Pharmacokinetics of Mirabegron, a β_3-Adrenoceptor Agonist for Treatment of Overactive Bladder, in Healthy East Asian Subjects

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ABSTRACT

Purpose: The objective of these studies was to evaluate the pharmacokinetic profile, safety, and tolerability of mirabegron, a β_3-adrenoceptor agonist for the treatment of overactive bladder, including food effects (low- or high-fat meals) and sex, in healthy East Asian subjects.

Methods: In total, 5 pharmacokinetic studies of mirabegron were conducted in healthy East Asian subjects. Food effects were assessed in 3 randomized, single-dose studies in young Japanese male subjects (study 1), male and female subjects (study 2), and young Taiwanese male and female subjects (study 3). In the other 2 single- and multiple-dose studies in young Chinese male and female subjects (study 4 and study 5), mirabegron was administered as a single dose under fasted conditions. After the washout period, mirabegron was administered once daily under fed conditions for 8 days. Pharmacokinetic parameters were determined using noncompartmental methods. Safety and tolerability assessments included physical examinations, vital signs, 12-lead ECG, clinical laboratory tests (biochemistry, hematology, and urinalysis), and adverse event monitoring.

Findings: After administration of single oral doses of mirabegron, exposure under fed conditions was lower than under fasted conditions in Japanese and Taiwanese subjects. In Japanese subjects, a greater reduction in mirabegron C_{max} and $AUC_{0-\infty}$ was observed after a low-fat meal compared with a high-fat meal. In Chinese subjects, C_{max} was reached at approximately 4.0 hours after single oral doses. Mirabegron accumulated 2- to 3-fold on once-daily dosing of multiple-dose relative to single-dose data. Steady state was reached within 7 days. After administration of mirabegron, mean values for C_{max} and AUC in female subjects were higher than those in male subjects. Mirabegron was well tolerated in Japanese, Taiwanese, and Chinese subjects.

Implications: Our studies confirm the higher exposure levels of mirabegron in female compared with male East Asian subjects as found earlier in Western subjects. Furthermore, the effects of food on the pharmacokinetic profiles appeared to be similar among the 3 populations tested in our studies. The findings suggest that there are no significant pharmacokinetic differences among the Japanese, Taiwanese, and Chinese populations. (*Clin Ther.* 2015;37:1031–1044) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: East Asia, healthy volunteers, mirabegron, pharmacokinetics, Ethnic difference.

INTRODUCTION

Mirabegron is a β_3-adrenoceptor (AR) agonist discovered by Astellas Pharma Inc in Japan.[1] The β_3-AR plays a role in the relaxation of the urinary bladder detrusor smooth muscle.[2] Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of β_3-AR, which increases bladder capacity.[1,3]

The pharmacokinetic profile of mirabegron after single and multiple oral doses has been reported in cohorts of Western, primarily white,[4,5] and Japanese[6]

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healthy adult subjects. Mirabegron had a greater than dose-proportional increase in mirabegron C_{max} and AUC after single and multiple oral doses, which was due to an increase in absolute bioavailability with increasing dose.[4,5] Mirabegron was cleared by multiple mechanisms (renal and possibly biliary excretion of unchanged drug and metabolism by multiple enzymes), with no single predominating clearance pathway.[7] It has been reported that mirabegron oral controlled absorption system (OCAS) tablets exhibited a decrease in mirabegron plasma exposure with food in healthy Western subjects.[8] In addition, weight is an important consideration when comparing different ethnic populations because weight affects mirabegron pharmacokinetic parameters.[5,6]

We conducted 3 food effect studies using single doses of 50 mg in Japanese male subjects (study 1), 50 and 100 mg mirabegron in healthy Japanese male and female subjects (study 2), and 50 mg mirabegron in healthy Taiwanese male and female subjects (study 3). In addition, we conducted 2 studies using single doses of 25 mg mirabegron (study 4) or 50 mg mirabegron (study 5) in healthy Chinese male and female subjects to evaluate the pharmacokinetic parameters, safety profile, and tolerability of mirabegron after single and multiple oral doses. The main purpose of these studies is to compare the pharmacokinetic parameters of mirabegron in East Asian subjects (Japanese, Taiwanese, and Chinese). In addition, the pharmacokinetic parameters of mirabegron in healthy East Asian subjects in these studies were subsequently compared with those previously reported for Western healthy subjects.[4,5,8]

PATIENTS AND METHODS

These studies were conducted in accordance with the ethical principles based on the Declaration of Helsinki[9] and Good Clinical Practice,[10] as defined by the Ministerial Ordinance concerning the standards for the implementation of clinical studies on pharmaceutical products, and the regulations stipulated in the Japanese, Taiwanese, and Chinese Pharmaceutical Affairs Law. These studies were conducted at single centers and approved by institutional review boards. Studies 1, 2, and 4 were conducted in Japan, study 3 in Taiwan, and study 5 in China.

Subjects

Subjects were eligible for inclusion in the studies if they met the following criteria: study 1, male Japanese subjects aged 20 through 44 years with a weight of 50.0 to $<$80.0 kg and a body mass index (BMI) of 17.6 to $<$26.4 kg/m^2; study 2, male and female Japanese subjects aged 20 through 54 years with a weight of 50.0 to $<$80.0 kg for male and 40.0 to $<$70.0 kg for female subjects and a BMI of 17.6 to $<$26.4 kg/m^2; study 3, male and female Taiwanese subjects aged 20 through 45 years, with a weight of at least 50 kg in male and 45 kg in female subjects and a BMI of 18.5 through 26.9 kg/m^2; study 4, male and female Chinese subjects aged 20 through 44 years with a weight of 50.0 to $<$80.0 kg for male and 40.0 to $<$70.0 kg for female subjects and a BMI of 17.6 to $<$26.4 kg/m^2; and study 5, male and female Chinese subjects aged 18 through 40 years with a weight of at least 50 kg and a BMI of 19 through 24 kg/m^2. All subjects provided written informed consent before screening.

Study Designs

Study 1 was a phase 1, randomized, open-label, single oral dose, 2-period, 2-sequence crossover study to evaluate the effect of food on the pharmacokinetic parameters of mirabegron in 24 Japanese male subjects. In each treatment period, 50 mg mirabegron was orally administered to subjects under fasting or fed (high-fat breakfast) conditions. The washout period between treatment periods 1 and 2 was 12 days or longer. The high-fat breakfast was $\geq$900 kcal, and fat comprised 35% of the total caloric content.

Study 2 was a phase 1, randomized, open-label, single oral dose, 3-period, 6-sequence crossover study to assess the effect of food on the pharmacokinetic parameters of mirabegron (50 or 100 mg) in 72 Japanese subjects (36 each for 50 and 100 mg). Under fed conditions, subjects received either low-fat meal (approximately 450 kcal) or a high-fat meal (960 kcal) at 30 minutes before receiving mirabegron. Each subject participated in 3 treatment periods, with washout periods of at least 12 days between periods 1 and 2 and between periods 2 and 3.

Study 3 was conducted as an open-label, randomized, crossover study to assess the effect of food on the pharmacokinetic parameters of single oral doses of mirabegron (50 mg) administered under fasted and fed conditions (low-fat breakfast of approximately 450 kcal) in 12 Taiwanese subjects (6 males and 6 females). Each subject participated in 2 treatment periods separated by a washout period of at least 8 days.

The design of studies 4 and 5 allowed assessment of mirabegron pharmacokinetic parameters after single oral dose administration under fasting conditions and multiple oral dose administration under fed conditions. Both studies enrolled 24 young, healthy, adult, male and female, Chinese subjects. A single oral dose of 25 mg (study 4) or 50 mg (study 5) mirabegron was administered under fasting conditions on day 1 of both studies. This was followed by a washout period of 9 days in study 4 and a washout period of 14 days in study 5. A low-fat meal (approximately 450 kcal) was served before each administration of study drug in the multiple dose administration period, which started on day 10 in study 4 and day 15 of study 5 and lasted for 8 days.

Method of Assigning Subjects to Treatment Groups

A person responsible for treatment assignment randomly assigned each subject to treatment sequences in studies 1, 2, and 3. For studies 4 and 5, no assignment or allocation was used in this study.

Sample Collection and Analysis

In all studies, blood samples for plasma mirabegron concentrations were collected into tubes that contained sodium-heparin as the anticoagulant and sodium fluoride as the stabilizer. In studies 1, 2, and 3, blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 36, 48, and 72 hours after dosing in each period. An additional sample was collected 7 and 96 hours after dosing in studies 2 and 3. In study 2, urine samples for measurement of unchanged mirabegron were collected no more than 12 hours before dosing and from 0 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 72 hours, and 72 to 96 hours after dosing. In studies 4 and 5, blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72, and 96 hours after dosing in the single-dose period and on the final day in the multiple-dose period, before the first administration of study drug in the multiple-dose period, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, and 24 hours after dosing on the first day in the multiple-dose period, and before dosing on days 5, 6, and 7 in the multiple-dose period. Plasma was collected by centrifugation, and plasma and urine samples were stored at –65°C or below until analysis. Liquid-liquid extraction was used to extract mirabegron from plasma constituents. Urine samples were diluted before analysis. Samples were assayed by validated liquid chromatography analytical methods coupled with LC-MS/MS using an atmospheric pressure chemical ionization interface, as described previously with minor modifications.[11] The calibration ranges were 0.20 to 100 ng/mL in plasma and 10.0 to 5000 ng/mL in urine. In the bioanalytical method validation studies, within-run precision (%CV) of quality control standards was $<6.6\%$ for plasma and $<8.4\%$ for urine. The within-run accuracy (relative error) of the assays over the quality control range ranged from -5.0% to 9.7% for plasma and -4.0% to 11.0% for urine.

Pharmacokinetic Analysis

The concentration of mirabegron in plasma or urine was analyzed by noncompartmental methods using WinNonlin Professional software, version 5.2.1 (studies 1 and 2) or a higher version (Pharsight Corporation, Mountain View, California). The following pharmacokinetic parameters were obtained as applicable and as appropriate for each study: C_{max}, T_{max}, AUC_{0-24} and $AUC_{0-\infty}$ after single dose administration, $AUC_{0-\tau}$, $t_{½}$, CL/F, cumulative percentage of unchanged drug excreted into the urine up to 96 hours after dosing, and renal clearance. Actual sampling times were used in all calculations that involved sampling times, and nominal sampling times were used for the mean concentration-time figures.

Safety and Tolerability Assessments

Tolerability was assessed based on physical examinations, vital signs (body temperature, supine blood pressure, and supine pulse rate), resting 12-lead ECGs, standard clinical laboratory tests (hematology, blood biochemistry, and urinalysis), and adverse event (AE) monitoring. Clinically significant adverse changes in any safety assessment, including symptoms and signs, vital signs, ECGs, and clinical laboratory tests, were considered AEs. The causal relationships for all AEs were categorized by the investigator as probable, possible, or not related.

Statistical Analysis

Plasma and urine pharmacokinetic parameters were analyzed using SAS software, version 8.2 (studies 1 and 2), version 9.2 (study 3), or version 9.1 (studies 4 and 5) (SAS Institute, Cary, North Carolina). Safety data were evaluated descriptively, and AEs were

described in their entirety. All randomized subjects who received at least 1 dose of study drug were included in the safety analyses. Summary statistics were calculated for all pharmacokinetic parameters by dose or food condition. The geometric mean ratio (GMR) (fed/fasting) of C_{max} and AUC and the 90% CI for the GMR were calculated to evaluate the effect of food on the pharmacokinetic parameters of mirabegron.

In studies 2, 3, 4, and 5, the GMR of the C_{max} and AUC for male versus female subjects (with 90% CIs) were estimated to evaluate the effect of sex on pharmacokinetic parameters.

In studies 4 and 5, the GMR of mirabegron C_{max} and $AUC_{0-\tau}$ on the last day versus C_{max} and AUC_{0-24} on the first day (with 90% CIs) were estimated to assess accumulation of mirabegron with multiple dosing.

RESULTS

Participant Disposition and Demographic Characteristics

The disposition and demographic characteristics of the subjects are summarized in Table I. A total of 24 healthy male subjects were enrolled in study 1; 23 subjects completed the study, and 1 subject discontinued the study during treatment period 2 because of AEs (headache, pyrexia, and diarrhea) under fasting conditions. A total of 36 subjects (18 males and 18 females) were randomized to each of the 50 and 100 mg dose groups in study 2, and 70 subjects completed the study. Two subjects discontinued the study, one to attend the funeral of a relative and the other because of work commitments. A total of 12 subjects (6 males and 6 females) were enrolled in study 3, and all completed the study. A total of 24 subjects (12 males and 12 females) were enrolled in studies 4 and 5, and all completed both studies.

Table I. Subject demographic characteristics.

Characteristic	Study 1	Study 2		Study 3	Study 4	Study 5
		50 mg	100 mg			
Subject population	Japanese	Japanese	Japanese	Taiwanese	Chinese	Chinese
Total No. of subjects (male/female)	24 (24/0)	36 (18/18)	36 (18/18)	12 (6/6)	24 (12/12)	24 (12/12)
Age, mean (range), y	26.4 (20–40)	33.3 (20–53)	32.4 (20–53)	27.0 (21.0–36.0)	25.0 (20–41)	23.4 (19–31)
Weight, mean (range), kg	63.90 (54.0–76.9)	57.92 (46.2–74.0)	59.89 (40.9–74.0)	63.4 (50.0–77.0)	58.38 (48.2–79.4)	59.26 (50.2–71.7)
Male		62.9 (52.5–74.0)	65.4 (57.4–74.0)	70.2 (62.0–77.0)	61.9 (53.1–78.5)	63.3 (52.1–71.7)
Female		53.0 (46.2–66.3)	54.3 (40.9–69.1)	56.6 (50.0–65.5)	54.4 (47.4–62.6)	55.3 (50.2–65.2)
BMI, mean (range), kg/m^2	21.55 (18.5–26.1)	21.13 (18.1–26.1)	21.88 (17.6–25.8)	22.9 (20.6–26.0)	20.94 (17.6–24.5)	21.17 (19.1–23.7)

BMI = body mass index.

Pharmacokinetic Parameters of Mirabegron

Studies in Japanese subjects (Studies 1 and 2)

A summary of the pharmacokinetic parameters of mirabegron in Japanese subjects under fasted or fed conditions is given in Table II. Mean plasma concentrations of mirabegron after single doses of 50 mg were similar between studies 1 and 2. Mean plasma concentrations of mirabegron after single doses of 50 and 100 mg mirabegron under fasted or fed conditions in study 2 are shown in Figure 1. After

Table II. Pharmacokinetic parameters of mirabegron after single oral doses of mirabegron OCAS in Japanese subjects (studies 1 and 2).*

	Study 1 (50 mg)		Study 2					
			50 mg			100 mg		
Parameter	Fasted (n = 23)	Fed (n =23)	Fasted (n = 35)	Low-Fat Meal (n = 35)	High-Fat Meal (n = 35)	Fasted (n = 35)	Low-Fat Meal (n = 35)	High-Fat Meal (n = 35)
C_{max}, ng/mL	29.40 (23.79)	10.28 (6.19)	35.37 (29.91)	13.40 (12.26)	16.31 (10.74)	103.29 (57.17)	42.86 (35.30)	52.31 (28.09)
T_{max}, h	3.5 (0.9)	4.7 (1.5)	3.55 (1.20)	4.89 (1.35)	4.91 (1.42)	3.57 (1.04)	5.32 (1.18)	5.63 (1.68)
AUC_{0-last}, ng·h/mL	214.91 (105.50)	100.96 (31.51)	330.45 (133.85)	158.09 (75.67)	222.38 (81.31)	841.16 (316.15)	431.53 (210.07)	589.78 (192.96)
$AUC_{0-\infty}$, ng·h/mL	246.82 (117.97)	122.13 (35.26)	387.13 (153.15)	195.60 (90.05)	272.50 (98.66)	944.53 (351.88)	506.16 (250.25)	674.36 (214.35)
$t_{½}$, h	28.1 (3.3)	30.7 (4.6)	39.9 (8.5)	43.4 (14.1)	43.7 (8.9)	36.3 (6.6)	37.1 (10.2)	35.6 (6.8)
CL/F, L/h	260.66 (143.36)	452.50 (178.19)	150.45 (59.48)	310.13 (136.67)	209.48 (81.39)	122.98 (53.54)	256.87 (149.74)	165.43 (61.46)

OCAS = oral controlled absorption system.
*Data are presented as mean (SD).

Figure 1. Mean (SD) plasma concentrations of mirabegron after single oral administration of mirabegron oral controlled absorption system at 50 mg (A) and 100 mg (B) under fasted or fed conditions in healthy Japanese subjects in study 2.

administration of 50 and 100 mg doses of mirabegron, the mean values for C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ after the low- and high-fat meals were lower than under fasted conditions (study 2). After administration of 50 mg doses of mirabegron after the high-fat meal, C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were approximately 53%, 32%, and 29% lower, respectively, than under fasted conditions. After the low-fat meal, C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were approximately 66%, 53%, and 51% lower, respectively, than under fasted conditions. After administration of 100 mg mirabegron after the high-fat meal, C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were approximately 49%, 29%, and 27% lower, respectively, than under fasted conditions. After administration of 100 mg mirabegron after the low-fat meal, C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ were approximately

64%, 51%, and 49% lower, respectively, than under fasted conditions (Table III). Thus, the low-fat meal resulted in a relatively greater reduction than the high-fat meal. Overall, there was high intersubject variability in C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ under all treatment conditions (%CV of C_{max}, 54%–91%; AUC_{0-last}, 33%–49%; and $AUC_{0-\infty}$, 32%–49%). Delays in the mean T_{max} were noted under the fed (low- and high-fat meals) conditions compared with fasted conditions in both the mirabegron 50 and 100 mg dose groups. Mean $t_{1/2}$ values were similar for both conditions (50 mg: 39.9 hours under fasted, 43.4 hours after low-fat meal, and 43.7 hours after high-fat meal; 100 mg: 36.3 hours under fasted, 37.1 hours after low-fat meal, and 35.6 hours after high-fat meal). In the 50 mg dose group, the percentage of unchanged drug excreted into the urine for mirabegron was 52% and 29% lower after the low- and high-fat meals, respectively, compared with the fasted conditions. In the 100 mg dose group, the mean cumulative percentage of unchanged drug excreted into the urine was 49% and 28% lower after the low- and high-fat meals, respectively, compared with the fasted conditions. Irrespective of mirabegron dose, mean renal clearance values were similar for the 3 treatment conditions (10.43–11.79 L/h).

Study in Taiwanese subjects (Study 3)

A summary of the pharmacokinetic parameters of mirabegron in Taiwanese subjects under fasted or fed conditions is given in Table IV. Mean plasma concentrations of mirabegron after single doses of 50 mg mirabegron under fasted or fed conditions in study 3 are shown in Figure 2. After a low-fat, low-calorie breakfast, mean T_{max} was increased by approximately 1 hour. The statistical analyses of food effect on the pharmacokinetic parameters of mirabegron are presented in Table III. Mean C_{max} decreased by approximately 29%, and mean $AUC_{0-\infty}$ decreased by 23%; the 90% CI of C_{max} and AUC fell outside the boundaries of 80% to 125%.

Studies in Chinese subjects (Studies 4 and 5)

A summary of the pharmacokinetic parameters of mirabegron in Chinese subjects is given in Table V. Mean plasma concentrations of mirabegron after single and multiple doses of 25 and 50 mg mirabegron in studies 4 and 5 are shown in Figure 3 and Figure 4, respectively.

Single dose

After single-dose administration of 25 or 50 mg mirabegron in the fasting state, the mean C_{max} was 9.70 and 37.13 ng/mL, the mean $AUC_{0-\infty}$ was 139.11 and 416.73 ng · h/mL, and the mean AUC_{0-24} was 64.09 and 208.49 ng · h/mL, respectively. The mean T_{max} occurred at approximately 4.0 hours after dosing across the tested dose range. The mean $t_{½}$ was approximately 41 hours. In both studies, mean estimates of CL/F decreased with increasing dose, whereas T_{max} and $t_{½}$ were independent of dose across the tested dose range.

Multiple dose

After the first dose of 25 mg mirabegron on day 10 and of 50 mg mirabegron on day 15 of the multiple-dose periods of studies 4 and 5, respectively, mirabegron reached its peak plasma concentration approximately 5 hours after dosing. The mean C_{max} was 4.69 and 16.06 ng/mL and the mean AUC_{0-24} was 33.75 and 109.97 ng · h/mL, respectively, after the first doses of 25 and 50 mg mirabegron, respectively, in the multiple-dose period. After multiple doses of 25 and 50 mg mirabegron, mirabegron reached a peak plasma concentration approximately 5 hours after doing on days 17 and 22, respectively. The mean C_{max} was 8.24 and 32.59 ng/mL and the mean $AUC_{0-\tau}$ was 98.96 and 320.99 ng · h/mL for the 25 and 50 mg doses, respectively. Mean C_{trough} almost reached steady state on days 17 and 21. The GMRs of C_{max} and AUC (day 17/day 10) were 1.800 and 2.946, respectively, for the 25 mg dose, whereas the GMRs of C_{max} and AUC (day 22/day 15) were 2.284 and 3.105, respectively, for the 50 mg dose. C_{max} and AUC of mirabegron were higher in female subjects than in male subjects. The GMR for female versus male subjects ranged from 1.136 to 1.412 for C_{max} and from 1.374 to 1.480 for AUC_{0-24} in study 4; the corresponding GMRs in study 5 ranged from 1.164 to 1.712 for C_{max} and from 1.354 to 1.675 for AUC_{0-24} (Table VI).

Tolerability

In study 1, one subject who received study drug under fasting conditions (fed-fasting sequence group, treatment period 2) experienced 3 serious treatment-emergent adverse events (TEAEs) (headache, pyrexia, and diarrhea), all of which were assessed as moderate in severity and possibly related to the study drug.

Table III. Effect of food on plasma pharmacokinetic parameters of mirabegron.

Variable	Study 1 (50 mg)	Study 2		Study 3 (50 mg)	Study 4 (25 mg)	Study 5 (50 mg)
		50 mg	100 mg			
Study population	Japanese	Japanese	Japanese	Taiwanese	Chinese	Chinese
C_{max}						
Fasted mean	29.40	35.37	103.29	27.03	9.70	37.13
Fed						
Low-fat meal						
Mean	—	13.40	42.86	20.23	4.69	16.06
GMR (90% CI)	—	0.342 (0.263–0.443)	0.357 (0.288–0.444)	0.7111 (0.4228–1.1958)	0.519 (0.409–0.658)	0.397 (0.292–0.539)
High[3]						
Mean	10.28	16.31	52.31	—	—	—
GMR[4] (90% CI)	0.389 (0.275–0.552)	0.474 (0.366–0.615)	0.514 (0.414–0.639)	—	—	–
AUC[*]						
Fasted mean	246.82	387.13	944.53	333.5	64.09	208.49
Fed						
Low-fat meal						
Mean	—	195.60	506.16	249.6	33.75	109.97
GMR (90% CI)	—	0.494 (0.440–0.555)	0.507 (0.459–0.560)	0.7684 (0.5865–1.0069)	0.547 (0.478–0.627)	0.489 (0.404–0.593)
High-fat meal						
Mean	122.13	272.50	674.36	—	—	–
GMR (90% CI)	0.532 (0.441–0.643)	0.712 (0.634–0.800)	0.728 (0.659–0.805)	—	—	—

GMR = geometric mean ratio.
[*]$AUC_{0-\infty}$ in studies 1, 2, and 3 and $AUC_{0-\tau}$ in studies 4 and 5.

Table IV. Pharmacokinetic parameters of mirabegron after single oral doses of mirabegron OCAS (50 mg) in Taiwanese subjects (study 3).*

Parameter	Fasted (n = 12)	Fed (Low-Fat Meal) (n = 12)
C_{max}, ng/mL	27.03 (18.05)	20.23 (15.11)
T_{max}, h	3.92 (0.79)	5.09 (0.79)
AUC_{0-last}, ng · h/mL	274.0 (131.8)	199.9 (97.9)
$AUC_{0-\infty}$, ng · h/mL	333.5 (154.5)	249.6 (116.2)
$t_{½}$, h	47.53 (15.60)	49.38 (15.54)
CL/F, L/h	194.91 (128.65)	237.58 (95.50)

OCAS = oral controlled absorption system.
*Data are presented as mean (SD).

All these events were confirmed to have resolved during the follow-up investigation conducted within 2 days of onset. The TEAEs occurred more frequently under fasting conditions. There was no specific pattern of changes in laboratory test results, and no clinically significant findings in vital signs or ECG were noted under fasting or fed conditions during the study.

In study 2, based on the incidence and type of AEs, results of clinical laboratory tests, vital sign assessment, and ECGs, single 50 and 100 mg doses of mirabegron administered under fasted and fed conditions (low- and high-fat meals) were well-tolerated in healthy Japanese male and female subjects. The mean supine pulse rate tended to increase in subjects receiving 100 mg at 6 hours after dosing under all treatment conditions. For the 100 mg dose group, maximum mean changes from baseline at 6 hours after dosing were 7.5, 5.5, and 5.4 beats/min under fasted, low-meal, and high-fat meal conditions, respectively.

In study 3, there were no serious AEs. Two subjects under fed conditions (16.7%) reported ≥1 TEAEs. The reported AEs in subjects receiving mirabegron included increased blood triglycerides, tachycardia, and abdominal tenderness. The occurrence rate of each event was 8.3%. All AEs in this study were mild in severity. Two of the 3 TEAEs observed were judged by the investigator to be possibly related to study drug. None of the subjects discontinued the study because of AEs. The number of reported TEAEs under fed conditions was higher than under fasted conditions. An increase in mean pulse rate 6 hours (11.1 and 8.5 beats/min from baseline under fasted and fed condition, respectively), 8 hours (approximately 11.9 and 7.2 beats/min from baseline under fasted and fed condition, respectively), and 12 hours (approximately 10.8 and 9.8 beats/min from baseline under fasted and fed condition, respectively) after administration of mirabegron was detected.

In study 4, single and multiple oral administration of 25 mg mirabegron was well tolerated in healthy Chinese volunteers. One TEAE (mild hordeolum) was reported in 1 of 24 subjects. The hordeolum was not considered to be related to the study drug and resolved at follow-up.

In study 5, single and multiple administration of the 50 mg mirabegron OCAS tablet was well tolerated in healthy Chinese volunteers. A total of 10 TEAEs were reported in 3 of the 24 subjects; drug-related TEAEs were reported in 2 subjects. There were no TEAEs reported in ≥2 subjects. Drug-related TEAEs included palpitations, tachycardia, abnormal hepatic function, and decreased white blood cell count. All TEAEs were mild in severity and resolved at follow-up. No serious AEs or AEs leading to study discontinuation were reported in these studies. In studies 4 and 5, no clinically meaningful tendencies were found in mean

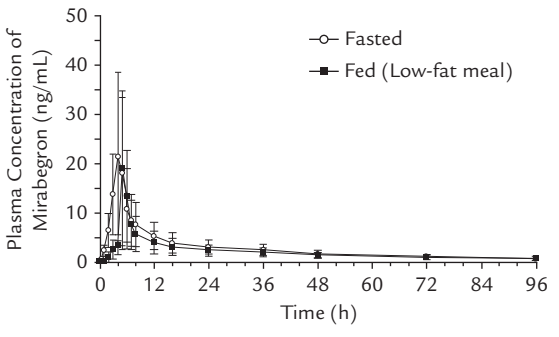

Figure 2. Mean (SD) plasma concentrations of mirabegron after single oral administration of mirabegron oral controlled absorption system 50 mg under fasted or fed conditions in healthy Taiwanese subjects in study 3.

Table V. Pharmacokinetic parameters of mirabegron after single oral doses of mirabegron OCAS under fasting conditions and multiple oral doses under fed conditions in Chinese subjects (studies 4 and 5).*

	Study 4 (25 mg)			Study 5 (50 mg)		
Parameter	Single (n = 24)	FD (Day 10) (n = 24)	LD (Day 17) (n = 24)	Single (n = 24)	FD (Day 15) (n = 24)	LD (Day 22) (n = 24)
C_{max}, ng/mL	9.70 (6.14)	4.69 (2.35)	8.24 (3.06)	37.13 (22.41)	16.06 (10.99)	32.59 (14.87)
T_{max}, h	3.88 (1.26)	4.92 (1.38)	5.42 (1.14)	4.00 (1.25)	5.21 (0.88)	5.42 (1.56)
$AUC_{0-\infty}$, ng · h/mL	139.11 (57.95)	—	—	416.73 (138.52)	—	—
AUC,† ng · h/mL	64.09 (29.80)	33.75 (11.16)	98.96 (28.72)	208.49 (79.18)	109.97 (53.70)	320.99 (113.66)
$t_{½}$, h	40.39 (8.75)	—	48.30 (9.04)	41.30 (8.27)	—	45.89 (11.00)
CL/F, L/h	207.61 (79.60)	—	282.51 (116.28)	134.14 (46.11)	—	192.69 (132.47)

FD = first day; LD = last day; OCAS = oral controlled absorption system.
*Data are presented as mean (SD).
†AUC_{0-24} for single dose and $AUC_{0-\tau}$ for multiple dose.

Figure 3. Mean (SD) plasma concentrations of mirabegron after oral administration of mirabegron oral controlled absorption system 25 mg in healthy Chinese subjects in study 4.

laboratory parameters. No clinically significant abnormalities in vital signs or ECG findings were reported.

DISCUSSION

These studies aimed to evaluate the pharmacokinetic parameters of mirabegron, including the effect of food, in healthy Japanese, Taiwanese, and Chinese subjects. In Japanese and Taiwanese studies (studies 1, 2, and 3), absorption of mirabegron was slightly delayed in the presence of food (mean T_{max} was 3.5 to 3.9 hours in fasted and 4.7 to 5.6 hours in fed).

Figure 4. Mean (SD) plasma concentrations of mirabegron after oral administration of mirabegron oral controlled absorption system 50 mg in healthy Chinese subjects in study 5.

Table VI. Effect of sex on the pharmacokinetic parameters of mirabegron after single (fasted) or multiple (fed) oral doses of mirabegron OCAS.

	Study 2 (Single Dose)		Study 3	Study 4			Study 5		
Variable	50 mg	100 mg	(Single Dose of 50 mg)	Single dose 25 mg	FD (Day 10) 25 mg	LD (Day 17) 25 mg	Single dose 50 mg	FD (Day 15) 50 mg	LD (Day 22) 50 mg
Study population	Japanese	Japanese	Taiwanese	Chinese	Chinese	Chinese	Chinese	Chinese	Chinese
C_{max}									
Mean of female	42.51	117.78	37.50	11.36	5.05	9.34	37.32	21.00	37.23
Mean of male	28.63	89.60	16.56	8.05	4.33	7.14	36.93	11.11	27.95
GMR (90% CI)[2]	1.276	1.452	2.211	1.276	1.136	1.412	1.164	1.712	1.521
	(0.877–1.856)	(1.053–2.002)	(1.149–4.254)	(0.828–1.965)	(0.811–1.591)	(1.048–1.904)	(0.764–1.772)	(0.991–2.957)	(1.019–2.271)
$AUC_{0-\infty}$									
Mean of female	446.32	1156.92	429.5	167.71	—	—	474.45	—	—
Mean of male	331.22	743.94	237.4	110.50	—	—	359.02	—	—
GMR (90% CI)[2]	1.337	1.600	1.869	1.432	—	—	1.347	—	—
	(1.078–1.658)	(1.334–1.918)	(1.174–2.974)	(1.121–1.830)			(1.081–1.680)		
AUC[a]									
Mean of female	—	—	—	78.81	38.95	114.48	236.76	135.80	388.09
Mean of male	—	—	—	49.38	28.56	83.45	180.22	84.14	253.88
GMR (90% CI)[2]	—	—	—	1.480	1.374	1.423	1.354	1.615	1.675
				(1.124–1.949)	(1.106–1.705)	(1.156–1.751)	(1.053–1.741)	(1.091–2.390)	(1.275–2.199)

FD = first day; GMR = geometric mean ratio; LD = last day; OCAS = oral controlled absorption system.
[2]Female/Male
[a]AUC_{0-24} for single dose and $AUC_{0-\tau}$ for multiple dose.

After administration of mirabegron in Japanese and Taiwanese subjects, C_{max} and $AUC_{0-\infty}$ under fed conditions were lower than under fasted condition, which indicated that there is a decrease in absorption when the drug is taken with food (C_{max} and $AUC_{0-\infty}$ were approximately 30% to 65% lower than under fasted conditions). In studies 4 and 5, C_{max} and AUC_{0-24} of mirabegron on the first day of multiple dosing under fed conditions were lower than those after a single dose under fasted conditions (mean C_{max} of 9.70 and 4.69 ng/mL and mean AUC_{0-24} of 64.09 and 33.75 ng · h/mL under fasted and fed conditions, respectively, for the 25 mg dose; mean C_{max} of 37.13 and 16.06 ng/mL and mean AUC_{0-24} of 208.49 and 109.97 ng · h/mL under fasted and fed conditions, respectively, for the 50 mg dose). Although the food effect on the pharmacokinetic parameters of mirabegron in Taiwanese subjects (in whom C_{max} and $AUC_{0-\infty}$ were 29% and 23% lower than under fasted conditions, respectively) was smaller than in Japanese subjects (in whom C_{max} and $AUC_{0-\infty}$ were 66% and 51% lower than under fasted conditions, respectively), the trend was similar for both Japanese and Taiwanese subjects. In study 2 in Japanese subjects, a greater reduction in mirabegron C_{max} and $AUC_{0-\infty}$ was observed after a low-fat meal than after a high-fat meal (50 mg: after the high-fat meal doses of mirabegron, C_{max} and $AUC_{0-\infty}$ were approximately 53% and 29% lower, and after the low-fat meal doses, C_{max} and $AUC_{0-\infty}$ were approximately 66% and 51% lower than under fasted condition, respectively; 100 mg: after the high-fat meal doses of mirabegron, C_{max} and $AUC_{0-\infty}$ were approximately 49% and 27% lower, and after the low-fat meal, C_{max} and $AUC_{0-\infty}$ were approximately 64% and 49% lower than under fasted condition, respectively), as observed in Western subjects.[8] According to the Biopharmaceutics Classification System, mirabegron may be considered class 3 with high solubility and low permeability.[12] Therefore, transporters may be important for mirabegron absorption. Mirabegron is a substrate of P-glycoprotein.[12] A postulated mechanism that may contribute to the observed food effect with mirabegron is unclear; however, it may in part be attributable to drug-transporter and food-transporter interactions.[13] Food intake may lead to a prolonged gastric residence time. In addition, luminal concentrations of mirabegron are likely to be lower and insufficient to saturate P-glycoprotein transporters, resulting in reduced bioavailability and plasma exposure compared with those in the fasted state. The differences in composition of the high-fat and low-fat meals may also differentially affect intestinal transport of mirabegron. Lipids, in particular monoglycerides, contained in a high-fat meal or its digests have been reported to inhibit P-glycoprotein transport.[14,15] Mirabegron has also previously been reported to have been adsorbed to food components, especially by components of low-fat meals.[8]

In studies in healthy Chinese subjects, mirabegron C_{max} was reached approximately 4 hours after oral administration of a single dose and approximately 5 hours after multiple-dose administration. Steady-state conditions were reached on days 7 to 8 after once-daily administration with mirabegron, and accumulation of mirabegron was approximately 2- to 3-fold. These findings are in accordance with previously published single- and multiple-dose studies in healthy Japanese male subjects.[6] Although the 25 and 50 mg dose studies were separately conducted, mirabegron C_{max} and $AUC_{0-\infty}$ increased more than proportionally with dose in Chinese subjects. In addition, after administration of mirabegron in Japanese, Taiwanese, and Chinese subjects, mean values for C_{max} and AUC in female subjects were higher than those in male subjects (**Table VI**). There were no apparent differences in the magnitude of the sex difference among the 3 populations. The mean weight of male subjects (61.9 to 70.2 kg) was higher than that of female subjects (53.0 to 56.6 kg) (**Table I**). The previous studies in Europe also found that female subjects generally had 44% greater mirabegron C_{max} and 38% greater AUC than males, which was partly related to sex differences in weight.[5] Weight-normalized values for C_{max} and AUC were 23% and 18% higher, respectively, in females than in males. Furthermore, absolute bioavailability of mirabegron in females tends to be larger than in males (approximately 12.7%). Sex differences in exposure could be explained by weight and absolute bioavailability.[4]

The mean C_{max} after a 50 mg dose of mirabegron under fasted conditions in male Japanese (study 2), Taiwanese (study 3), and Chinese (study 5) subjects was 35.37, 27.03, and 37.13 ng/mL, respectively. The mean $AUC_{0-\infty}$ was 387.13, 333.5, and 416.73 ng · h/mL, respectively. Therefore, the pharmacokinetic profiles of mirabegron are similar in healthy Japanese, Taiwanese,

and Chinese subjects. These findings are reasonable in view of mirabegron's drug disposition in which the elimination of mirabegron is likely to be through both biliary and renal excretion of unchanged drug and metabolism.[7] Renal clearance accounts for approximately 25% of total clearance from plasma.[4] The rest of its elimination occurs through metabolism and excretion of unchanged drug in feces. Indeed, metabolism is one of the major elimination pathways of mirabegron.

The results of in vitro and in vivo studies suggest involvement of butyrylcholinesterase, UDP-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase in the metabolism of mirabegron.[7,16] In addition, cytochrome 450 (CYP) 3A4 is the primary isoenzyme responsible for the hepatic oxidative metabolism of mirabegron in vitro, with a minor role of CYP2D6.[16] Mirabegron is cleared by multiple metabolic enzymes with no single enzyme dominant.

From the results of the clinical studies, mirabegron is not considered a sensitive substrate of CYP3A in vivo because ketoconazole increased mirabegron exposure by <2-fold. In addition, the effect of the CYP2D6 phenotype on mirabegron exposure is small and likely of limited clinical importance.[17] There is a report that subjects native to Japan, China, and Korea can be expected to have similar metabolic ratios for drugs primarily cleared by major CYPs, including CYP3A4 and CYP2D6.[18] In addition, it seems that ethnic differences in CYP3A4 polymorphisms, particularly in Asians, are very rare and do not appear to fully explain the large individual variation in CYP3A4 activity.[19] Therefore, CYP polymorphism may not play a role in the pharmacokinetic variability of mirabegron in an East Asian population.

Both human butyrylcholinesterase and UGTs are metabolic enzymes for mirabegron. Butyrylcholinesterase is coded by the *BCHE* gene included some mutations lead to catalytic disturbance.[20,21] UGTs are well known to have 4 subfamilies: UGT1, UGT2, UGT3, and UGT8.[22] It is unclear whether there are ethnic differences in these enzymes among Asian populations. Because mirabegron is cleared by multiple pathways, differences in enzymatic metabolism due to ethnicity might also be expected to have a small effect on the pharmacokinetic parameters of mirabegron in East Asian populations.

On the other hand, several aspects of these studies, such as extrinsic ethnic factors, have to be considered when comparing their results. First, they were conducted in different countries, at different centers, and at different times, although evaluation of food effect on the pharmacokinetic parameters was performed with similar food content. The pharmacokinetic parameters of mirabegron are similar among Japanese, Taiwanese, and Chinese subjects. This information is important for use of mirabegron in East Asian countries.

To compare the Western[5] and East Asian populations, the subject demographic characteristics were compared. The mean ages of the Western (27.6 to 30.3 years) and East Asian (23.4 to 33.3 years) male and female subjects were similar (Table I). The mean weight of young Western male and female subjects (68.9 to 77.1 kg and 58.8 to 64.6 kg, respectively) was higher than that of young East Asian male and female subjects (61.9 to 70.2 kg and 53.0 to 56.6 kg, respectively) (**Table I**). A comparison of mirabegron exposure in East Asian and Western healthy subjects revealed that the mean AUC values for mirabegron in East Asian male and female subjects after single 50 mg doses were higher than those observed in Western male and female individuals as reported previously.[5] Weight might be one of the factors that affect these differences in exposure. In a previous report of Japanese single- and multiple-dose studies, the differences in mirabegron exposure were smaller when values were normalized for weight between Japanese and Western subjects.[6] These findings are in accordance with previously published pharmacokinetic profiles in healthy Western subjects.[5,6,8]

The effects of food and sex on bioavailability of mirabegron were not clinically relevant. Mirabegon is used without dose adjustment based on sex and food consumption in clinical practice.[23,24] Mirabegron was well tolerated in healthy Japanese, Taiwanese, and Chinese subjects.

CONCLUSIONS

Our studies indicate higher exposure levels of mirabegron in female compared with male Japanese, Taiwanese, and Chinese subjects as found earlier in Western subjects. Furthermore, the effects of food on the pharmacokinetic parameters of mirabegron appeared to be similar among the 3 populations tested in our studies. A greater reduction in mirabegron C_{max} and $AUC_{0-\infty}$ was observed after a low-fat meal compared with a high-fat meal in Japanese subjects. The overall findings suggest that there

are no significant pharmacokinetic parameter differences among Japanese, Taiwanese, and Chinese populations. Mirabegron was well tolerated in healthy Japanese, Taiwanese, and Chinese subjects.

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CONFLICTS OF INTEREST

The studies were sponsored by Astellas Pharma Inc. The authors of this article disclose the following conflicts of interest: H. Iitsuka, M. Katashima, S. Takusagawa, and T. Sawamoto are full-time employee of Astellas Pharma Inc and M. van Gelderen is a full-time employee of Astellas Pharma Global Development.

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