 – 7.14) | 1.89 | 29.6 | 6.86 (6.52 – 7.21) |
| $V/F = \theta_{V/F} \cdot (\theta_{v\_pop})^{pop} \cdot (WT/75.3)^{\theta WT}$<br>V/F (L) | 180 (173 – 187) | 2.08 | 39.2 | 179 (170 – 189) |
| Effect of CLD subjects on V/F (Ratio) | 1.65 (1.52 – 1.78) | 4.13 | – | 1.66 (1.53 – 1.81) |
| Effect of body weight on V/F (Power function) | 0.371 (0.226 – 0.516) | 19.9 | – | 0.363 (0.175 – 0.543) |
| First-order absorption rate constant for suspension - Ka (1/h) | 5.50 Fixed | – | 23.5 | – |
| Effect of 1G & 2G tablets on Ka | 0.258 Fixed | – | – | – |
| Zero-order absorption duration - D1 (h) | 4.08 Fixed | – | 50.3 | – |
| Lag time in absorption (h) | 0.389 Fixed | – | 100 | – |
| F1 – Bioavailability for 1G and 2G tablet relative to suspension | 0.745 Fixed | – | 41.6 | – |
| F1 - Bioavailability for 1G tablet (Lot No. 56789-101) relative to suspension | 0.213 Fixed | – | 64.1 | – |
| Inter-subject variability in CL/F (%CV) [a] | 28.8 | 9.19 | – | 28.5 (22.6 – 34.8) |
| Inter-subject variability in V/F (%CV) [a] | 25.0 | 11.0 | – | 24.6 (19.0 – 30.6) |
| Inter-subject variability in Ka (%CV) [a] | 137.0 | 7.22 | – | 141 (113 – 175) |
| Inter-subject variability in D1 (%CV) [a] | 21.7 | 13.1 | – | 22.1 (16.4 – 29.3) |
| Inter-subject variability in F1 for 1G and 2G tablet (%CV) [a] | 35.9 | 13.2 | – | 36.1 (29.6 – 40.5) |
| Inter-subject variability in F1 for 1G (Lot No. 56789-101[c]) (%CV) [a] | 67.7 | 16.8 | – | 67.8 (55.4 – 78.9) |
| Inter-occasion variability for F1 for 1G and 2G tablet (%CV) [a] | 41.1 | – | – | – |
| Proportional residual variability in avatrombopag concentrations (%CV) [a] | 16.9 | 0.380 | – | 17.1 (15.5 – 18.7) |
| Additive residual variability in avatrombopag concentrations (SD in ng/mL) | 0.395 | 7.18 | – | 0.378 (0.228 – 0.504) |
| Proportional residual variability in avatrombopag concentrations for TAD ≤ 4 h (%CV) [a] | 56.3 | 1.73 | – | 56.4 (52.3 – 60.1) |
| Additive residual variability in avatrombopag concentrations for TAD ≤ 4 h (SD in ng/mL) | 0.338 | 8.77 | – | 0.371 (0.0032 – 0.712) |

ALB, albumin; AST, aspartate aminotransferase; CI, confidence interval; CLD, etiology of chronic liver disease; CL/F, apparent clearance; CV, coefficient of variation; D1, duration for zero-order absorption; F1, relative bioavailability; Ka, absorption rate constant; %CV, percent coefficient of variation; %RSE, percent relative standard error; POP, population (healthy subjects vs patients); SD, standard deviation; TAD, time after dose; V/F, apparent central volume, WT, body weight.

a: %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance × 100. The approximation is due to the expansion of the exponential function only to first-order. b: %RSE was calculated as the S.E. divided by the parameter estimate × 100. c: One lot of the 1G tablet formulation (Lot 56789-101) was found to have manufacturing issues related to powder flow and content uniformity with reduced bioavailability relative to other 1G and 2G lots; therefore, this lot was distinguished for modeling purposes.

The population mean value for avatrombopag CL/F was estimated to be 6.89 L/h (percent coefficient of variation, 28.8%). Avatrombopag CL/F was similar between healthy subjects and patients with CLD. Avatrombopag V/F was observed to increase with increasing body weight (power = 0.371) and was 65% higher in patients compared to healthy subjects. The bioavailability of 1G and 2G tablet was 74.5% relative to suspension. The absorption rate constant for the 1G and 2G tablets was 25.8% of that for the suspension.

## 2) PK/PD Model for Platelet Count

The final PK/PD model was a 6-compartment life-span model parameterized with slope for linear drug effect, $K_{in}$ and $K_{out}$ with an effect of East Asians (Japanese, Chinese, and Korean), TPO levels, and albumin on drug effect parameter of slope was selected as the final PK/PD model for avatrombopag effect on platelet count (Figure 3-1).

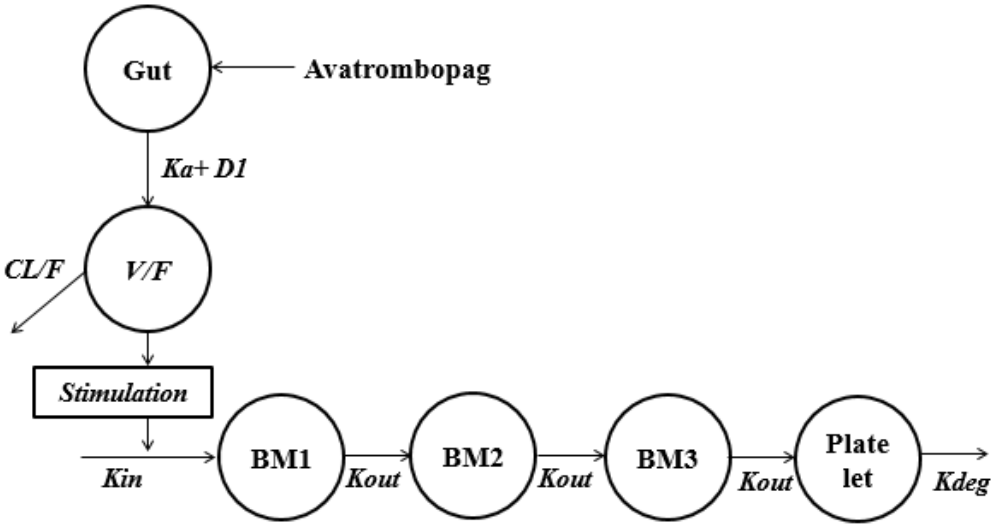


**Figure 3-1 Illustration of compartments for the PK/PD life-span model of avatrombopag.**

Stimulation defined the relationship between avatrombopag concentration and megakaryocyte production, calculated as 1+slope×plasma concentration. The production of platelet precursors increases in avatrombopag plasma concentration proportional manner. BM1, one precursor production compartment; BM2, two-transit compartment; BM3, maturation compartment; CL/F, apparent clearance; D1, duration of absorption; Gut, gastrointestinal tract; Ka, absorption rate constant; $K_{deg}$, first-order degradation rate of platelet count estimated as $K_{in}$/baseline platelet count; $K_{in}$, zero-order production rate of platelet precursors; $K_{out}$, first-order maturation rate of platelet precursors.

The parameter estimates and the results of the visual predictive check for the final PK/PD model are presented in Table 3-5 and Figure 3-2, respectively. Avatrombopag increased the rate of platelet production in a linear manner and the production rate increases 1.17% per 1 ng/mL increase in plasma avatrombopag concentrations. The linear effect of avatrombopag concentration on platelet production (slope) was approximately 32% lower in East Asians than non–East Asians and decreased with TPO levels and albumin expressed as $(TPO/100)^{-0.445}$ and $(ALB/34)^{-0.938}$, respectively.

**Table 3-5 Population PK/PD Model Parameters for Avatrombopag in Patients with Chronic Liver Disease**

| Parameter | Estimate (95% CI) | %RSE[c] | Shrinkage (%) | Bootstrap Median (95% CI) |
|---|---|---|---|---|
| Slope = $\theta_{slope} \cdot \theta_{East\ Asian}^{RACE} \cdot (TPO/100)^{\theta TPO} \cdot (ALB/34)^{\theta ALB}$ Slope (mL/ng) | 0.0117 (0.0110 – 0.0124) | 3.01 | 20.5 | 0.0121 (0.0101 – 0.0138) |
| Effect of East Asian[a] on Slope | 0.678 (0.554 – 0.802) | 9.35 | – | 0.654 (0.507 – 0.797) |
| Effect of TPO on Slope | -0.445 (-0.606 – -0.284) | 18.4 | – | -0.357 (-0.669 – -0.124) |
| Effect of ALB on Slope | -0.938 (-1.23 – -0.644) | 16.0 | – | -0.669 (-1.91 – 0.0685) |
| Kin (Gi/L/h) | 1.40 (1.29 – 1.51) | 4.11 | 50.0 | 1.69 (0.931 – 2.85) |
| Kout ($h^{-1}$) | 0.0160 (0.0153 – 0.0167) | 2.09 | 49.9 | 0.0158 (0.0140 – 0.0177) |
| Inter-subject variability in BASE (%CV)[b] | 15.3 | 6.72 | – | 14.7 (11.0 – 17.3) |
| Inter-subject variability in SLOP (%CV)[b] | 60.2 | 6.58 | – | 58.8 (46.3 – 73.9) |
| Inter-subject variability in Kin (%CV)[b] | 101 | 19.2 | – | 108 (2.90 – 158) |
| Inter-subject variability in Kout (%CV)[b] | 21.2 | 13.3 | – | 21.1 (7.20 – 30.5) |
| Proportional residual variability in platelet count (%CV)[b] | 14.0 | 4.28 | – | 13.9 (11.2 – 15.9) |
| Additive residual variability in platelet count (*$10^9$/L) | 3.38 | 8.95 | – | 3.41 (1.52 – 4.75) |

ALB, albumin; a: East Asian is included in Japanese, Chinese and Korean; b: %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order.; c: %RSE was calculated as the standard error divided by the parameter estimate x 100.

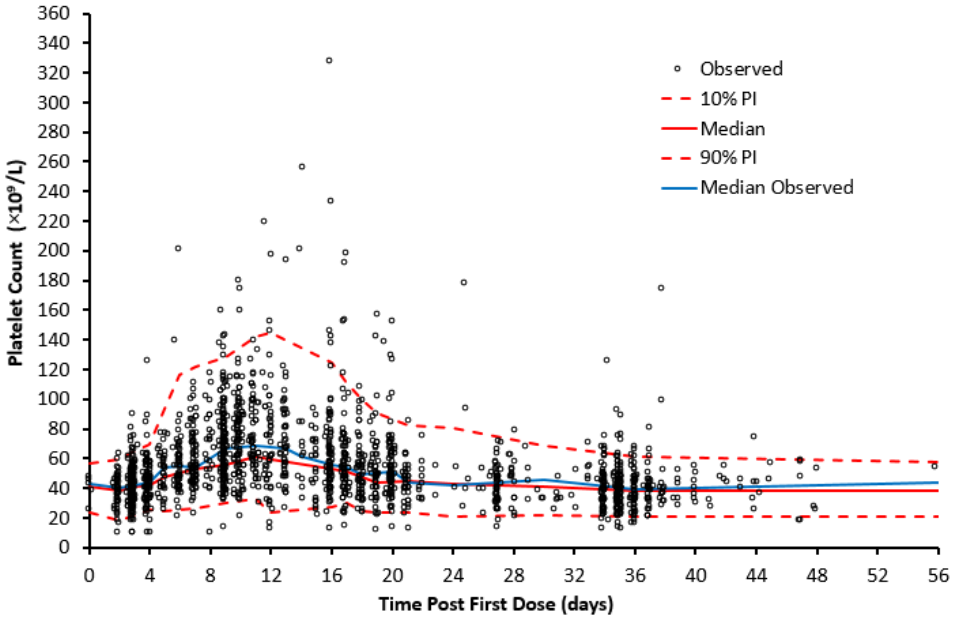


**Figure 3-2 Visual predictive check of observed and model-predicted platelet count in patients with chronic liver disease (N = 394).**
PI, prediction interval.

## Discussion

In order to characterize the PK profile of avatrombopag, pooled PK data from 14 studies were modeled. The PK of avatrombopag was best described by a 1-compartment

model with simultaneous first- and zero-order absorption and linear elimination. Patients with CLD had, on average, a 65% higher avatrombopag V/F than healthy subjects. V/F increased with increasing body weight; however, PK simulations showed no clinical relevance of this effect on exposure. CL/F was similar between healthy subjects and patients, and hence exposure (AUC) of avatrombopag is comparable when these subjects receive the same doses. The following intrinsic and extrinsic factors had no significant effect on avatrombopag PK: age, race, renal function, liver function, prothrombin international normalization ratio, and concomitant administration of proton pump inhibitors or $H_2$ blockers. Although coadministration with strong CYP3A inhibitors/inducers was shown to affect avatrombopag PK in previous clinical study and physiologically based PK simulations of Chapter 2, the effect of concomitant administration of these drugs could not be estimated in the population PK analysis due to the very limited number of subjects in the PK data set receiving concomitant CYP3A inhibitors/inducers, which is attributed to the short treatment duration of 5 days with avatrombopag.

The PK/PD relationship between avatrombopag concentrations and platelet count in patients with CLD disease following once-daily dosing was well described by a 6-compartment PK/PD life-span model, in which the stimulation of platelet count was linearly related to avatrombopag concentrations. Due to explain the delayed PD response, this life-span model was superior to a model with an $E_{max}$ function at the process of model development. East Asian race showed a 32% lower slope than others in this PK/PD model. However, the primary efficacy end points of phase 3 studies, that is, the proportion of subjects not requiring a platelet transfusion, demonstrated similarity between all patients and subgroup patients categorized by race (White, black, Asian, and other). The magnitude of race effect is within the intersubject variability for slope (60.2%), and, hence, overall the effect of East Asians was considered minimal and of no clinical relevance. An inverse relationship was identified for drug effect on slope with increasing albumin and TPO levels, with the power function of -0.938 and -0.445, respectively. However, PK/PD simulations demonstrated these effects to be of no clinical relevance. Neither age, sex, Model for End-Stage Liver Disease score, Child-Turcotte-Pugh score, etiology of CLD, hepatocellular carcinoma, splenomegaly,

nor steroid coadministration had any statistically significant effect on any of the PK/PD parameters in patients with CLD.

# Chapter 4 PK/PD Simulation and Optimal Dose Adjustment Guide

## Introduction

In a clinical drug-drug interaction study in healthy subjects (Chapter 2), coadministration with CYP2C9 and CYP3A inhibitors/inducers was shown to affect avatrombopag PK. Fluconazole (a dual inhibitor of CYP2C9 and CYP3A) and rifampin (a dual inducer of CYP2C9 and CYP3A) resulted in an approximately 2-fold increase and 0.5-fold decrease in avatrombopag area under the plasma drug concentration-time curve, respectively; no clinically important drug interactions were observed following coadministration with CYP3A or P-glycoprotein inhibitors.

With the intent to further and fully assess the clinical relevance of potential drug-drug interactions, platelet count following avatrombopag administration with and without concomitant medication was simulated using the final population PK/PD model to explore potential dose adjustments.

## Method

Deterministic simulations of platelet count were performed using the final PK/PD model empirical Bayes estimated parameters with intra- and intersubject variabilities and characteristics of patients with CLD with baseline platelet count of 20 to $<40\times10^9$/L and 40 to $<50\times10^9$/L. Concomitant drugs used for the simulation were itraconazole (CYP3A inhibitor)[22], verapamil (CYP3A inhibitor)[32], fluconazole (CYP2C9 and CYP3A dual inhibitor)[18], sulfaphenazole (CYP2C9 inhibitor)[33], and rifampin (CYP3A and CYP2C9 dual inducer)[34]. The apparent clearance values used in the simulations following coadministration of inhibitors/inducers were obtained from the actual clinical data in Chapter 2. Regarding the interacting drugs which were not used in the clinical DDI study, the exposures were predicted using PBPK simulation and were used in the final population PK/PD model. PD simulations were performed using the dose regimens included in phase 3 studies of avatrombopag, with and without concomitant medication, with dosing 60 mg for 5 days for patients with baseline platelet count of $<40\times10^9$/L and 40 mg for 5 days for patients with baseline between 40 and

$<50\times10^9$/L. A comparison of the median, 10%, and 90% prediction intervals (PIs) of platelet count-time profiles were made to assess the impact of changes in covariates on platelet count.

## Results

Predicted platelet count following avatrombopag administration in patients with CLD in the presence or absence of CYP2C9 and CYP3A inhibitors are shown in Figure 3-3 and Figure 3-4. Elevations in platelet count when avatrombopag was coadministered with fluconazole and sulfaphenazole were predicted to be slightly higher compared to corresponding doses of avatrombopag administration alone. The medians of maximal increase in platelet count following avatrombopag alone and concomitantly with fluconazole and sulfaphenazole in patients with a baseline platelet count of 20 to $<40\times10^9$/L were $65\times10^9$/L, $96\times10^9$/L and $80\times10^9$/L, respectively. Median of maximal increase in platelet count following avatrombopag alone and concomitantly with fluconazole and sulfaphenazole in patients with a baseline platelet count of 40 to $<50\times10^9$/L were $77\times10^9$/L, $104\times10^9$/L, and $89\times10^9$/L, respectively. In addition to predicting a higher median effect on platelet count, coadministration with the above 2 inhibitors and itraconazole (only patients with a baseline platelet count of 40 to $<50\times10^9$/L) also resulted in the upper limit of the 90% PI exceeding $200\times10^9$/L, the safety threshold used for risk of portal vein thrombosis in patients. Simulations showed that avatrombopag administered for 5 days with concomitant CYP3A or CYP2C9 inhibitors (fluconazole, itraconazole, sulfaphenazole, or verapamil) is predicted to achieve comparable elevations in platelet count to those following corresponding doses of avatrombopag administration alone for 5 days, standard regimen, with the percentage of patients with a CLD exceeding $200\times10^9$/L at <10% (patients with a baseline platelet count of 40 to $<50\times10^9$/L; <1% in avatrombopag alone vs <10%, <6%, <8%, and <3% in fluconazole, itraconazole, sulfaphenazole, and verapamil, respectively). Meanwhile, elevations in platelet count when avatrombopag was coadministered with dual strong CYP3A4 and moderate CYP2C9 inducer (rifampin) at standard regimen were predicted to be lower compared to corresponding doses of avatrombopag administered alone. The medians of maximal increase in platelet count following avatrombopag alone and concomitantly with rifampin in patients with a baseline platelet count of 20 to $<40\times10^9$/L were

$66\times10^9$/L and $47\times10^9$/L, respectively, and in patients with a baseline platelet count of 40 to<$50\times10^9$/L, the corresponding medians for maximal increase were $77\times10^9$/L and $61\times10^9$/L, respectively, indicating that despite the decrease in exposure with concomitant rifampin, the majority of patients will achieve a target platelet count above $50\times10^9$/L.

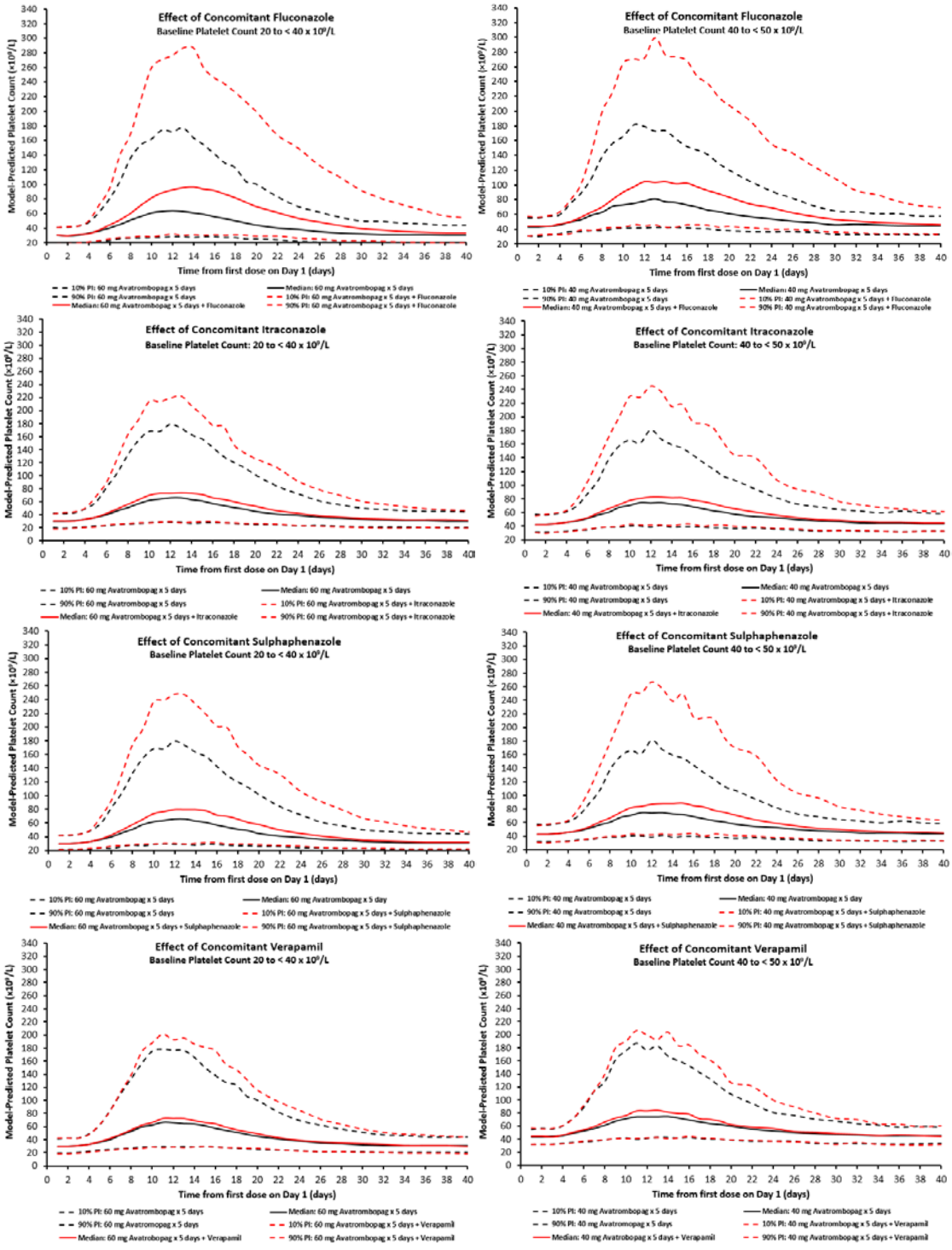


**Figure 4-1 Predicted platelet count following avatrombopag administration in patients with chronic liver disease in the presence or absence of CYP2C9 and CYP3A inhibitors.**

PI, prediction interval.

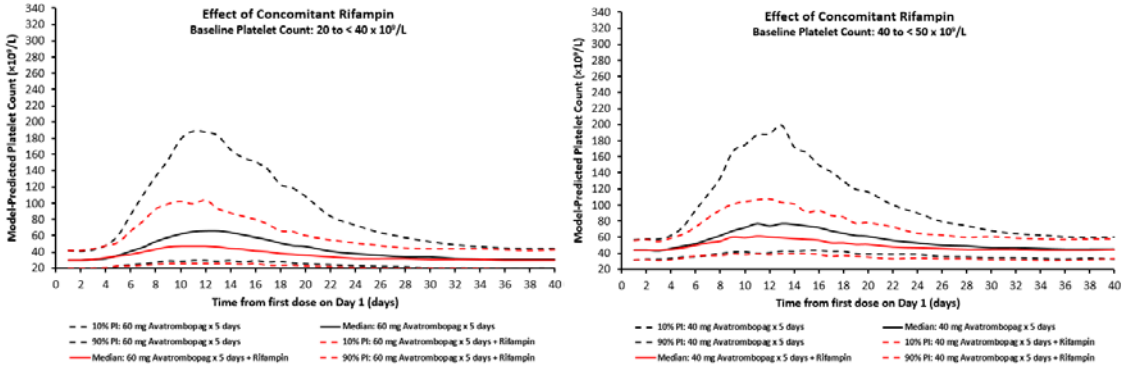


**Figure 4-2 Predicted platelet count following avatrombopag administration in patients with chronic liver disease in the presence or absence of CYP2C9 and CYP3A inducers.**

PI, prediction interval.

## Discussion

Based on the population PK/PD simulations of platelet count and the percentage of CLD subjects predicted to exceed a platelet count of $>200\times10^9$/L, the safety threshold used for risk of portal vein thrombosis in patients, a comparable increase in platelet count was achieved with and without concomitant CYP3A and CYP2C9 inhibitors for the same dosing regimens of 60 mg for 5 days with baseline platelet count between 20 and $<40\times10^9$/L and 40 mg for 5 days for baseline platelet count between 40 and$<50\times10^9$/L. Simulations demonstrated that coadministration with strong CYP3A and moderate CYP2C9 inducers resulted in lower elevation in platelet count compared to corresponding doses of avatrombopag administered alone, and the median difference was approximately $20\times10^9$/L. However, considering the short duration (5 days) of avatrombopag treatment subjects with CLD are administered prior to their planned surgery and confirmation that target platelet elevation was achieved, this difference is not clinically important.

# Overall Discussion and Conclusion

Author mainly conducted clinical studies to clarify the characteristics of avatrombopag PK and PD; propose and develop a study design of Chapter 1 and Chapter 2; lead authorship of all clinical-related documents (e.g., clinical protocols, study reference manual, study reports, and publication); interpret the population PK/PD modeling and simulation of Chapter 3 and Chapter 4. The following conclusions were obtained from these clinical studies:

In Chapter 1, the PK and PD properties of single dose were characterized in healthy subjects. Avatrombopag showed linear PK across a range of 20 to 60 mg dose, relatively slow absorption with peak exposure at 6 to 8 h postdose, and elimination with approximately 19 h of $t_{½}$; $t_{max}$ and $t_{½}$ were constant and independent of dose increase. Considering avatrombopag characteristics such as poor aqueous solubility and the slow absorption, avatrombopag might be partially absorbed via the lymphatics. Food intake affected reduction of inter- and intrasubject variability in PK without influencing the rate or extent of absorption; this finding was considered clinically important, therefore administration under fed condition was recommended for clinical use. Platelet count increased dose-proportionally, reaching a maximum by 11 days postdose and then returning to baseline level by 27 days postdose. This delayed response of platelet count was expected based on the mechanism of action. The PK and PD of avatrombopag were similar between Japanese and White subjects.

In vitro data indicated that avatrombopag is primarily metabolized by CYP3A and CYP2C9. Physiologically based PK modelling predicted a potential for clinically important interactions, but left uncertainty as to whether or not clinically important effects were limited to strong inhibitors and/or inducers of these pathways. Therefore, in Chapter 2, a 3-Part clinical drug-drug interaction study assessing three different interacting drugs was proposed to provide insights into the relative role of CYP2C9 and CYP3A in metabolic clearance of avatrombopag. Itraconazole, a strong CYP3A inhibitor which does not impact CYP2C9, was found to have a milder effect on the avatrombopag PK than that of fluconazole, which is known to moderately inhibit both CYP3A and CYP2C9 activity[19,20]. Hence, these results suggested that CYP2C9 may play a more predominant role in metabolic clearance of avatrombopag than CYP3A.

Taken together with drug interactions seen with inhibitors, the reduction in exposure of avatrombopag following codaministration with rifampin, a dual inducer of CYP2C9 and CYP3A, is also likely to be driven primarily by CYP2C9 induction. Relative to the magnitude of these interactions on avatrombopag PK, coadministration with inhibitors/inducers resulted in smaller magnitude of effects on avatrombopag PD. This could be attributed to the indirect effect of avatrombopag on platelet count. To further examine these PK and PD relationships, a PK/PD model was planned.

In Chapter 3, a population PK/PD model was developed to characterize the relationship between plasma avatrombopag concentrations and platelet count in patients with CLD patients. The final population PK/PD model was well described by a 6-compartment life-span model, in which the stimulation of platelet count was linearly related avatrombopag concentrations, and was included statistically effects of body weight and CLD population on avatrombopag V/F, East Asian race, TPO level and albumin on the PK/PD slope parameter. The magnitude of these covariates was within the intersubject variability for relative bioavailability (41.1%) and slope (60.2%), hence, overall the effects of these covariates was considered minimal and of no clinical relevance. It also can be explained that the effects of these covariates is no clinically meaningful since the subgroup analysis of phase 3 did not show the racial differences and simulation using the various covariate values showed no clinical relevance on PK and platelet count.

Although coadministration with CYP2C9 and CYP3A inhibitors/inducers was shown to affect avatrombopag PK in clinical drug-drug interaction study, the effect of concomitant administration of these drugs could not be estimated in the population PK analysis due to the very limited number of subjects in the PK data set receiving concomitant inhibitors/inducers. Therefore, in Chapter 4, deterministic simulations of platelet count were performed using the final PKPD model in order to investigate further drug-drug interaction for guiding safe and effective dose. A safety threshold of platelet count used for risk of portal vein thrombosis in patients is known as $200 \times 10^9$/L. PK/PD simulations showed comparable elevation in platelet count with and without concomitant CYP2C9 and CYP3A inhibitors for the dosing regimens of 40 and 60 mg for 5 days, with less than 10% frequency of platelet with CLD exceeding platelet count $>200 \times 10^9$/L. Meanwhile, despite the decrease in exposure (i.e., 0.5-fold decrease of AUC) with concomitant rifampin, the majority of patients were predicted to achieve a

target platelet count $>50\times10^9/L^7$. Consequently, author concluded that dose adjustment is not necessary with concomitant use of CYP2C9 and CYP3A interacting drugs considering the short treatment duration (i.e., 5 days) and lack of significant safety concerns in CLD patients.

This clinical pharmacology program not only clarified the characteristics of PK and PD but also provided critical assessments guiding the appropriate avatrombopag dosage regimen. Although nonclinical (in vitro) data can identify CYP isoforms associated with metabolism, these data cannot clarify accurately the relative proportion of elimination related to each pathway. PBPK modelling predicted a potential for clinically important interactions, but left uncertainty as to whether or not clinically important effects were limited to strong inhibitors and/or inducers of these pathways. Hence, author conducted the clinical drug-drug interaction study to assess the clinically important effects in healthy subjects. The results from this study suggested that dose/duration adjustment is recommended when avatrombopag is coadministered with CYP2C9 and CYP3A inhibitors, and coadministration with strong inducers is not recommended. However, author eventually concluded no dose adjustment of avatrombopag was needed with CYP2C9 and CYP3A inhibitors/inducers in patients based on the population PK/PD simulation. The reason for different conclusion is that PD simulation was performed using platelet count of actual patients with CLD, unlike clinical study in healthy subjects. Although an analysis of clinical data only from healthy subjects is insufficient to evaluate the safety and to optimize the dosage regimen, the present integrated PK and PD analyses would enable improved pharmacotherapy by predicting effectiveness, safety, and optimized dosage for the target patient.

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# List of Main Publication

The content of a doctoral degree application thesis is written based on the following published papers;

1. Nomoto, M., Nomoto, M., Pastino, G., Rege, B., Aluri, J., Ferry, J., and Han, D. Pharmacokinetics, pharmacodynamics, pharmacogenomics, safety, and tolerability of avatrombopag in healthy Japanese and White subjects. Clin Pharm Drug Dev. 7: 188-195 (2018)

2. Nomoto, M., Zamora, CA., Schuck, E., Boyd, P., Chang, M-K., Aluri, J., Siu, YA., Lai, WG., Yasuda, S., Ferry, J., and Rege, B. Pharmacokinetic/pharmacodynamic drug-drug interactions of avatrombopag when co-administered with dual or selective CYP2C9 and CYP3A perpetrators. Br J Clin Pharmacol. 84: 952-960 (2018)

3. Nomoto, M., Ferry, J., Hussein, Z. Population Pharmacokinetic/Pharmacodynamic Analyses of Avatrombopag in Patients with Chronic Liver Disease and Optimal Dose Adjustment Guide with Concomitantly Administered CYP3A and CYP2C9 Inhibitors. J Clin Pharmacol. 58: 1629-1638 (2018)

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