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.