Pharmacokinetic Properties of Mirabegron, a β_3-Adrenoceptor Agonist: Results From Two Phase I, Randomized, Multiple-Dose Studies in Healthy Young and Elderly Men and Women

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ABSTRACT

Background: Mirabegron (YM178) is a β_3-adrenoceptor agonist for the treatment of overactive bladder (OAB). As part of the clinical development program for mirabegron, 2 human volunteer studies were performed to derive detailed data on the multiple-dose pharmacokinetic (PK) properties of mirabegron.

Objective: Two randomized Phase I studies were conducted to evaluate the PK properties of mirabegron, including metabolic profile and effects of age and sex, following multiple oral doses in healthy subjects.

Methods: In study 1, mirabegron oral controlled absorption system (OCAS) tablets were administered once daily to healthy young subjects (18–55 years) at doses of 50, 100, 200, and 300 mg and in elderly subjects (65–80 years) at 50 and 200 mg in a double-blind placebo-controlled, parallel-group design. In study 2, mirabegron OCAS was administered once daily to healthy young (18–45 years) and older (≥55 years) subjects at doses of 25, 50, and 100 mg in an open-label crossover design. Blood samples were collected up to 72 hours (study 1) and 168 hours (study 2) after the last dose. Urine samples were collected up to 24 hours after the last dose. Plasma and urine concentrations of mirabegron and its metabolites (study 2 only) were analyzed by LC-MS/MS. PK parameters were determined using noncompartmental methods. Tolerability assessments included physical examinations, supine blood pressure and pulse rate, orthostatic stress testing (study 1), resting 12-lead ECGs, clinical laboratory tests (biochemistry, hematology, and urinalysis), and adverse-events (AE) monitoring using investigators' questionnaires and subjects' spontaneous reports.

Results: Thirty-two young male (mean age, 30.3 years; mean weight, 77.1 kg), 32 young female (27.6 years; 64.6 kg), 16 elderly male (69.8 years; 79.3 kg), and 16 elderly female (68.1 years; 67.4 kg) subjects were enrolled in study 1. Eighteen young male (mean age, 28.6 years; mean weight, 68.9 kg), 18 young female (28.7 years; 58.8 kg), 21 older male (63.4 years; 72.6 kg), and 18 older female (65.1 years; 62.3 kg) subjects were enrolled in study 2. Most of the subjects were white (91% in study 1 and 88% in study 2). Mirabegron plasma concentrations peaked at ~3 to 5 hours and declined multiexponentially with a $t_{1/2}$ of ~32 hours in study 1 and 60 hours in study 2. Steady state was achieved within 7 days of once daily administration, with an accumulation ratio of ~2. Mirabegron and its metabolites demonstrated a greater–than–dose-proportional increase in C_{max} and $AUC_{0-\tau}$ after multiple-dose administration. Two major circulating metabolites were observed, representing 17% and 10% of total drug-related $AUC_{0-\tau}$. Excretion of unchanged mirabegron in urine over the 24-hour dosing interval ($Ae_{0-\tau}\%$) increased from approximately 7% at 25 mg to 18% at 300 mg once daily in young subjects. Renal clearance (CL_R) of mirabegron was independent of dose and averaged ~13 L/h. Mirabegron C_{max} and $AUC_{0-\tau}$ were similar in older and young subjects. Women exhibited ~40% higher mirabegron C_{max} and $AUC_{0-\tau}$ than men; weight-corrected values were ~20% higher in women. Mirabegron was generally

well tolerated up to 300 mg once daily. No clear trends for increased incidence of AEs occurred with higher doses of mirabegron. The AE with the highest incidence was headache.

Conclusion: Oral mirabegron exhibited a greater–than–dose-proportional increase in exposure. Sex but not age significantly affected mirabegron exposure. ClinicalTrials.gov identifier: NCT01478503 (Study 1) and NCT01285596 (Study 2). (*Clin Ther.* 2012;34:2144–2160) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: β_3-adrenoceptor, elderly, gender, mirabegron, pharmacokinetics, overactive bladder.

INTRODUCTION

Overactive bladder (OAB) is a syndrome affecting the filling phase of the bladder and is characterized by symptoms of urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia.[1] OAB has a profound influence on patients' physical, social, and emotional well-being, and the disease burden creates a substantive cost to society.[2] An estimated 10.7% of the 2008 worldwide population (4.3 billion) was affected by OAB,[3] with the overall prevalence being greater in women than men.[3–5] The prevalence of OAB increases with age, affecting 30% to 40% of the population >75 years of age.[1]

Currently available medical treatment options are muscarinic receptor antagonists, for example solifenacin, tolterodine, oxybutynin, and darifenacin.[6] However, their clinical use is often limited by common adverse events, including dry mouth, blurred vision, and constipation, that can affect adherence. An insufficient response to treatment is another factor that can affect the utility of antimuscarinics. Mirabegron is the first of a new class of agents approved for the treatment of OAB.[7,8] Mirabegron is an agonist of the human β_3-adrenergic receptor (AR), as demonstrated by in vitro laboratory experiments using the cloned human β_3 AR.[9] 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.[9,10] A Phase II dose-finding study demonstrated efficacy of mirabegron oral controlled absorption system (OCAS) modified-release tablets at once-daily doses of 25, 50, and 100 mg (ClinicalTrials.org identifier: NCT00527033).[11] Two, large-scale, 12-week, Phase III studies demonstrated the efficacy and

tolerability of mirabegron at once-daily doses of 50 and 100 mg in patients with OAB in Europe and Australia[12] and in North America.[13]

As part of the clinical development of mirabegron, the pharmacokinetic (PK) properties of multiple-dose mirabegron OCAS tablets were characterized in healthy subjects in 2 clinical studies. In particular, because the OAB population consists of a large proportion of elderly patients and affects both sexes, these studies evaluated the effects of age and sex on the PK properties of mirabegron. Information from these studies was required to understand the PK profile of mirabegron, help define dosing recommendations, and support regulatory submissions. The present article reports the results of these 2 studies.

SUBJECTS AND METHODS
Subjects

Subjects in study 1 were healthy and young (18–55 years, inclusive) or elderly (65–80 years, inclusive) men and women with a body weight between 60 and 100 kg for men and between 50 and 90 kg for women, and a body mass index (BMI) of 18 to 30 kg/m^2 for both sexes. Subjects in study 2 were healthy and young (aged 18–45 years inclusive) or older (aged ≥55 years, of whom at least 25% were required to be ≥70 years) men and women with a BMI of 18.5 to 30 kg/m^2. Female subjects were of nonchildbearing potential or willing to take adequate contraceptive measures. All subjects were in good health (as determined by medical history, physical examination, electrocardiography, and clinical laboratory measurements) and were willing and able to comply with study requirements.

Study Designs

Study 1 was conducted at Pharma Bio-Research Group BV, Zuidlaren, The Netherlands, and Kendle, Utrecht, The Netherlands, between May and October 2005; study 2 was conducted at SGS Aster, Paris, France, between March and November 2009.

Study 1 was a double-blind, randomized, placebo-controlled, multiple dose–escalation study in 6 separate dose groups. In each dose group, 12 subjects (6 men and 6 women) were randomly assigned with the use of a computer-generated randomization scheme to receive mirabegron OCAS tablets (50, 100, 200, and 300 mg [as 1 × 100 mg + 1 × 200 mg tablet] in young subjects and 50 and 200 mg in elderly subjects) and 4 subjects (2 men and 2 women) were randomly assigned

to receive placebo. Treatment assignment was concealed from all study personnel until data analysis had been completed. Each subject received a single dose of mirabegron or placebo on day 1, followed by a 3-day washout and once-daily oral doses for 10 days (days 4–13). Subjects were fasted for 10 hours prior to dosing and remained fasted until 4 hours postdose on days 1 and 13. On all other days, subjects were allowed breakfast at least 30 minutes postdose. Subjects were confined to the study site from 2 nights before dosing until 72 hours after the last dose. Subjects underwent a poststudy visit within 7 to 14 days after discharge or after early discontinuation. Study 2 was an open-label, randomized, 2-way crossover study in 36 young (18 men and 18 women) and 39 older subjects (21 men and 18 women). Subjects were randomized to 1 of 6 treatment sequences with the use of a computer-generated randomization scheme. Randomization was stratified by age and sex. Each subject received 2 of 3 possible doses of mirabegron OCAS tablets (25, 50, and 100 mg) in random sequence separated by a minimum of 14 days. On each occasion, subjects received an oral dose of mirabegron twice daily (loading dose) on day 1, followed by multiple oral doses once daily for 6 days (days 2–7). On days 6 and 7, subjects were fasted for 8 hours prior to and 4 hours after dosing. On all other days, study drug was administered 30 minutes after a standardized breakfast. Subjects were confined to the study site from 2 nights before dosing until 168 hours after the last dose of each period. Subjects underwent a poststudy visit 7 to 14 days after discharge of period 2 or after early discontinuation.

In both studies, concurrent medication was not allowed, with the exception of oral contraceptives and the incidental use of paracetamol (acetaminophen). All studies were carried out in accordance with the Declaration of Helsinki[14] and the Good Clinical Practice Guidelines,[15] and all subjects provided written informed consent before entering a study and before any study-specific procedures were performed. Protocols were approved by the Independent ethics review committee or institutional review board at the sites where the studies were conducted. Subjects received pro rata compensation for their participation.

Blood and Urine Collection

In study 1, blood samples for measurement of mirabegron plasma concentrations were obtained predose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 16, 24, 36, 48, 60,

and 72 hours after dosing on days 1 and 13, and predose on days 10 to 12. Urine samples for measurement of unchanged mirabegron were collected within ~30 minutes prior to dosing and from 0 to 6, 6 to 12, 12 to 24, 24 to 48, and 48 to 72 hours postdose on day 1, and from 0 to 6, 6 to 12, and 12 to 24 postdose on day 13. In study 2, blood samples for measurement of plasma concentrations of mirabegron and metabolites were obtained predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 132, and 168 hours after dosing on day 7. Urine samples for measurement of unchanged mirabegron and metabolites were collected within ~30 minutes prior to dosing on day 7 and from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose.

In both studies, blood samples were collected into tubes containing sodium-heparin as anticoagulant and sodium fluoride as stabilizer and centrifuged within 30 minutes of collection, and the plasma was stored at −70°C pending analysis. Urine containers were kept refrigerated during collection. Samples from each urine collection period were stored at −70°C pending analysis. Frozen samples were shipped on dry ice for analysis at Astellas Pharma Europe (Leiderdorp, The Netherlands) for study 1 and study 2 (metabolites only), and PPD (Richmond, Virginia) for study 2 (mirabegron only).

Sample Analysis

Plasma and urine samples were analyzed for concentrations of mirabegron and eight metabolites (M5 [deacylated mirabegron (M16)-N^{ω}-acetylated], M8 [mirabegron-N-α-oxidation body (phenylacetic acid derivative)], M11 [mirabegron-O-glucuronide], M12 [mirabegron ketone oxidation body (M18)-N-COO-glucuronide], M13 [mirabegron-N-COO-glucuronide], M14 [mirabegron-N^{ω}-glucuronide], M15 [mirabegron-N-O-glucuronide], and M16 [deacylated mirabegron] [study 2 only]) using 4 separate validated LC-MS/MS methods, as described previously[16]: (1) mirabegron; (2) M5 and M16; (3) M8; and (4) M11, M12, M13, M14, and M15. Technicians were masked to the treatment as the assays were completed. Either solid phase extraction or liquid–liquid extraction was used to extract the analytes of interest from matrix constituents. For mirabegron, an Inertsil C8-3 analytical column (ATAS GL International BV, Eindhoven, The Netherlands) was used and detection was performed using a triple-quad mass spectrometer

equipped with an atmospheric pressure chemical ionization interface. For the metabolite assays, chromatographic separation was performed through a Phenomenex Synergi Fusion-RP C18 analytical column (Phenomenex, Macclesfield, Cheshire, United Kingdom) and detection was performed using a triple-quad mass spectrometer equipped with a heated electro spray ionization interface. The calibration ranges for mirabegron were 1.0 to 500 ng/mL in plasma and 2.0 to 1000 ng/mL in urine for study 1, and 0.2 to 100 ng/mL in plasma and 10 to 5000 ng/mL in urine for study 2. The calibration ranges for the metabolites (study 2) in plasma were 1.0 to 200 ng/mL for M8; 0.5 to 250 ng/mL for M11, M12, M13, and M15; 1.0 to 500 ng/mL for M14; and 0.5 to 100 ng/mL for M5 and M16. The ranges in urine were 5.0 to 1000 ng/mL for M8, M5, and M16; and 5.0 to 2000 ng/mL for M11 to M15. Precision of quality control (QC) standards assayed during sample analysis of mirabegron and its metabolites, expressed as percentage relative SD, was <6.9% and <6.7% for study 1 and study 2, respectively, for plasma, and <7.1% and <5.9% for study 1 and study 2, respectively, for urine. The accuracy (relative error) of the assays over the QC range ranged from −2.3% to 1.7% and from −7.9% to 2.4% for study 1 and study 2, respectively, for plasma, and from −5.1% to 2.9% and from −10.2% to 4.5% for study 1 and study 2, respectively, for urine.

Pharmacokinetic Methods

Concentration data of mirabegron and metabolites in plasma and urine were analyzed by noncompartmental methods using WinNonlin version 4.1 or higher (Pharsight Corporation, Mountain View, California) and SAS version 8.2 or higher (SAS Institute, Cary, North Carolina) to obtain values for the following PK parameters,[17,18] as applicable and as appropriate for each study: C_{max}, T_{max}, C_{min}, AUC_{0-24h}, AUC_{0-inf} after single-dose administration, $AUC_{0-\tau}$ after multiple-dose administration (all calculated using the linear-log trapezoidal method), accumulation ratio (R_{acc}) (assessed as $AUC_{0-\tau}$, day 13/AUC_{0-24h}, day 1 for study 1), metabolic ratio (MR_t) (assessed as metabolite $AUC_{0-\tau}$ divided by total $AUC_{0-\tau}$ of mirabegron and metabolites), $t_{1/2}$, amount of drug as percentage of the dose excreted in the urine (Ae%) from time zero to infinity (Ae_{0-inf}%) after single-dose administration, Ae% over the 24-hour dosing interval ($Ae_{0-\tau}$%) after multiple-dose administration, and renal clearance

(CL_R). Weight-normalized mirabegron C_{max} and AUC were calculated as the corresponding PK parameters divided by the body weight of the individual subject. Actual sampling times were used for the calculation of PK parameters, and nominal sampling times were used for the mean concentration−time figures.

Statistical Methods

No formal sample size calculations were performed. Sample sizes were chosen as a compromise between combinations of the following: (1) the need to minimize the exposure of human subjects to a new chemical entity; (2) the need to provide sufficient tolerability data; and (3) PK considerations. Summary statistics were calculated for all PK parameters for mirabegron and its metabolites by dose, sex, and age group.

For study 1, log-transformed AUC values of mirabegron were evaluated by ANOVA to estimate ratios of $AUC_{0-\tau}$, day 13/AUC_{0-inf}, day 1. These ratios provide an estimate of the extent of change in bioavailability and/or clearance with time during repeated administration. For linear PK properties with time, the $AUC_{0-\tau}$ at steady state is equal to the AUC_{0-inf} following a single dose (ie, a ratio of 1).[17] Log-transformed data were back-transformed to provide the ratio between day 13 and day 1 and associated 95% CIs.

AUC and C_{max} values for mirabegron in study 1 were analyzed to determine dose proportionality using the power model, ln(parameter) $= \alpha + \beta \cdot$ ln(dose), where $\alpha =$ intercept, and $\beta =$ dose-proportionality coefficient.[19] Dose proportionality was concluded if the 95% CI for β included 1.[20] The corresponding model for study 2 included, in addition, period and subject as fixed effects to reflect the difference in study design and was also applied to metabolites of mirabegron. These models were fit for the overall population (study 2 only) and separately for each sex and age group.

Age and sex effects in study 2 were evaluated by an ANOVA model on log-transformed $AUC_{0-\tau}$ and C_{max} values of mirabegron and metabolites with terms for period, dose, sex, age group, and subject nested within sex and age group, and interaction terms for sex by age, dose by sex, and dose by age. Subjects aged ≥55 years were the primary older population defined in the study protocol for the effect of age analyses. The analyses were repeated for a subpopulation of the older subjects who were ≥65 years (the current age cutoff for elderhood in the International Conference on Harmo-

nization [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E7).[21] The 90% CI of the ratio of $AUC_{0-\tau}$ and C_{max} for female versus male and elderly versus young subjects were calculated on the original scale after back-transforming the log scale results. Absence of age and/or sex effect was concluded if the corresponding 90% CI was entirely within the default equivalence limits of 0.80 and 1.25,[22,23] although the study was not powered for this. The effect of age and sex on the PK properties of mirabegron and its metabolites was also analyzed separately by sex and age group (including a dose-by-sex or dose-by-age group interaction term). All statistical analyses were performed using SAS version 8.2 or higher.

Tolerability Assessments

Tolerability was assessed based on physical examinations, supine vital signs (blood pressure and pulse rate), orthostatic stress testing (study 1), resting 12-lead ECGs, standard clinical laboratory tests (biochemistry, hematology, and urinalysis), and AE monitoring. AEs were recorded from the time of admission to the study site until the end of the study. All AEs collected on investigators' questionnaires or subjects' spontaneous reports were assessed by the investigators with respect to severity, course, outcome, seriousness, and relationship to the study drug and were recorded regardless of the suspected relationship to the study drug. Physical examinations were conducted at screening and the end-of study visit (follow-up). Vital signs were measured after the subject had rested for at least 5 minutes in the supine position at screening, 1 day before drug administration (day −1), on days 1, 2, 10 to 17 and follow-up in study 1, and at screening, admission (day −2), on days −1 and 1 to 7, at discharge and at follow-up in study 2. Orthostatic vital signs in study 1 were measured at screening and on days −1, 1, and 13 and included pulse and blood pressure measurements taken after the subject had been lying supine for 5 minutes; the subject then sat for 2 minutes, stood for 2 minutes, and had pulse and blood pressure measurements repeated while standing. A positive orthostatic test associated with standing was defined as any symptoms of dizziness or light-headedness, associated with a decrease in systolic blood pressure (SBP) of >20 mm Hg and an increase in pulse rate of ≥20 beats/min. A standard 12-lead ECG that included heart rate (HR) and interval measurements (ie, PR, QRS, QT, QTc)

was performed at screening, on days −1, 1, and 13, and at discharge and follow-up in study 1, and at screening and on days −1, 1, 6, and 7 of each period in study 2. Standard clinical laboratory assessments were conducted at screening, on day −1, and at discharge and follow-up in study 1, and at screening, on day −2, and at follow-up in study 2. Laboratory analyses were performed by Pharma Bio-Research Group BV, Zuidlaren, The Netherlands, and Analytico-Medinet, Breda, The Netherlands (study 1), and Thebault Laboratory, Choisy-Le-Roi, France (study 2). If an abnormality was observed in vital signs, ECG, or clinical laboratory tests, the investigators subsequently assessed the clinical significance and the relationship to the study drug.

RESULTS
Study Population

Subject characteristics are summarized in Table I. In study 1, a total of 96 healthy subjects were enrolled and all completed the study. Three subjects used concomitant medications that were not allowed as per the study protocol: 1 subject received an intramuscular injection of tetanus immunoglobulins following a wrist fracture, and 2 subjects used acyclovir topically for the treatment of herpes labialis. The use of these concomitant medications was not considered to have influenced the results of the study.

In study 2, 75 subjects were enrolled and 67 subjects completed the study. Eight subjects prematurely discontinued the study—1 due to withdrawal of consent, 1 due to a serious AE (SAE), and 6 due to hematocrit measurements below the normal range prior to treatment period 2. Three subjects received concurrent medications that were not allowed as per the study protocol—1 subject received 2 topical applications of diclofenac for treatment of a leg contusion, 1 subject received oral fosfomycin for a urinary tract infection, and 1 subject received 3 cutaneous daily doses of pentosan polysulfate in 2 separate periods for treatment of venous forearm indurations. These concurrent medications were received after study drug administration was completed and were not expected to affect the results of the study. All 75 enrolled subjects were included in the PK and tolerability assessments.

Pharmacokinetic Properties of Mirabegron

Mean mirabegron T_{max} was 2.7 to 5.0 hours across the dose range, both after the administration of a single

Table I. Demographic and baseline characteristics.

| Characteristics	Study 1				Study 2					
	Young Males (n = 32)	Young Females (n = 32)	Elderly Males (≥65 y) (n = 16)	Elderly Females (≥65 y) (n = 16)	Young Males (n = 18)	Young Females (n = 18)	Older Males (≥55 y) (n = 21)	Older Females (≥55 y) (n = 18)	Elderly Males (≥65 y) (n = 8)	Elderly Females (≥65 y) (n = 9)
Age, mean (range), y	30.3 (18–55)	27.6 (18–53)	69.8 (65–77)	68.1 (65–73)	28.6 (19–45)	28.7 (19–45)	63.4 (55–72)	65.1 (57–77)	68.5 (65–72)	70.0 (65–77)
Race, no.										
White	30	27	16	14	14	14	19	18	7	9
Black	2	3	0	0	1	3	1	0	0	0
Asian	0	0	0	2	0	0	1	0	1	0
Other	0	2	0	0	3	1	0	0	0	0
Weight, mean (range), kg	77.1 (60–93)	64.6 (55–89)	79.3 (69–90)	67.4 (52–80)	68.9 (54–84)	58.8 (50–70)	72.6 (62–88)	62.3 (48–83)	70.3 (62–80)	64.6 (48–83)
BMI, mean (range), kg/m²	23.1 (19–28)	22.5 (19–27)	26.1 (23–30)	25.1 (21–30)	22.7 (19–26)	21.8 (20–26)	24.9 (22–30)	24.1 (19–31)	23.9 (22–28)	25.4 (22–31)

BMI = body mass index.
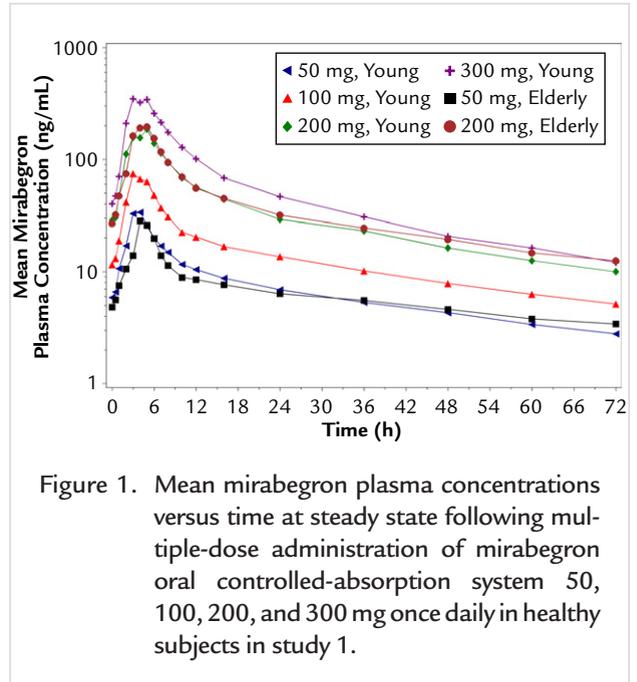
Figure 1. Mean mirabegron plasma concentrations versus time at steady state following multiple-dose administration of mirabegron oral controlled-absorption system 50, 100, 200, and 300 mg once daily in healthy subjects in study 1.

dose (50−300 mg) and at steady state (25−200 mg once daily). T_{max} was similar between young, older (≥55 years), and elderly (≥65 years) subjects and between men and women (Figures 1 and 2, Tables II and III). Plasma exposure was generally higher in women compared with men, while no apparent differences
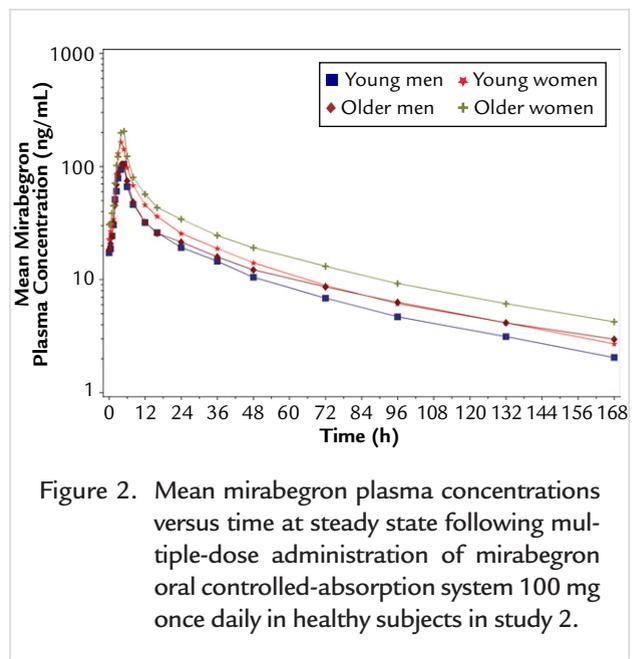

Figure 2. Mean mirabegron plasma concentrations versus time at steady state following multiple-dose administration of mirabegron oral controlled-absorption system 100 mg once daily in healthy subjects in study 2.

Table II. Summary of selected pharmacokinetic parameters for mirabegron following single- and multiple-dose administration (study 1). Values are mean (%CV) unless otherwise noted.

Dosing/Sex/Parameter	Young				Elderly ($\geq$65 y)	
	50 mg	100 mg	200 mg	300 mg	50 mg	200 mg
Single Dose						
Male						
n*	6	6	6	6	6	6
C_{max}, ng/mL	23.7 (51)	61.9 (28)	158 (48)	287 (59)	34.2 (43)	150 (63)
T_{max}, h[†]	3.5 (1.76)	3.0 (1.10)	2.7 (0.49)	3.0 (1.10)	4.3 (0.52)	3.7 (1.36)
AUC_{0-inf}, ng · h/mL	302 (33)	600 (23)	1190 (42)	1800 (36)	297 (—)	1070 (40)
$t_{1/2}$, h	28.8 (20)	34.6 (26)	29.4 (17)	27.9 (16)	30.3 (—)	33.5 (15)
Ae_{0-inf}, %	9.10 (19)	9.20 (23)	8.30 (43)	9.79 (27)	3.13 (—)	6.35 (26)
CL_R, L/h	15.7 (19)	15.8 (22)	13.9 (19)	17.0 (24)	6.75 (28)	12.8 (30)
Female						
n*	6	6	6	6	6	6
C_{max}, ng/mL	40.1 (77)	78.6 (46)	200 (34)	461 (40)	33.2 (54)	235 (47)
T_{max}, h[†]	3.0 (0.89)	3.3 (1.03)	3.0 (0.89)	3.3 (0.82)	4.2 (1.17)	3.7 (0.82)
AUC_{0-inf}, ng · h/mL	397 (39)	602 (32)	1650 (31)	2940 (33)	308 (26)	1790 (29)
$t_{1/2}$, h	30.7 (14)	32.5 (19)	31.4 (19)	27.6 (12)	42.1 (20)	35.5 (11)
Ae_{0-inf}, %	9.00 (35)	8.17 (34)	9.21 (35)	11.9 (39)	4.23 (51)	8.74 (31)
CL_R, L/h	11.4 (15)	13.8 (19)	11.2 (23)	12.2 (20)	8.21 (44)	9.83 (15)
Multiple doses						
Male						
n*	6	6	6	6	6	6
C_{max}, ng/mL	32.8 (48)	72.0 (23)	220 (27)	381 (42)	36.9 (41)	205 (65)
T_{max}, h[†]	2.7 (1.51)	3.2 (0.75)	3.0 (1.26)	3.2 (1.17)	4.7 (0.82)	4.0 (0.90)
$AUC_{0-\tau}$, ng · h/mL	262 (40)	519 (28)	1440 (28)	2470 (28)	231 (33)	1460 (42)
$t_{1/2}$, h	36.7 (10)	36.8 (13)	32.7 (25)	29.2 (19)	48.3 (21)	35.5 (13)
R_{acc}	2.45 (72)	1.53 (20)	2.28 (39)	2.13 (16)	1.95 (35)	2.33 (13)
$Ae_{0-\tau}$, %	7.41 (36)	9.82 (23)	12.9 (50)	12.2 (41)	3.96 (50)	9.73 (25)
CL_R, L/h	14.4 (23)	19.6 (22)	17.3 (34)	15.3 (36)	8.78 (38)	14.6 (30)
Female						
n*	6	6	6	6	6	6
C_{max}, ng/mL	45.6 (58)	112 (58)	264 (59)	530 (34)	36.5 (28)	290 (44)
T_{max}, h[†]	3.3 (0.82)	3.3 (1.03)	3.7 (1.63)	3.7 (1.21)	4.0 (1.25)	3.5 (1.03)
$AUC_{0-\tau}$, ng · h/mL	368 (49)	800 (37)	2040 (49)	3890 (22)	274 (17)	2110 (38)
$t_{1/2}$, h	36.5 (24)	32.0 (10)	29.8 (23)	26.3 (25)	45.0 (28)	34.9 (15)
R_{acc}	1.84 (12)	2.50 (35)	1.84 (32)	2.01 (33)	2.19 (32)	2.02 (42)
$Ae_{0-\tau}$, %	10.1 (47)	11.9 (34)	14.3 (54)	18.0 (26)	4.59 (26)	10.4 (25)
CL_R, L/h	14.0 (12)	15.4 (25)	14.0 (16)	14.0 (18)	8.72 (37)	10.5 (24)

Ae_{0-inf} = amount of drug as percentage of the dose excreted in the urine from time zero to infinity; $Ae_{0-\tau}$ = amount of drug as percentage of the dose excreted in the urine over the 24-hour dosing interval; CL_R = renal clearance; R_{acc} = accumulation ratio.
*Number of subjects with evaluable data may vary for some parameters.
[†]Mean (SD).

Table III. Summary of selected pharmacokinetic parameters for mirabegron following multiple-dose administration (study 2). Values are mean (%CV) unless otherwise noted.

Dose/Parameter	Young		Older (≥55 y)		Elderly (≥65 y)	
	Male	Female	Male	Female	Male	Female
25 mg once daily						
n*	11	11	13	12	4	7
C_{max}, ng/mL	21.6 (49)	20.1 (28)	11.7 (39)	19.7 (30)	13.6 (42)	19.7 (32)
Weight-corrected C_{max}, ng/mL · kg	1430 (43)	1150 (26)	827 (36)	1230 (30)	906 (38)	1260 (32)
T_{max}, h[†]	4.1 (0.84)	3.9 (0.78)	4.7 (0.9)	3.9 (1.1)	5.0 (0.8)	4.3 (0.5)
$AUC_{0-\tau}$, ng · h/mL	165 (39)	163 (28)	113 (31)	182 (31)	146 (27)	191 (38)
Weight-corrected $AUC_{0-\tau}$, ng · h/mL · kg	11080 (35)	9300 (26)	8010 (27)	11250 (28)	9790 (22)	12040 (34)
$t_{1/2}$, h	54.3 (15)	64.8 (12)	64.7 (21)	70.7 (18)	61.8 (12)	73.1 (19)
$Ae_{0-\tau}$, %	7.17 (28)	6.57 (23)	4.63 (30)	6.04 (25)	5.61 (29)	5.89 (19)
CL_R, L/h	11.3 (15)	10.4 (20)	10.4 (19)	8.62 (27)	9.70 (21)	8.28 (28)
50 mg once daily						
n*	12	12	11	11	4	5
C_{max}, ng/mL	54.4 (45)	58.1 (27)	43.5 (43)	66.3 (41)	42.7 (45)	56.3 (46)
Weight-corrected C_{max}, ng/mL · kg	3890 (49)	3430 (26)	3160 (44)	4150 (38)	2990 (46)	3880 (45)
T_{max}, h[†]	3.9 (0.87)	4.6 (1.00)	3.9 (1.3)	4.5 (0.8)	2.9 (1.3)	4.2 (0.8)
$AUC_{0-\tau}$, ng · h/mL	413 (36)	471 (19)	341 (21)	512 (35)	377 (18)	498 (46)
Weight-corrected $AUC_{0-\tau}$, ng · h/mL · kg	29050 (37)	27960 (21)	24830 (22)	32070 (32)	26340 (21)	33660 (41)
$t_{1/2}$, h	58.3 (25)	58.0 (14)	59.7 (21)	66.4 (22)	61.9 (32)	63.7 (24)
$Ae_{0-\tau}$, %	10.2 (33)	10.7 (37)	7.87 (30)	8.84 (35)	7.97 (30)	7.03 (33)
CL_R, L/h	12.7 (17)	11.2 (26)	11.8 (23)	9.03 (26)	9.51 (15)	7.75 (30)
100 mg once daily						
n*	11	11	14	11	7	5
C_{max}, ng/mL	134 (44)	215 (28)	130 (27)	259 (32)	142 (29)	272 (31)
Weight-corrected C_{max}, ng/mL · kg	8810 (35)	12860 (33)	9590 (26)	15610 (36)	9880 (23)	15990 (22)
T_{max}, h[†]	3.6 (1.11)	4.0 (0.77)	4.0 (1.1)	4.1 (0.9)	4.3 (1.4)	4.3 (1.1)
$AUC_{0-\tau}$, ng · h/mL	947 (24)	1370 (19)	992 (24)	1680 (25)	1100 (24)	1820 (25)
Weight-corrected $AUC_{0-\tau}$, ng · h/mL · kg	63360 (19)	81210 (23)	72770 (22)	100980 (21)	77150 (20)	109030 (25)
$t_{1/2}$, h	54.1 (18)	56.2 (14)	58.2 (12)	61.7 (11)	56.6 (11)	63.4 (14)
$Ae_{0-\tau}$, %	10.5 (22)	14.8 (18)	11.0 (22)	13.0 (31)	10.5 (38)	10.8 (21)
CL_R, L/h	11.4 (20)	11.0 (17)	11.4 (25)	7.92 (33)	9.51 (15)	6.09 (22)

Ae_{0-inf} = amount of drug as percentage of the dose excreted in the urine from time zero to infinity; $Ae_{0-\tau}$ = amount of drug as percentage of the dose excreted in the urine over the 24-hour dosing interval; CL_R = renal clearance; R_{acc} = accumulation ratio.

*Number of subjects with evaluable data may vary for some parameters.

[†]Mean (SD).

were observed between young and older or elderly subjects. Plasma concentrations exhibited at least a biphasic decline, with estimated mean $t_{1/2}$ values in young subjects ranging from ~26 to 37 hours in study 1 and 54 to 65 hours in study 2 across the dose range. study 2, which was performed later in the development program, used a longer sampling duration and a lower assay limit of quantification compared with study 1. As mirabegron exhibits multicompartmental elimination with a faster and slower elimination phase, this led to improved definition of the terminal elimination phase of the plasma concentration−time profile of mirabegron in study 2. Hence, the differences in $t_{1/2}$ values between the 2 studies is likely artefactual. In both studies, mean $t_{1/2}$ of mirabegron was generally slightly longer in elderly compared with young subjects, and in study 2, the $t_{1/2}$ tended to be longer in women compared with men. Mean mirabegron $Ae_{0-\tau}$% increased with dose and ranged from 6.6% of the dose with the 25 mg once daily to 18% with the 300 mg once daily in young subjects. $Ae_{0-\tau}$% was generally lower in older and elderly subjects compared with young subjects and tended to be higher in women compared with men. Mean estimates of CL_R were independent of dose and ranged from 10.4 to 19.6 L/h in young subjects. CL_R was generally lower in older and elderly subjects, and lowest in elderly women. The PK properties of mirabegron exhibited moderate intersubject variability with mean coefficients of variation (%CV) for C_{max} and AUC parameters ranging from 17% to 77%.
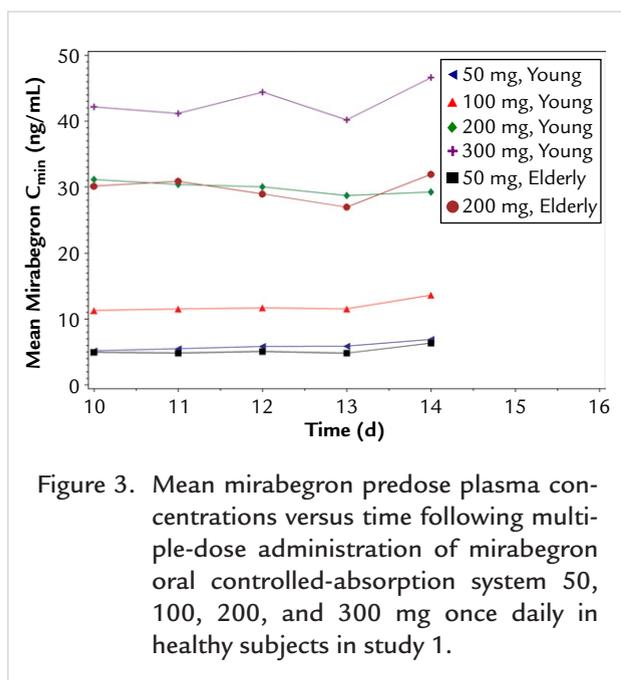
Figure 3. Mean mirabegron predose plasma concentrations versus time following multiple-dose administration of mirabegron oral controlled-absorption system 50, 100, 200, and 300 mg once daily in healthy subjects in study 1.

Steady state was visually assessed to have been achieved within 7 days (day 10 in study 1) of once-daily dosing (Figure 3). Comparison between AUC values following a single dose and at steady state indicated a ~2-fold accumulation of mirabegron with once-daily dosing (Table II). Accumulation ratios were comparable across doses (50–300 mg once daily), and no differences were observed between men and women or between young and elderly subjects. The geometric mean ratio of $AUC_{0-\tau}$ at steady state to AUC_{0-inf} after a single dose in young subjects was 1.0 with the 50-mg dose and greater than unity with doses of 100 to 300 mg (Table IV), although most of the 95% CIs contained unity. The difference between steady-state $AUC_{0-\tau}$ and first-dose AUC_{0-inf} suggests nonlinear PK properties over time at doses of ≥100 mg. Similar ratios were obtained in elderly subjects. No apparent change in $t_{1/2}$ or CL_R was observed with repeat dosing of mirabegron.

The increase in single-dose AUC_{0-inf} of mirabegron was approximately dose proportional, but there was evidence of greater-than-proportional increases in single-dose and steady-state C_{max} and steady-state $AUC_{0-\tau}$ over the dose range studied (Figures 4 and 5, Table V). For study 1, the dose-proportionality coefficients (β) were 1.43 for steady-state C_{max} and 1.33 for $AUC_{0-\tau}$ in the overall population of young men and women, resulting in a predicted 2.7-fold increase in

C_{max} and a 2.5-fold increase in $AUC_{0-\tau}$ for every 2-fold increase in dose within the range of 50 to 300 mg once daily. Slightly higher estimates for β were obtained in study 2 (Table V). In the overall population, mirabegron C_{max} and $AUC_{0-\tau}$ were estimated to increase by factors of 3.2- and 2.8-fold with a doubling of the dose within the dose range of 25 to 100 mg once daily. Deviations from dose proportionality were similar between young, older, and elderly subjects and between men and women. In accordance with the greater-than-dose proportional increases in $AUC_{0-\tau}$, $Ae_{0-\tau}$% increased with dose, whereas the PK parameters T_{max}, $t_{1/2}$, and CL_R showed no dose dependency.

Pharmacokinetic Properties of Metabolites

For all measured metabolites, plasma concentrations were lower than parent concentrations at all time points and all doses (Figures 2 and 6). Pharmacokinetic parameters for metabolite M8 were determined only in the 100-mg dose group of study 2, as a limited part of the PK profiles was quantifiable at the lower doses. Metabolite T_{max} values were either observed at times comparable to mirabegron (M8, M13, and M15) or were delayed by ~1 to 1.5 hours (M5, M11, M12, M14, and M16), with mean T_{max} values ranging between 4.2 and 5.7 hours (Figure 6, Table VI). The plasma concentration–time profiles of the metabolites were truncated at various time points when the metabolite concentrations fell below the lower limit of quantification, resulting in highly variable $t_{1/2}$ values that increased with dose and were apparently shorter than the parent $t_{1/2}$ (Table VI). The apparent dose dependency of metabolite $t_{1/2}$ estimates is attributed to improved definition of the terminal phase at the higher doses of mirabegron. Greater-than-dose proportional increases in metabolite C_{max} and $AUC_{0-\tau}$ were observed, similar to mirabegron, resulting in relatively constant metabolic ratios across the dose range of 25 to 100 mg once daily for all metabolites. Two of the metabolites, M11 and M12, each accounted for at least 10% of the total drug-related exposure (parent drug and its metabolites) in plasma across all tested dose levels and, as such, were designated major metabolites according to the ICH M3 (R2) guidance.[24] Small amounts of metabolites were found in urine ranging between <1% (M8, M12, M13, M14, M15, and M16) and ≤2% (M5 and M11) of the dose after the admin-

Table IV. Ratios of mirabegron steady state $AUC_{0-\tau}$ to first dose $AUC_{0\text{-inf}}$ after multiple-dose administration in healthy subjects (study 1).

Dose/Age Group/Population	n	GMR	90% CI
Young			
50 mg once daily			
Male	4	0.96	0.75–1.24
Female	5	1.03	0.89–1.21
Overall	9	1.00	0.90–1.11
100 mg once daily			
Male	6	0.86	0.77–0.95
Female	6	1.32	0.97–1.78
Overall	12	1.06	0.88–1.29
200 mg once daily			
Male	6	1.26	0.82–1.93
Female	6	1.13	0.71–1.80
Overall	12	1.19	0.92–1.55
300 mg once daily			
Male	6	1.39	1.21–1.61
Female	6	1.36	1.03–1.82
Overall	12	1.38	1.21–1.57
Elderly (≥65 y)			
50 mg once daily			
Male	1	1.18	—
Female	3	0.91	0.72–1.15
Overall	4	0.97	0.76–1.24
200 mg once daily			
Male	6	1.34	1.13–1.58
Female	6	1.14	0.84–1.55
Overall	12	1.23	1.06–1.44

GMR = geometric mean ratio.

istration of multiple mirabegron doses of 25 to 100 mg once daily. For all metabolites, the $Ae_{0-\tau}\%$ increased with increasing mirabegron dose, whereas CL_R was not affected by dose.

Age and Sex Effects

Comparison of mirabegron $AUC_{0-\tau}$ and C_{max} between older subjects ≥55 years and young subjects by analysis of variance showed no significant differences in mirabegron exposure across multiple doses of 25 to 100 mg (Table VII). The 90% CI for mirabegron $AUC_{0-\tau}$ and C_{max} ratios (both sexes) fell within the default equivalence limits of 0.80 and 1.25. Similar results were obtained for the elderly subpopulation aged ≥65 years. An analysis by sex demonstrated no significant exposure differences between older and elderly women compared with young women. A small decrease for mirabegron C_{max} was observed in older and elderly men compared with young men, whereas mirabegron $AUC_{0-\tau}$ was slightly decreased in older but not in elderly men. No significant age-related differences in plasma exposure to the metabolites M12, M13, and M16 were observed (Table VII for M11 and M12). Metabolite exposure was higher in older and elderly subjects than in young subjects for M5, M8, M11, M14, and M15, with mean increases in $AUC_{0-\tau}$ in older compared with young subjects ranging from 27% for M14 to 62% for M8.
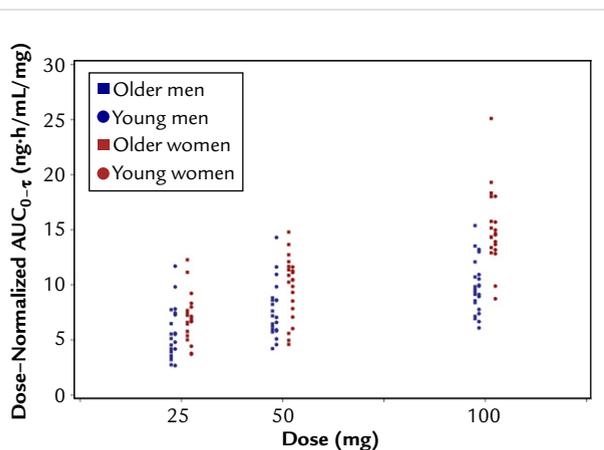
Figure 4. Dose-normalized individual $AUC_{0-\tau}$ following multiple-dose administration of mirabegron oral controlled-absorption system 25, 50, and 100 mg once daily in healthy subjects in study 2.

ANOVA revealed significantly (44% and 38%) higher C_{max} and $AUC_{0-\tau}$, respectively, in women (all age groups) compared with men (**Table VIII**). This exposure difference between men and women appeared more pronounced in older and elderly subjects than in young subjects. Smaller differences attributable to sex were apparent after normalizing mirabegron C_{max} and $AUC_{0-\tau}$ by body weight. Weight-normalized values for C_{max} and $AUC_{0-\tau}$ were ~23% and 18% higher in women compared with those in men. For all circulating mirabegron metabolites with the exception of M13, C_{max} and $AUC_{0-\tau}$ were higher in women than in men (**Table VIII** for M11 and M12).

Tolerability

Mirabegron was generally well tolerated when given as single and multiple oral doses up to 300 mg in young men and women, and single and multiple doses up to 200 mg in elderly men and women (the maximum doses studied in each age group). AEs reported were infrequent, mild to moderate in severity, and generally not considered by the investigators to be related to study drug. The most frequently reported treatment-related AEs were headache (30% of subjects), dizziness (18%), palpitations (14%), abdominal pain (10%), and diarrhea (10%) in study 1, and hot flushes (7%) and dry mouth (4%) in study 2. One SAE (reported by the investigator as essential epilepsy) occurred in study 2 and was considered by the investigator to be possibly

related to study drug. One day after the completion of mirabegron dosing (100 mg once daily), a 77-year old female subject experienced a generalized tonic−clonic seizure. The subject had no relevant medical history and had no previous history of episodes of epilepsy. The subject recovered without receiving drug treatment for the event but was hospitalized and withdrawn from the study. No other subjects were withdrawn from either study due to an AE. There were no qualitative differences in the incidence of any AE from placebo (study 1) and no increases in the incidence of AEs (overall or of any specific type) with increasing dose. In addition, there was no evidence of any significant differences in the tolerability profile in older or elderly subjects compared with the younger subjects. Mirabegron increased supine pulse rate in a dose-dependent manner, with a greater effect in young compared with elderly subjects. Women generally demonstrated a higher increase in pulse rate than men, which is consistent with their higher mirabegron plasma exposure compared with men. Modest blood pressure increases were observed that were not clearly correlated with increases in dose. None of the subjects showed a positive orthostatic stress test in study 1. There were no clinically significant findings in 12-lead ECG or physical examination results. Analysis of clinical laboratory parameters did not reveal any safety issues.
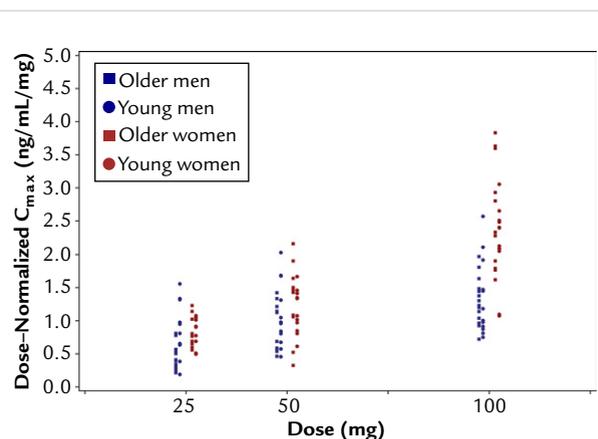

Figure 5. Dose-normalized individual C_{max} following multiple-dose administration of mirabegron oral controlled-absorption system 25, 50, and 100 mg once daily in healthy subjects in study 2.

Table V. Dose proportionality of mirabegron pharmacokinetic parameters.

Dosing/Population	Dose-Proportionality Coefficient β (95% CI)	
	AUC*	C_{max}
Single dose (day 1): 50, 100, 200, 300 mg once daily (study 1)		
Young male	0.98 (0.75–1.21)	1.39 (1.09–1.70)
Young female	1.17 (0.92–1.42)	1.49 (1.09–1.90)
Young overall	1.07 (0.90–1.25)	1.44 (1.19–1.70)
Multiple doses		
50, 100, 200, 300 mg once daily (study 1)		
Young male	1.30 (1.09–1.52)	1.44 (1.17–1.70)
Young female	1.35 (1.07–1.63)	1.43 (1.04–1.82)
Young overall	1.33 (1.14–1.51)	1.43 (1.21–1.66)
25, 50, 100 mg once daily (study 2)		
Older ($\geq$55 y)	1.58 (1.48–1.68)	1.83 (1.64–2.02)
Elderly ($\geq$65 y)	1.51 (1.41–1.62)	1.82 (1.60–2.03)
Young	1.43 (1.34–1.51)	1.54 (1.37–1.71)
Male	1.47 (1.36–1.57)	1.62 (1.42–1.83)
Female	1.54 (1.46–1.63)	1.75 (1.60–1.90)
Overall	1.51 (1.44–1.57)	1.69 (1.56–1.81)

*AUC_{0-inf} for single dose; $AUC_{0-\tau}$ for multiple doses.

DISCUSSION

The primary objective of these studies was to evaluate the PK properties of multiple-dose mirabegron OCAS modified-release tablets in healthy individuals of differing ages and sexes.

Steady-state plasma concentrations of mirabegron were achieved by 7 days of once-daily dosing at all doses. Plasma exposure at steady state was approximately double that seen after a single dose. The PK properties of mirabegron did not change over time with repeated administration at a dose of 50 mg. At higher doses, a small increase (ranging from 6% at 100 mg to 38% at 300 mg) in $AUC_{0-\tau}$ at steady state compared with first dose AUC_{0-inf} was observed, suggesting that mirabegron may exhibit time-dependent PK properties (ie, an increase in bioavailability and/or a decrease in clearance with time) at doses >50 mg.[25] As mirabegron CL_R was not changed over time, this finding may be possibly attributed to autoinhibition of its metabolism via mechanism-based inactivation of the cytochrome P450 (CYP) 2D6 isozyme. Mirabegron is a
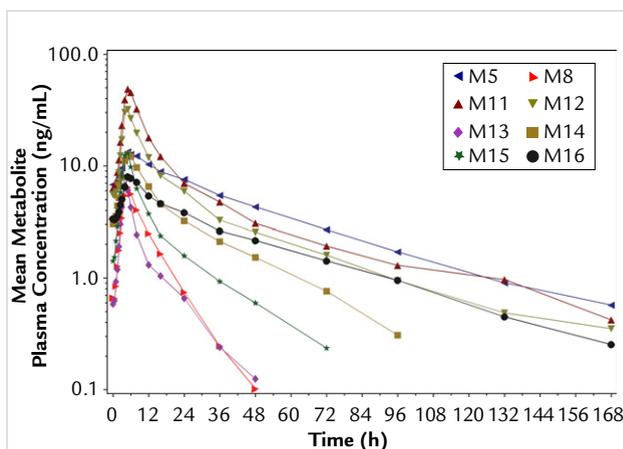

Figure 6. Mean mirabegron metabolite plasma concentrations versus time at steady state following multiple-dose administration of mirabegron oral controlled-absorption system 100 mg once daily in healthy subjects in study 2.

Table VI. Summary of selected pharmacokinetic parameters for mirabegron metabolites following multiple-dose administration of mirabegron in healthy subjects (study 2). Values are mean (%CV) unless otherwise noted.

Dose/Parameter	M5	M8	M11	M12	M13	M14	M15	M16
25 mg once daily								
n^*	44	47	47	47	22	46	43	44
C_{max}, ng/mL	2.17 (54)	–	4.54 (45)	2.83 (72)	0.87 (50)	2.80 (41)	1.63 (47)	1.19 (41)
T_{max}, h[†]	5.3 (1.1)	–	5.7 (1.2)	5.3 (1.4)	4.7 (1.2)	5.1 (1.1)	4.5 (1.0)	5.3 (1.0)
$AUC_{0-\tau}$, ng · h/mL	36.3 (61)	–	55.3 (44)	33.7 (71)	2.55 (104)	20.0 (58)	10.3 (86)	17.3 (59)
MR_t	0.11 (44)	–	0.17 (21)	0.10 (46)	0.01 (80)	0.06 (38)	0.03 (59)	0.05 (46)
$t_{1/2}$, h	37.1 (38)	–	27.6 (58)	20.9 (61)	3.22 (40)	6.36 (59)	7.99 (114)	32.1 (60)
$Ae_{0-\tau}$, %	1.21 (54)	0.62 (45)	0.67 (42)	0.13 (65)	0.03 (93)	0.17 (38)	0.06 (58)	0.42 (51)
50 mg once daily								
n^*	46	46	46	46	44	46	46	46
C_{max}, ng/mL	5.06 (51)	–	14.7 (50)	9.21 (74)	2.06 (72)	5.94 (33)	4.41 (41)	3.14 (52)
T_{max}, h[†]	5.3 (0.9)	–	5.5 (0.9)	5.1 (1.0)	4.5 (0.9)	5.2 (1.0)	4.5 (1.0)	5.5 (1.1)
$AUC_{0-\tau}$, ng · h/mL	86.2 (57)	–	151 (51)	97.9 (71)	11.1 (109)	63.9 (35)	35.2 (52)	49.5 (57)
$t_{1/2}$, h	36.5 (30)	–	40.5 (50)	30.9 (38)	5.86 (90)	16.3 (72)	13.8 (63)	40.5 (34)
MR_t	0.09 (41)	–	0.16 (22)	0.10 (45)	0.01 (84)	0.07 (29)	0.04 (30)	0.05 (31)
$Ae_{0-\tau}$, %	1.46 (47)	0.89 (43)	0.94 (43)	0.18 (67)	0.05 (72)	0.20 (36)	0.09 (46)	0.61 (61)
100 mg once daily								
n^*	48	48	48	48	48	48	48	48
C_{max}, ng/mL	13.6 (50)	6.84 (47)	51.9 (42)	35.0 (50)	7.89 (61)	13.7 (29)	14.6 (45)	831 (43)
T_{max}, h[†]	5.1 (1.0)	4.7 (0.9)	4.9 (0.8)	4.6 (0.7)	4.2 (0.8)	5.0 (0.8)	4.4 (0.6)	5.2 (0.8)
$AUC_{0-\tau}$, ng · h/mL	234 (56)	60.9 (58)	463 (43)	313 (54)	47.2 (60)	155 (31)	108 (49)	126 (44)
$t_{1/2}$, h	40.6 (27)	10.8 (71)	52.1 (33)	44.6 (37)	11.9 (61)	30.6 (43)	20.5 (43)	47.0 (25)
MR_t	0.09 (38)	0.02 (31)	0.17 (18)	0.11 (40)	0.02 (47)	0.06 (27)	0.04 (27)	0.05 (31)
$Ae_{0-\tau}$, %	2.00 (58)	1.23 (41)	1.37 (36)	0.26 (49)	0.07 (52)	0.23 (40)	0.12 (43)	0.74 (41)

– = not evaluable; M5 = deacylated mirabegron (M16)-N^ω-acetylated; M8 = mirabegron-N-α-oxidation body (phenylacetic acid derivative); M11 = mirabegron-O-glucuronide; M12 = mirabegron ketone oxidation body (M18)-N-COO-glucuronide; M13 = mirabegron-N-COO-glucuronide; M14 = mirabegron-N^ω-glucuronide; M15 = mirabegron-N-O-glucuronide; M16 = deacylated mirabegron.
*Number of subjects with evaluable data may vary for some parameters.
[†]Mean (SD).

moderate inhibitor of CYP2D6 in vivo.[26] In addition, in vitro experiments have indicated that the CYP2D6-inhibitory effect of mirabegron was increased following preincubation with human liver microsomes in the presence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), suggesting that mirabegron may act as a (quasi-) irreversible, metabolism-dependent inhibitor of CYP2D6.[27] CYP2D6 is involved in mirabegron metabolism to a minor extent. There was a small difference (19%) in mirabegron plasma exposure between extensive and poor metabolizers of CYP2D6 receiving a single 160-mg dose of mirabegron,[28] which is consistent with the small increases in steady-state $AUC_{0-\tau}$ compared with first-dose AUC_{0-inf} observed in study 1. As the degree of nonlinearity in the PK properties of mirabegron over time was small to negligible at clinically relevant doses, the clinical meaningfulness of the finding is likely to be limited.

Mirabegron exposure (C_{max} and $AUC_{0-\tau}$) increased in a greater-than-proportional manner across the dose range studied. These data are consistent with previous data from single-dose studies, which demonstrated that the greater-than-dose proportional increase in mirabegron exposure resulted from increased bioavailability (29% at 25 mg to 45% at 150 mg).[29] In study 2, mirabegron metabolites also demonstrated a more-than-dose proportional increase in C_{max} and $AUC_{0-\tau}$, similar to parent, indicating that the greater-than-dose proportional increase in mirabegron exposure is not caused by saturable first-pass metabolism. Mirabegron is a substrate for the intestinal efflux transporter P-glycoprotein (P-gp) in vitro.[30] A postulated mechanism for the supraproportionality is saturation of P-gp−mediated efflux as the dose of mirabegron increases and concentrations in the gut lumen increase.

Two major metabolites, M11 and M12, were identified according to the ICH M3 (R2) guidance[24]; both

Table VII. Effect of age on pharmacokinetic parameters of mirabegron and major metabolites by sex (study 2). Values are least squares mean ratios (90% CI).

Compound/Sex	Older (≥55 y) Versus Young		Elderly (≥65 y) Versus Young	
	$AUC_{0-\tau}$	C_{max}	$AUC_{0-\tau}$	C_{max}
Mirabegron				
Male	0.86 (0.79–0.93)	0.76 (0.65–0.90)	0.97 (0.88–1.08)	0.78 (0.63–0.97)
Female	1.14 (1.06–1.22)	1.10 (0.98–1.23)	1.16 (1.08–1.24)	1.06 (0.94–1.20)
Overall	0.98 (0.93–1.04)	0.91 (0.82–1.01)	1.07 (1.01–1.13)	0.92 (0.82–1.03)
M11				
Male	1.26 (1.14–1.39)	1.09 (0.94–1.25)	1.41 (1.24–1.61)	1.10 (0.91–1.35)
Female	1.57 (1.46–1.68)	1.40 (1.28–1.54)	1.71 (1.57–1.86)	1.43 (1.28–1.58)
Overall	1.40 (1.32–1.49)	1.23 (1.13–1.34)	1.56 (1.46–1.68)	1.26 (1.14–1.40)
M12				
Male	0.87 (0.78–0.96)	0.72 (0.62–0.83)	1.14 (1.02–1.28)	0.79 (0.65–0.97)
Female	1.27 (1.13–1.42)	1.12 (1.00–1.25)	1.37 (1.22–1.53)	1.11 (0.98–1.27)
Overall	1.05 (0.97–1.13)	0.89 (0.82–0.97)	1.26 (1.17–1.37)	0.95 (0.85–1.06)

Table VIII. Effect of sex on pharmacokinetic parameters of mirabegron and major metabolites by age group (study 2). Values are least squares mean ratios (90% CI).

Compound/Age Group	Female Versus Male		Female Versus Male, Body Weight–Corrected	
	$AUC_{0-\tau}$	C_{max}	$AUC_{0-\tau}$	C_{max}
Mirabegron				
Young	1.19 (1.11–1.28)	1.19 (1.03–1.37)	1.02 (0.95–1.10)	1.02 (0.89–1.17)
Older (≥55 y)	1.59 (1.46–1.73)	1.72 (1.47–2.01)	1.36 (1.25–1.48)	1.47 (1.26–1.72)
Elderly (≥65 y)	1.42 (1.30–1.54)	1.61 (1.32–1.98)	1.29 (1.19–1.41)	1.47 (1.20–1.81)
Overall	1.38 (1.31–1.45)	1.44 (1.30–1.59)	1.18 (1.12–1.25)	1.23 (1.11–1.36)
M11				
Young	1.26 (1.16–1.37)	1.26 (1.11–1.42)	1.08 (0.99–1.17)	1.08 (0.95–1.22)
Older (≥55 y)	1.57 (1.43–1.72)	1.63 (1.44–1.84)	1.34 (1.22–1.47)	1.39 (1.24–1.57)
Elderly (≥65 y)	1.51 (1.35–1.69)	1.61 (1.34–1.94)	1.38 (1.24–1.54)	1.47 (1.23–1.77)
Overall	1.40 (1.32–1.49)	1.43 (1.32–1.55)	1.20 (1.13–1.28)	1.23 (1.13–1.33)
M12				
Young	0.94 (0.86–1.03)	0.95 (0.83–1.09)	0.81 (0.74–0.88)	0.82 (0.72–0.93)
Older (≥55 y)	1.38 (1.23–1.55)	1.49 (1.31–1.69)	1.18 (1.05–1.32)	1.27 (1.12–1.44)
Elderly (≥65 y)	1.12 (1.01–1.24)	1.33 (1.10–1.60)	1.02 (0.92–1.13)	1.21 (1.01–1.46)
Overall	1.14 (1.05–1.22)	1.19 (1.09–1.30)	0.97 (0.90–1.05)	1.02 (0.93–1.11)

are glucuronides representing 17% and 10%, respectively, of total drug-related exposure in plasma. There was no evidence of metabolites with a longer $t_{1/2}$ than mirabegron, suggesting that all 8 circulating metabolites are most likely to show formation-rate limited kinetics. Structure identification studies have shown that mirabegron is metabolized via multiple pathways involving *N*-dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis.[31] On the basis of the metabolite recoveries in urine in study 2, the predominant primary metabolic reaction of mirabegron in humans is estimated to be amide hydrolysis (M5 and M16), accounting for 48% of the circulating metabolites recovered in urine after multiple mirabegron doses of 50 mg once daily, followed by glucuronidation (M11, M12, M13, and M14) and *N*-dealkylation or oxidation of the secondary amine (M8 and M15), accounting for 34% and 18% of the metabolites, respectively.

The results of both studies demonstrate that female subjects generally show greater mirabegron C_{max}, single-dose AUC_{0-inf}, and steady-state $AUC_{0-\tau}$ than do men, which was partly related to sex differences in body weight. Weight-normalized values for C_{max} and $AUC_{0-\tau}$ were ~23% and 18% higher, respectively, in women compared with those in men. This remaining increased exposure is attributed to a higher absolute bioavailability of mirabegron in women than in men.[29] The sex difference appeared more pronounced in the older subjects than in young subjects, which may partly be explained by a lower CL_R in women, especially in elderly women, than in men. A lower CL_R in women was expected, as mirabegron CL_R has been shown to be correlated with renal function,[32] and clearance by all renal routes (glomerular filtration, tubular reabsorption, and secretion) decreases with age and is lower in women than in men at all ages.[33] Except for M13, no marked differences in metabolic ratios between men and women were observed for any of the measured circulating metabolites. As M13 is a minor metabolite representing only ~2% of total drug-related material in plasma and 0.07% of the dose in urine, these data suggest that there are no marked sex differences in the degree of metabolism of mirabegron. Dosing modifications based on sex are not needed[7,8]; the efficacy and tolerability of mirabegron have been demonstrated in both men and women with OAB.

There were no significant age-related differences in mean C_{max} and $AUC_{0-\tau}$ of mirabegron. Across the doses studied, CL_R was lower in older subjects than in young subjects, consistent with the generally lower renal capacity in older subjects. As indicated previously, physiologic changes in renal function associated with advanced age are well recognized. Except for then metabolites M12, M13, and M16, metabolite exposure was higher in older and elderly subjects than in young subjects. These observations are consistent with metabolism accounting for a larger percentage of overall elimination in elderly subjects, to compensate for their reduced CL_R of mirabegron. Together, the results suggest that mirabegron can be administered without regard to age, and support the currently available prescribing information for mirabegron,[7,8] which indicates that dosing modifications are not needed for elderly patients with OAB.

CONCLUSIONS

Mirabegron and metabolites exhibited a greater-than-dose proportional increase in exposure after multiple oral doses of mirabegron OCAS, resulting in relatively constant metabolic ratios. Two major metabolites were observed in plasma; both are pharmacologically inactive glucuronides. Mirabegron accumulated ~2-fold on once-daily dosing. No clinically meaningful changes in the PK properties of mirabegron over time were observed. The PK properties of multiple-dose mirabegron were unaffected by age. The increased plasma exposure to mirabegron observed in female subjects was not considered clinically important based on available efficacy and tolerability data in patients with OAB. Based on these findings, no dose adjustments based on age and sex are needed.

REFERENCES

1. Wein AJ, Rovner ES. The overactive bladder: an overview for primary care health providers. *Int J Fertil Womens Med*. 1999;44:56–66.

2. Hu TW, Wagner TH, Bentkover JD, et al. Estimated economic costs of overactive bladder in the United States. *Urology*. 2003;61:1123–1128.

3. Irwin DE, Kopp ZS, Agatep B, et al. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. *BJU Int*. 2011;108:1132–1138.

4. Kim SH, Boye M, Bhattacharyya SK, et al. Medical visits among adults with symptoms commonly associated with an overactive bladder. *BJU Int*. 2006;97:551–554.

5. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20:327–336.

6. Athanasopoulos A, Giannitsas K. An overview of the clinical use of antimuscarinics in the treatment of overactive bladder. *Adv Urol*. 2011;2011:820816.

7. Betanis (mirabegron) tablets [prescribing information] [in Japanese]. http://www.info.pmda.go.jp/go/pack/2590014F1021_1_02/. Accessed July 31, 2012.

8. Myrbetriq (mirabegron) [prescribing information]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202611s000lbl.pdf. Accessed September 25, 2012.

9. Takasu T, Ukai M, Sato S, et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]-ethyl} acetanilide (YM178), a novel selective β3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther*. 2007;321:642–647.

10. Yamaguchi O, Chapple CR. β₃-adrenoceptors in urinary bladder. *Neurourol Urodyn*. 2007;26:752–756.

11. Chapple C, Wyndaele JJ, Van Kerrebroeck P, et al. Dose-ranging study of once-daily mirabegron (YM178), a novel selective β₃-adrenoceptor agonist, in patients with overactive bladder (OAB). *Eur Urol Suppl*. 2010;9:249.

12. Khullar V, Cambronero J, Stroberg P, et al. The efficacy and tolerability of mirabegron in patients with overactive bladder—results from a European-Australian Phase III trial. *Eur Urol Suppl* 2011;10:278–279. Abstract 886.

13. Nitti V, Herschorn S, Auerbach S, et al. The efficacy and safety of mirabegron in patients with overactive bladder syndrome—results from a North-American Phase III trial. *Eur Urol Suppl*. 2010;10:278. Abstract 885.

14. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly and amended by 48th WMA General Assembly, Somerset West, South Africa, October 1996. http://www.wma.net/en/30publications/10policies/b3/ index.html. Accessed July 31, 2012.

15. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for Good Clinical Practice E6(R1). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed July 31, 2012.

16. van Teijlingen R, Meijer J, Takusagawa S, et al. Development and validation of LC-MS/MS methods for the determination of mirabegron and its metabolites in human plasma and their application to a clinical pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2012;887–888:102−111.

17. Rowland M, Tozer TN. *Clinical Pharmacokinetics: Concepts and Application*. 3rd ed. Baltimore, Md: Lippincott Williams & Wilkins; 1995.

18. Gabrielsson J, Weiner D. *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*. 4th ed. Stockholm, Sweden: Swedish Pharmaceutical Press; 2007.

19. Gough K, Hutchison M, Keene O, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. *Drug Inf J*. 1995;29:1039–1048.

20. Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17:1278–1283.

21. European Medicines Agency (EMA). ICH Topic E7: Studies in support of special populations: geriatrics. CPMP/ICH/379/95 European Medicines Agency. March 1994. http://www.ema.europa.eu/docs/en_GB/document_library/2009/09/WC500002875.pdf. Accessed May 30, 2012.

22. US Food and Drug Administration (FDA). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. March 1, 2003. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf. Accessed August 16, 2012.

23. European Medicines Agency (EMA). Guideline on the investigation of bioequivalence. January 20, 2010. http://www.ema.europa.eu/docs/en_GB/document_library/

Scientific_guideline/2010/01/WC500070039.pdf. Accessed August 16, 2012.

24. European Medicines Agency (EMA). ICH Topic M3 (R2): Non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. CPMP/ICH/286/95. June 2009. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf. Accessed May 30, 2012.

25. Levy R. Time-dependent pharmacokinetics. In "Pharmacokinetics: Theory and Methods," Rowland M, Tucker G, eds. in The International Encyclopedia of Pharmacology and Therapeutics. Oxford, UK: Pergamon Press; 1982.

26. Krauwinkel WJ, van Gelderen EM, Groen MJ, et al. An open-label, one-sequence crossover study to evaluate the effect of multiple doses of mirabegron on the pharmacokinetics of the CYP2D6 substrate desipramine in healthy subjects. *Clin Pharm Ther*. 2010; 87(Suppl 1):S88.

27. Takusagawa S, Yajima K, Miyashita A, et al. Identification of human cytochrome P450 isoforms and esterases involved in the metabolism of mirabegron, a potent and selective β_3-adrenoceptor agonist. *Xenobiotica*. 2012;42:957–967.

28. van Gelderen E, Li Q, Meijer J, et al. An exploratory comparison of the single dose pharmacokinetics of the β_3-adrenoceptor agonist mirabegron in healthy CYP2D6 poor and extensive metabolizers. *Clin Pharmacol Ther*. 2009;85(Suppl 1):S88.

29. Eltink C, Lee J, Schaddelee M, et al. Single dose pharmacokinetics and absolute bioavailability of mirabegron, a β_3-adrenoceptor agonist for treatment of overactive bladder. *Int J Clin Pharmacol Ther*. 2012 Sep 4. [Epub ahead of print].

30. Ushigome F, Takusagawa S, Li Q, et al. Mirabegron, a potent and selective β_3-adrenoceptor agonist, is a P-glycoprotein (P-gp) substrate: characterization of its efflux transport in Caco-2 and Human P-gp expressing cells and BCRP and MRP2 expressing vesicles. *Drug Metab Rev*. In press.

31. Takusagawa S, van Lier JJ, Suzuki K, et al. Absorption, metabolism and excretion of [^{14}C]mirabegron (YM178), a potent and selective β_3-adrenoceptor agonist, after oral administration to healthy male volunteers. *Drug Metab Dispos*. 2012; 40:815–824.

32. Dickinson J, Lewand M, Sawamoto T, et al. Effect of renal or hepatic impairment on the pharmacokinetics of mirabegron. *Clin Drug Invest*. In press.

33. Schwartz JB. Clinical pharmacology. In: Gerstenblith G, ed. *Cardiovascular Disease in the Elderly*. Totowa, NJ: Humana Press Inc; 2005: 335–362.

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