CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202611Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Consultation for NDA 202611

DATE: March 07, 2012

FROM: Rajanikanth Madabushi, Ph.D., Team Leader,
Division of Clinical Pharmacology I, OCP

Preston Dunnmon, M.D., Medical Officer,
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Division Director,
Division of Cardiovascular and Renal Products, HFD-110

TO: Nenita Crisostomo, RHPM / Roger Wiederhorn, MO
Division of Reproductive & Urologic Products (DRUP)

NDA:	202611
Drug Name:	YM178
Trade Name:	Mirabegron
Formulation:	25 mg and 50 mg extended release tablets
Dose:	50 mg once daily (reduced to 25 mg daily for patients with severe renal or moderate hepatic insufficiency)
Sponsor:	Astellas Pharma US, Inc
Consult requesting division:	Division of Reproductive and Urologic Products

Reference ID: 3143395

Background:

The Division of Reproductive and Urologic Products (DRUP) consulted us to provide an assessment of the cardiovascular risk associated with the increases in systolic blood pressure for mirabegron. The Division of Cardiovascular and Renal Products (DCRP) provided advice to the sponsor[1] with regard to the cardiovascular risk assessment using the Cox Proportional Hazards model described by D'Agostino et al[2]. In the current document, the cardiovascular risk projection based on the blood pressure data pooled from 3 Phase III trials of 12 weeks duration (178-CL-046, 178-CL-047 and 178-CL-074) is presented. In an attempt to characterize the blood pressure effects of mirabegron, Study 178-CL-031 and Study 178-Cl-077 (Thorough QT study) are evaluated[3]. The changes in the projected cardiovascular risk based on the blood pressure effect derived from the TQT study are also performed.

Key Questions:

1) What is the effect of mirabegron on blood pressure?

Based on the results of the phase I studies Study CL-178-031, mirabegron demonstrates an exposure-dependent increase in blood pressure (systolic as well as diastolic) as shown in the Figure 1 below.

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[1] *Teleconference dated 02/09/2012 and 03/01/2012*

[2] *General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Ralph B. D'Agostino et al. Circulation 2008;117;743-753*

[3] *Analyses performed by Jiang Liu, Ph.D., Pharmacometrics Reviewer, OCP. For details see the Clinical Pharmacology AC Background Document.*

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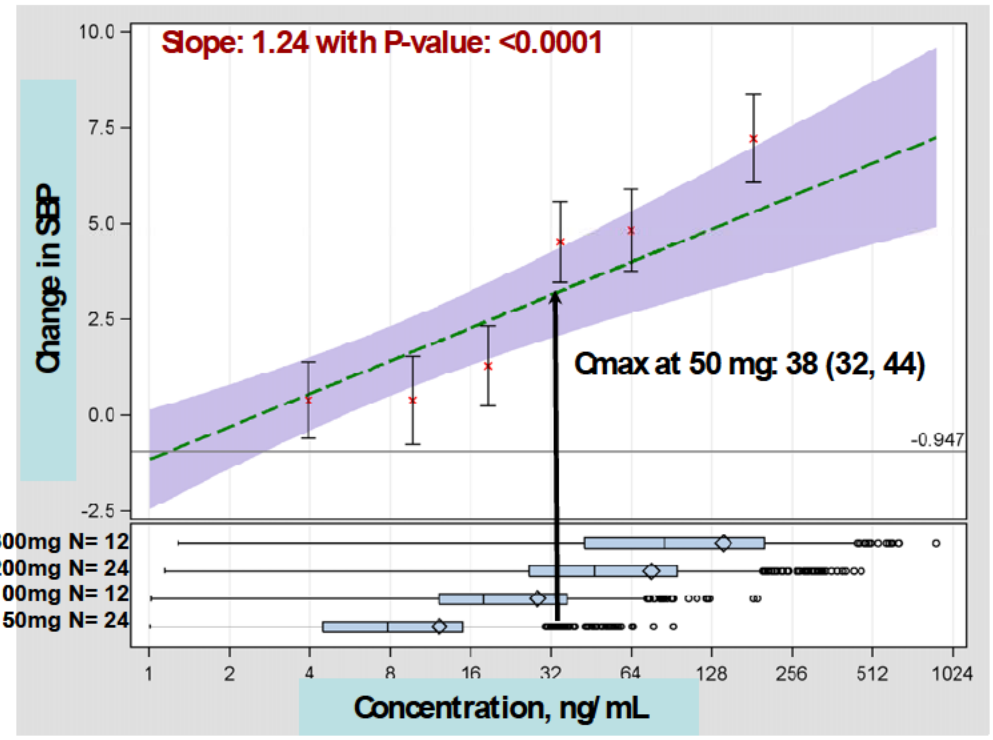

Figure 1: A concentration-dependent increase in blood pressure is observed over the range of doses studied in Study CL-178-031. *For the purpose of plotting, the data are divided in to 6 equal bins of observed mirabegron concentration. The red cross (x) and the associated error bars represent the mean change in systolic blood pressure (SBP) corresponding to the median concentration for each bin and the corresponding 95% confidence intervals. The dashed green line represents regression mean for the entire data and the purple band is the associated 95% confidence interval. (Source: OCP AC Background Document)*

The increase in blood pressure was similar between younger subjects (18 – 55 years) and older subjects (65 – 77 years) after correction for the placebo effects[3]. The maximum blood pressure effects coincided with the peak concentration following the administration of mirabegron. A consistent dose-response relationship was also noted in the TQT study (Study 178-CL-077) at steady-state (Day 14) as shown in Figure 2.

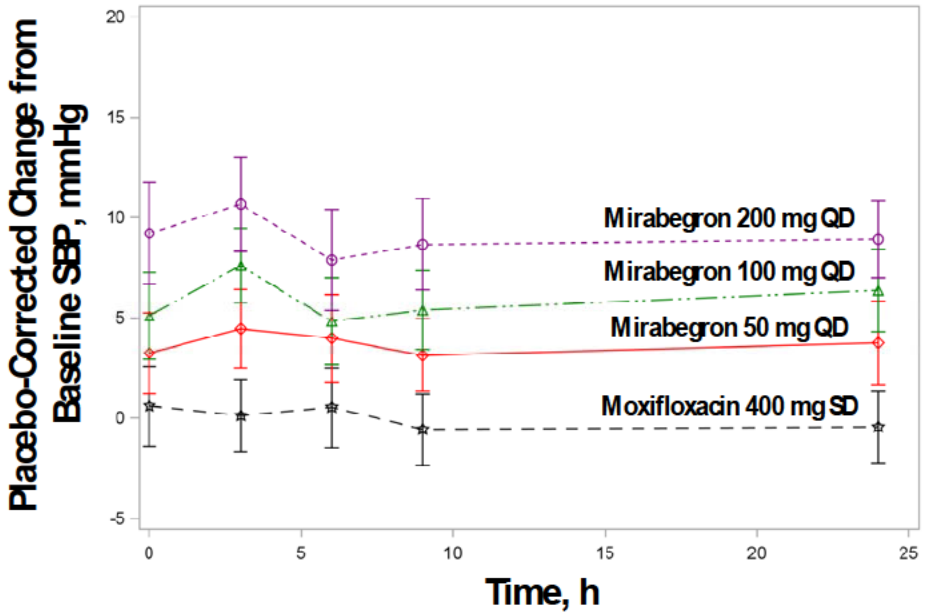

Figure 2: Dose dependent increase in SBP observed in the Study CL-178-077 at steady-state (Day 14). ***The error bars represent 95% confidence interval.***

It should be noted that moxifloxacin (active control for the QT part of the study) showed no change in blood pressure as expected. The maximum change in SBP with mirabegron 50 mg QD was 4.0 mmHg (1.64, 6.43). The 24-hour average effects are presented in Table 1 below:

Treatment	24 hour average change in SBP, mmHg Mean (SD)
Moxifloxacin 400 mg QD	0.02 (11.2)
Mirabegron 50 mg QD	3.0 (10.2)
Mirabegorn 100 mg QD	5.5 (10.6)
Mirabegron 200 mg QD	9.7 (11.7)

Table 1: Summary of the 24 hour change in SBP at steady state in Study 178-CL-077

The effects of different treatment arms on SBP for the Phase III trials are discussed in detail in the Consult Review by Dr. Dunnmon, hence will not be discussed in detail in this document. The only additional point of interest is that in the pooled phase III data there is a consistent trend

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for increase in average SBP over 12-week trial durations for mirabegron 50 mg QD and mirabegron 100 mg QD treatment arms compared to placebo as shown in the Figure 3 below.

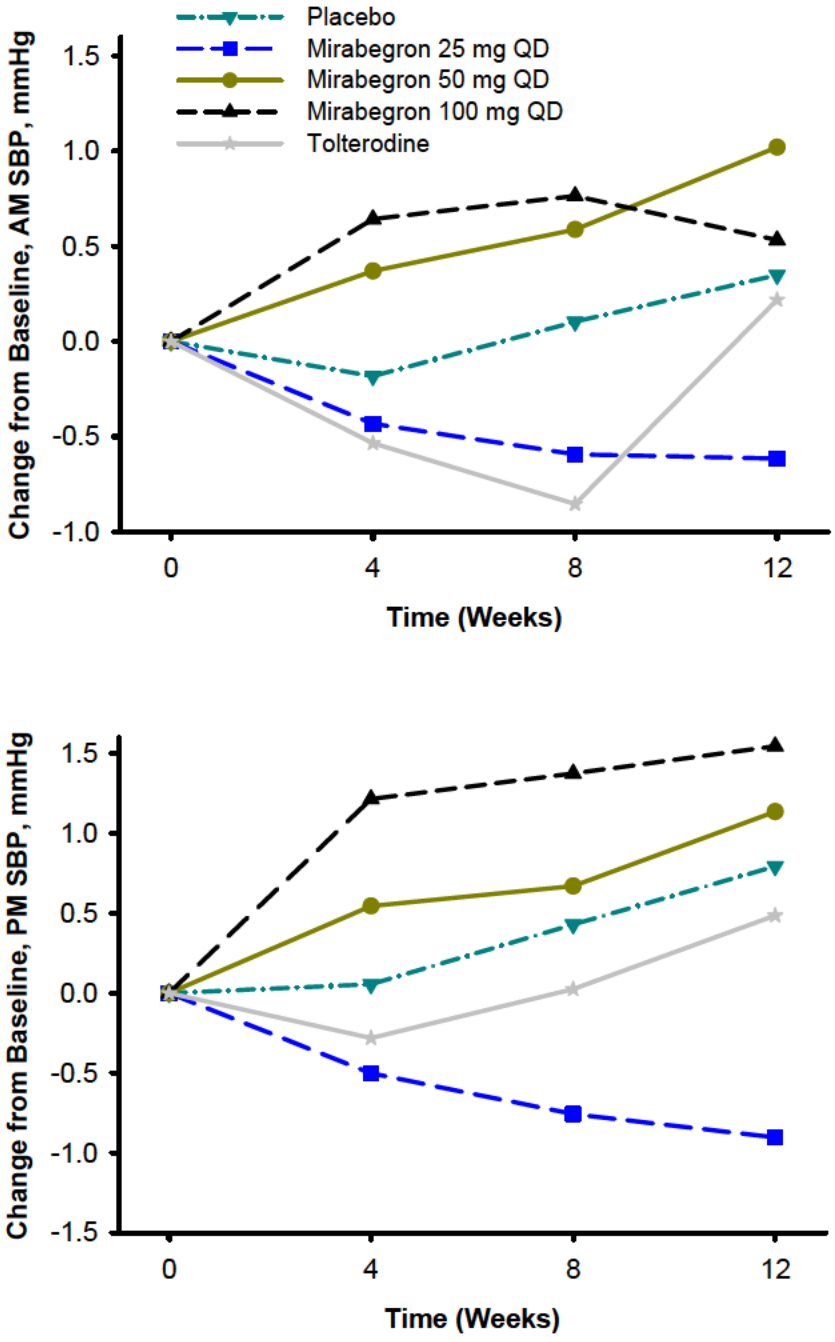

Figure 3: Time course for mean AM (above) and PM (below) SBP in phase III (pooled data from studies 178-CL-046, 178-CL-047 and 178-CL-074)

It should be noted that none of these differences are statistically significant compared to placebo and are lower than the effects observed in the TQT study. The potential reasons for under-estimating the blood pressure effects in phase III studies, as compared to what was demonstrated in the TQT study, are:

1) Use of different measurement techniques for blood pressure (self measurement in phase III versus office measurements in TQT study with time matched-baseline).

2) Timing of the blood pressure measurement. In TQT study, relatively more measurements within the inter-dosing interval allowed for assessment of drug effect at peak and trough. In the phase III studies, vital signs were collected by the subject during the AM (after waking up in the morning before the morning dose) and PM (between 2 PM and 6 PM) in a 5-day vital sign diary using a self-measurement device. This sampling scheme did not allow for the assessment of the peak effects which generally occurred around 3 – 4.5 hours coinciding with the peak mirabegron concentrations post-dose, as demonstrated by the histogram of post-dose timing of the afternoon blood pressure reading in the figure below.

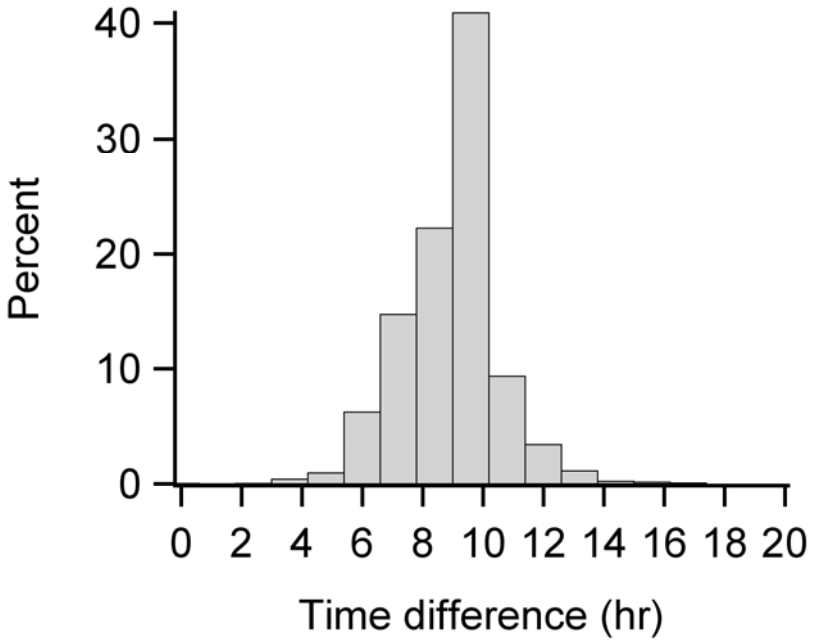

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Figure 4: The peak effects are not assessed for most of the patients in the phase III trials at week 12. The time of the AM measurement is used as a reference for dosing time.

For the purpose of cardiovascular risk assessment in phase III, AM SBP (morning SBP obtained from the vital signs collected via Patient Diary) is utilized. This typically represents the trough SBP (SBP at the trough exposure of the treatment). For the treatment effect, the maximum AM SBP (the maximum of the three visits post-baseline derived from the ISS database; AVISIT = 7777) is considered. A brief description of the derivation of the SBP measurement from the patient diary is provided in the Appendix.

The cumulative distribution of the change from baseline in morning SBP for the pooled Phase III trials (178-CL-046, 178-CL-047 and 178-CL-074) for Placebo and the mirabegron 50 mg QD, the dose for which approval is being sought is shown in the figure below. As expected based on the time-course, the cumulative distribution curve for mirabegron is shifted to the right by a small change in SBP of 0.5 mmHg (95%CI: -0.21, 1.16). These results suggest that SBP effect greater than 1.16 mm Hg can be ruled out with a certain confidence under the specific design used for blood pressure measurement in the Phase III trials.

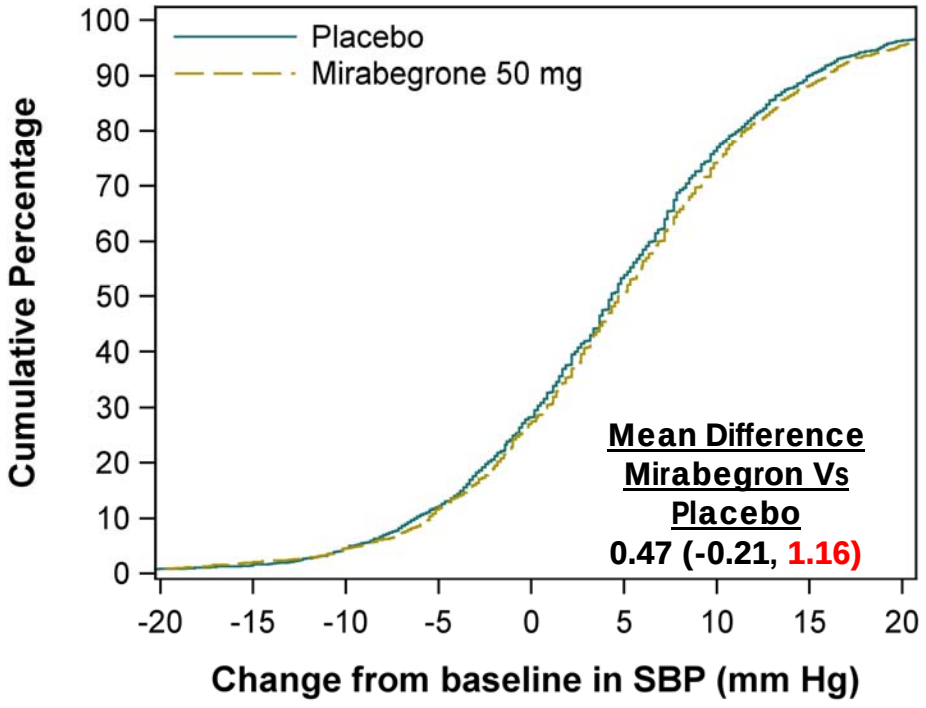

Figure 5: Cumulative distribution of maximum mean change from baseline AM SBP for the pooled phase III trials (178-CL-046, 178-CL-047 and 178-CL-074). ***The X-axis is truncated to -20 mmHg on the lower end and 20 mmHg on the higher end.***

2) What is the impact of change in SBP on the cardiovascular risk?

To assess the potential impact of the changes in SBP, the Cox-Proportional hazards model developed by D'Agostino et al was utilized[2]. This model provides a quantitative relationship between various risk factors and the probability of developing cardiovascular disease (CVD). CVD is defined as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral arterial disease (intermittent claudication), and heart failure. The various predictors of risk are sex, age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking and diabetes status. Using this model, 10-year general CVD risk can be assessed.

CVD risk assessment based on SBP effect observed in the 12-week phase III trials:

The change in 10-year general CVD risk was computed on the pooled Phase III data (178-CL-046, 178-CL-047 and 178-CL-074), taking into account various patient-specific risk factors and changes in AM SBP. The AM SBP typically represented the trough SBP during the trial. The SBP for the treatment effect was the maximum mean AM SBP observed post-baseline (explained on Page 4) obtained from the vital signs collected via Patient Diary. Patients receiving either systemic Beta Blockers or agents acting on Renin Angiotensin System (RAS) at baseline were flagged as receiving treatment for hypertension. The same definition was used for baseline and post-baseline visit. Patients with a history of diabetes at baseline were flagged for diabetes status.

In the Phase III trials, total cholesterol, high density lipoprotein, and smoking status were not collected. For the purpose of this analysis, the mean total cholesterol value and mean HDL cholesterol value by age and gender based on the National Health and Nutrition Examination

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Surveys (NHANES) [Carroll et al, 2005[4]] was used for each patient. Patients between the ages of 18 and 19 years are not covered by NHANES, so they were assigned the mean total cholesterol value and mean HDL cholesterol value for the age group of 20 to 29 years by gender based on NHANES. Smoking status was based on the age- and gender-specific average percentage of current cigarette smokers in 2010 for the United States from the National Health Interview Survey (NHIS)[5]. These imputations were proposed by the sponsor and accepted by the Agency.

The change in 10-year general CVD risk was also computed for patients with high baseline risk. High risk patients were defined as those patients in the upper 25% of the baseline risk. For the pooled Phase III studies this comprised patients with a 10-year CVD risk greater than 19.9%.

A summary of the available baseline risk factors for the pooled phase III trials is presented in Table 2 below.

Patient Characteristics	**Placebo N = 1329**	**Mirabegron 50 mg N = 1327**
Age, yrs (Mean, [SD])	59 (13)	60 (13)
SBP, mmHg (Mean, [SD])	126 (17)	126 (17)
Gender, M/F	363/966	383/944
Antihypertensive Treatment, %	40	39
Diabetes Status, %	8.0	9.0

Table 2: Summary of the available baseline risk factors for assessment of 10-year general CVD risk by treatment for the pooled phase III trials

The small increases in SBP for the pooled twelve-week phase III trials translate into a small increase in the 10–year general CVD risk a shown in Figure 6 below. The absolute increase in the mean 10-year CVD risk

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[4] Carroll et al. Trends in serum lipids and lipoproteins of adults, 1960-2002. JAMA. 2005;294(4):1773-81.

[5] Centers for Disease Control and Prevention. Vital signs: current cigarette smoking among adults aged ≥ 18 years --- United States 2005 – 2010. MMWR. 2011;60(35):1207-12.

on an average is 0.19% (or 0.19 CVD events per 1000 patient-years) and fails to achieve statistical significance.

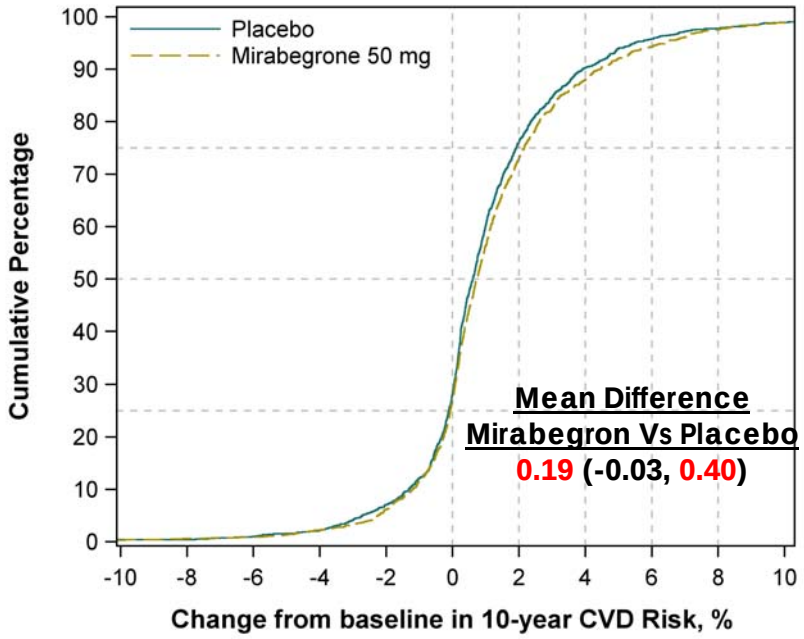

Figure 6: Cumulative distribution plots for change from baseline in 10-year general CVD risk for Placebo and Mirabegron 50 mg QD based on the SBP effects observed in the twelve-week phase III trials

The prevalence of OAB is estimated to be 34 million in the United States[6]. When this increase in the CVD risk of 0.19 events/1000 patient-years is extended to an OAB population (with risk characteristics similar to those in the phase III studies) of a million patients on treatment with mirabegron 50 mg QD for 1 year, 187 additional CVD events are projected, per the figure below.

[6] *Irwin et al. Understanding the elements of overactive bladder: questions raised by the EPIC study. BJU Int. 2008;101:1381–1387*

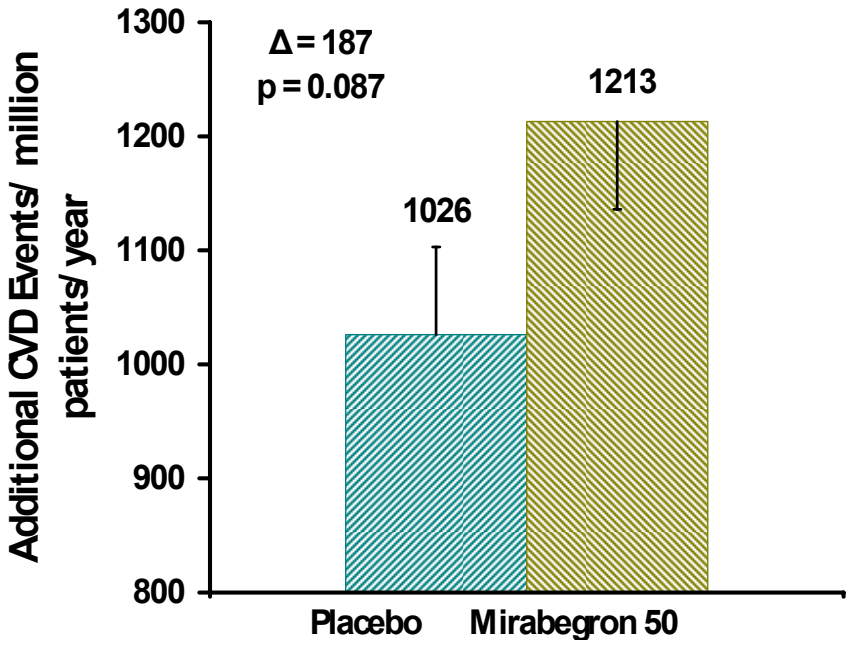

Figure 7: Projection of the cardiovascular impact of the increase in 10-year CVD risk based on the SBP effects observed in the twelve-week phase III trials

This increase in the CVD risk is magnified in patients with a higher baseline risk (patients in the upper 25th percentile of baseline CVD risk) as shown in the Figures 8 & 9 below. These patients in general tend to demonstrate more advanced age (median: 70 years), higher baseline AM SBP (median: 141 mmHg), a greater proportion of diabetes (22 – 23%), more treatment for hypertension (67 – 68%) and higher baseline 10-year CVD risk (median: 30.6%). Accordingly, in these higher risk patients on treatment with mirabegron 50 mg QD for 1 year, an additional 556 CVD events are projected per million patients (still not statistically significant, p-value derived based on 25% of the total sample size in the Phase III trials).

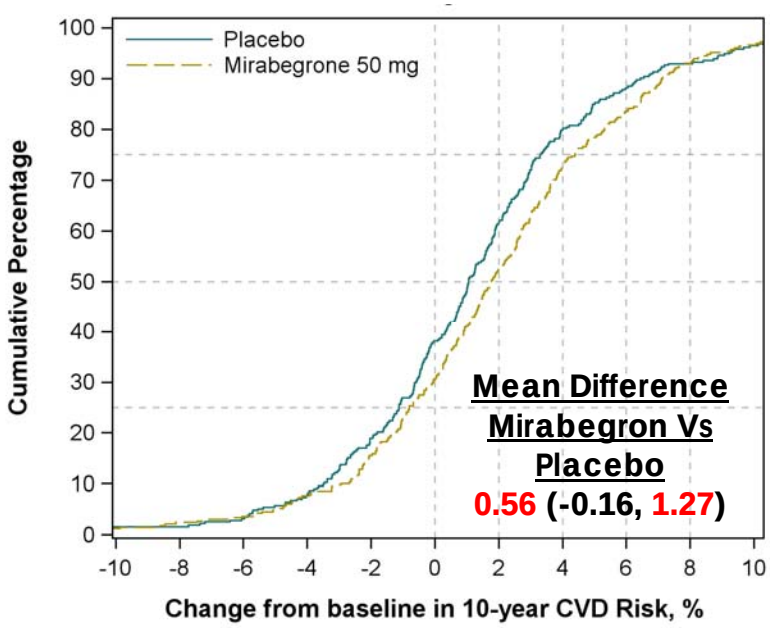

Figure 8: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 50 mg QD in high risk patients based on the SBP effects observed in the twelve-week phase III trials

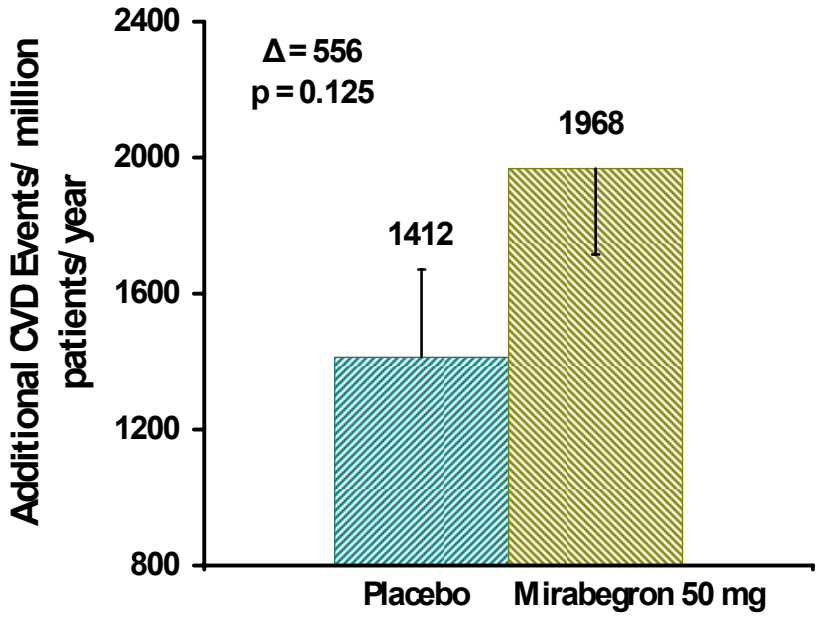

Figure 9: Projection of the cardiovascular impact of the increase in 10-year CVD risk for placebo and mirabegron in high risk patients based on the SBP effects observed in the twelve-week phase III trials

CVD risk assessment based on SBP effect observed in the TQT Study:

The blood pressure effects observed in the TQT study represent a relatively precise estimate of the blood pressure effects of mirabegron as these results were obtained under tightly controlled conditions. It is not unreasonable to assume that the effects observed in this study are representative of the true SBP effects of mirabegron. The design and conduct of phase III trials generally do not allow detection of peak or mean effects. The analysis presented below represents an effort to understand the potential cardiovascular impact of the blood pressure effects observed in the TQT study.

Blood pressure effects associated with the treatment of placebo and mirabegron 50 mg QD were simulated based on the results presented in Table 1 assuming normal distributions. The 24-hour average (corrected for placebo and baseline) change in blood pressures represented the change from the baseline AM SBP (i.e., trough) for the pooled phase III data. The effect observed for the moxifloxacin arm in the TQT study (Mean [SD]: 0.02 mmHg [11.2]) was used to simulate the placebo effect for the placebo arm (N =1329) while that observed for mirabegron 50 mg QD (Mean [SD]: 3.0 [10.2]) was used for the mirabegron arm (N = 1327) for the pooled phase III trial data. All the other risk factors at baseline and end or treatment were retained from the observed phase III data.

The projection of the change in the 10-year CVD risk and its impact per-million patient-years are presented in the Figures below for the overall population (Figures 10 and 11) and patients with high baseline risk (Figures 12 and 13).

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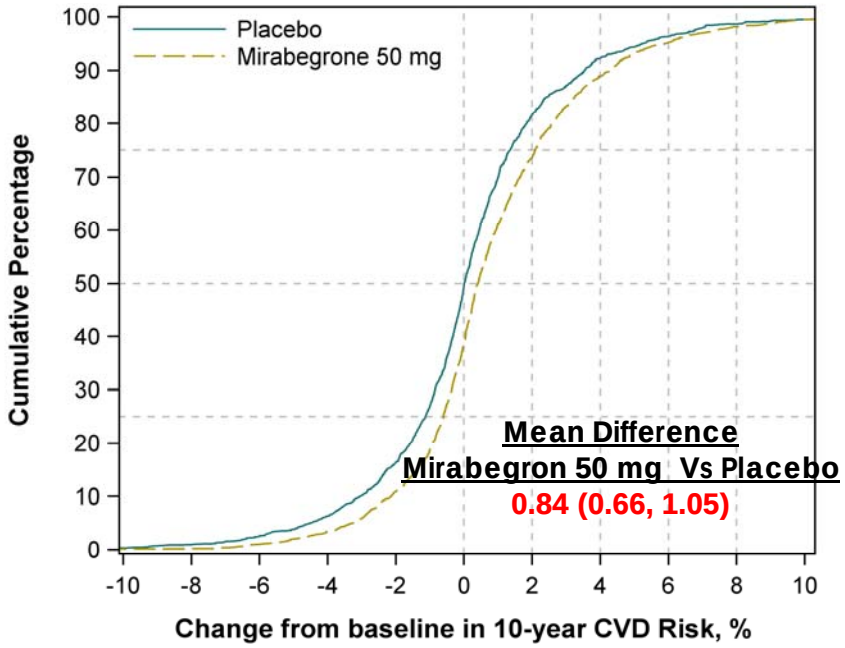

Figure 10: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 50 mg QD based on the simulated blood pressure effects derived from TQT study

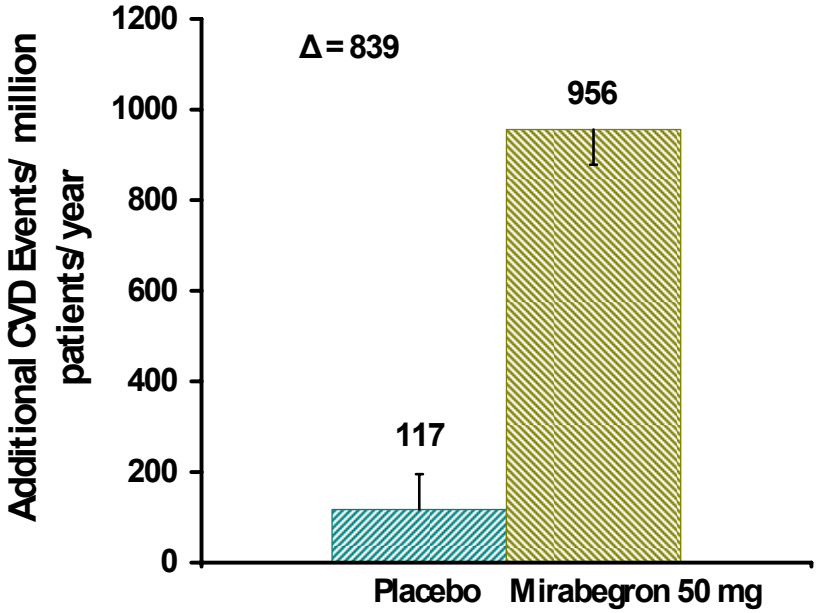

Figure 11: Projection of the cardiovascular impact of the increase in 10-year CVD risk based on the simulated blood pressure effects derived from TQT study

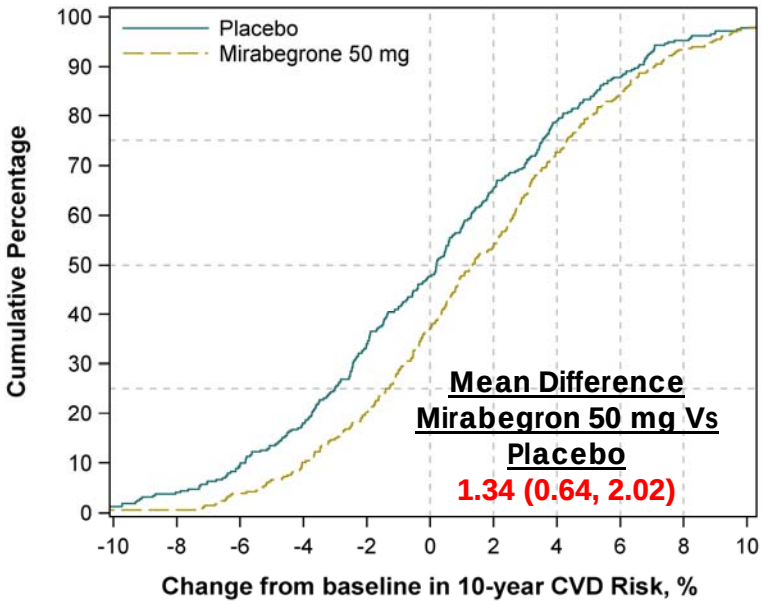

Figure 12: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 50 mg QD based on the simulated blood pressure effects derived from TQT study in high risk patients

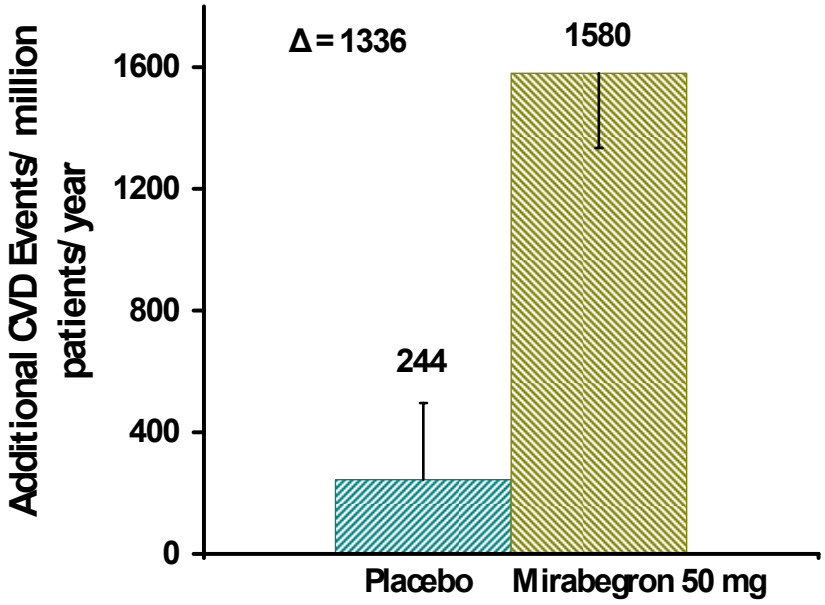

Figure 13: Projection of the cardiovascular impact of the increase in 10-year CVD risk based on the simulated blood pressure effects derived from TQT study in high risk patients

As would be expected, the higher demonstrated blood pressure elevation in the TQT study predicts a higher risk of CVD events than did the phase III data.
Monte Carlo simulations of 100,000 trials based on the SBP effects observed in the TQT study showed that the 10-year CVD risk projections were reasonable.

	10-year CVD Risk (Additional Events/1000 pt-years)		
Population	**2.5th Percentile**	**50th Percentile**	**97.5th Percentile**
All	0.45	0.66	0.87
High Risk	0.53	1.19	1.87

Table 3: Summary of the Monte Carlo simulation of 100,000 trials

3) What is the impact of Mirabegron 25 mg QD on the cardiovascular risk?

At the Advisory Committee Meeting held on April 5th, 2012, several experts opined on the utility of Mirabegron 25 mg QD as a starting dose. During the internal deliberations, the review team requested that we compute the potential CV risk anticipated with Mirabegron 25 mg QD.

The cumulative distribution of the change from baseline in morning SBP for the pooled Phase III trials (178-CL-046, 178-CL-047 and 178-CL-074) for placebo and for mirabegron 25 mg QD are shown in the figure below.

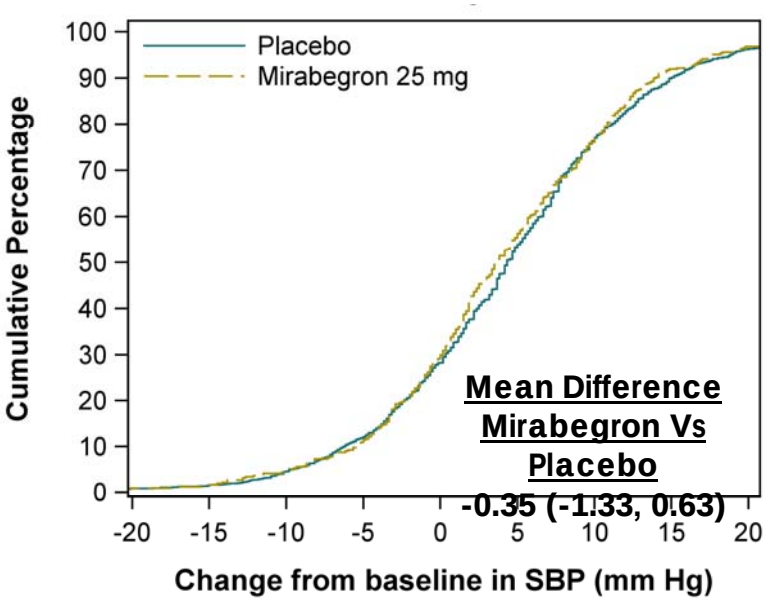

Figure 14: Cumulative distribution of maximum mean change from baseline AM SBP for the pooled phase III trials (178-CL-046, 178-CL-047 and 178-CL-074). ***The X-axis is truncated to -20 mmHg on the lower end and 20 mmHg on the higher end.***

As seen from the figure, a small decrease in the SBP is observed with mirabegron 25 mg unlike that seen with the higher dose of 50 mg (see Figure 5). The impact of this small change in SBP is presented below for the overall population and the high risk group. It can be seen that the potential for CVD risk associated with mirabegron 25 mg QD is very small and comparable to that of placebo.

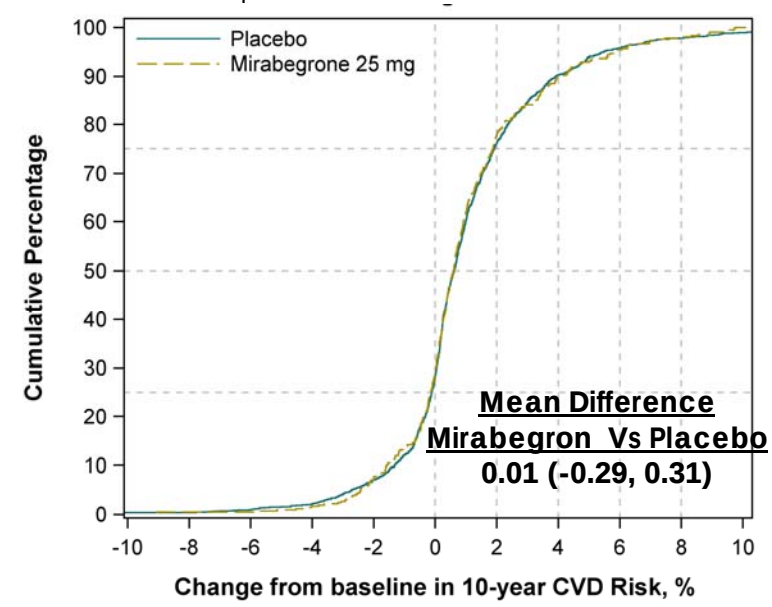

Figure 15: Cumulative distribution plots for change from baseline in 10-year general CVD risk for Placebo and Mirabegron 25 mg QD based on the SBP effects observed in the twelve-week phase III trials

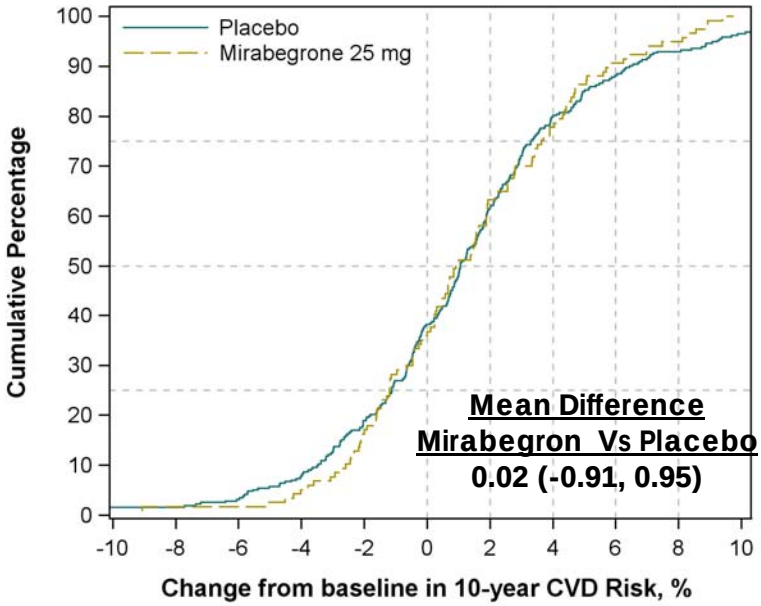

Figure 16: Cumulative distribution plots for change from baseline in 10-year general CVD risk for placebo and mirabegron 25 mg QD in high risk patients based on the SBP effects observed in the twelve-week phase III trials

Appendix:

The following is a brief description of the systolic blood pressure collection and the calculation of the average excerpted from sponsor's Integrated Summary of Safety.

"**Vital Sign Conventions**

The vital sign collection method and conventions described below are applicable to the EU/NA OAB 12-week Phase 3 and EU/NA Long-term Controlled populations.

Vital sign measurements (systolic and diastolic blood pressure and pulse rate) are collected in two ways. For the ISS, diary measurements will be used for all analyses of vital signs. Each subject records vital sign measurements in a 5-day diary period preceding the study visit (e.g., for the 12-week studies: Randomization Visit, Week 4, Week 8, Week 12, and Final Visit) using a self-measurement device. For each diary day, the subject will collect AM measurements (after waking in the morning but prior to breakfast and double-blind study drug intake) and PM measurements (between 2 pm and 6 pm in the afternoon). Subjects are to take 3 readings which are approximately 2 minutes apart for both the AM and PM measurements."

"Averaging Vital Signs Measurement

Diary Measurement

An average will be calculated for AM and PM measurements separately for each vital sign variable (SBP, DBP and pulse rate). The average for each day will first be calculated and then the average over the diary days will be calculated.

The last 2 vital sign values measured each day for AM and PM with the subject's self-measurement device will be utilized for the AM and PM analyses. If only 1 or 2 measurements are taken in the AM or PM, then all values will be utilized in the AM or PM analyses.

If a subject recorded a vital sign measurement for ≥ 4 diary days for AM or PM, an average will be calculated based on the last 3 diary days provided they are within the analysis window for a given visit. If a vital sign measurement is recorded for only 1 to 3 diary days, an average will be calculated based on all diary days within the analysis window for a given visit."

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/s/

RAJANIKANTH MADABUSHI
06/11/2012

PRESTON M DUNNMON
06/11/2012

NORMAN L STOCKBRIDGE
06/11/2012

Final
(May 11, 2012)
Clinical Pharmacology Review
Office of Clinical Pharmacology (OCP)

NDA: 202611 **Date of Submission:** August 26, 2011 (cover letter)

Generic Name:	Mirabegron
Proposed Brand Name:	TBD
Formulation:	Extended Release Tablet
Strengths:	25 mg and 50 mg
OCP Division:	Division of Clinical Pharmacology 3
Office of New Drug (OND) Division:	Division of Reproductive and Urologic Products
Route of Administration:	Oral
Indication:	Treatment of Overactive Bladder
Dosage and Administration:	50 mg daily (QD)
Type of Submission:	Original NDA (New Molecular Entity, NME)
Sponsor:	Astellas Pharma, Deerfield, IL
Primary Clinical Pharmacology Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Secondary OCP Reviewers/Signers:	E. Dennis Bashaw, Pharm.D. Myong-Jin Kim, Pharm.D.
Pharmacometric Primary Reviewer:	Jiang Liu, Ph.D.
Pharmacometric Secondary Reviewer:	Yaning Wang, Ph.D.
Pharmacogenomics Primary Reviewer:	Christian Grimstein, Ph.D.
Pharmacogenomics Secondary Reviewer:	Mike Pacanowski, Pharm.D. M.P.H.

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable.

1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no post-marketing commitments are indicated for this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

Mirabegron (also known as YM178) Oral Controlled Absorption System (OCAS) is modified release film coated tablet to be available in two dosage strengths of 25 mg and 50 mg. This is a new chemical entity and first-in-class compound as a selective agonist for human beta 3-adrenoceptor (beta 3-AR). It is being developed for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency. The proposed initial dose is 25 mg once daily for 8 weeks prior to titrating up to 50 mg daily with or without food. However, a dose of 25 mg is reserved for patients with severe renal or moderate hepatic impairment with no increase to 50 mg.

The sponsor conducted 41 studies consisting of 29 Phase 1 and 2 clinical pharmacology studies and 12 global safety and efficacy studies. The Phase 1 studies consist of 6 biopharmaceutics studies and 23 human PK studies including extensive PK/PD modeling and simulation. The primary/pivotal safety and efficacy studies are 178-CL-046, 047, and 074. In addition to the standard clinical pharmacology studies, the sponsor conducted two thorough QT (TQT) studies (# 178-CL-037 and 077). Additional analysis was performed to evaluate the cardiovascular effects (e.g., blood pressure and heart rate).

In addition to human *in vivo* studies, the sponsor conducted numerous *in vitro* studies using human biomaterials (e.g., microsomes and cell lines) to characterize the drug metabolic pathways, potential drug-drug interaction (DDI), to identify the isoezymes responsible for the metabolism of mirabegron, and transport mechanisms.

Basic PK Information:

While Mirabegron has a chiral center (R and S) the product under review is the R-enantiomer. It should be noted that no chiral inversion was observed *in vivo*. The plasma protein binding is 71%. The drug binds to albumin and alpha-1 acid glycoprotein. Erythrocytes concentration is 2-fold higher than in the plasma (*in-vitro* data). The drug is widely distributed in the body with large volume of distribution of approximately 1670 L. The terminal elimination half life of mirabegron on average is approximately 50 hours.

The time to reach maximum concentration (Tmax) is 3-4 hours. Based on the Biopharmaceutics Classification System (BCS) mirabegron may be considered Class 3 with high solubility and low

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permeability (see ONDQA review). The absolute bioavailability is approximately 29% at 25 mg dose and 35% at 50 mg dose (i.e., dose dependent). Also, the bioavailability appears to be higher in females than in males. Overall, the exposure in females is approximately 40% to 50% higher than in males (uncorrected for body weight). However, when corrected for body weight, the difference is reduced to approximately 20% to 30%.

Absorption is dependent on the fat content of food; the effect being greater following a low fat meal compared to a high fat meal. The maximum concentration (Cmax) and the area under the concentration-time curve (AUC) were reduced by approximately 45% and 17% following high fat meal compared to fasting, respectively. However, when low fat meal was consumed, the Cmax was reduced by 75% and AUC was reduced by 51%. This may cause potential day-to-day fluctuation in mirabegron plasma concentration compared to fasting condition.

Irrespective of this unpredictability in mirabegron systemic exposure due to inconsistencies in food contents and the associated dose dependency in bioavailability, the sponsor's proposed label states that the drug may be given with or without food. It should be noted that pivotal Phase 3 studies were conducted irrespective of food consumption.

Metabolism:

Approximately 55% of radioactivity (^{14}C) is recovered in urine and 34% in feces. The drug is extensively metabolized to approximately 10 metabolites. Approximately 25% of dose was excreted unchanged in urine. None of these metabolites appears to be active in reference to 3-AR. There appear to be several metabolic pathways involved in the metabolism of mirabegron. These include dealkylation, oxidation, and glucuronidation, and amid hydrolysis. Also, these pathways involve several enzymes and isoenzymes such as butyrylcholinesterase, uridine diphospho-glucuronosyltransferase (UGT), CYP3A4, and CYP2D6, and alcohol dehydrogenase. However, CYP3A4 appears to be the primary responsible isoenzyme.

Dose-Exposure and Specific Population:

It appears, in general, that steady state plasma concentrations are reached within 7 days after once daily (QD) dosing. There was no apparent difference in PK in relation to age (18-55 vs. 65-80 years). Cross study analysis reveals that the exposure in Japanese subjects appears to be higher than that of Westerner subjects (Studies 178-CL-41 and 078). There were no apparent differences in PK between Caucasians and African Americans.

In patients with mild, moderate, and severe renal impairment the AUC increased by 31%, 66%, and 118% and the Cmax increased by 6%, 23%, and 92% compared to healthy subjects, respectively. In patients with mild hepatic impairment (Child-Pugh Class A) the Cmax and AUC were increased by 9% and 19% and in moderate (Child-Pugh Class B) they were increased by 175% and 65% compared to healthy subjects, respectively. No study was conducted in severe hepatic impairment patients (Child-Pugh Class C). Based on these studies, the recommended dose is only 25 mg QD in severe renal and moderate hepatic impairment with no titration up to 50 mg dose. However, mirabegron is **not recommended** in patients with severe hepatic impairment (Child-Pugh Class C).

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Drug-Drug Interaction (DDI) Findings:

The sponsor conducted several *in vivo* and *in-vitro* drug-drug interaction studies to establish the effect of other drugs on the PK of mirabegron and the effect of mirabegron on other drugs.

Ketoconazole, as a potent CYP3A4 and P-glycoprotein (P-gp) inhibitor, increased the Cmax and AUC of mirabegron by 45% and 81% while rifampin as a potent enzyme inducer reduced the Cmax and AUC by 35% and 44%, respectively. Other tested drugs such as metformin, solifenacin, and tamsulosin had no effect on mirabegron PK.

From the genetic polymorphism perspective, there was no apparent difference in mirabegron exposure between CYP2D6 poor metabolizers and extensive metabolizers. Based on these findings, the sponsor did not conduct study with CYP2D6 inhibitors. Therefore, no dose adjustment is needed when the drug is co-administered with CYP2D6 inhibitors or patients who are CYP2D6 poor metabolizers.

Mirabegron increased the Cmax and AUC of two CYP2D6 substrates, metoprolol and desipramine. The Cmax and AUC of metoprolol increased by 90% and 229% and of desipramine by 79% and 241%, respectively. This shows that mirabegron is a moderate inhibitor of CYP2D6. Therefore, metoprolol, desipramine, and other CYP2D6 substrates with a "narrow therapeutic index" should be used with caution and will require titration when coadministered with mirabegron.

The Cmax and AUC of tamsulosin (a CYP2D6 and CYP3A4 substrate) was increased by 60% when co-administered with mirabegron. Other studies showed that mirabegron has minimal or no effect on other drugs such as: combined oral contraceptives (COC) containing ethinyl estradiol and levonorgestrel or other *in vivo* probes of metabolism such as: solifenacin (CYP3A4 substrates), warfarin (probe substrate for CYP2C9), metformin, and digoxin.

Exposure-Response and Cardiovascular/QT Data:

An analysis of the data in reference to the effect on blood pressure was performed by the cardio-renal and the clinical pharmacology team. Based on this analysis, mirabegron shows concentration dependent increase in systolic blood pressure (SBP) in healthy subjects from Phase 1 studies and specifically in TQT study (Study # 178-CL-077). This analysis is performed in details in joint documents from the cardio-renal and clinical pharmacology team (reviews dated January 20, 2012 and February 28, 2012). This issue was also discussed in details at the Advisory Committee (AC) meeting held on April 5, 2012 (see background materials, presentation slides, and transcript at http://www.fda.gov/AdvisoryCommittees/Calendar/ucm291237.htm.

As the dose of mirabegron increased from 50 mg to 200 mg, the observed increase in heart rate over baseline was approximately 6.7 beats per minutes (bpm) to 17.3 bpm. PK/PD modeling showed that heart rate and blood pressure increased with increasing mirabegron plasma concentration, especially in TQT study (178-CL-077).

Based on an Emax model, it appears there is a dose separation in micturation frequency and mean volume voided across the dose range of 25mg, 50 mg, and 100 mg equal to 52%, 85%, and 98% of the Emax (maximum efficacy), respectively. However, the exposure-response relationship for incontinence episodes per 24 hours was flat across the 25 to 100 mg doses range. All doses were associated with approximately 26% reduction in the rate of incontinence compared to placebo.

Synopsis of the Advisory Committee:

On April 5, 2012 a Reproductive Health Drugs Advisory Committee meeting was held for mirabegron. The background materials and presentation slides can be retrieved at http://www.fda.gov/AdvisoryCommittees/Calendar/ucm291237.htm.

The focus of the discussion was on the efficacy and safety (in particular the cardiovascular risk and the increase in blood pressure associated with mirabegron). Overall, the committee members were in favor for the marketing of mirabegron to provide an alternative treatment for OAB patients who fail on other therapy.

The transcript and voting scores can be found on-line.

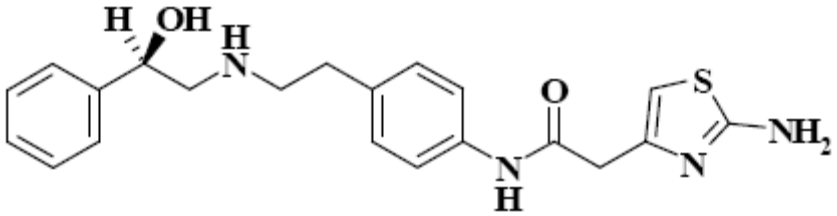
2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Mirabegron (YM178) is a selective agonist for human beta 3-adrenoceptor (beta 3-AR). It is a new chemical entity, first-in-class compound with a different mechanism of action compared with pharmacotherapy, primarily antimuscarinics, for the treatment of symptoms associated with OAB.

The chemical name is 2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide, the molecular formula is $C_{21}H_{24}N_4O_2S$ and the chemical structure is as follows:



The drug product is formulated as Oral Controlled Absorption System (OCAS) tablets. OCAS is a modified release system (also referred as extended-release or prolonged-release) that allows the release of drug from the tablets for an extended period. The tablets are film coated at doses of 25 and 50 mg. From the Biopharmaceutics Classification System (BCS) perspective mirabegron is classified as Class III compound of high solubility and low permeability.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.2.1 Mechanism of Action:

Mirabegron is an agonist of human beta 3-adrenoceptors (AR). It relaxes the detrusor smooth muscle during the urinary bladder fill-void cycle by activation of beta 3-AR without interfering with the voiding contraction.

2.1.2.2.2 Indications:

The proposed indication is for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency

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2.1.3 What are the proposed dosage(s) and route(s) of administration?

According to the sponsor's proposed label, the initial recommended dose of mirabegron is 25 mg daily for 8 weeks prior to the titration up to 50 mg once daily with or without food. A dose of 25 mg once daily with no titration up to 50 mg with or without food is recommended in the following populations:

- Severe renal impairment (CLcr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m2)
- Moderate hepatic impairment (Child-Pugh Class B).

Mirabegron should be taken with liquid and swallowed whole. It should not be chewed, divided or crushed.

2.1.4. What are the Core Studies Submitted in this NDA?

The clinical pharmacology program consist of *in vitro* studies that were conducted with human biomaterials and clinical studies to characterize the absorption, distribution, metabolism and excretion (ADME) of mirabegron in healthy volunteers, special populations and subjects with OAB. It also, includes PD studies investigating mirabegron's effects on cardiovascular parameters and intraocular pressure (IOP), and several drug-drug interaction studies.

2.1.4.1 What are the Studies Used Human Biomaterials (*In Vitro* and *Ex Vivo* Studies)?

The sponsor conducted several *in vitro* studies using human biomaterials. The purposes of these studies are to investigate several characteristics including but not limited to the following: permeability, transport, mechanism of hepatic uptake, plasma protein binding, metabolism, effect on cytochrome P450 (CYP) isoforms and transporters, effect of mirabegron on transporters, and chiral inversion.

From all these studies migrabegron was found to be substrate for P-glycoprotein (P-gp), organic cation transporters (OCT 1, 2, and 3) and transported via P-gp. The uptake was saturable. Mirabegron was found weak inhibitory of P-gp and OCT1 and 2. In plasma, the drug binds mainly to albumin and alpha-1 acid glycoprotein.

Mirabegron was found to breakdown to approximately 10 metabolites. Most of these metabolites were <10% of dose which are inactive toward beta-3 adrenergic receptor (3-AR). The drug is metabolized through several metabolic pathways including but not limited to the following: oxidation (or *N*-dealkylation) of secondary amine; (2) amide hydrolysis and acetyl conjugation of the amine generated; (3) glucuronidation of the hydroxyl group or the primary amine, or carbamate glucuronidation of the secondary amine; (4) oxidation of the hydroxyl group to carbonyl group. Esterases, and in particular butyrylcholinesterase (BChE) are involved in the hydrolysis of mirabegron.

In vitro, mirabegron was found to be a moderate inhibitor of CYP2D6 and a weak inhibitor of CYP3A4. These findings were confirmed in *in vivo* human studies using two CYP2D6 substrates, metoprolol and desipramine and CYP3A4 substrates using combined oral contraceptives (COC) and solifenacin (see Section 2.4.1.2 effect of mirabegron on other drugs).

For metoprolol, the Cmax and AUC were increased by 90% and 229% (Study 178-CL-005) and for desipramine by 79% and 241% (Study 178-CL-058) when co-administered with mirabegron, respectively. There was minimal effect on COC and solifenacin (Study 178-CL-068).

In vitro studies showed no potential DDI between sulfonylurea hypoglycemic agents such as glibenclamide, glipizide and tolbutamide and mirabegron in both directions. Mirabegron is not an inducer of CYPs. *In vitro* data showed no chiral inversion.

2.1.4.2 What are the Highlights of Studies Conducted in Human (*In Vivo Human* Studies)?

The clinical development of mirabegron consisted of 41 studies. The clinical pharmacology Phase 1 program consists of 29 studies as listed below:

- 18 clinical pharmacology studies which used the Oral Controlled Absorption System (OCAS) formulation
- 5 clinical pharmacology studies which used an oral solution or immediate release (IR) solid dosage formulations
- 6 biopharmaceutic (bioavailability, food effect and *In-Vitro-In-Vivo* Correlation [IVIVC]) studies which used OCAS formulations with varying release rates.

In addition, there were 2 thorough QT (TQT) studies (# 178-CL-037 and 077) and PK/PD modeling and simulation reports.

IR formulations of mirabegron were used in the initial studies. Subsequently, the development was focused on modified release formulations leading to the development of mirabegron OCAS. The proposed to-be-marketed formulation of mirabegron is the OCAS medium-release formulation. In this NDA and throughout the review it has also been referred to as "OCAS-M", "OCAS target" or simply "OCAS".

The safety and efficacy was evaluated in 6 global, 12 week Phase 2b and Phase 3 studies. The following are the three pivotal efficacy studies in patients with OAB conducted in North America and Europe: 178-CL-046, 047, and 074. The following Sections give the synopsis of the clinical pharmacology studies per subjects:

2.1.4.2.1 PK Studies in Healthy Subjects:

The single- and multiple-dose PK of mirabegron were assessed in several phase 1 studies. Study 178-CL-001, the first-in-human study of mirabegron given as an IR formulation, was conducted in 2 parts. The first part studied the PK of escalating single doses of mirabegron IR and also assessed dose proportionality of the IR formulation. Part 2 of the study examined the effects of food. Dose proportionality after single and multiple doses of the OCAS formulation was assessed in several dose escalation studies (178-CL-031, 066, 034, 076, 077, and 072).

In Studies 033 and 076, the PK of mirabegron after intravenous administration was characterized. The mass balance study conducted to determine the disposition of a 160 mg oral dose as solution of ^{14}C-labeled mirabegron in study 007. The effect of food on the PK of IR and

OCAS mirabegron formulations has been evaluated in multiple studies. However, the pivotal two studies using OCAS tablets were study 041 in Westerners (conducted in USA) and study 078 in Japanese (conducted in Japan).

2.1.4.2.2 PK Studies in Special Population (Intrinsic Factors Studies):

The sponsor conducted several clinical pharmacology studies to characterize the PK of mirabegron in special populations. These studies include:

Age: The PK in healthy elderly volunteers was examined in studies 178-CL-031 and 072. The effect of age on mirabegron PK was also assessed in an exploratory pooled analysis across phase 1 studies and in a population PK analysis of sparse sampling data obtained in patients with OAB (Report # 178-PK-015).

Gender: Study 072 was dedicated to investigating the PK in healthy male and female volunteers. The effect of sex on mirabegron PK after intravenous and oral administration of mirabegron was examined in Study 178-CL-076. The effect of sex on mirabegron PK was also assessed in a population PK analysis of sparse sampling data obtained in patients with OAB (Report # 178-PK-015).

Race: The influence of race on the PK of mirabegron was explored in the thorough QT (TQT) study 178-CL-077. In addition, the effect of race was assessed in an exploratory pooled analysis across phase 1 studies and in a population PK analysis of sparse sampling data obtained in patients with OAB (Report # 178-PK-015). Studies 178-CL-064, 078, 066 and 034 examined the PK and food effect of single and multiple doses of mirabegron in healthy Japanese volunteers; PK parameters were compared to those obtained in Western volunteers in comparable studies.

Weight: The effect of body weight on mirabegron PK was assessed in a population PK analysis of sparse sampling data obtained in patients with OAB (Study report 178-PK-015).

Genetic Polymorphism: *In vitro* data indicated a minor involvement of CYP2D6 in the metabolism of mirabegron (Study 178-ME-002). The PK in healthy subjects genotyped and phenotyped as poor (PM) or extensive metabolizers (EM) for CYP2D6 was examined in Study 178-CL-005 and several other studies for which genotyping for CYP2D6 was performed. An exploratory pooled analysis was conducted to assess the potential impact of the derived phenotype (i.e. poor, intermediate (IM), extensive or ultrarapid (UM) metabolizer) on the PK of mirabegron.

Renal Impairment: The human mass balance study indicated that mirabegron and its metabolites are substantially eliminated renally (Study 178-CL-007). The PK in volunteers with varying degrees of impaired renal function (mild to severe) was examined in Study 178-CL-038. Subjects with End Stage Renal Disease (ESRD) were not studied. In addition, population PK analysis of sparse sampling data obtained in patients with OAB was used to examine the influence of renal function on the PK parameters (Study report # 178-PK-015).

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Hepatic Impairment: *In vitro* and *in vivo* data suggested that mirabegron is cleared through multiple metabolic pathways and possibly biliary excretion of unchanged drug. The PK in volunteers with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment was examined in Study 178-CL-039. Subjects with severe hepatic impairment were not studied.

Drug-drug interaction (DDI) studies were designed based on *in vitro* transporter and metabolism studies and the potential for concomitant use of specific agents with mirabegron.

2.1.4.2.3 Studies of Drug-Drug Interaction-DDI (Extrinsic Factors)

In vitro hepatic oxidative metabolism is primarily mediated by CYP3A4, with a minor role of CYP2D6 (Study 178-ME-002). In addition, mirabegron is a substrate for P-glycoprotein (P-gp) (Studies 178-ME-031, 178-ME-132). DDI studies were performed with ketoconazole, a potent CYP3A4 and P-gp inhibitor (Study 178-CL-036) and rifampin, a potent CYP3A4 and P-gp inducer (Study 178-CL-070) to assess the contribution of CYP3A4 to the overall metabolic clearance of mirabegron.

Mirabegron is a moderate inhibitor of CYP2D6 *in vitro* (Studies 178-ME-009, 178-ME-015, 178-ME-068). To evaluate the *in vivo* relevance of these findings, the potential impact of mirabegron on the PK of the probe CYP2D6 substrates metoprolol (Study 178-CL-005) and desipramine (Study 178-CL-058) was assessed. In addition, *in vitro* studies showed that mirabegron is a weak inhibitor of CYP3A4 at concentrations greatly exceeding those observed *in vivo*. Given the widespread use of combination oral contraceptives (COC) and the fact that the components of the most widely used COC, ethinyl estradiol and levonorgestrel, are substrates of CYP3A4, the effect of mirabegron on the PK of the ethinyl estradiol and levonorgestrel containing COC Minidril® (non- US approved product) was investigated in Study 178-CL-068.

The CYP2D6- and CYP3A4-inhibitory potential of mirabegron was further explored in interaction studies with the urologic products solifenacin (Study 178-CL-069), which is predominantly eliminated by CYP3A4-mediated metabolism, and tamsulosin (Study 178-CL-080), which is eliminated by CYP2D6- and CYP3A4-mediated metabolism. These studies also assessed the effect of solifenacin and tamsulosin on the PK of mirabegron. In addition, study 178-CL-080 evaluated the potential cardiovascular PD interactions between mirabegron and tamsulosin.

In vitro studies suggested that mirabegron may have weak inhibitory effects on P-gp-mediated drug transport (Study 178-ME-032). The *in vivo* P-gp inhibitory potential of mirabegron was investigated in Study 178-CL-059, using digoxin as a probe P-gp substrate. Other studies were conducted to investigate the potential interactions of metformin, which, like mirabegron, is a renally secreted organic cation (Study 178-CL-006). Given the narrow therapeutic index of warfarin, the effects of mirabegron on warfarin PK, prothrombin time (PT) and International Normalized Ratio (INR) were examined in Study 178-CL-040.

In addition, the potential influence of co-medication on mirabegron PK parameters was tested using population PK analysis of sparse sampling data in patients with OAB (Study Report # 178-PK-015).

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2.1.4.2.4 PK Studies in Subjects with Overactive Bladder (OAB)

Population PK analysis methods were used to characterize the clinical PK of mirabegron in subjects with OAB (Study Reports # 178-PK-004, 012, 015). The population analyses included data from subjects enrolled in 3 phase 2 studies (178-CL-008 (IR formulation), 044, and 045) and 4 phase 3 studies (178-CL-046, 047, 048, and 074) that evaluated the efficacy and safety of mirabegron in OAB. The data were derived from sparse sampling strategies used in these studies. Also rich sampling data from healthy subjects were included to help the model development.

2.1.4.2.5 Pharmacodynamic (PD) Studies:

It was observed that mirabegron causes dose-dependent increases in heart rate and blood pressure in healthy subjects. In order to explore the mechanism of the increase in heart rate, a single oral dose of mirabegron was administered before and after beta adrenoreceptor (AR) blockade with the nonselective beta 1/2-AR antagonist propranolol or the selective beta 1-AR antagonist bisoprolol (Study 178-CL-053). The mirabegron associated heart rate effects in the presence of beta-AR blockade were compared to those seen in placebo pretreated subjects. In addition, impedance cardiography (ICG) was used to evaluate the cardiovascular response induced by mirabegron. Initial experience with impedance cardiography was obtained in study 178-CL-072 (see Medical Officer's review).

As mirabegron is a new chemical entity, electrocardiographic assessments, with particular emphasis on QT intervals, were evaluated in the TQT studies 178-CL-037 and 077 (This will be discussed in later sections of this review and for more details please also see Pharmacometric review and QT-IRT review dated January 24, 2012).

A thorough evaluation of the potential for mirabegron to affect intraocular pressure or induce glaucomatous events was conducted. A phase 1b study (Study 178-CL-081) was conducted to address the potential imbalance in glaucoma-type events observed in the mirabegron phase 2/3 clinical program (see medical Officer's review).

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2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

The efficacy of mirabegron in the treatment of patients with symptoms of OAB, including urge urinary incontinence, urgency, and urinary frequency was evaluated in 9 studies including 3 primary phase 3 studies, 1 supportive phase 3 study, 2 supportive phase 2b studies, 1 phase 2a proof-of-concept study, 1 phase 3 active-controlled long-term safety study, and 1 phase 3 open label, long-term safety study.

It should be noted that of the three primary 3 studies, only one study (074) included mirabegron 25 mg dose. Therefore, the doses studied in Phase 3 are 25, 50, and 100 mg administered daily for 12 weeks.

The efficacy of mirabegron in reducing mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours as compared with placebo was demonstrated across these studies. It appears that all three doses demonstrated superiority compared with placebo. However, there was no much separation between 25 mg and 50 mg doses and 100 mg dose demonstrated slight superiority over 50 mg dose. **Figures 2.2.1.1 and 2.2.1.2** show the mean primary endpoints from studies 074 and 047 as examples.

Figure 2.2.1.1 Mean Incontinence Frequency in Studies 074 and 047
A: Study 074 **B: Study 047**

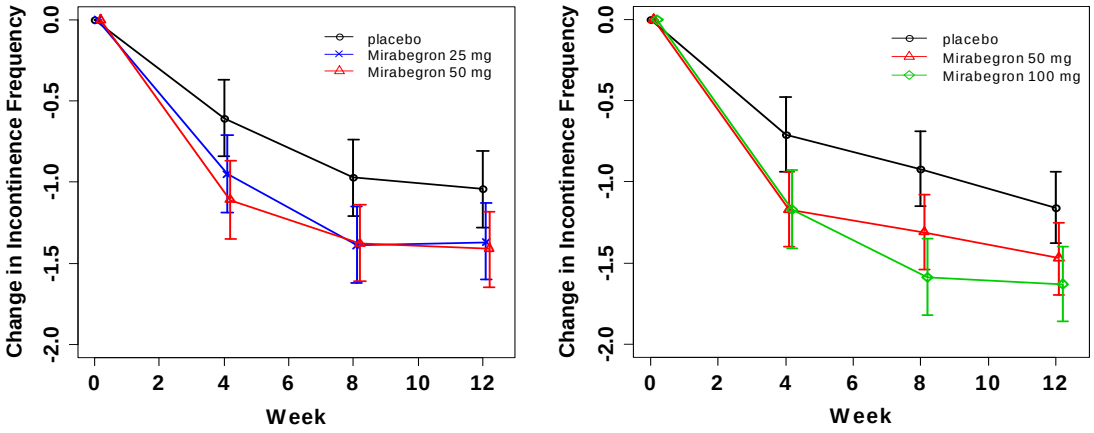
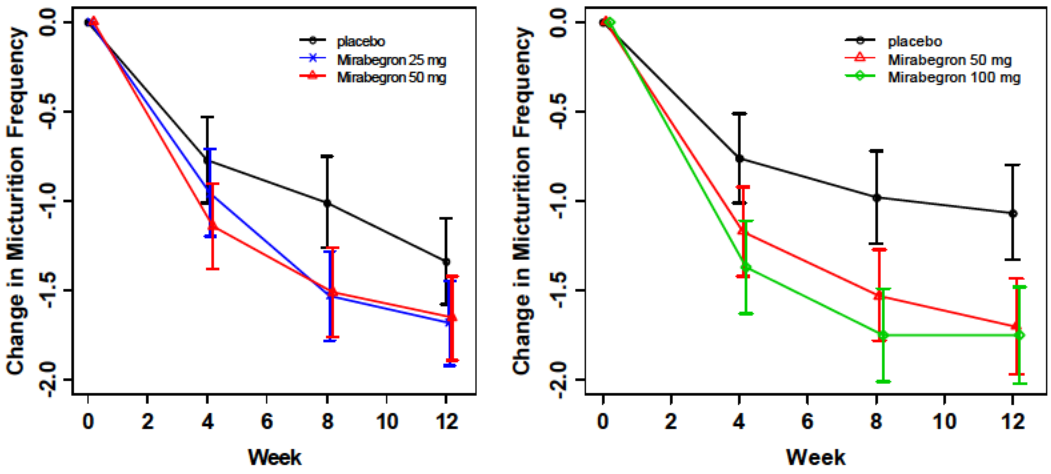
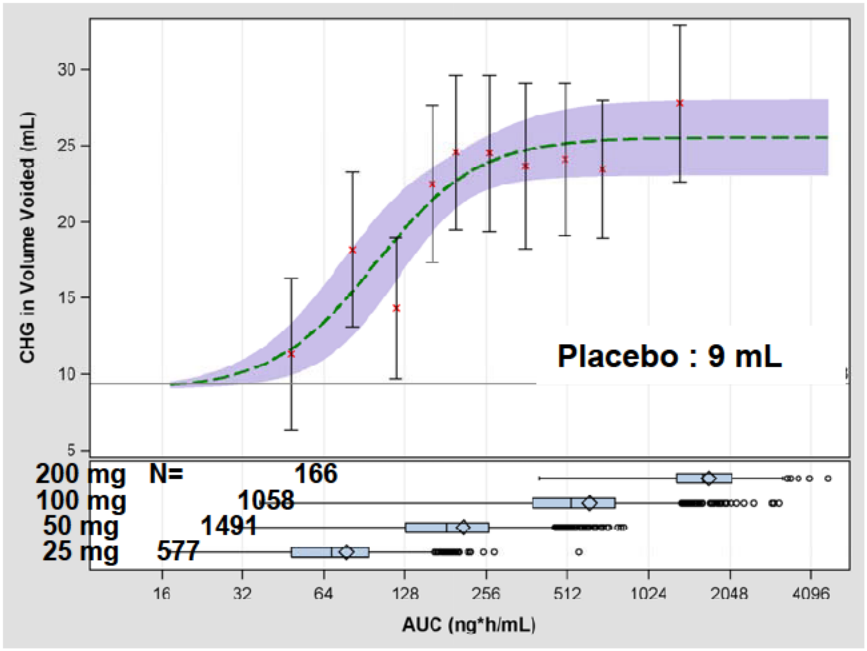


Figure 2.2.1.2. Mean Micturation Frequency in Studies 074 and 047
A: Study 074 **B: Study 047**



The analysis of the data from four Phase 3 studies (178-CL-044, 046, 047, and 074) shows a sigmoid E_{max} shape for exposure-response relationship in reference to volume voided (**Figure 2.2.1.3**). As a secondary efficacy endpoint (i.e., change from baseline to final visit in mean volume voided per micturition), higher mirabegron exposure (i.e. AUC) was associated with larger volume voided. However, doses higher than 50 mg do not seem to offer further advantage. The same conclusion can be reached for the supportive efficacy end point (e.g., number of urgency episodes per 24 hours, the mean level of urgency, and treatment satisfaction-visual analog scale).

Figure 2.2.1.3. Mirabegron Exposure (AUC) –Response Relationship for Volume Voided From for Studies 178-CL-044, 046, 047, and 074.



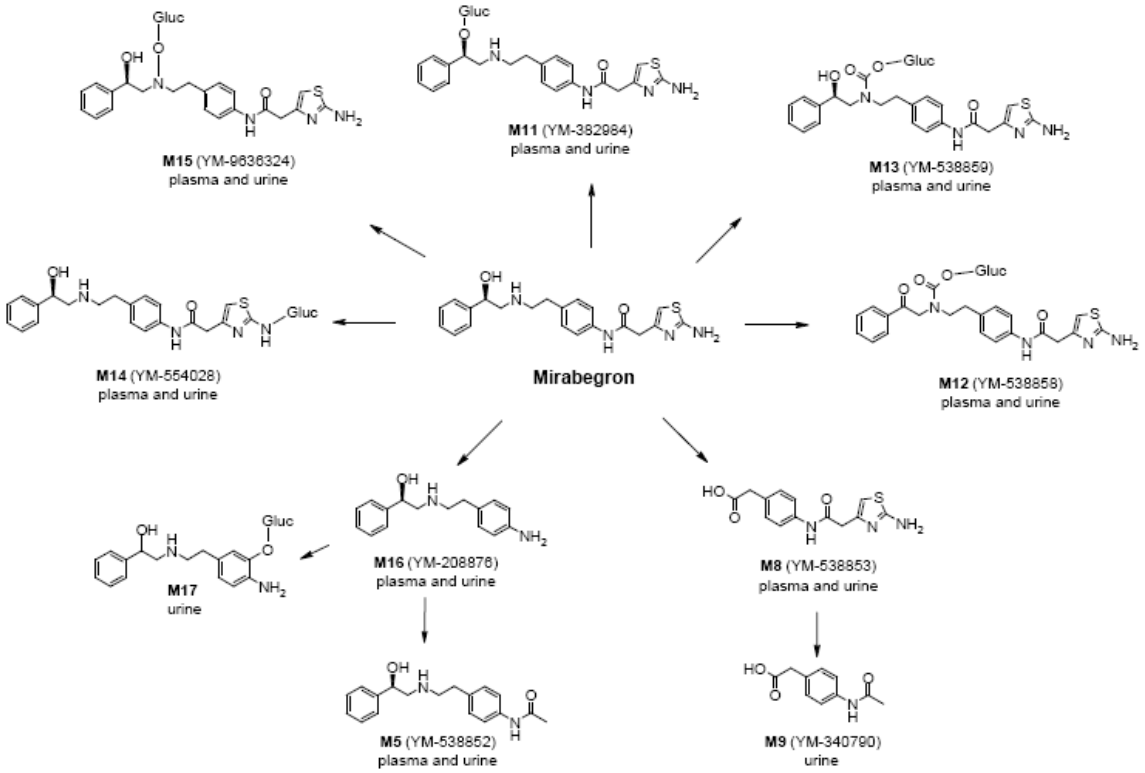
For details of Phase 3 trials and each study, please see the Medical Officer's review. Based on these data, the initial dose is 25 mg once daily for 8 weeks and then titrated up to 50 mg once daily as needed. However, the 25 mg once daily dose is reserved for severe renal impairment and moderate hepatic impairment with no titrating to 50 mg dose.

2.2.2 What are the Characteristics of Drug Metabolism?

As discussed earlier in this review, mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, glucuronidation, and amide hydrolysis. Urinary excretion data suggest that butyrylcholinesterase is involved in the hydrolysis of mirabegron, in addition to contributions from uridine diphospho-glucuronosyltransferase (UGT), CYP3A4 and CYP2D6 enzymes and possibly alcohol dehydrogenase. CYP3A4 is the primary responsible isoenzyme for *in vitro* hepatic oxidative metabolism of mirabegron, along with CYP2D6.

Mirabegron was the major circulating component in the plasma following a single radioactive dose of mirabegron. A total of 10 metabolites (M5, M8, M9, M11, M12, M13, M14, M15, M16 and M17) were identified in human urine. Eight of these (M5, M8, M11, M12, M13, M14, M15, and M16) were also observed in human plasma after oral administration. The postulated metabolic pathways of mirabegron in humans are shown in **Figure 2.2.2.1**.

Figure 2.2.2.1. Metabolic Pathways of Mirabegron in Humans



It should be noted that the metabolite-to-parent AUC ratios were relatively constant across multiple oral doses of 25 to 200 mg QD, indicating that the metabolism of mirabegron is not

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saturable over this dose range. The 2 glucuronidated metabolites, M11 and M12, are considered major metabolites which representing 16% and11% of total exposure in plasma, respectively. None of the metabolites observed in plasma were pharmacologically active toward 3AR (see pharmTox review).

Following the administration of 160 mg ^{14}C-mirabegron solution to healthy volunteers (n=4) in a mass balance study, approximately 89% of the administered radioactive dose was recovered: 55% in the urine and 34% in the feces (Study 178-CL-007, **Table 2.2.2.1**), 25% of the dose was excreted unchanged in urine.

Table 2.2.2.1 Summary of Plasma, Blood, Urinary and Fecal PK Parameters of Mirabegron and Total Radioactivity (Study 178-CL-007)

PK parameter (unit)	Plasma Mirabegron	Urine Mirabegron	Plasma Total Radioactivity	Blood Total Radioactivity	Urine Total Radioactivity	Feces Total Radioactivity
t_{max} (hr)	1.00 (0.71)	NA	2.25 (1.44)	2.13 (1.44)	NA	NA
C_{max} (ng/mL)	371 (96)	NA	879 (279)[†]	777 (211)[†]	NA	NA
AUC_{inf} (ng·hr/mL)	2285 (250)	NA	10443 (2328)[†]	13896 (2979)[†]	NA	NA
$t_{1/2}$ (hr)	47.9 (8.1)	72.9 (13.0)	28.2 (5.4)	30.5 (4.0)	84.5 (11.6)	NA
CL_R (L/hr)	NA	17.7 (2.14)	NA	NA	NA	NA
Ae_{last} urine (%)	NA	25.0 (0.83)	NA	NA	55.0 (2.66)	NA
Ae_{last} feces (%)	NA	NA	NA	NA	NA	34.2 (2.28)

2.2.3 Does this Drug Prolong the QT or QTc Interval?

The sponsor conducted a thorough QT (TQT) study to investigate the effect of mirabegron on the QTc (Study 178-CL-077). The study was conducted in 352 healthy subjects (176 women and176 men) following 10 days daily dosing of 50 mg, 100 mg, 200 mg mirabegron or corresponding each strength placebo and a single oral dose of 400 mg of the active control, moxifloxacin or its placebo. Overall, based on this study mirabegron does not appear to cause QT prolongation at the tested doses. However, a small signal was observed, in females at 200 mg dose.

This study was reviewed by the FDA Interdisciplinary Review Team for QT (IRT-QT) which it confirmed that there are no major QTc prolongation signals of clinical concern. **Table 2.2.3.1** and **Figure 2.2.3.1** are extracted form IRT-QT review which summarized the QTc data from this study.

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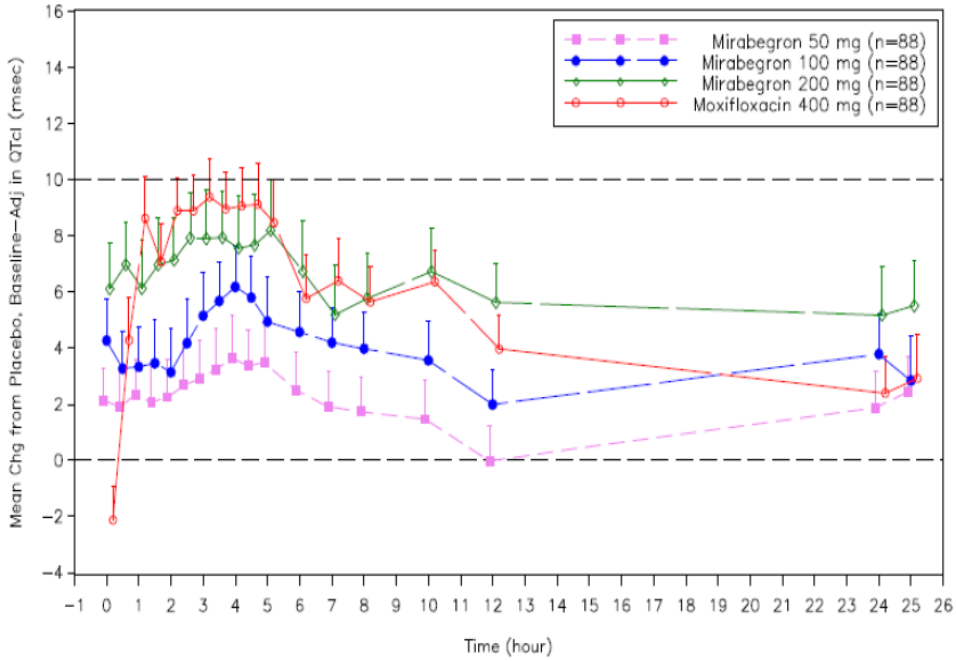
Table 2.2.3.1 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Mirabegron and the Largest Lower Bound for Moxifloxacin (FDA Analysis, IRT-QT review dated January 24, 2012))

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Mirabegron 50 mg	4	3.7	(2.3, 5.1)
Mirabegron 100 mg	4	6.1	(4.7, 7.6)
Mirabegron 200 mg	5	8.1	(6.3, 9.8)
Moxifloxacin 400 mg*	3	9.4	(8.1, 10.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.6.

Figure 2.2.3.1 Mean Change in QTc from Placebo for Mirabegron (Study 178-CL-077)



However, it should be noted that throughout this NDA females appear to have higher exposure than males for mirabegron. Overall, the exposure in females is approximately 40% to 50% higher compared to males, *uncorrected for body weight* (**Figure 2.2.3.2** and **Table 2.2.3.2**). This may explains the larger effect of mirabegron on QTc for females. However, based on IRT-QT review, this difference is of no clinical significance at the proposed 50 mg dose.

Figure 2.2.3.2. Mean (± SD) Concentration-Time Profiles of Mirabegron on Day 10, by Gender (Study 178-CL-077)

A: 50 mg Dose **B: 200 mg Dose**

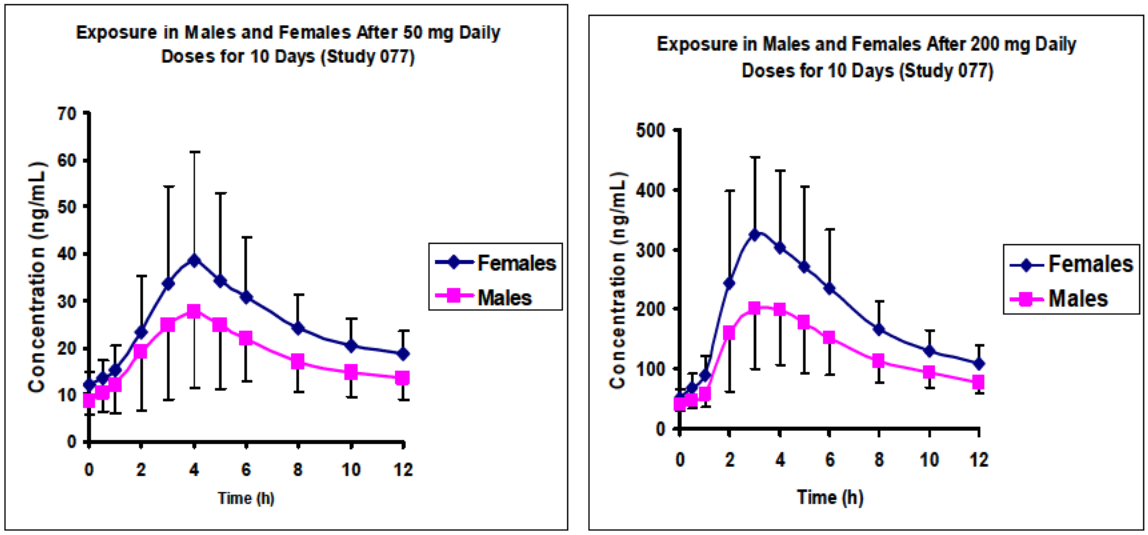


Table 2.2.3.2: Summary of Plasma PK Parameters of Mirabegron on Day 10, by Gender (Study 178-CL-077)

Parameter	50 mg (n=84)		100 mg n=82		200 n=83	
	Female (n= 41)	Male (n=43)	Female (n=41)	Male (n=41)	Female (n=40)	Male (n=43)
AUC (ng.h/ml) (SD)	503.4 (138.42)	361.0 (126.80)	1386.9 (342.53)	916.6 (296.69)	3273.7 (836.52)	2237.0 (586.90)
Cmax (ng/ml) (SD)	47.90 (25.601)	36.20 (17.919)	171.68 (53.927)	105.62 (46.266)	409.21 (139.37)	266.51 (94.420)

It appears that mirabegron increases heart rate in a dose-dependent manner. The maximum mean difference from placebo after adjusting for baseline (90% confidence interval) is 6.7 (5.3, 8.1), 11 (9.4, 12.6) and 17 (15.3, 18.7) bpm for 50 mg, 100 mg and 200 mg, respectively. For female subjects only, the maximum mean difference (90% confidence interval) is 8.3 (6.0, 10.7), 13.6 (11.2, 16.0) and 20.0 (17.6, 22.3) bpm for 50 mg, 100 mg and 200 mg, respectively. The increase in heart rate occurred between 5 and 6 hours post-dose. However, it should be noted that the Cmax of mirabegron occurs between 3 to 4 hours post dose.

The effect of mirabegron on heart rate as well as blood pressure was further analyzed jointly by the Division of Cardio-Renal products and clinical pharmacology team in separate documents (see below summary).

2.2.3.1 Does this Drug Have Effect on Cardiovascular Vital Signs?

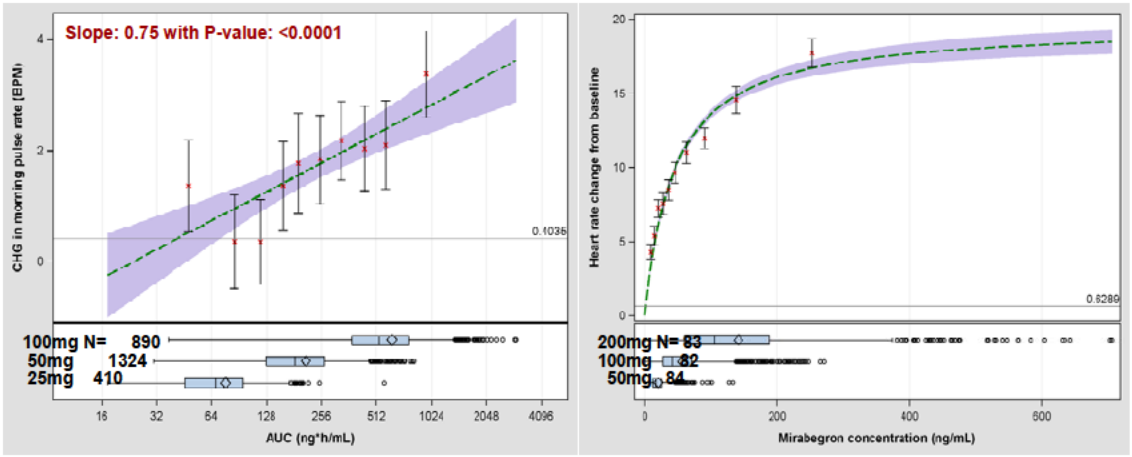
It appears that mirabegron increases blood pressure in healthy subjects as well as heart rate (**Figures 2.2.3.1.1 and 2.2.3.1.1**). These were observed in several studies and further analyzed by the Division of Cardio-Renal Products and by the Office of Clinical Pharmacology, Pharmacometrics Group (**Appendix 1).**

Pharmacometrics Analysis:

As shown from this analysis, higher mirabegron exposure was significantly associated with pulse rate increase in OAB patients (**Figure 2.3.1.1 A**). The pulse rate increased with increasing mirabegron plasma concentration in healthy subjects. This change was more pronounced in healthy subjects compared to the pulse rate change observed in OAB patients (**Figure 2.2.3.1 B**).

Figure 2.2.3.1.1 Effect of Mirabegron Exposure (AUC) on Pulse Rate and Heart Rate (Data from TQT study 178-CL-077)

A: Pulse Rate[a] **B: Heart Rate[b]**



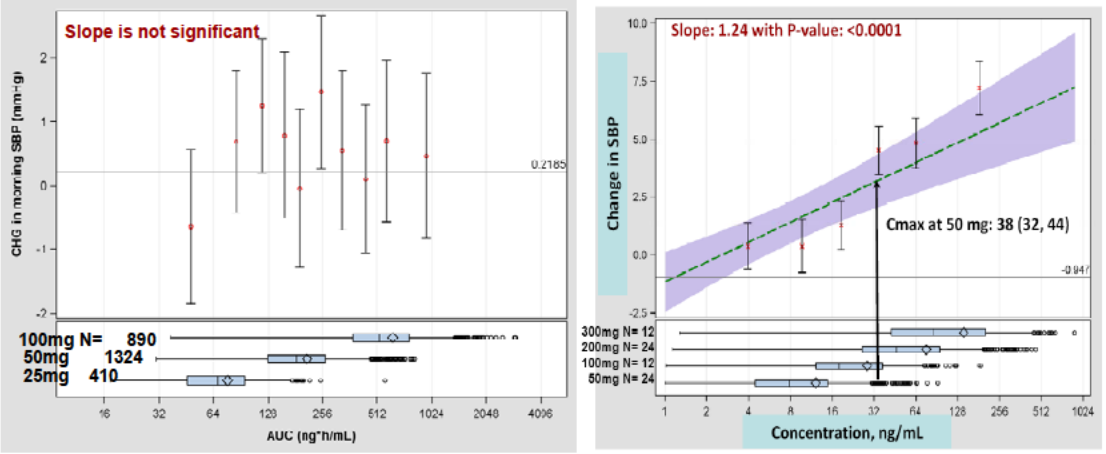
[a] *AUC-pulse rate analysis was conducted in pooled Phase 3 studies (AUC is predicted based on Population PK analysis)*

[b] *Concentration-heart rate analysis was conducted in the TQT study (178-CL-077)*

Analyses of Phase 3 data show no clear relationship between mirabegron exposure (AUC) and systolic blood pressure (SBP) in patients with OAB (**Figure 2.2.3.1.2 A**). However, there was significant increase in SBP with mirabegron plasma concentration in healthy subjects in Phase 1 studies (**Figure 2.2.3.1.2 B**, Study 178-CL-031).

Figure 2.2.3.1.2 Effect of Mirabegron Exposure on Blood Pressure in Phase 3 Trials in OAB Patients and Phase 1 Study 178-CL-031

A: Phase 3 OAB Patients **B: Phase 1[c]**



[a]*AUC-SBP analysis was conducted in pooled Phase 3 studies (AUC is predicted based on Population PK analysis)*

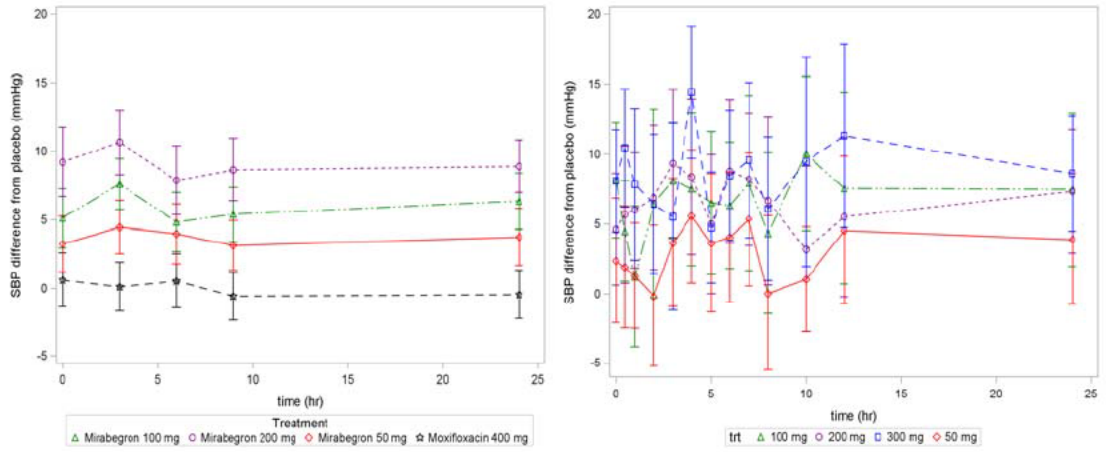
[b]*Concentration-SBP analysis was conducted in Phase 1 Study (178-CL-031)*

[c]*For the purpose of plotting, the data are divided in to 6 equal bins of observed mirabegron concentration. The red cross (x) and the associated error bars represent the mean change in systolic blood pressure (SBP) corresponding to the median concentration for each bin and the corresponding 95% confidence intervals. The dashed green line represents regression mean for the entire data and the purple band is the associated 95% confidence interval.*

The effect of dose on SBP data from Phase 1 studies (077 and 031) shows dose proportional increase in SBP at doses of 50, 100, and 200 mg. Correcting the SBP increase for the placebo effect shows that at a dose of 50 mg there is approximately 4 mmHg increase in SBP during 3 to 6 hours after dosing in healthy subjects (**Figure 2.2.3.1.3**).

Figure 2.2.3.1.3 Changed from Placebo of Systolic Blood Pressure (SBP) After Mirabegron 50, 100, and 200 mg Doses in Healthy Subjects in two Phase 1 Studies

A: TQT Study (178-CL-077) **B: Study 178-CL-031**



The potential reasons for observing different exposure-BP relationship between healthy subjects from Phase 1 studies and OAB patients from Phase 2b and 3 studies include:

- Different in population: Healthy subjects from Phase 1 studies are young and have relatively low BP baseline.
- Different in BP measurement: Self measurement of sitting BP in Phase 3 versus clinic measurements of supine BP in Phase 1 studies.
- Timing of the blood pressure sampling. In Phase 1 studies, relatively more measurements within the inter-dosing interval allowed for assessment of drug effect at peak and trough. In the Phase III studies, vital signs were collected by the subject during the AM (after waking up in the morning before the morning dose) and PM (between 2 PM and 6 PM) in a 5-day vital sign diary using a self-measurement device. This sampling scheme did not allow for the assessment of the peak effects which generally occurred around 3-4 hours coinciding with the peak mirabegron concentrations post-dose.

Based on the Cardio-Renal review, it was noted that categorical changes from baseline was numerically higher percentage of patients at final visit systolic blood pressure (SBP) and diastolic blood pressure (DBP) elevation on 50 mg mirabegron than for tolterodine, a commonly used anticholinergic drug for the treatment of OAB or placebo. When the data from 50 mg dose is compared to placebo, the differences in final visit categorical SBP/DBP elevation rates are less < 2%. The effect of mirabegron on SBP/DBP was similar to those of tolterodine. Also, there was a dose response in SBP/DBP effects between 50 mg and 100 mg mirabegron.

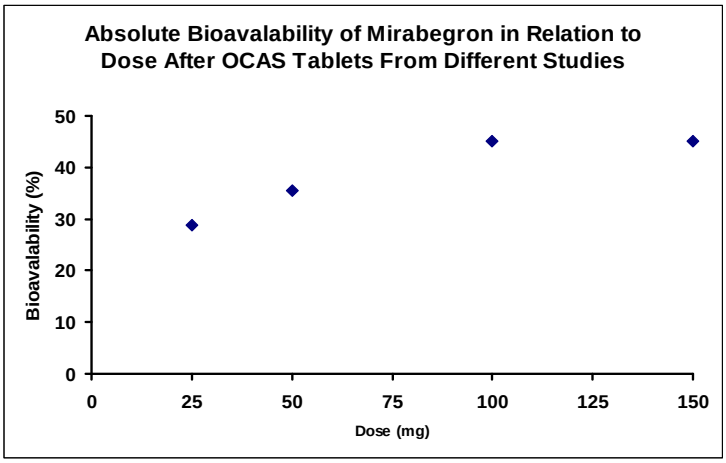
Therefore, the Cardio-Renal team recommends that the sponsor put the target population's characteristics into a Framingham risk model so that they can predict what the likely impact will be on cardiovascular event rates for the observed blood pressure effects (see cardio-renal review dated January 20, 2012). This comment, among others, was conveyed to the sponsor during the T-con held on February 9th, 2012 and other correspondences during the review cycle. Furthermore, this model was discussed in detail at the Advisory Committee meeting held on April 5, 2012 (se meeting transcript and FDA background package at http://www.fda.gov/AdvisoryCommittees/Calendar/ucm291237.htm.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of mirabegron and its metabolites? How do the PK parameters change with time following chronic dosing?

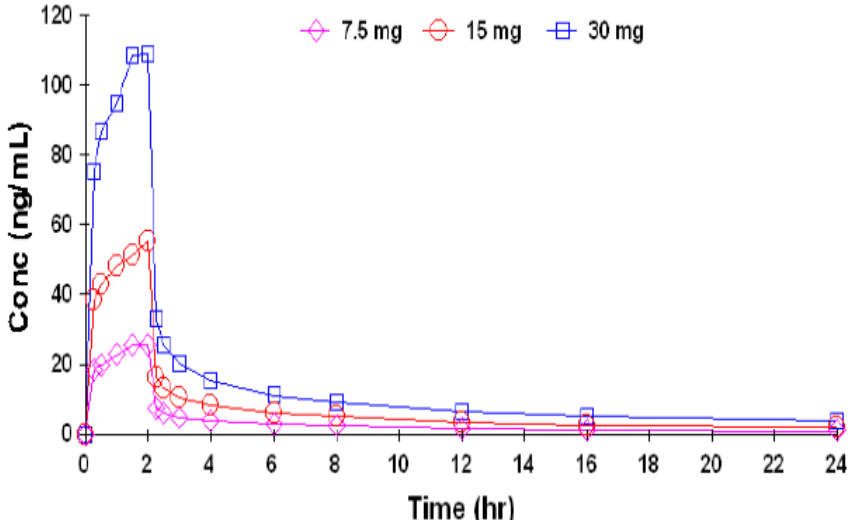
The sponsor conducted several studies following single- and multiple-dose to assess the PK profiles of mirabegron. Initially the sponsor conducted PK studies with IR formulation to assess dose proportionality after a single dose escalation (Study 178-CL-001) and after multiple escalating doses (178-CL-002). Later in the development, dose proportionality studies were conducted with OCAS formulation after single and multiple/repeat dose escalation (Studies 178-CL-031, 066, 034, 076, 072, and 077). The absolute bioavailability of mirabegron is approximately 35% after 50 mg dose, but it appears to be dependent on the dose (**Figure 2.2.4.1**).

Figure 2.2.4.1.7 Mirabegron Compiled Bioavailability and Dose from Several Studies OCAS Tablets



After intravenous (IV) infusion of 7.5, 15, 30 mg, and 50 mg there was no deviation was observed from dose proportionality (**Figures 2.2.4.1.1 and 2.2.4.1.2,** Studies 178-CL-076 and 033). It should also be noted that there was no evidence of deviation from linearity for the dose normalized ratio up to 30 mg. Further, the ratio for females was slightly higher than males. However, the magnitude of difference between females and males after IV infusion appears to be much smaller than that observed after oral administration (see later discussion under effect of gender-sex, **Section 2.3.1.2**).

Figures 2.2.4.1.1: Mean Plasma Concentration-Time Profiles of Mirabegron After IV Infusion to 30 Human Subjects (Study 178-CL-076)



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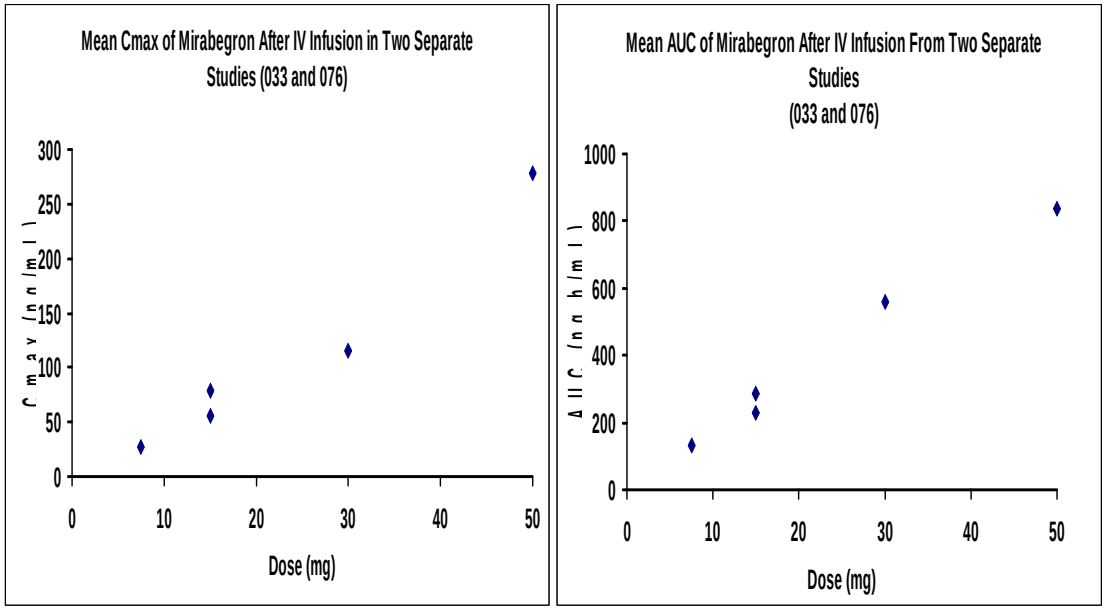
Figures 2.2.4.1.2: Mean Cmax and AUC of Mirabegron After IV Infusion Over 120 Minutes in 30 Human Subjects From Two Studies: Study 178-CL-076 Doses Were 7.5, 15, and 30 mg Study 178-CL-033 Doses Were 15 mg and 50 mg.

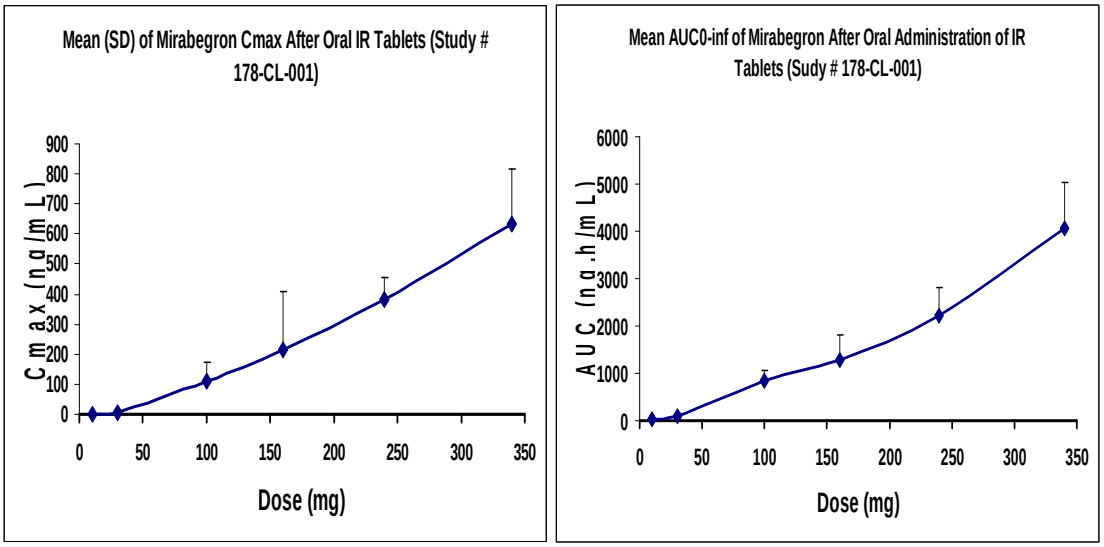
A: Cmax **B: AUC**



Unlike IV administration, the deviation from dose proportionality was more evident after oral administration. For example, following oral administration of 10 to 340 mg single doses of the IR tablet administered in the fasted state, a greater than proportional increase in mean AUC and Cmax was observed (**Figures 2.2.4.1.3, Study 178-CL-001**). Similarly, greater than dose proportional increase was observed after multiple dose administration of 40 mg to 240 mg doses of IR tablets (Study 178-CK-002).

Figure 2.2.4.1.3 Mean (SD) Cmax and AUC of Mirabegron After Oral Administration of IR Tablets (Study 178-CL-001)

A: Cmax **B: AUC**



The same trend was seen in several studies after single doses of 25 mg to 400 mg and repeated administration of 25 mg to 300 mg of OCAS tablets (Studies 178-CL-031, 033, 034, 066, 072, and 077, **Figures 2.2.4.1.4 and 5**).

Figure 2.2.4.1.4 Mean Plasma Concentration-Time Profiles of Mirabegron After Oral Administration of Single Doses of OCAS-M Tables on First Day and Last Day in Young Subjects (Study 178-CL-031)

A: First Day (Day 1) **B: Last Day (Day 14)**

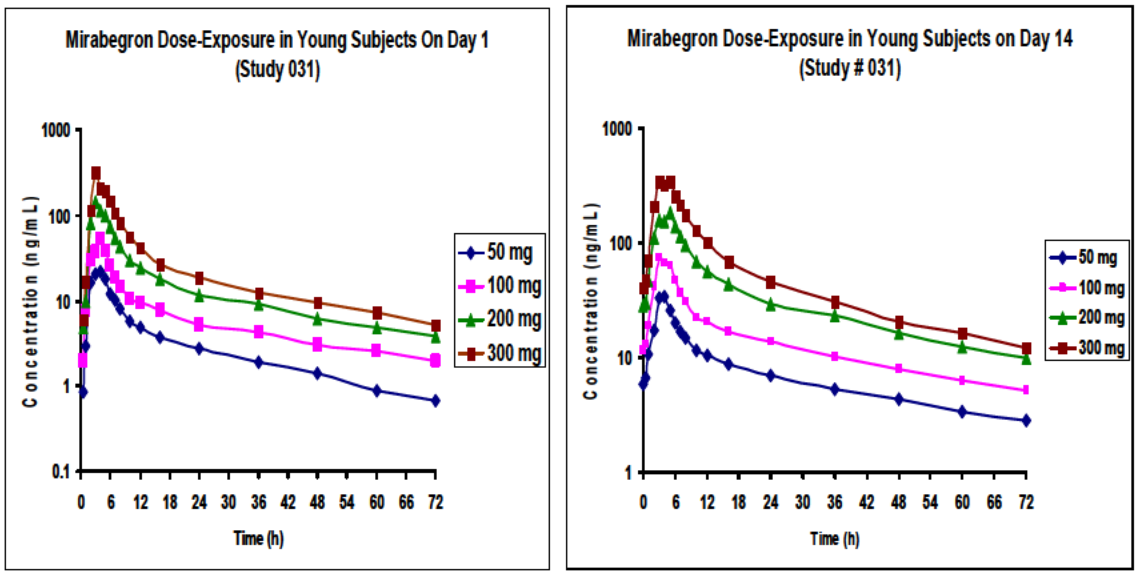
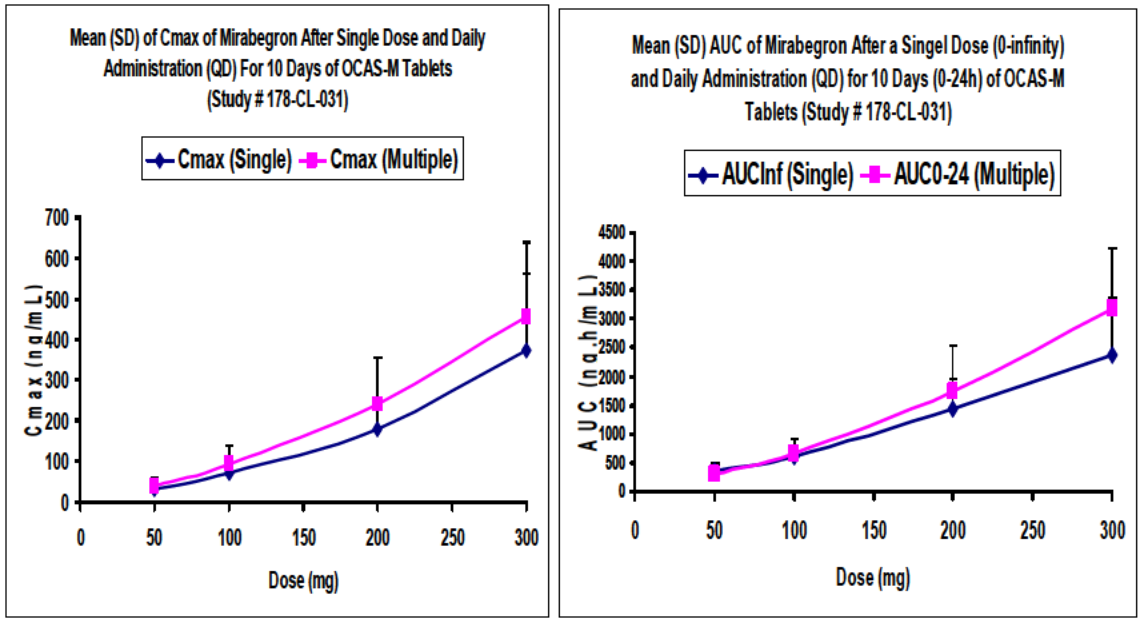


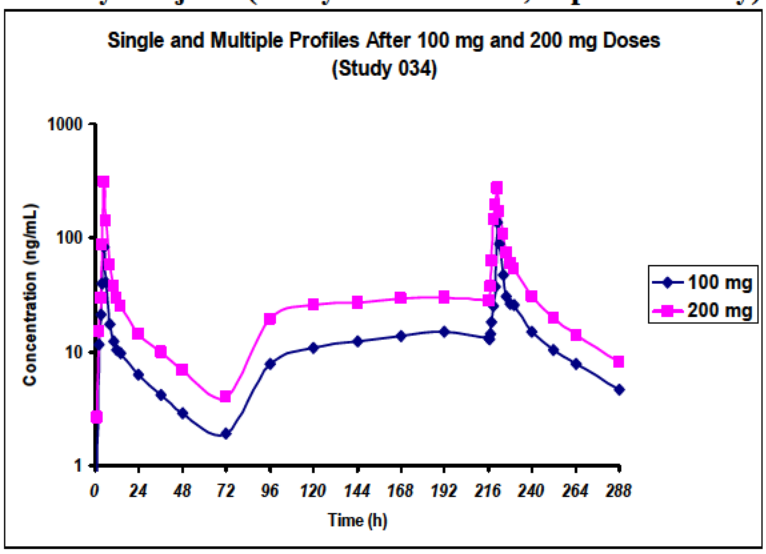
Figure 2.2.4.1.5 Mean (SD) Cmax and AUC of Mirabegron After a Oral Administration of Single and Multiple Doses of OCAS-M Tablets (Study 178-CL-031)

A: Cmax **B: AUC**



In terms of steady state concentration, the data from two studies show that it is achieved within 7 days of once daily dosing (Studies 178-CL-031 and 034, **Figure 2.2.4.1.6).**

Figure 2.2.4.1.6 Mean Plasma Concentration-Time Profiles of Mirabegron After Single and Multiple Doses in Healthy Subjects (Study# 178-CL-034, Japanese Study).



Reviewer's Comments:

Overall, after oral administration, a greater than dose-proportional increase in mirabegron Cmax and AUC was observed with increasing dose above 50 mg dose. These observations are predominantly seen after oral than after IV administration and in particular after OCAS tablets. This finding suggests that the observed non-linearity is not related to capacity limited elimination but due to an increase in bioavailability with increasing oral doses (possibly due to an effect on transporters). As dosing will be capped at 50mg, these findings are not relevant to clinical use.

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

2.3.1.1 Effect of Age:

Age has no clinically relevant impact on mirabegron exposure. A pooled analysis across 15 phase 1 studies was conducted using only the treatment arms where mirabegron OCAS was administered alone and under fasted conditions to healthy subjects (**Table 2.3.1.1.1**).

Table 2.3.1.1.1. Across Studies Pooled Analysis for the Effect of Age on Mirabegron PK After Multiple Doses of 50 mg and 100 mg (Pooled Data From Several Studies)

Dose	Parameter	18-45 years	46-64 years	65-74 years	>75 years
Single Dose					
n		**145**	**18**	**11**	**1**
50 mg	Cmax (±SD) (ng/ml)	33 (35.9)	29.1 (21.8)	32.1 (15.2)	51.5
	AUC (±SD) (ng.h/ml)	340 (237)	314 (165)	308 (79.4)	297
Multiple Dose					
n		**35**	**14**	**19**	**2**
50 mg	Cmax (±SD) (ng/mL)	50.4 (22.3)	58.1 (26.9)	41.7 (19.1)	50.1 (4.24)
100 mg	AUC (±SD) (ng.h/mL)	401 (146)	410 (144)	318 (148)	494 (202)

Reviewer's Comments:

Although the data from this NDA shows no clear trend on the influence of age on any of the PK parameters, population PK analysis showed slight increase (~11%) in mirabegron exposure in subjects with advanced age (Report # 178-PK-015).

2.3.1.2 Effect of Gender:

Overall, it was observed from this NDA that mirabegron Cmax and AUC are approximately 40% to 50% higher, respectively, in females compared with males. However, when the data is normalized for body weight, the difference becomes smaller ranging from 20% to 30% (depending on the study). Therefore, the observed difference in exposure appears to be partially associated with body weight and other unknown factors.

The study 178-CL-072 was conducted in healthy male and female subjects at doses of 25 mg, 50 mg, and 100 mg QD for 7 days (a loading dose as BID on day 1, then QD for 6 days). The data from all three doses were consistent in which the exposure of mirabegron and its metabolites were higher in females than in males.

For the 50 mg dose, the ***overall*** mean Cmax and AUC in young or elderly females were numerically higher than that in the corresponding male subjects, the elderly subjects having a more pronounced difference. Specifically, the observed mean Cmax was 54.4, 58.1 in young males and females and 43.5, and 66.3 in elderly males and females, respectively. For AUC the mean was 413, 471 in young males and females, and 341 and 512 in elderly males and females, respectively. In addition, the half life tended to be longer in females (mean values, 59.0 to 67.9 hr) compared with males (mean values, 56.3 to 60.0 hr).

As described earlier similar results were also obtained in the TQT study 178-CL-077 (**Figure 2.2.3.2**, Section 2.2.3). After multiple doses of 50 mg to 200 mg QD, the observed AUC was

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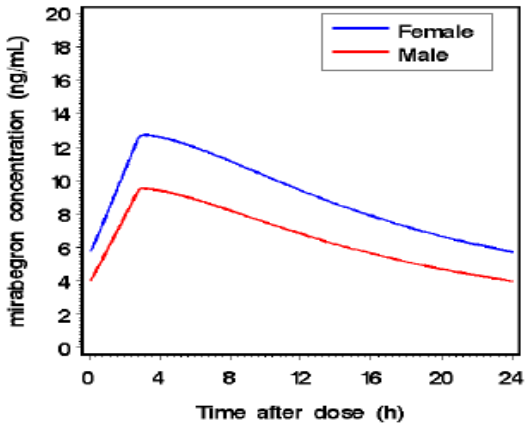
approximately 39% to 51% and the Cmax was approximately 32% to 63% higher in female compared to male volunteers across all doses.

In one of the formulation development study, the sex difference in the PK of mirabegron was shown to be more pronounced after oral administration compared with intravenous administration (Study 178-CL-076). This study was conducted after single IV doses of 7.5 mg, 15 mg or 30 mg of mirabegron. The mean Cmax and AUC were approximately 20% and 27% higher in female subjects compared to male subjects across all dose levels. However, after oral administration of 25 mg, 50 mg or 100 mg of mirabegron, the mean Cmax and AUC were approximately 49% and 64% higher in female subjects compared to male subjects across all dose levels. The absolute bioavailability from this study was 35.0% and 53.0% in females and 24.6% and 40.3% in males at 25 and 100 mg doses, respectively. No differences in bioavailability were observed at the 50 mg dose.

The gender differences in exposure observed in these studies are consistent across studies submitted in this NDA as illustrated from the Pop PK analysis of Phase 2 and 3 data (Report #178-PK-015, **Figure 2.3.1.2.1**). From this analysis, females had a 38% higher AUC than males, although the magnitude of the difference did differ with age and dose as shown above.

Figure 2.3.1.2.1 Influence of Sex on Typical Male and Female Subject's Steady State Plasma Concentration versus Time Profile after Receiving a 50 mg Dose of Mirabegron (Pop PK Analysis, Report #178-PK-015)



Based on the overall drug safety and efficacy shown in Phase III studies in which the majority of subjects enrolled in all these studies were females, no dose adjustment is needed based on gender.

2.3.1.3 Effect of Race:

The influence of race on mirabegron plasma exposure was explored in the TQT study 178-CL-077. This study included a similar number of Caucasians and African American subjects. After multiple doses of 50 mg, 100 mg or 200 mg, there were no notable differences in mean Cmax and AUC between Caucasian subjects and African American subjects. The numbers of subjects in other racial categories were too small for an informative analysis.

The influence of race on the PK of mirabegron was further explored in a pooled analysis across phase 1 studies. In this analysis only healthy subjects receiving mirabegron OCAS alone at single or multiple doses under fasted conditions were included. No consistent trend was seen among all treatments between the subjects classified for race. While numerical differences were seen, these differences did not rise to the level of anticipated clinical significance.

Several single-dose and multiple-dose PK studies and food effect studies with mirabegron were conducted in healthy Japanese subjects (178-CL-034, 066, 064 and 078). The food effect study 078 was of similar design as the food effect study 041 performed in Western (i.e. non-Asian) subjects. This allows a direct comparison of single-dose PK parameters between Japanese and Western subjects (**Table 2.3.1.3.1**). Mean Cmax and AUC values in Japanese subjects were approximately 54% to 177% and 42% to 119% higher, respectively, than those observed in Western subjects after single doses of mirabegron (50 mg and 100 mg) under fasted conditions.

This difference in exposure is largely related to differences in body weight. Weight-normalized values for Cmax were about 14% to 64% higher in Japanese subjects compared to those in Western subjects, whereas mean AUC values were 38% higher at the 50 mg dose and 5% lower at the 100 mg dose. Half life was comparable for the Japanese and Western populations, consistent with the comparable degree to which mirabegron accumulated in plasma after once daily dosing in these subjects.

Similar results were obtained after multiple doses of mirabegron. Mean values for Cmax and AUC in healthy young Japanese participants who received mirabegron 100 or 200 mg for 7 days [Study 178-CL-034] were higher compared with healthy young Western subjects who received mirabegron 50 to 300 mg qd for 10 days [Study 178-CL-031]. Mean Tmax and half life values were similar between the 2 populations.

Further analysis of the data between Japanese and Westerners (North American) can be seen in the Biopharmaceutics **Section 2.5.3** (Effect of Food).

Table 2.3.1.3.1 Comparison of PK Parameters in Male Japanese and Western Subjects after Single-Dose Administration of Mirabegron In Fasted Subjects (Studies 041 and 078)

PK parameter	178-CL-078 (Japanese)		178-CL-041 (Western)	
	50 mg n=18	100 mg n=18	50 mg n=17	100 mg n=15
C_{max} (ng/mL)	28.6 (17.3)	89.6 (57.6)	12.8 (5.08)	66.7 (35.8)
Dose and Weight-adjusted C_{max} (ng/mL/(mg/kg))	35.1 (19.2)	58.5 (37.1)	21.4 (8.0)	51.2 (22.9)
AUC_{inf} (ng·hr/mL)	331 (122)	744 (261)	177 (62.1)	668 (270)
Dose and Weight-adjusted AUC_{inf} (ng·hr/mL/(mg/kg))	407 (135)	485 (168)	296 (103)	514 (161)
$t_{1/2}$ (hr)	39.1 (6.7)	34.0 (4.9)	41.5 (7.9)	38.1 (9.3)

Values of PK parameters are mean (SD).

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Reviewer's Comments:

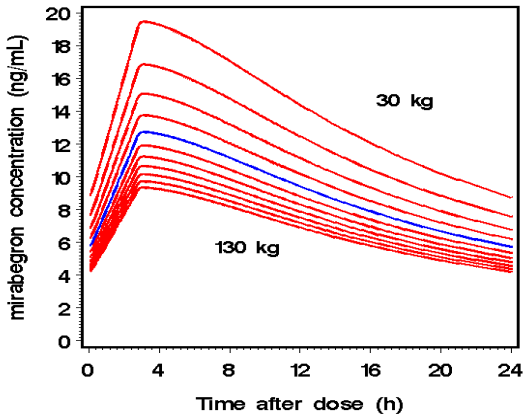
While there is inconsistent trend in exposure between African Americans and Caucasians, there appears to be consistent trend between Japanese and Westerners (North Americans) in which the observed exposure in Japanese is higher than in North Americans. However, in Japan, the approved doses are the same as those proposed for marketing in the United States. Based on this data no dose adjustment is necessarily with regards to race and specifically among African Americans and Caucasians for mirabegron.

2.3.1.4 Effect of Body Weight:

As described in Section 2.3.1.2 above (i.e., effect of gender), the magnitude of the observed mirabegron exposure differences between male and female volunteers and between Japanese and Western volunteers was attenuated with correction for body weight.

The influence of weight (including other body size measures such as body mass index, lean body mass and height) has been investigated across a number of population PK analysis using data from healthy subjects and patients with OAB who received IR or OCAS formulations (178-PK-003, 012, 015). In the population PK analysis of phase 2 and 3 data it was shown that body weight affected mirabegron exposure (Study 015). Relative to a subject with a body weight of 70 kg, AUC was about 53% higher in subjects with body weight of 30 kg and approximately 17% lower in subjects with body weight of 100 kg (**Figure 2.3.1.4.1**).

Figure 2.3.1.4.1 Influence of Weight on a Typical Subject's Steady State Plasma Concentration Versus Time Profile after Receiving a 50 mg Dose of Mirabegron (Pop PK analysis 178-PK-015).



Reviewer's Comments:

Based on the data of gender differences, Japanese study, and Pop PK analysis mirabegron exposure appears to be higher in low body weight and surface area than in average weight of 70 kg subjects. Considering the variability in the data and the data from the clinical trials it appears there is no strong safety signal of concern.

Reference ID: 3129601

2.3.1.5 Effect of Genetic Polymorphism:

The effect of CPY2D6 genetic polymorphism was studied as part of the TQT study following 50, 100, and 200 mg doses of OCAS formulation (Study 178-CL-077). At a dose of 50 mg the mean AUC was approximately 30% lower in ultrarapid metabolizers (UM) and 8% higher in PM compared to EM subjects (**Table 2.3.1.5.1**). A similar pattern was also seen for 100 mg and 200 mg. However the number of UMs and PMs was very small in comparison to EMs. Similar trends were observed Phase 1 studies.

Table 2.3.1.5.1 Mirabegron PK Parameters in CYP2D6 Phenotyped Subjects After Multiple-Dose Administration in TQT Study 178-CL-077

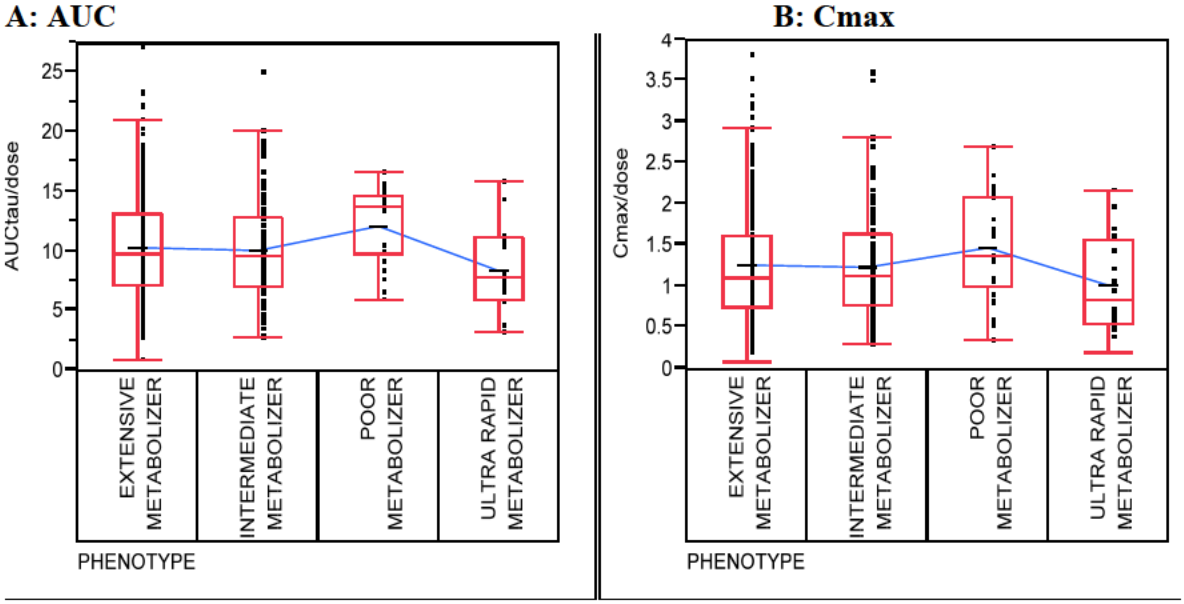
Dose	PK parameter	Predicted CYP2D6 Phenotype				
		UM	EM	IM	PM	INC
50 mg qd	n	5	56	18	3	2
	C_{max} (ng/mL)	30.0 (5.07)	43.0 (26.4)	39.9 (9.87)	43.8 (20.0)	59.0 (17.4)
	AUC_{tau} (ng·hr/mL)	306 (91.7)	438 (167)	417 (89.3)	475 (83.5)	587 (85.1)
	CL/F (L/hr)	182 (77.7)	147 (141)	126 (29.4)	108 (21.0)	86.1 (12.5)
100 mg qd	n	5	43	22	10	2
	C_{max} (ng/mL)	74.4 (48.7)	141 (58.9)	149 (58.1)	147 (63.0)	88.0 (26.3)
	AUC_{tau} (ng·hr/mL)	667 (307)	1170 (375)	1170 (415)	1310 (353)	820 (223)
	CL/F (L/hr)	184 (95.6)	95.4 (37.1)	101 (60.2)	84.0 (33.3)	127 (34.5)
200 mg qd	n	3	62	16	0	2
	C_{max} (ng/mL)	348 (117)	334 (142)	344 (138)	-	274 (37.3)
	AUC_{tau} (ng·hr/mL)	2510 (910)	2760 (949)	2800 (612)	-	1840 (102)
	CL/F (L/hr)	89.5 (40.2)	81.1 (27.2)	75.5 (20.1)	-	109 (6.07)

Values of PK parameters are mean (SD). EM: extensive metabolizer; IM: intermediate metabolizer; INC: inconclusive; PM: poor metabolizer; UM: ultrarapid metabolizer. - : no data.

An additional analysis was conducted by pooling data from three multiple dose studies following administration of OCAS tablets (Studies 178-CL-037, -072, -077). Based on this analysis there was no difference in dose normalized Cmax and AUC based on CYP2D6 phenotype (**Figure 2.3.1.5.1**).

Reference ID: 3129601

Figure 2.3.1.5.1 Variability Chart for Dose-Normalized AUC and Cmax



Reviewer's Comments:

Despite limited clinical data in PM subjects, these results indicate that genetic polymorphism for the CYP2D6 isozyme has little to no impact on mirabegron PK, which is consistent with the multiple elimination pathways for mirabegron (for detail discussion please see **Appendix II**).

2.3.1.6 Effect of Renal Impairment

The sponsor conducted a study to characterize the effect of impaired renal function on the single-dose PK of mirabegron (Study 178-CL-038). Mirabegron was administered at a single dose of 100 mg to subjects with normal renal function (eGFR $\geq$ 90 mL/min/1.73 m2), mild renal impairment (60 to 89 mL/min/1.73 m2), moderate renal impairment (30 to 59 mL/min/1.73 m2), and severe renal impairment (15 to 29 mL/min/1.73 m2). Subjects with normal renal function were approximately comparable to subjects in the renal impairment groups as regards to age, sex and body mass index (BMI). Subjects with end-stage-renal-disease (ESRD) were not studied.

The plasma exposure of mirabegron was slightly higher in subjects with mild renal impairment (Cmax 6% and AUC 31%) and was noticeably increased in moderate (Cmax 23% and AUC 66%) and severely (Cmax 92% and AUC 118%) impaired subjects relative to those in healthy controls (**Figure 2.3.1.6.1 and Table 2.3.1.6.1 and 2.3.1.6.2**).

Figure 2.3.1.6.1 Mean Plasma Concentration–Time Profiles Up to 12 Hours of Mirabegron in Subjects with Varying Degrees of Renal Function Following Single-Dose Administration of 100 mg Mirabegron (Study 178-CL-038)

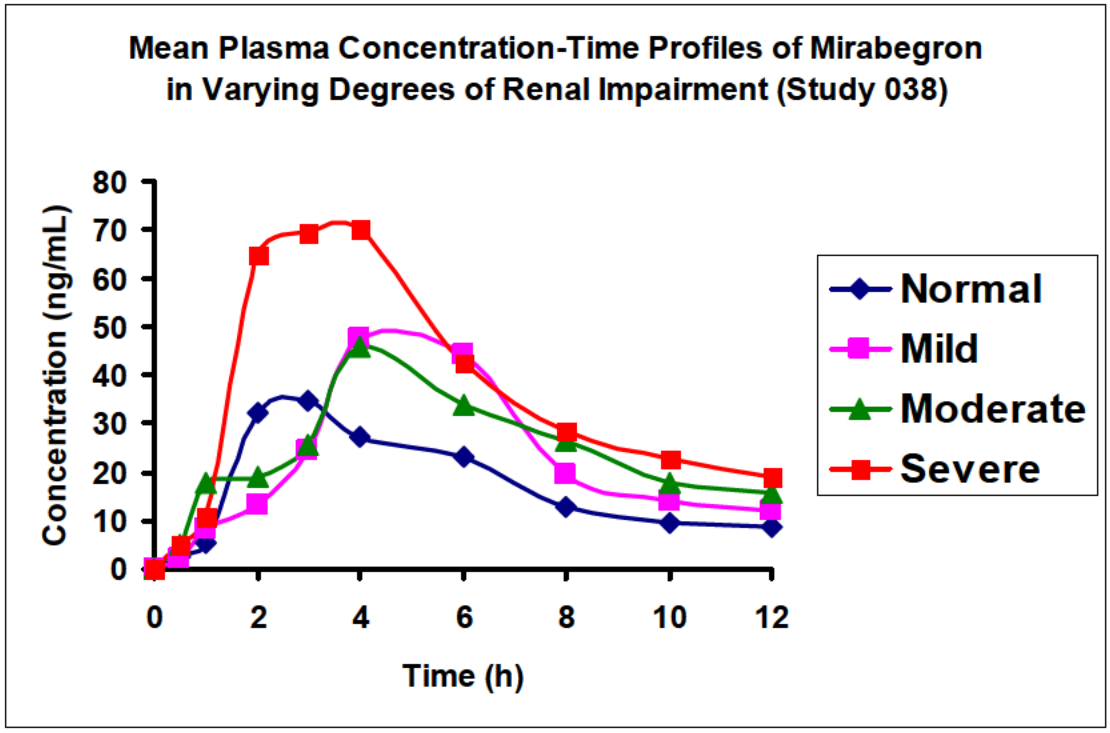


Table 2.3.1.6.1 Mean (SD) Cmax and AUC in Subjects with Varying Degrees of Renal impairment

Parameters	Normal (N=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)
Cmax (ng/mL)	45.2 (± 26.94)	57.0 (± 49.99)	60.8 (± 41.95)	93.8 (± 70.12)
AUC (ng.h/mL)	558 (± 249.3)	771 (± 479.6)	992 (± 512.0)	1239 (± 654.2)

Table 2.3.1.6.2 Statistical Analysis of the Effect of Renal Impairment on PK of Mirabegron

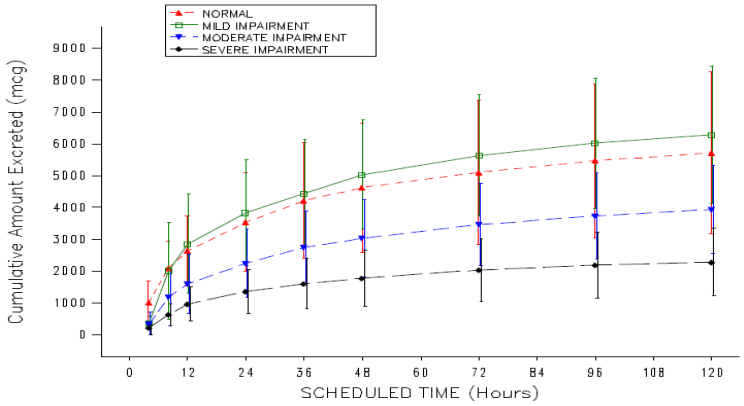
Parameter (unit)	Test Group/ Reference Group	Test Group n	Test Group Geometric Mean †	Reference Group n	Reference Group Geometric Mean †	Ratio of Test Group/Reference Group ‡	90% CI for Ratio ‡
AUC_{inf} (hr·ng/mL)	Mild/Normal	8	654.58	8	500.92	130.68	(77.73, 219.69)
	Moderate/Normal	8	832.84	8	500.92	166.26	(98.90, 279.52)
	Severe/Normal	8	1092.77	8	500.92	218.15	(129.76, 366.75)
C_{max} (ng/mL)	Mild/Normal	8	40.39	8	38.12	105.94	(53.36, 210.33)
	Moderate/Normal	8	46.88	8	38.12	122.96	(61.93, 244.12)
	Severe/Normal	8	73.24	8	38.12	192.12	(96.77, 381.43)
AUC_{last} (hr·ng/mL)	Mild/Normal	8	566.76	8	448.40	126.39	(77.09, 207.23)
	Moderate/Normal	8	723.54	8	448.40	161.36	(98.42, 264.56)
	Severe/Normal	8	944.89	8	448.40	210.72	(128.53, 345.49)
CL/F (L/hr)	Mild/Normal	8	152.77	8	199.63	76.53	(45.52, 128.65)
	Moderate/Normal	8	120.07	8	199.63	60.15	(35.78, 101.12)
	Severe/Normal	8	91.51	8	199.63	45.84	(27.27, 77.06)

Mean mirabegron elimination half life was slightly increased from approximately 43 h in healthy control to 52 h in severe renal impairment patients.

Renal impairment increased exposure of 8 major mirabegron metabolites, M5, M8, M11, M12, M13, M14, M15 and M16. The extent of exposure was more pronounced in those metabolites that appear to be CYP-mediated such as M8 and glucuronidated metabolites such as M14**.** For example, the metabolic ratio (MR) as defined by the metabolite AUC divided by the parent AUC for M8 and M14 was 13% and 62% in severe group compared to 2% and 16% in normal group, respectively.

Urinary excretion of mirabegron appears to follow the same pattern of the plasma data. The mean cumulative amounts of mirabegron excreted into urine over 120 hours post-dose were comparable between the normal and mild groups but was much lower in moderate and severe groups (**Figure 2.3.1.6.2**).

Figure 2.3.1.6.2. Mean (Standard Deviation) Cumulative Amounts of Mirabegron Excreted Into Urine in Subjects with Varying Degrees of Renal Functions



Since mirabegron is extensively metabolized the urinary excretion of unchanged fraction is expected to be small but with similar patterns as that of plasma relative to renal function. Therefore, as expected, the average percentage of unchanged mirabegron excreted in urine was 5.7%, 6.3%, 3.9% and 2.3% of the administered dose in the normal, mild, moderate and severe groups, respectively. From this data it shows that the amount excreted in urine is reduced with the severity of renal function.

Based on these data, the sponsor's proposed label is to reduce the dose to 25 mg in patients with severe renal impairment.

2.3.1.7 Effect of Liver Function (Hepatic Impairment)

The sponsor conducted one study in patients with hepatic impairment that were matched to healthy control subjects with respect of sex, age and body mass index (BMI). Two groups of hepatic impairment were studied: mild (Child-Pugh Class A) and moderate Child-Pugh Class B). No patients with severe hepatic impairment (Child-Pugh Class C) were included in this study. All subjects received a single dose of 100 mg mirabegron (Study # 178-CL-039).

Reference ID: 3129601

Plasma exposure of mirabegron was slightly higher in subjects with mild hepatic impairment, and was increased in moderately impaired subjects relative to those in matching controls (**Figure 2.3.1.7.1**). Mean mirabegron Cmax and AUC were increased by 9% and 19% in mild and 175% and 65% in moderate hepatic impairment relative to subjects with normal hepatic function (**Tables 2.3.1.7.1).** Point estimates and CIs for group comparisons of PK parameters in subjects with varying degrees of hepatic function are presented in **Table 2.3.1.7.2**.

Figure 2.3.1.7.1 Mean Plasma Concentration–Time Profiles of Mirabegron in Control and Hepatic Impairment Subjects Following Administration of a 100 mg Dose (Study 178-CL-039)

A: Mild **B: Moderate**

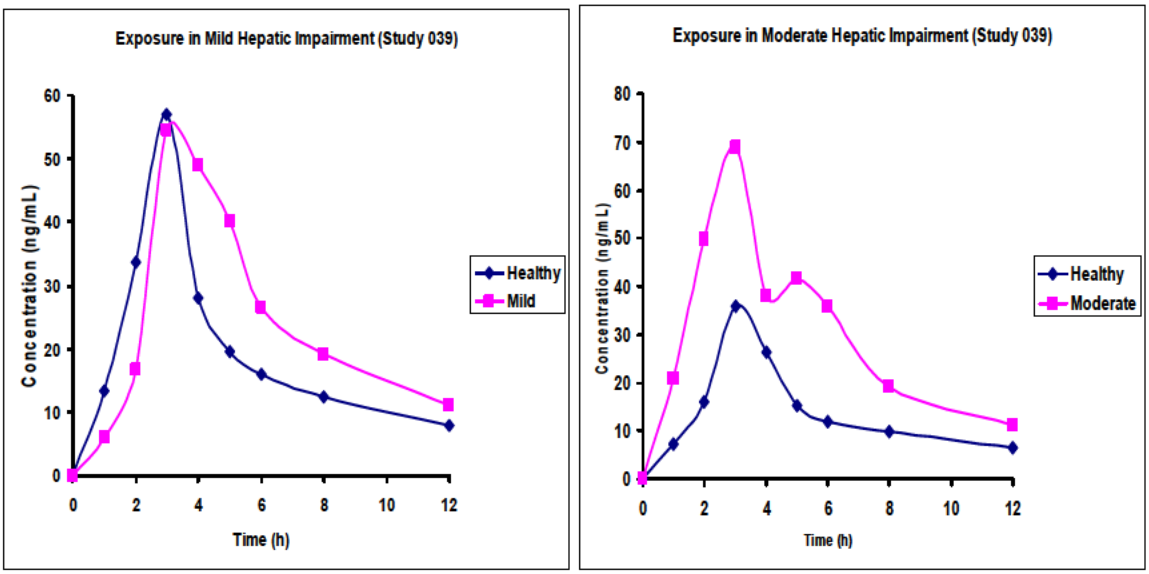


Table 2.3.1.7.1 Mean (SD) Cmax and AUC in Subjects with Varying Degrees of Hepatic Function (Study 178-CL-039)

Parameters	Mild (N=8)	Matching Healthy (n=8)	Moderate (n=8)	Matching Healthy (n=8)
Cmax (ng/mL)	71.9 (± 50.5)	66.9 (± 74.4)	113 (± 68)	41.5 (± 31.8)
AUC (ng h/mL)	770 (± 391)	615 (± 370)	784 (± 363.0)	486 (± 248)

Reference ID: 3129601

Tables 2.3.1.7.2 Summary of PK Statistical Analysis (90% CI) of Mirabegron in Subjects with Varying Degrees of Hepatic Function (Study 178-CL-039)

Hepatic Function		Least Square Means[a]			
		Healthy	Impaired	Ratio (Impaired/Healthy)	90% CI
Mild	Cmax) (ng/mL)	46.6	50.7	1.09	0.42, 2.80
	AUC (ng.h/mL)	550	655	1.19	0.69, 2.05
Moderate	Cmax) (ng/mL)	31.7	87.1	2.75	1.08, 6.98
	AUC (ng.h/mL)	424	699	1.65	0.95, 2.85

[a]**Least Square Means**

The urinary excretion of unchanged mirabegron slightly increased in patients with hepatic impairment compared to control. The percentage of unchanged mirabegron excreted in urine was about 6.8% of the administered dose in controls, 6.3% in mild, and 9.3% in moderate hepatic impairment. The difference between the normal and moderately impaired hepatic function groups was statistically significant. In addition, plasma concentrations of the eight known metabolites were increased in both mild and moderate hepatic impairment, but as they are considered to be inactive.

Reviewer's Comments:

Given its metabolic profile, it would be expected that the exposure of mirabegron would be increased in hepatic impairment patients. Based on these data, the sponsor's proposed recommendation is to reduce the dose to 25 mg once daily in patients with moderate hepatic impairment. However, mirabegron is **not recommended** in patients with severe hepatic impairment (Child-Pugh Class C) as it has not been studied in this population.

2.4 Extrinsic factors

2.4.1 What extrinsic factors such as drugs influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The sponsor conducted several studies to characterize the effect of other drugs and food on mirabegron PK profiles and also the effect of mirabegron on the PK of other drugs.

Ketoconazole, a potent CYP3A and P-gp inhibitor, causes increase in mirabegron exposure by approximately 45% for Cmax and 80% for AUC (**Table 2.4.1.1,** Study 178-CL-036). However, the co-administration of potent inducers of CYP3A and P-gp such as rifampin, the exposure for

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mirabegron is decreased by approximately 35% for Cmax and 44% for AUC (**Table 2.4.1.1**, Study 178-CL-070).

Table 2.4.1.1 Effect of Co-administered Drugs on the PK of mirabegron

Coadministered drug and dose	n	Mirabegron dose	Ratio (%) with/without Coadministered drug (90% CI)	
			C_{max}	AUC
CYP3A and/or P-gp Inhibitors				
Ketoconazole 400 mg qd	23	100 mg sd	145 (123, 172)	181 (163, 201)
CYP3A and/or P-gp Inducers				
Rifampin 600 mg qd	24	100 mg sd	65 (50, 86)	56 (49, 65)
Other				
Metformin 500 mg bid	12	160 mg IR qd	79 (68, 93)	79 (70, 90)
Solifenacin 10 mg qd	20	100 mg sd	99 (78, 126)	115 (101, 130)
Tamsulosin 0.4 mg qd	24	100 mg sd	85 (71, 103)	84 (74, 95)

The other significant drug-drug interaction studies in this NDA demonstrating mirabegron is a moderate inhibitor of CYP2D6. In two studies, mirabegron increased the exposure of CYP2D6 substrates such as metoprolol and desipramine. For metoprolol, the exposure was increased by 90% for Cmax and 229% for AUC (Study 178-CL-005) and for desipramine the Cmax was increased by 79% and AUC by 241% (Study 178-CL-058).

Food appears to decrease mirabegron Cmax by 45% to 75% and AUC by 17% to 51%. However, this effect is dependent on the fat contents of food (see Section 2.5, Biopharmaceutics for detail discussion)

The most relevant DDI studies are individually summarized below in this section under two major sub-sections:
A: Effect of other drugs on mirabegron PK
B: Effect of mirabegron on the PK of other drugs

2.4.1.1 What is the Effect of Other Drugs on Mirabegron?

2.4.1.1.1 What is the Effect of CYP3A and P-gp Inhibitors on Mirabegron PK?

Study 178-CL-036 was conducted to evaluate the effect of ketoconazole as a potent CYP3A and P-gp inhibitor on the PK of mirabegron. In this study, ketoconazole was administered daily at a dose of 400 mg for 9 days prior to the administration of a single dose of 100 mg of mirabegron. The coadministration of ketoconazole resulted in higher mirabegron plasma exposure (45% higher Cmax and 81% higher AUC) than when given alone (**Table 2.4.1.1.1.1 and Figure 2.4.1.1.1.1**).

Reference ID: 3129601

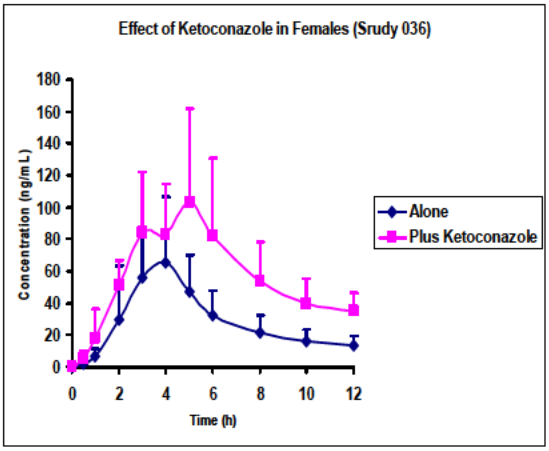
Table 2.4.1.1.1.1 Mean Cmax and AUC of Mirabegron With and Without Ketoconazole (Study 178-CL-036).

Parameter Gender	LSM† YM178 Alone	LSM† YM178 + Keto	YM178 + Keto/ YM178 Alone‡	90% Confidence Interval‡
AUC_{inf}				
Overall (n = 23)	679.7	1229.6	180.9	[162.6, 201.2]
Females (n = 11)	827.8	1655.0	199.9	[175.2, 228.1]
Males (n = 12)	567.3	936.4	165.0	[139.6, 195.1]
C_{max}				
Overall (n = 23)	57.7	83.7	145.0	[122.5, 171.5]
Females (n = 11)	69.8	115.5	165.5	[128.5, 213.2]
Males (n = 12)	48.5	62.3	128.4	[101.0, 163.1]

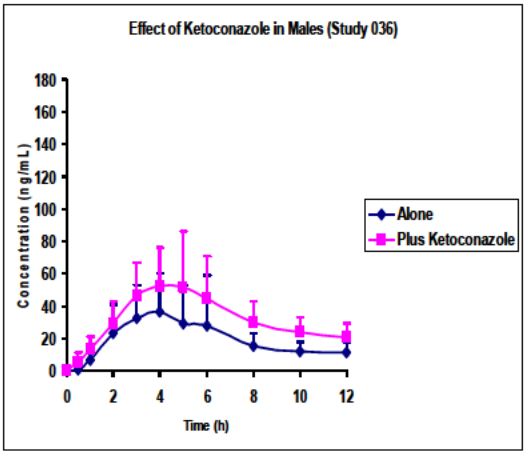
†Least Square Means

Figure 2.4.1.1.1.1 Mean (± SE) Mirabegron Plasma Concentration-Time Profiles When Administered Alone in Period 1 (P1) and When Administered After 9 Days of 400 mg Daily Administration of Ketoconazole in Period 2 (P2)

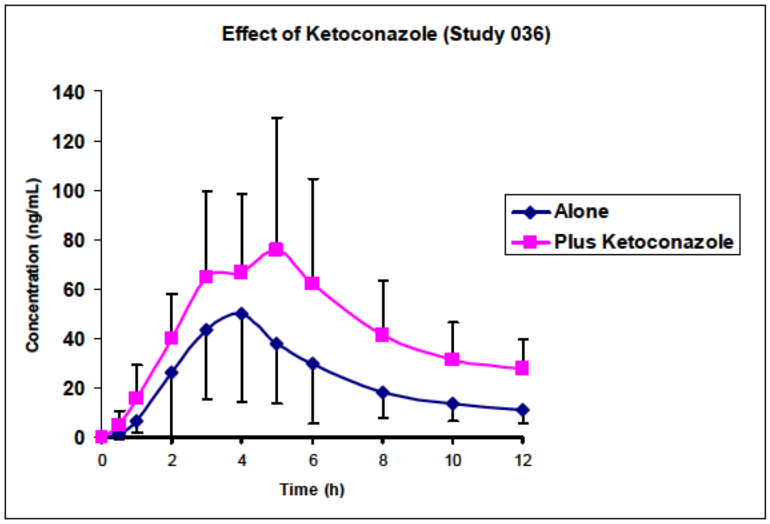
A: Females



B: Males



C: All Subjects



As consistently observed in this NDA, female subjects exhibited higher plasma concentrations compared with male subjects. Mirabegron Cmax and AUC in females in the presence of ketoconazole were increased by 66% and 100% compared to 28% and 65% in males, respectively.

Reviewer's Comments:

The study design was optimal to evaluate the effect of ketoconazole on the PK of mirabegron. From this study, it does not appear that ketoconazole show dramatic effect on the PK of mirabegron.

Considering the safety margins of mirabegron as demonstrated in several clinical trials and TQT study, no dose adjustment is needed when mirabegron is co-administered with ketoconazole or perhaps other CYP3A inhibitors

2.4.1.1.2 What is the Effect of CYP3A and P-gp Inducers on Mirabegron PK?

The sponsor conducted a study to assess the effect of repeat doses of the potent enzyme and transporter inducer rifampin on the PK of mirabegron and its metabolites. In this study, rifampin was administered daily at a dose of 600 mg for 11 days (Days 5 to 15). Mirabegron was administered on Day 1 (alone) and on Day 12 (with rifampin) as a single dose of 100 mg each time (Study 178-CL-070).

Rifampin decreased mirabegron Cmax by approximately 35% and AUC by 44% (**Figures 2.4.1.1.2.1 and Tables 2.2.1.1.2.1**). In addition, the urinary cumulative excretion of mirabegron was also reduced on Day 12 compared to Day 1 (**Figures 2.4.1.1.2.2).**

The mechanism of this interaction appears to be associated with decrease in the bioavailability of mirabegron when coadministered with rifampin. It should also be noted that due to the enzyme induction, the exposure to mirabegron metabolites was markedly increased and in particular CYP-mediated metabolite M8. Furthermore, rifampin appears to induce the glucuronidation pathways. The exposure of some of mirabegron glucuronides such as M11, M13, and M14 were increased. Other mechanisms may also be involved such as induction of intestinal P-gp efflux as well as some effect on the renal secretion of the metabolites.

Reference ID: 3129601

Figures 2.4.1.1.2.1 Mean Plasma Concentration-Time Profiles of Mirabegron on When administered Alone (Day 1) and after 11 Days of Daily Administration of Rifampin (Day 12) (Study 178-CL-070)

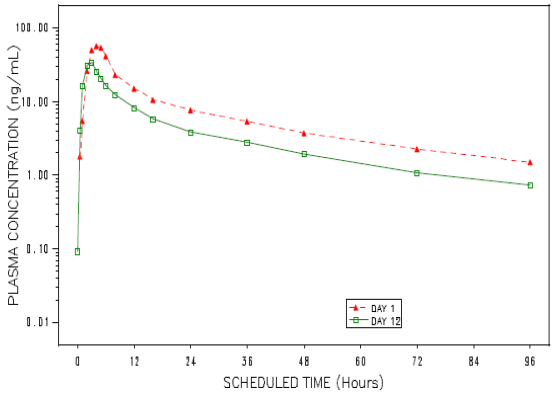
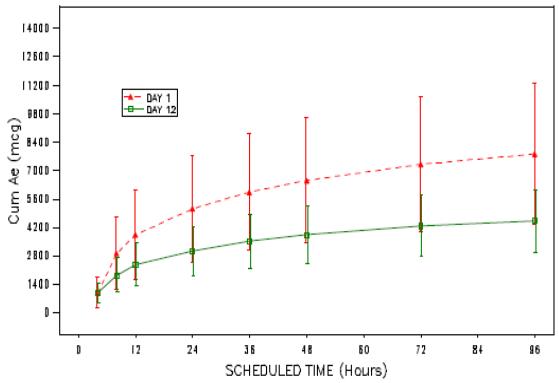


Table 2.4.1.1.1 Statistical Data for Cmax and AUC of Mirabegron When Administered Alone (Day 1) and after 11 Days of Daily Administration of Rifampin (Day 12) (Study 178-CL-070)

Pharmacokinetic Parameter (unit)	Mirabegron Alone		Mirabegron + Rifampin		Ratio‡ (Mirabegron + Rifampin/ Mirabegron Alone)	90% CI of Ratio‡
	n	LS Mean†	n	LS Mean†		
AUC_{inf} (hr·ng/mL)	22	711.10	24	401.42	56.45	(49.07, 64.94)
C_{max} (ng/mL)	24	61.02	24	39.85	65.31	(49.82, 85.62)

Figures 2.4.1.1.2.2 Mean (± SD) Cumulative Amounts of Mirabegron Excreted in Urine When Administered Alone (Day 1) and after 11 Days of Daily Administration of Rifampin (Day 12) (Study 178-CL-070)



Reviewer's Comments:

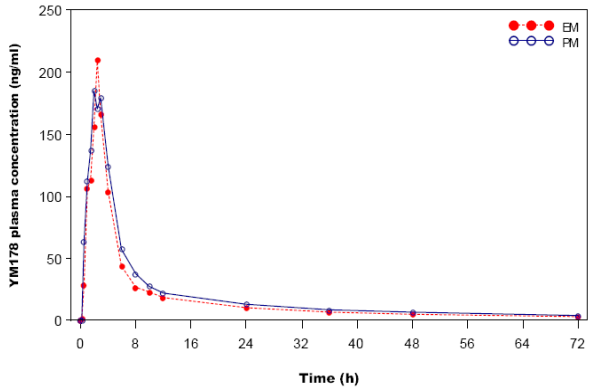
Although there was a reduction in mirabegron exposure which is associated with increase in mirabegron metabolites, no dose adjustment is necessary. Since the metabolites are known to be inactive (see PharmTox review), the increase in their exposure may not be of safety concern at this time.

Reference ID: 3129601

2.4.1.1.3 What is the Effect of CYP2D6 Inhibitors on Mirabegron PK?

The sponsor did not conduct a study to evaluate the effect of potent CYP2D6 inhibitors on the PK of mirabegron., the rationale being that CYP2D6 PMs exhibited similar or only slightly higher mirabegron exposure compared to EMs after a single oral dose of 160 mg mirabegron (**Figure 2.4.1.1.3.1**, Study 178-CL-005). This study will be discussed in more details later in the subsequent Section under "Effect of Mirabegron on Other Drugs-CYP2D6 Substrates/metoprolol).

Figure 2.4.1.1.3.1 Mean Plasma Concentration-Time Profiles of Mirabegron in PMs and EMs of CYP2D6 Following a Single 160 mg Dose of Mirabegron (Study 178-CL-005)



Reviewer's Comments:

The data from this study appears to be convincing that the exposure in CYP2D6 PMs is similar to that of the EMs. This may mimic the inhibition potential of potent CYP2D6 inhibitors.

2.4.1.1.4 What is the Effect of Renally Secreted Drugs on Mirabegron PK?

Interaction with Metformin (Study 178-CL-006):

Like mirabegron, metformin is a renally secreted cation and substrate of OCTs. Therefore, the PK of mirabegron may be altered when co-administered with metformin.
Therefore, study was conducted in which metformin was co-administered with mirabegron for 11 days at a 500 mg BID and 160 mg daily dose of mirabegron IR tablets (Study 178-CL-006). The study was placebo controlled.

Mirabegron exposure was only reduced by approximately 20% when co-administered with metformin. It should also be noted that the PK profile of meformin was not affected by the presence of mirabegron.

Reviewer's Comments:

The difference is about 20% reduction in mirabegron Cmax and AUC when co- administered with meformin. This difference may not be of clinical significance. Therefore, no dose adjustment is necessary when mirabegron is co-administered with metformin at the most commonly used dose of 500 mg.

2.4.1.1.5 Interaction with Other Urologic Drugs

Interaction with Solifenacin:

Solifenacin is currently marketed by the same sponsor (Astellas Pharma) and was approved in November 19, 2004 for the treatment of over active bladder (NDA 021518). Study 178-CL-069 was conducted with two main objects:

- To evaluate the effect of steady state concentrations of mirabegron on the single dose PK of solifenacin.
- To evaluate the effect of steady state concentrations of solifenacin on the single dose PK of mirabegron.

The rationales for this study are of two folds:

1. The sponsor is considering development of combination product of solifenacin and mirabegron in the future.
2. Mechanistically, solifenacin is a muscarinic receptor antagonist. Therefore, it is anticipated to inhibits GI motor activity and prolong gastric residence and transit time. From these actions, solifenacin like other muscarnic antagonists, may increase the bioavailability of mirabegron. Furthermore, solifenacin is predominantly metabolized by CYP3A4. This will also assess the competitive interaction with CYP3A4 mediated metabolism with both drugs.

Study Design:

Arm 1: Subjects received a single dose of 10 mg solifenacin on Day 1 and were discharged on Day 9 with washout period until Day 15. Mirabegron was administered daily at a dose of 100 mg as a film coated tablet for 9 consecutive days (Day 15 to Day 23). On Day 9^{th} (Day 23) a single dose of 10 mg solifenacin was administered together with 100 mg daily dose of mirabegron until Day 38.

Arm 2: Subjects received a single dose of 100 mg mirabegron as a film coated tablet on Day 1 with a washout period of 6 days. Solifenacin was administered at a daily dose of 20 mg for 10 consecutive days (Day 7 to Day 16). On the 10th day of solifenacin dosing (Day 16) subjects received a single dose of 100 mg as a film coated tablet of mirabegron together with solifenacin. Solifenacin dosing continued until Day 20^{th}.

The plasma concentration-time profiles and the PK parameters of mirabegron were almost similar when administered alone or in combination with solifenacin. The AUC of mirabegron was increased by 15% when administered with solifenacin. It should be noted there was minimal effect of mirabegron on solifenacin PK as the Cmax and AUC increased by approximately 23% and 26%, respectively.

Reference ID: 3129601

Reviewer's Comments:

From this study, it can be concluded that no dose adjustment is necessary for both drugs when concomitantly administered.

Interaction with Tamsulosin:

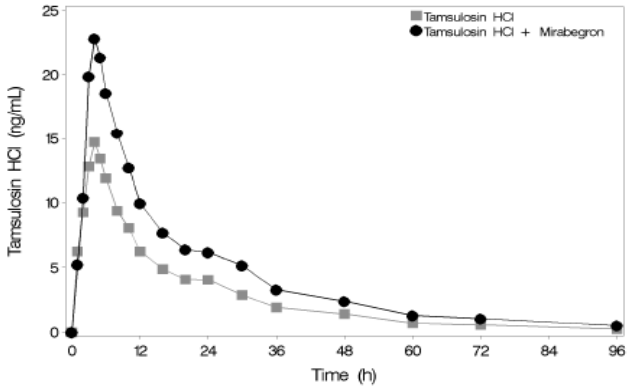
Tamsulosin is an alpha-1 adrenoceptor antagonist for the treatment of benign prostatic hyperplasia (BPH). The rationale for this study is that tamsulosin is eliminated by CYP2D6 and mirabegron is a moderate inhibitor of CYP2D6.

The sponsor conducted a study to investigate the cardiovascular effect and the PK of mirabegron and tamsulosin when coadministred together (Study 178-CL-080). The study was conducted in 48 healthy males as two arms (n=24 in each arm) as follows:

Arm 1: Single doses of tamsulosin were given alone and after 9 days of dosing with 100 mg doses of mirabegron.
Arm 2: Single doses of mirabegron were given alone and after 5 days of dosing with tamsulosin 0.4 mg doses.

On the day of the combination dose, tamsulosin and mirabegron were administered together. From this study there was no effect of tamsulosin on the plasma concentration-time profiles of mirabegron or its PK Parameters. In terms of effect of mirabegron on tamsulosin PK, there was about 1.6 fold increase in exposure (Cmax and AUC) of tamsulosin (**Figure 2.4.1.1.5.1)**.

Figure 2.4.1.1.5.1. Mean Plasma Concentration Time Profiles of Tamsulosin Single Dose and Combination Dosing with Mirabegron – Treatment Arm 1 (Study 178-CL-080)



Reviewer's Comments:

From this study the effect of tamsulosin on mirabegron PK was minimal as the Cmax and AUC decreased by approximately 15%. However, mirabegron increased the exposure of tamsulosin by approximately 1.6 fold. Overall, there is no need for dose adjustment when mirabegron and tamsulosin are administered together.

Reference ID: 3129601

2.4.1.2 What is the Effect of Mirabegron on Other Drugs?

Based on *in vitro* DDI studies and the potential for predicting *in vivo* drug interaction, several studies were conducted to evaluate the effect of mirabegron on other drugs that are likely to be co-administered with mirabegron. These studies are briefly described below:

2.4.1.2.1 Studies with CYP2D6 Substrates:

Two studies were conducted using two known CYP2D6 substrates: metoprolol (Study 178-CL-005) and desipramine (Study 178-CL-058).

Metoprolol (Study 178-CL-005):

As described in the previous Section, this study was conducted into two parts: one part to compare the PK of mirabegron in CYP2D6 PM and EM subjects and the second part was to evaluate the effect of multiple doses of mirabegron on the PK/metabolism of metoprolol as a model substrate for CYP2D6. The focus of this Section is on the second part.

This was a cross-over design, in 12 healthy male subjects genotyped and phenotyped as EM for CYP2D6. Each subject received a single 100 mg dose of metoprolol tartrate as a model substrate on the first day of dosing (Day 1). After a 1-day washout mirabegron 160 mg IR tablet was given alone and once a day for 4 days (Days 3-6) and in combination with metoprolol tartrate 100 mg for 1 day (Day 7). The PK profile of metoprolol tartrate was assessed on the first day and on the last day of dosing. Plasma concentrations of mirabegron were measured on the last day of monotherapy and during the combination treatment of mirabegron with metoprolol tartrate.

From this study there was a marked increase in the plasma concentration-time profiles of metoprolol when coadministered with mirabegron (**Figure 2.4.1.2.1**). The mean Cmax and AUC of metoprolol were increased by 90% and 229% respectively in the presence of mirabegron (**Tables 2.4.1.2.1 and 2.4.1.2.2).**

Figure 2.4.1.2.1 Mean metoprolol and α-hydroxymetoprolol plasma concentration-Time Profiles in the Absence and Presence of Mirabegron (Study 178-CL-005)

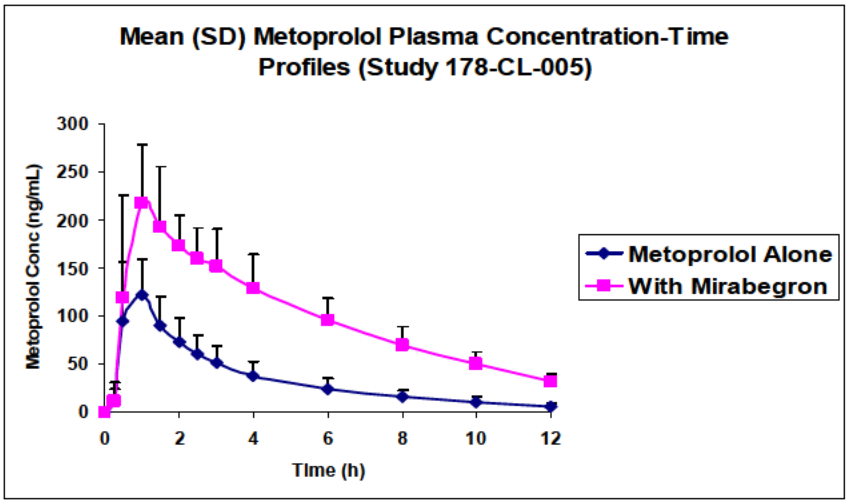


Table 2.4.1.2.1 Summary of PK parameters of metoprolol in the absence and presence of Mirabegron (Study 178-CL-005)

Treatment	Statistic	t_{max}[1] (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	$AUC_{0\text{-}inf}$ (ng.h/ml)	$t_{1/2}$ (h)	CL/F (l/h)	V_z/F (l)
Metoprolol	Mean	0.79	132	408	439	2.96	200	844
	(SD, CV)	(0.26)	(41, 31%)	(147, 36%)	(153, 35%)	(0.35, 12%)	(70, 35%)	(288, 34%)
	Range	0.5 – 1.0	64 – 180	212 – 606	240 – 657	2.3 – 3.5	119 – 325	485 – 1271
	Median	1.0	155	377	402	2.93	195	821
Metoprolol and YM178	Mean	1.25	247	1242	1389	4.11	58.6	346
	(SD, CV)	(0.69)	(67, 27%)	(317, 26%)	(286, 21%)	(0.24, 6%)	(13, 22%)	(72, 21%)
	Range	0.5 – 3.0	133 – 352	821 – 1809	986 – 1845	3.6 – 4.4	42 – 79	250 – 470
	Median	1.0	226	1220	1399	4.17	55.9	321

1. For t_{max} CV was not calculated.

Table 2.4.1.2.2. Statistical Analysis

Analysis Population	Substance	PK parameter	Ratio with/without YM178			Coefficient of variation (%)
			Point estimate	90% Confidence interval		
				Lower	Upper	
PPS	Metoprolol	$AUC_{0\text{-}inf}$	3.285	2.699	3.998	27.3
PPS	Metoprolol	C_{max}	1.897	1.543	2.332	28.7

Reviewer's Comments:

This study confirms the *in vitro* findings that mirabegron is a moderate inhibitor of CYP2D6. The data demonstrates that mirabegron reduces the clearance of metoprolol by inhibition of CYP2D6 and increases its bioavailability by reducing the first-pass effect. Based on the data from this study, metoprolol dose should be adjusted and/or titrated when co-administered with mirabegron.

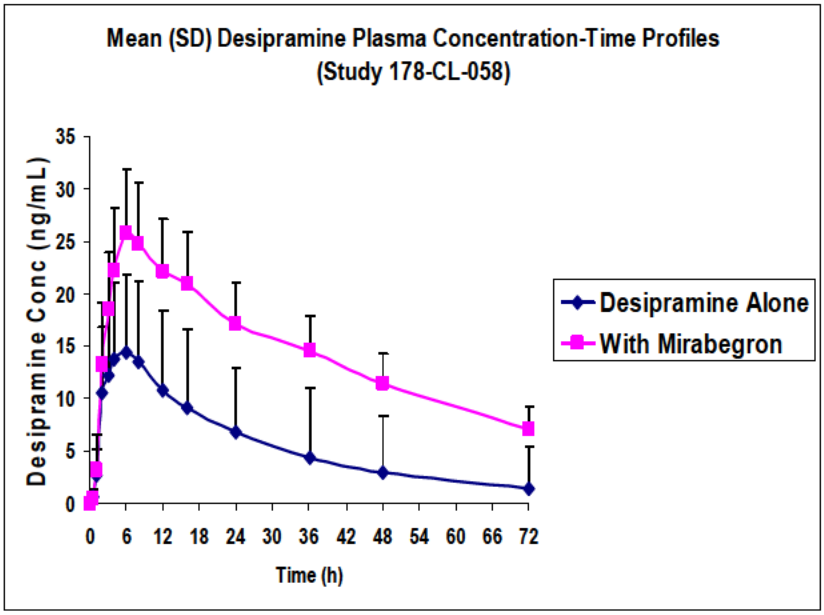
Desipramine (Study 178-CL-058):

This study was a cross-over design with two periods. In period 1, subjects received a single oral dose of 50 mg desipramine on Day 1. From Day 5 up to and including Day 23, subjects received daily oral doses of 100 mg mirabegron. A single dose of
50 mg desipramine was given in combination with mirabegron on Day 18 (13 days after the first dose of mirabegron). In period 2 (after 13 days washout), subjects received a single oral dose of 50 mg desipramine on Day 38.

When coadministerd with mirabegron, there was a marked increase in the plasma concentration-time profiles of desipramine (**Figure 2.4.1.2.2).** The mean Cmax and AUC of desipramine were increased by 79% and 241%, respectively.

Reference ID: 3129601

Figure 2.4.1.2.2 Mean Plasma Desipramine Concentration-Time Profiles Following Single Dose Administration of 50 mg Desipramine on Days 1, 18 and 38 (Study 178-CL-058)



Reviewer's Comments:

As discussed above in the case of metoprolol, the data for desipramine is additional confirmatory evidence that mirabegron is a CYP2D6 inhibitor. In this case, the dose of desipramine also may need to be adjusted or titrated.

Overall, based on these data from the two studies, caution should be advised when mirabegron is coadministered with metoprolol and desipramine or with CY2D6 substrates, especially those drugs that are known to exhibits a narrow therapeutic index.

It should be noted that in the sponsor's proposed label of the highlight section states the following:

"Caution is advised if mirabegron is co-administered with medication significantly metabolized by CYP2D6 with a narrow therapeutic index (e.g., thioridazine, flecainide, propafenone"

In a tabulated section of the label, the sponsor's recommendation is "caution" for both desipramine and metoprolol.

2.4.1.2.2 Studies with CYP3A4 Substrates:

The potential of mirabegron to inhibit CYP3A *in vivo* was examined with the CYP3A4 substrates ethinyl estradiol (EE) and levonorgestrel (LNG), components of combined oral contraceptive (COC), and solifenacin a muscarinic receptor antagonist (see earlier Section on the effect of other urologic drugs on mirabegron PK).

Effect of Mirabegron on Oral Contraceptives (Study 178CL-068):

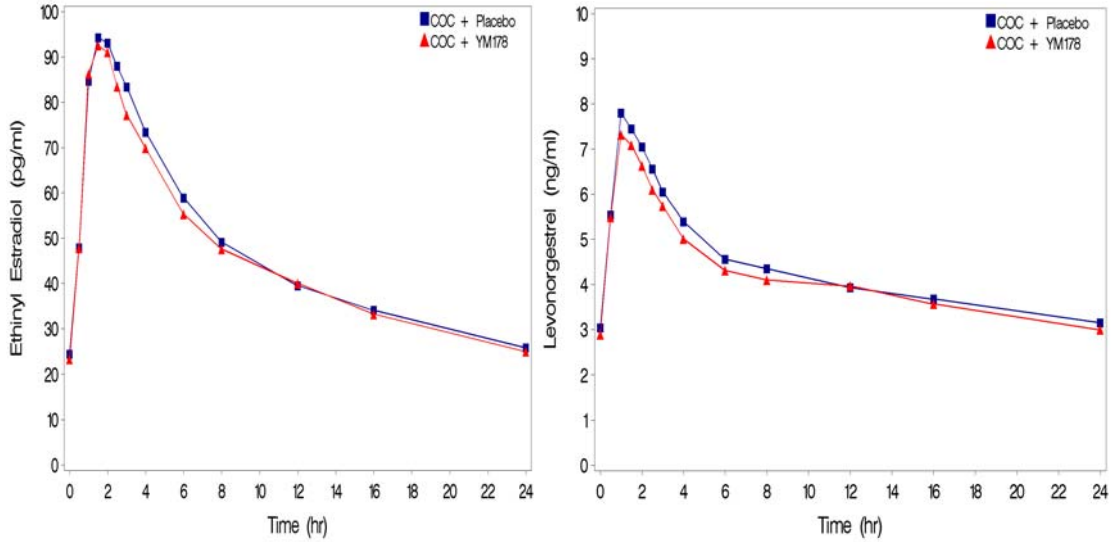
The objective of this study was to determine the effect of multiple doses of 100 mg mirabegron on the PK of EE and LNG containing COC.

The study was a double-blind cross-over design. All subjects received a study COC (Minidril®, not US approved) containing 30 mcg EE and 150 mcg LNG. Subjects started their study COC on Day 1 and continued for 21 days in the first study period. After 7 days (without a COC) to allow for break-through bleeding, they re-started the COC for 21 days in the second study period. In each study period, starting on the 12th day of receipt of the COC, subjects received either mirabegron (100 mg once daily) or matching placebo, for 10 days.

The co-administration of mirabegron had no effect on the plasma concentration-time profiles or the PK parameters of EE and LNG on Day 21 (**Figures 2.4.1.2.1).** The ratio of least square means for Cmax and AUC values with and without mirabegron were 0.958 and 0.961, respectively, for EE, and 0.938 and 0.955, respectively, for LNG. The 90% confidence intervals of the treatment ratios were contained entirely within the predefined equivalence limits of 0.80-1.25 (**Table 2.4.1.2.2).**

Figure 2.4.1.2.1 Mean Steady-State Plasma Concentration-Time Profiles for EE and LNG Following Administration of COC Alone or in Combination with Mirabegron 100 mg QD (Study 178-CL-068)

A: EE **B: LNG**



Reference ID: 3129601

Table 2.4.1.2.2 Statistical Analysis of the Effect of Mirabegron 100 mg Administered QD on PK of EE and LNG on Day 21 (Study 178-CL-068)

Hormone	Parameter	Least Square Means: COC with Placebo (n=23)	Least Square Means: COC with Mirabegron (n=24)	Ratio with/without Mirabegron	90% Confidence Interval
EE	C_{max} (pg/mL)	95.5	91.5	0.958	0.874-1.050
	AUC_{tau} (pg·hr/mL)	1060	1019	0.961	0.886-1.043
LNG	C_{max} (ng/mL)	7.99	7.49	0.938	0.862-1.021
	AUC_{tau} (ng·hr/mL)	98.5	94.0	0.955	0.883-1.032

Reviewer's Comments:

Based on this study mirabegron is not expected to impair hormonal contraceptive efficacy of a combination oral contraceptive containing EE and LNG. However, the data may not be extrapolated to other COC that contains other than EE and LNG. Overall, from this study it can be anticipated that mirabegron may have minimal effect on CYP3A4 substrates.

Effect of Mirabegron on Solifenacin (Study 178CL-069):

This study was described early in the section related to the effect of mirabegron on the urologic drugs. Therefore, the study design will not be repeated here. Based on this study the plasma concentration-time profiles of solifenacin and the PK parameters were minimally affected by the co-administration of mirabegron (**Figure 2.4.1.2.2 and Table 2.4.1.2.2**). Solifenacin Cmax and AUC were increased by 23% and 26% as a result of co-administration with mirabegron, respectively.

Figure 2.4.1.2.2 Mean Solifenacin Plasma Concentration-Time Profiles Following Administration of Solifenacin 10 mg Alone (Day 1) or in Combination with Mirabegron 100 mg QD (Day 23) (Study 178-CL-069)

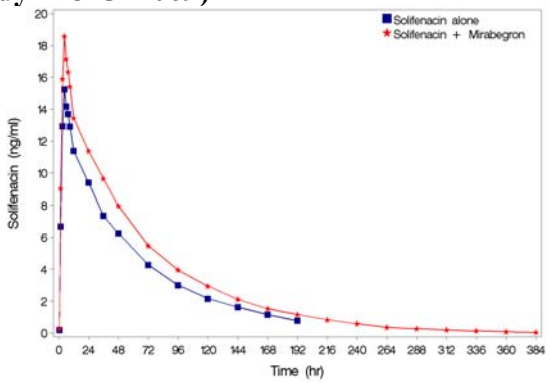


Table 2.4.1.2.2 Statistical Analysis of PK Parameters of Solifenacin Following Administration of Solifenacin 10 mg Alone (Day 1) or in Combination with Mirabegron 100 mg QD (Day 23) (Study 178-CL-069)

Parameter	Least Square Means		Ratio (%) with/without Mirabegron	90% Confidence Interval
	Solifenacin Alone	Solifenacin with Mirabegron		
C_{max} (ng/mL)	15.3	18.8	1.23	1.15, 1.31
AUC_{inf} (ng·hr/mL)	838	1055	1.26	1.17, 1.35

Reviewer's Comments:

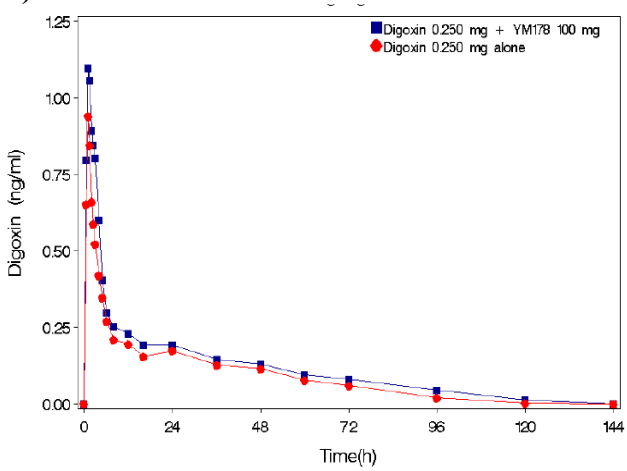
These data further support the observed effect on COC in which mirabegron has minimal effect on CYP3A4. Therefore, mirabegron can be administered with drugs known to be metabolized by CYP3A4.

2.4.1.2.3 Studies with P-gp Substrates:

To investigate the clinical effect of mirabegron on P-gp, the PK of digoxin (single dose of 0.250 mg), was studied with and without coadministration of mirabegron (100 mg qd) [Study 178-CL-059].

The study was crossover at a single oral dose of 0.250 mg digoxin that was administered on Day 1. The PK profile of digoxin was followed up to 144 hours when given alone. On Day 10 up through Day 23, subjects received daily oral doses of 100 mg mirabegon. On Day 18, a single 0.250 mg dose of digoxin was given again in combination with mirabegron (i.e., 8 days after the first dose of mirabegron). The PK profile of digoxin was again followed up to 144 hours. On Day 16 through Day 19, blood samples for mirabegron were collected. There was no change in the plasma concentration-time profiles of digoxin or any of its PK parameters (**Figure 2.4.1.3.1)**

Figure 2.4.1.3.1 Mean Plasma Digoxin Concentration-Time Profiles Following Single Dose Administration of 0.250 mg Digoxin Alone or in Combination with Mirabegron 100 mg Dose (Study 178-CL-059)



Reviewer's Comments:

The results from this study indicate that the inhibitory effect of mirabegron on P-gp is weak. However, as digoxin is a drug with narrow therapeutic index it is recommended that serum digoxin concentrations be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. In addition, it is recommended that the lowest dose for digoxin should initially be used when intended to be co-administered with mirabegron.

2.4.1.2.4 Other Commonly Used Drugs

Interaction with Warfarin (Study 178-CL-040):

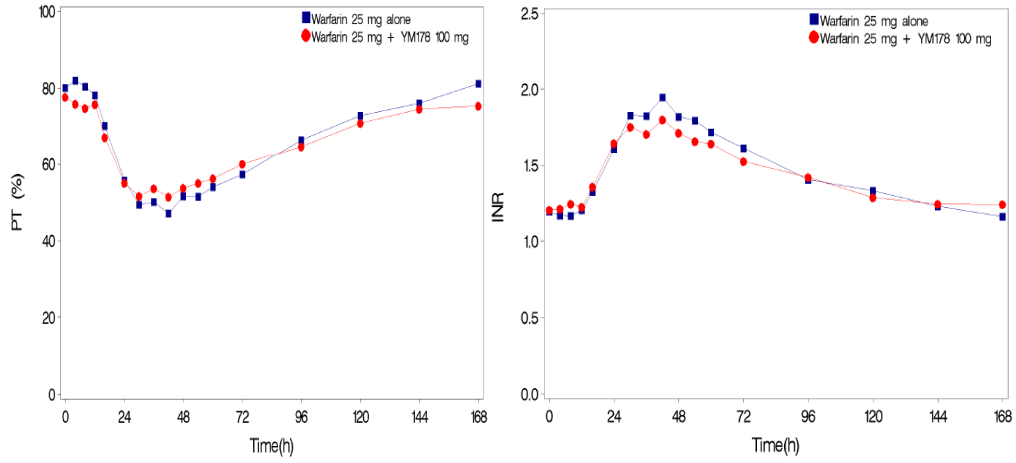
Warfarin is a commonly used drug as anticoagulant and it is known as a CYP2C9 substrate. This study was designed as a crossover following a supratherapeutic single dose of 25 mg of warfarin and in combination with 100 mg mirabegron administered once daily.

On Day 1 and Day 23 warfarin was administered as a single 25 mg dose followed by a PK sampling post dosing in each day. From Day 15 to Day 30 mirabegron 100 mg daily doses were administered. Thus, warfarin was co-administered with mirabegron only on Day 23.

Mirabegron had no effect on the PK profiles or parameters of S- or R- warfarin. The mean ratios for Cmax were 1.05 and 1.04 (R- and S-warfarin, respectively) and for AUC were 1.10 for both R- and S-warfarin; the bounds of the 90% CIs were contained within the predefined limits for equivalence (0.80-1.25). In addition, mirabegron did not affect the pharmacodynamic (PD) effect of warfarin such as prothrombin time (PT) and international normalized ratio (INR) (**Figure 2.4.2.4.1**).

Figure 2.4.1.2.4.1 Mean Pharmacodynamic (PD) Profiles Following Single Dose Administration of 25 mg Warfarin with and without 100 mg Mirabegron (Study 178-CL-040)

A: PT **B: INR**



Reviewer's Comments:

This study clearly demonstrates that mirabegron had no effect on CYP2C9 substrates as warfarin is well known probe for this isoenzyme. There was no effect on either PK or PD (PT or INR) profiles of warafrin.

Reference ID: 3129601

2.5 General Biopharmaceutics

2.5.1 What is the Effect of Food on the BA of Mirabegron?

The effect of food on the bioavailability of mirabegron was evaluated in 6 Phase 1 studies. The focus of this review is on the pivotal two studies that were conducted in Western (Studies 178-CL-041) and Japanese (178-CL-078) subjects. The other studies are irrelevant as they were conducted using IR tablets. Also, the focus of the review is on the highest recommended dose strength of 50 mg tablet.

Overall, mirabegron OCAS tablets exhibited a decrease in plasma exposure when given with food. However, the extent of absorption is dependent on meal composition and specifically the fat contents (i.e., low-fat versus high-fat). Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron Cmax and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron Cmax and AUC by 75% and 51%, respectively. Similar results were obtained with a 100 mg dose of mirabegron. It should be noted that there was no food restrictions in the primary Phase 3 studies to establish the safety and efficacy of mirabegron.

Study 178-CL-41 was a crossover designed at a dose of 50 mg or 100 mg administered under fasted or fed conditions (high-fat and low-fat breakfasts). The study was conducted in 72 healthy subjects where 18 men and 18 women were enrolled in each arm, 50 mg or 100 mg dose. From this study it can be seen that food in general caused reduction in the bioavailability of mirabegron, the highest effect was noted after taking the drug with low fat food content (**Figures 2.5.1.1 and 2.5..12 and Tables 2.5.1.1**). The same trend was also seen for urine excretion data for mirabegron in the same study (**Figure 2.5.1.2**).

It should also be noted that food had similar effect in the Japanese study, but the mirabegron plasma levels were higher than in Westerners (Compare scale in **Figures, 2.5.1.3 vs 2.5.1.1,** 178-CL-078). The study was also conducted after 50 mg and 100 mg OCAS tablets and of similar design as that of the Westerners study (041).

Reference ID: 3129601

Figure 2.5.1.1 Mean Plasma Mirabegron Concentration-Time Profiles Following Single 50 mg Doses of Mirabegron under Fasted and Fed Conditions in Western Subjects (Study 178-CL-41)

A: Time scale 0-96 hours **B: Time scale 0-12 hours**

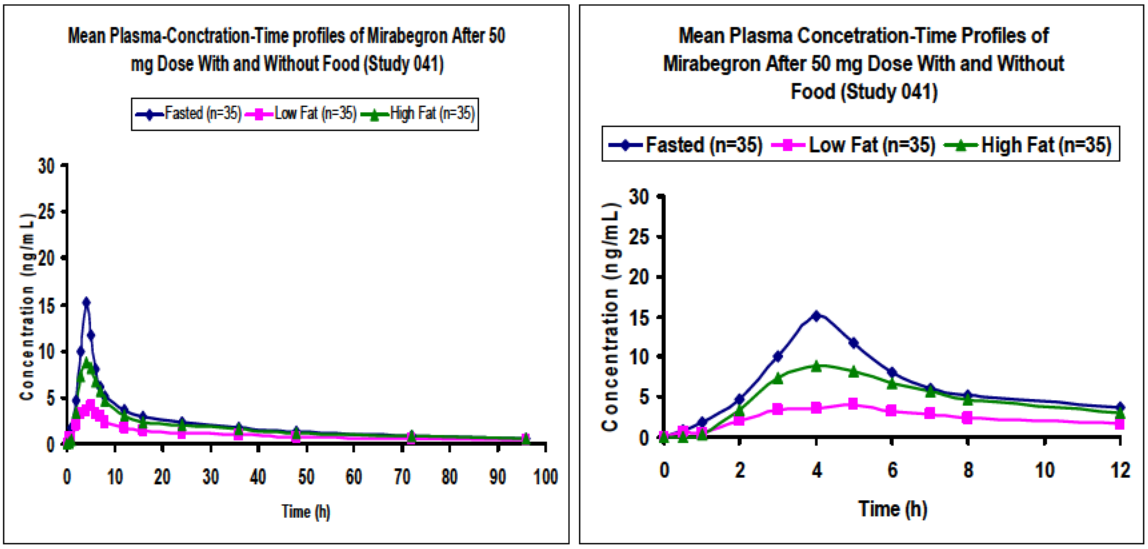


Table 2.5.1.1 Statistical Analysis of the Effect of Food on Plasma Mirabegron PK Parameters Following Administration of 50 mg Dose under Fasted and Fed Conditions In Western Subjects (Study 178-CL-041)

Parameter (unit)	Treatment	n	LS Mean†	Comparison	LS Mean Ratio (%)‡	90% CI of Ratio (%)‡
AUC_{inf} (hr·ng/mL)	Fasted	35	227.44	Low-fat/Fasted	48.66	(43.32, 54.67)
	Low-fat	36	110.68	High-fat/Fasted	83.24	(74.16, 93.42)
	High-fat	36	189.31	High-fat/Low-fat	171.05	(152.47, 191.89)
AUC_{last} (hr·ng/mL)	Fasted	35	188.42	Low-fat/Fasted	44.29	(38.90, 50.42)
	Low-fat	36	83.45	High-fat/Fasted	80.32	(70.61, 91.36)
	High-fat	36	151.33	High-fat/Low-fat	181.35	(159.52, 206.17)
C_{max} (ng/mL)	Fasted	35	17.75	Low-fat/Fasted	24.96	(19.89, 31.33)
	Low-fat	36	4.43	High-fat/Fasted	54.76	(43.69, 68.65)
	High-fat	36	9.72	High-fat/Low-fat	219.38	(175.08, 274.89)

Figure 2.5.1.2 Mean (SD) Mirabegron Urinary Cumulative Excretion Profiles Following Single 50 mg Doses of Mirabegron under Fasted and Fed Conditions in Western Subjects (Study 178-CL-41)

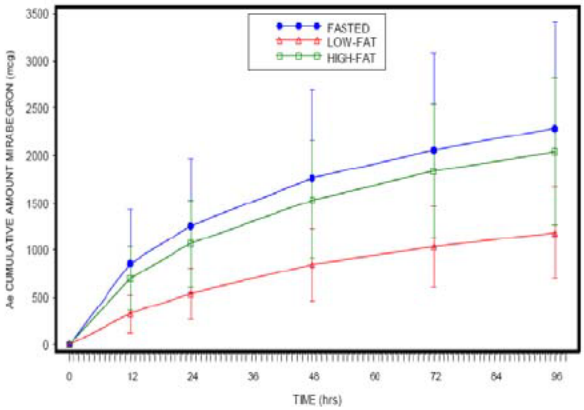
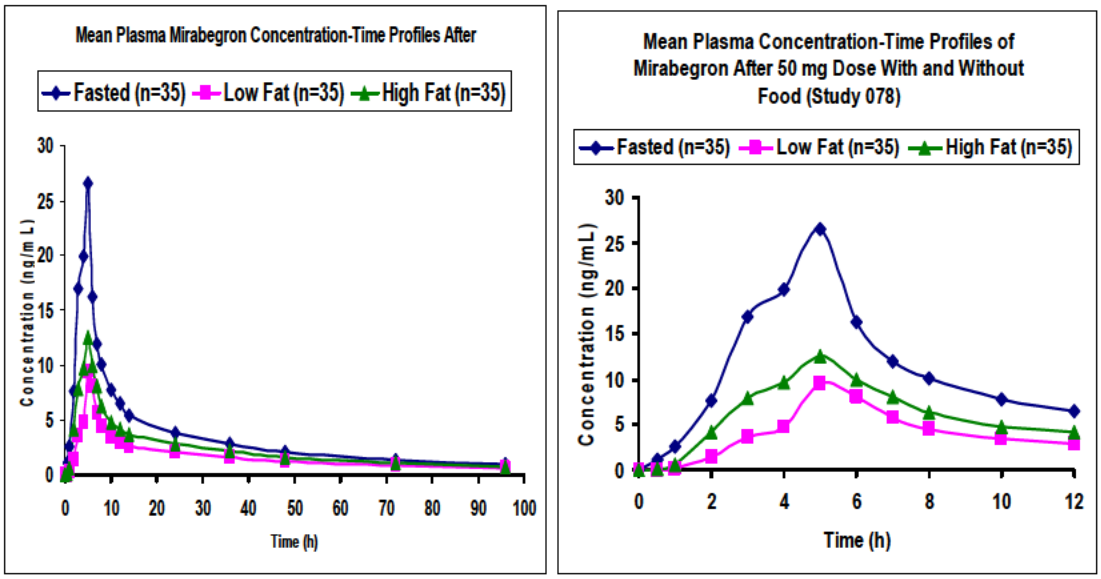


Figure 2.5.1.3 Mean Plasma Mirabegron Concentration-Time Profiles Following Single 50 mg Doses of Mirabegron under Fasted and Fed Conditions In Japanese Subjects (Study 178-CL-078)

A: Time scale 0-96 hours **B: Time scale 0-12 hours**



Reviewer's Comments:

Food has similar and consistent pattern on the absorption of mirabegron in the above two studies and in all other studies conducted with mirabegron, irrespective of formulation. As stated above, the second pivotal study was in Japanese subjects. **Figures 2.5.1.4 to 2.5.1.7** shows the comparison in exposure for mirabegron between Japanese and Westerners following the same 50 mg OCAS dose of mirabegron for the observed and dose and weight normalized (ratio) for Cmax and AUC.

Figure 2.5.1.4 Comparison of the Effect of Food on Cmax of Miragebron in Westerns (Study 041) and Japanese (Study 078). Data is Expressed as Mean (±SD) of Observed Cmax (Left) and Cmax Normalized by Weight-Adjusted Dose (Right)
A: Observed Cmax B: Cmax normalized by Weight-Adjusted Dose

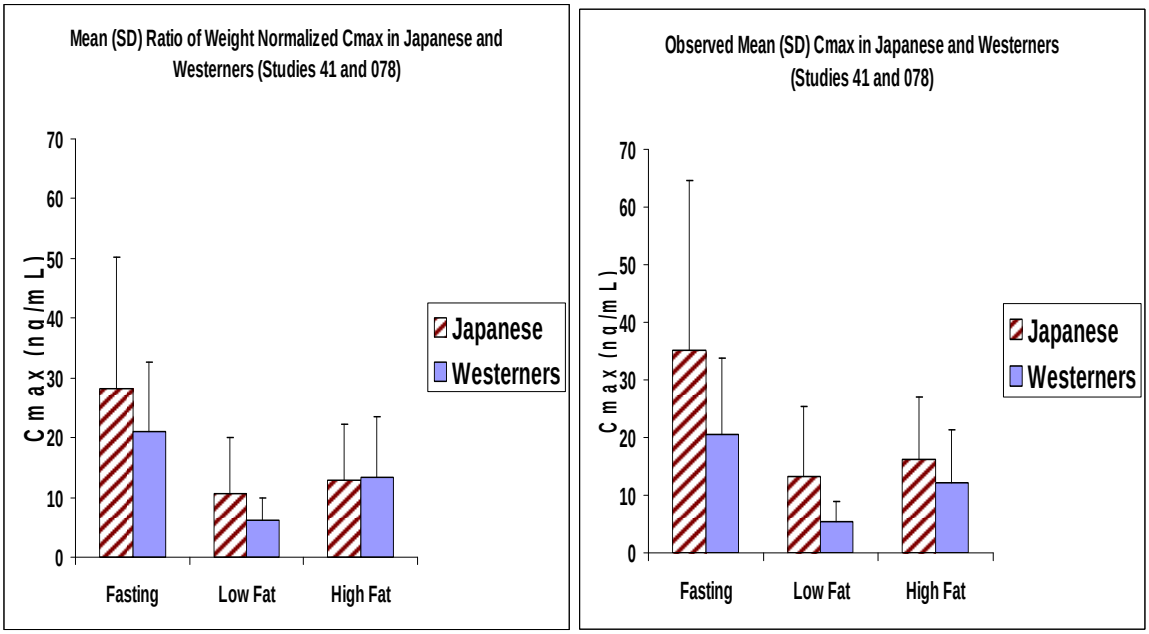
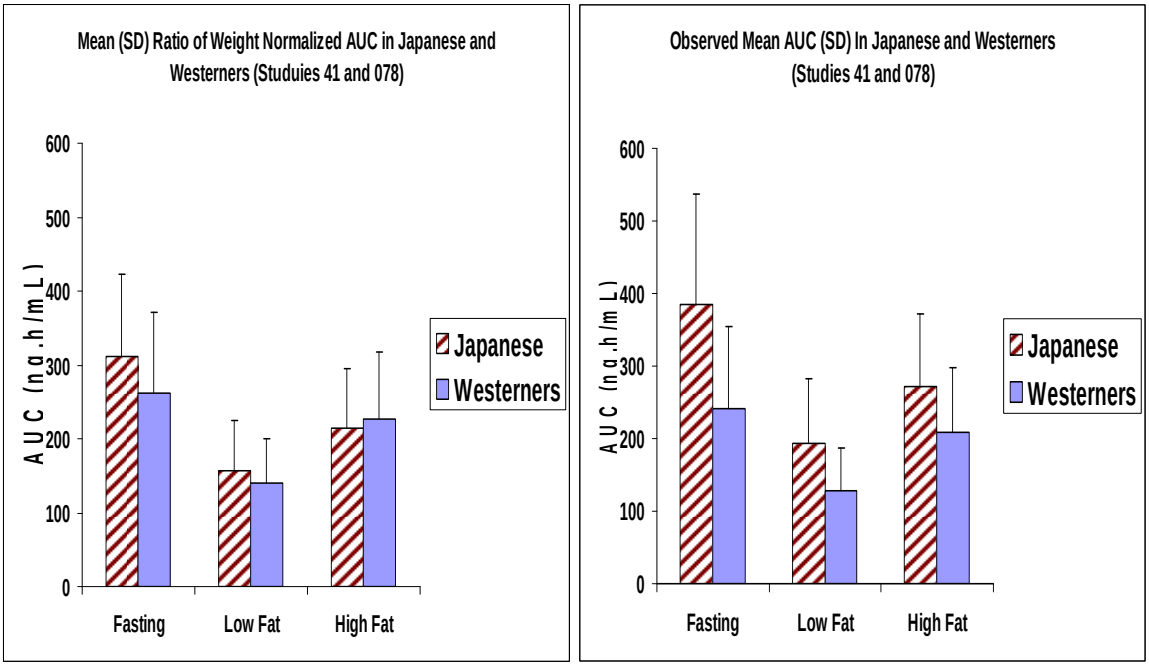


Figure 2.5.1.5 Comparison of the Effect of Food on AUC of Miragebron in Westerns (Study 041) and Japanese (Study 078). Data is Expressed as Mean (±SD) of Observed AUC (Left) and AUC Normalized by Weight-Adjusted Dose (Right)
A: Observed AUC B: AUC Normalized by Weight-Adjusted Dose



Reference ID: 3129601

Figure 2.5.1.6 Comparison of Individual Cmax of Miragebron in Westerns (Study 041) and Japanese (Study 078) Subjects in Fasting Condition. Data is Expressed as Individual Observed Cmax (Left) and Individual Cmax Normalized by Weight-Adjusted Dose (Right)

A: Observed Cmax **B: Weight-Adjusted Dose Cmax**

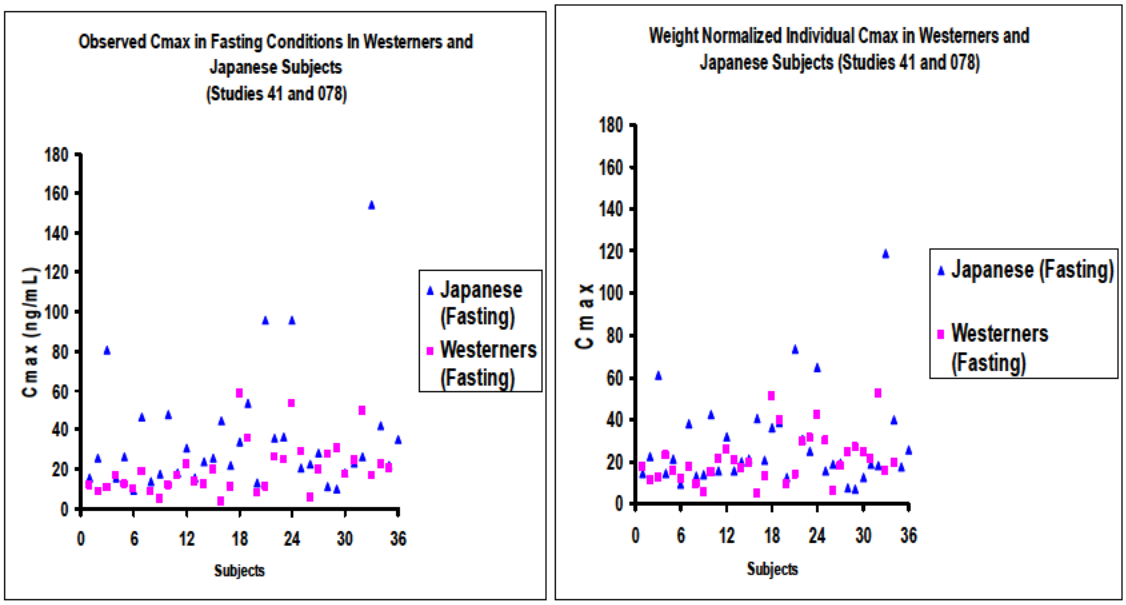
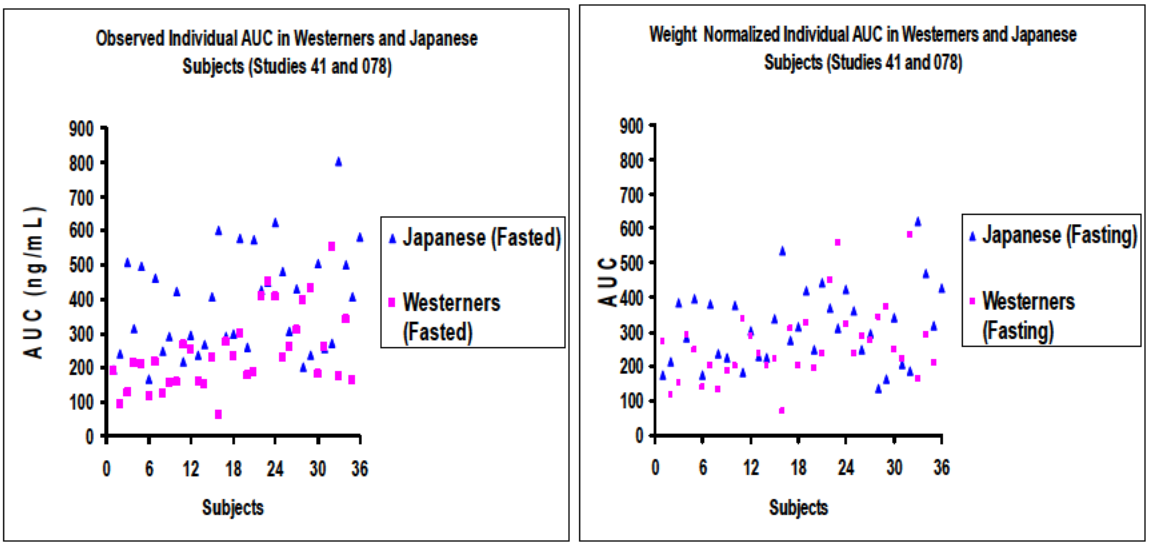


Figure 2.5.1.7 Comparison of Individual AUC of Miragebron in Westerns (Study 041) and Japanese (Study 078) Subjects in Fasting Condition. Data is Expressed as Individual Observed AUC (Left) and Individual AUC Normalized by Weight-Adjusted Dose (Right)

A: Observed AUC **B: Weight-Adjusted Dose AUC**



Reference ID: 3129601

The mean Cmax and AUC were normalized by weight and dose using the observed data from studies 41 and 078 following 50 mg dose in average normal body weight of **70 kg** as follows:

Ratio A (weight-adjusted dose ratio centered at 70 kg) = 70/subject weight
Ratio B (exposure normalized by the weight-adjusted dose) = AUC or Cmax/Ratio A (i.e., weight-adjusted dose ratio centered at 70 kg)

The analysis was performed as two sets. One set for the mean Cmax and AUC and mean body weight in respective study and treatment. The second set was for individual observed Cmax and AUC and individual weights at a respective treatment. It should be noted that the mean body weight in Japanese study was 57.92 Kg ranging from 46.2-74.0 Kg and in Westerners study the mean body weight was 77.31 Kg ranging from 55.2 to 103.6 kg.

By normalizing the mean Cmax for mean body weight adjusted dose in each study the difference between Japanese and Westerners subjects became minimal for the mean and individual Cmax and AUC data, especially after food. Based on this analysis, it appears that the observed difference in exposure between Japanese and Westerners can be explained by weight difference between the two populations. It should be noted that based on the pharmacogenomic review no genetic factors were found to be associated with the PK and/or the metabolism of mirabegron (**Appendix II**)

To conclude, in all studies the data is conclusive that food reduces the absorption of mirabegron. Also it was consistently observed that low fat content appears to lower the bioavailability of mirabegron at greater extent than high fat content. Overall, the exposure of mirabegron is consistently higher in Japanese compared to Westerners following the same dose. It should be noted that the pivotal Phase 3 studies were conducted irrespective food or food contents and the sponsor proposed label states that mirabegron is to be taken with or without food.

2.5.2 Was the to-be-Marketed Formulation Used in the Clinical Trials?

Various dosage forms and formulations of mirabegron have been used through different stages of clinical development.

The early clinical studies were conducted with immediate release (IR) capsules and tablets. An aqueous solution was used for the human mass balance study. Since the IR formulations showed a considerable decrease in plasma exposure with food and high peak-to-trough fluctuations in plasma concentrations with once daily dosing, a modified release tablet using Oral Control Absorption System (OCAS) technology was developed. OCAS modified release formulation is also referred to as extended-release or prolonged-release. Several OCAS formulations, with differing dissolution profiles were screened in one study (Study 178-CL-030).

Based on the data from 178-CL-30 study, an OCAS tablet with an intermediate dissolution rate (OCAS-M) was selected for further development. The release rate of mirabegron from this OCAS formulation resulted in a PK profile with a slower rate of absorption than the IR tablet, an attenuated food effect with a high-fat meal and reduced fluctuations in plasma concentrations compared with once daily mirabegron IR.

Reference ID: 3129601

The OCAS-M tablet was used in the phase 2 and 3 efficacy studies and all clinical pharmacology studies, with the exception of those investigating the effect of CYP2D6 genotype and drug-drug interactions (DDIs) with metoprolol (Study 178-CL-005) and metformin (Study 178-CL-006), and the mass balance study (Study 178-CL-007).

The sponsor made minimal changes to the OCAS-M tablet formulation during clinical development. There were minor differences in the formula and granulating method between OCAS-M tablets used in the initial phase 1 studies and those used during the phase 2b stage of clinical development. *In vitro* release of mirabegron was not influenced by these changes (see ONDQA review). It is important to note that 50-mg tablets used in phase 2b and Phase 3 were identical in terms of composition and manufacturing process.

For 25 mg and 100 mg strengths, used in Phase 2b and Phase 3 were differed only in film-coating agents used to improve the visual identification for the final products. Dissolution profiles demonstrated that these formulations exhibited similar release characteristics *in vitro* (See ONDQA review).

The proposed mirabegron 25 mg and 50 mg commercial formulations are identical to the tablets used in the phase 3 stage, except that the commercial product will be debossed. Dissolution testing of plain and debossed tablets demonstrated that **debossing does not affect** *in vitro* drug release (see ONDQA review). **Figure 2.5.21** shows representative dissolution profiles imported from ONDQA review. **Table 2.5.22** shows the composition of the final to be marketed formulation (OCAS-M) for 25 mg and 50 mg tablets.

Reference ID: 3129601

Figure 2.5.4.1 Representative Dissolution data and Profiles for 25 mg and 50 mg tablets (source: ONDQA review)

Table P.5.6-14 Basket Dissolution Data Summary of Representative Commercial Batches

Dose		25 mg	50 mg
Number of dissolution data for calculation		14	14
Mean rates (min. – max.) from all batches (%)	3 h	30.5 (b) (4)	27.7 (b) (4)
	5 h	58.0	54.0
	8.5 h	99.0	95.3

Figure P.5.6-4 Representative Dissolution Profiles with Basket Method at 100 rpm

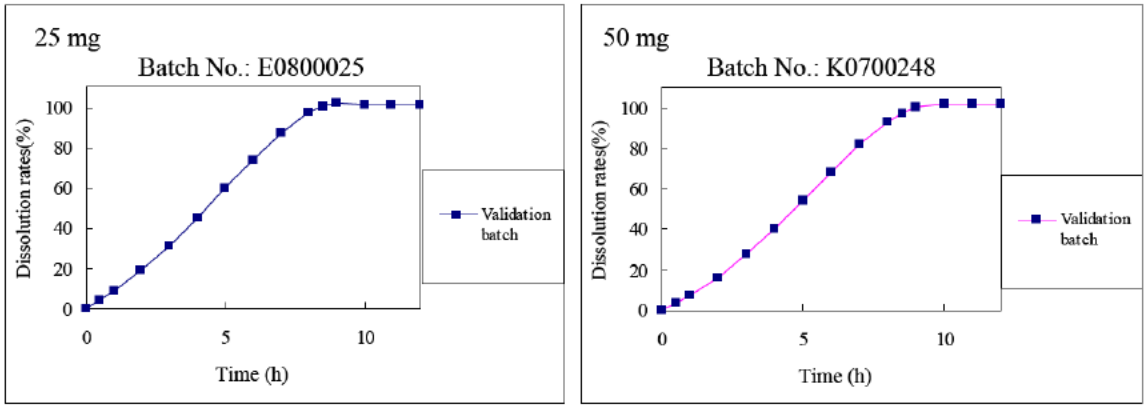


Table 2.5.4.2 Composition of the Final To-be-Marketed Mirabegron OCAS-M Formulation for 25 mg and 50 mg Tablets

Components	Reference Quality Standard	Function	Quantity (mg/tablet)	
			Mirabegron OCAS tablets 25 mg	Mirabegron OCAS tablets 50 mg
Mirabegron	In house	Active Ingredient	25.0	50.0
Polyethylene Oxide (b) (4)	NF/In house	(b) (4)		
Polyethylene Glycol (b) (4)	NF			
Hydroxypropyl Cellulose	NF			
Purified Water	USP			
Butylated Hydroxytoluene	NF			
Magnesium Stearate	NF			
(b) (4)	In house			
	In house			
	USP			
Total tablet weight (mg)			257.5	257.5

NF: National Formulary; USP: United States Pharmacopeia; -: material not used

(b) (4)

2.5.3 Is there Dosage Strength Equivalency?

The sponsor did not conduct dosage-strength equivalency study between 2 x 25 mg tablets and 1 x 50 mg tablet. However, to establish similarity between the two tablet strengths the sponsor conducted *in vitro* dissolution data and performed *in-vitro-in-vivo*-correlation (IVIVC) analysis. The dissolution profiles for both strengths were similar (**Figure 2.5.3.1**) and the similarity factor (f2) was >50 for all tested batches of both strengths (**see ONDQA Review**).

2.5.3.1 Dissolution Profiles of Mirabegron OCAS Tablets with Different Media (Left: 25 mg, Right: 50 mg)

(b) (4)

Reviewer's Comments:

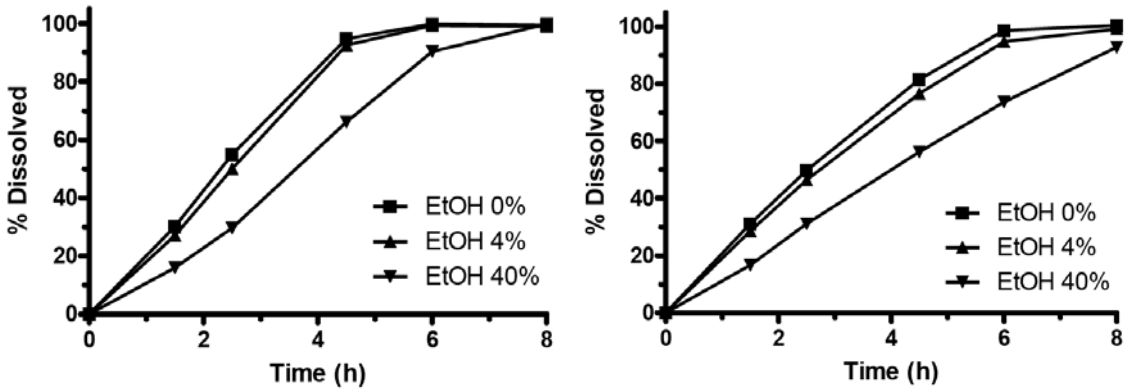
Based on the *in vitro* data presented in ONDQA review and the overall safety and efficacy profiles of mirabegron and the data from QTc study at a high dose there is no need to conduct a separate study to specifically evaluate the dosage-strength equivalency between 2 x 25 mg and 1 x 50 mg tablets. Therefore, the *in vitro* data alone in this case is acceptable (see also ONDQA review).

2.5.4. Is there Potential for Dose Dumping with Alcohol?

Alcohol is unlikely to accelerate mirabegron dissolution and release from the OCAS formulation (for details please see ONDQA review). The addition of 4% ethanol to the dissolution medium showed similar dissolution profiles for mirabegron OCAS tested at the lowest tablet strength of 25 mg and the highest tablet strength of 200 mg compared to buffer, whereas the addition of 40% ethanol showed delayed dissolution profiles (**Figure 2.5.4.1**). A similar trend was seen for intermediate tablets strengths. Therefore, there is no potential for dose dumping.

Figure 2.5.4.1 Dissolution Profiles of Mirabegron OCAS Tablets 25 mg in USP Phosphate Buffer (pH 6.8) Containing Ethanol

A: 25 mg tablet **B: 200 mg tablet**



2.5.6 Are the method and dissolution specifications supported by the data provided by the sponsor?

The method proposed for *in vitro* dissolution is summarized below:

Apparatus:	I (40 mesh baskets)
Media:	USP pH 6.8 phosphate buffer
Speed:	100 RPM
Volume:	900 mL
Temperature:	37 ± 0.5 ºC

ONDQA will assess the adequacy of the final method and specifications.

2.6 Analytical Section

The plasma concentrations of mirabegron were determined by a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. The lower limit of quantitation (LLOQ) of the assays is 0.2 ng/mL. The calibration curve is linear over a concentration ranging from 0.2 to 100 ng/mL. The inter- and intra-day assay %CV is <10% (ranging from 3.6% to 7.8%). The accuracy at a concentration of 0.2 ng/mL (LLOQ) was 95% to 109% and at 80 ng/mL was 102.6% to 108.1%. All other assay validation data are satisfactory. Blood samples of the majority of the PK studies were assayed at Astellas Pharma Europe BV (Leiderdorp, The Netherlands) and (b) (4)

Reference ID: 3129601

3.0 Labeling Comments (preliminary):

Labeling comments will be made directly into the label during the internal labeling meetings.

4.0 Appendices
4.1 Sponsor's Proposed Label
4.2. Individual Study Review (Selected Studies)
4.3 Consult Reviews:
4.3.1 Appendix I: Pharmacometric Review
4.3.2 Appendix II: Genomics Group Review
4.3 Filing memo

7 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3129601

4.2. Individual Study Review (Selected Studies)

4.2.1 Study 178-CL-031 (Single and Multiple Doses):

Study Title: "Double-Blind, Randomized, Placebo-Controlled, Exploratory Study to Investigate the Pharmacokinetics, Safety and Tolerability of Multiple Doses of YM178 OCAS-M in Healthy Young Male and Female Subjects and Healthy Elderly Male and Female Subjects: Phase I YM178 OCAS Dose-Proportionality Study"

Objectives:

Primary
- To evaluate the PK of mirabegron after single and multiple oral administrations.

Secondary
- To evaluate the safety and tolerability
- To compare the PK of mirabegron between healthy elderly and young subjects.

Study Design:

This was a double blind, randomized, placebo controlled design comprised 96 subjects. The study consisted of healthy young and elderly male and female subjects. The study was conducted in two centers. The subjects were distributed among the two sites in a balanced manner (see Table below for the demographic data). The following is a synopsis of the study:

Arm 1: Healthy Young Males and Females:

In this arm mirabegron was administered among 4 groups of young subjects (A, B, C and D). Each group was treated with one dose level and contained 16 subjects: 8 male subjects (6 on active treatment and 2 on placebo) and 8 female subjects (6 on active treatments and 2 on placebo). The young subjects were treated with the following dose levels:

Group A: 50 mg
Group B: 100 mg
Group C: 200 mg
Group D: 300 mg

Arm 2: Healthy Elderly Males and Females Subjects

This arm consists of two groups. Each group was treated with one dose level and contained 16 subjects: 8 male subjects (6 on active treatment and 2 on placebo) and 8 female subjects (6 on active treatments and 2 on placebo) as follows:

Group E: 50 mg
Group F: 200 mg

Reference ID: 3129601

Each subject participated in one dose group only. Each subject received a single dose of mirabegron or placebo on Day 2, followed by multiple dosing once daily for 10 days (Days 5-14). The doses were administered under fasted conditions on PK days (Days 2 and 14).

The following Table shows the demographic Data of the study:

		Young					Elderly		
		OCAS-M					OCAS-M		
		50 mg (N=12)	100 mg (N=12)	200 mg (N=12)	300 mg (N=12)	Placebo (N=16)	50 mg (N=12)	200 mg (N=12)	Placebo (N=8)
Gender	Male	6 (50%)	6 (50%)	6 (50%)	6 (50%)	8 (50%)	6 (50%)	6 (50%)	4 (50%)
	Female	6 (50%)	6 (50%)	6 (50%)	6 (50%)	8 (50%)	6 (50%)	6 (50%)	4 (50%)
Age (years)	Mean	28.1	28.3	32.4	26.8	28.9	68.6	68.3	70.4
	Range	18-53	20-50	18-52	18-55	19-55	65-77	65-73	65-77
Weight (kg)	Mean	71.4	69.8	73.8	69.9	69.4	70.9	76.0	72.9
	Range	54.8-89.6	57.9-93.0	55.0-91.8	54.8-88.5	55.6-91.8	51.8-87.7	60.0-85.4	54.6-90.0
Height (cm)	Mean	173.7	178.3	175.7	178.9	174.0	167.3	170.8	169.0
	Range	158-189	166-191	162-189	161-195	160-187	152-184	158-184	158-180
BMI (kg/m^2)	Mean	23.70	21.93	23.83	21.73	22.80	25.31	26.10	25.39
	Range	19.7-28.1	19.4-26.3	20.0-26.5	19.6-23.8	19.0-26.7	22.0-29.7	23.9-28.9	21.1-29.3

Results:

There was increase in exposure as the dose increase in all subjects (**Figures 4.2.1.1 and 4.2.1.2 and Table 4.2.1.1**). There was no noticeable difference in exposure between young and elderly. However, females had higher exposure than males. There was greater than dose proportional increase in exposure with minimal accumulation after multiple doses compared to a single dose (**Figures 4.2.1.3 and 4.2.1.4**).

Reference ID: 3129601

Figure 4.2.1.1 Mean Plasma Concentration-Time profiles of Mirabegron after the First Dose in Young and Elderly (Study 031)

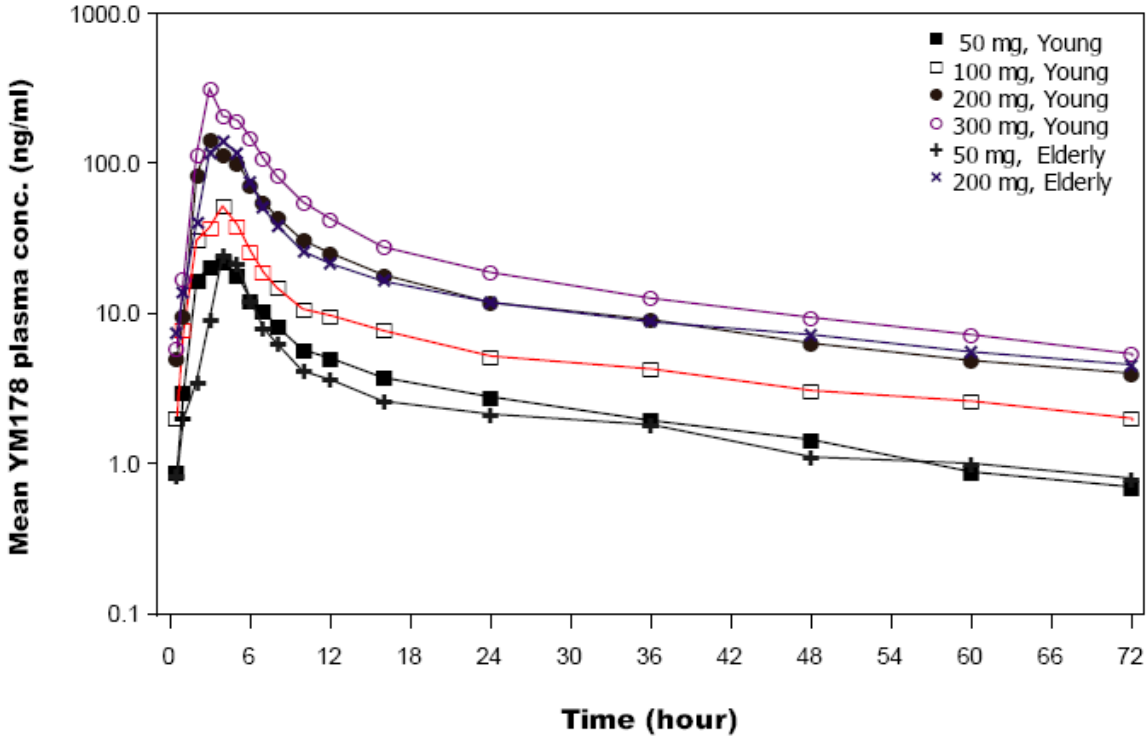
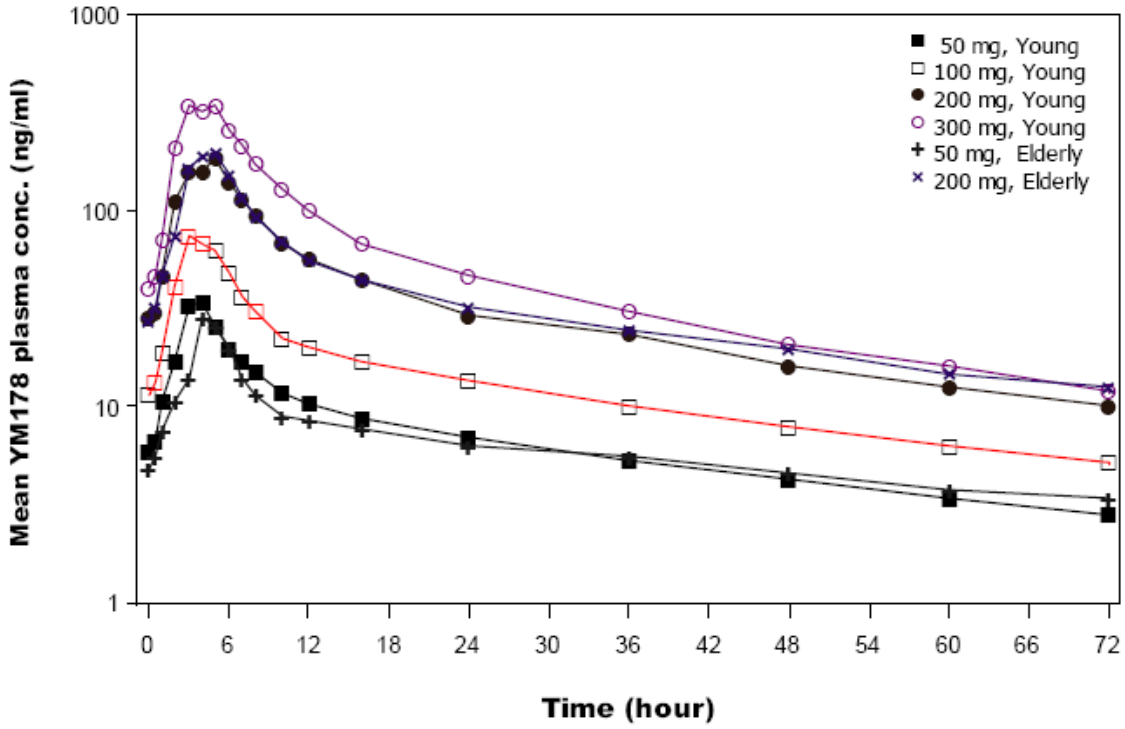


Figure 4.2.1.1 Mean Plasma Concentration-Time profiles of Mirabegron after the Last Dose in Young and Elderly (Study 031)



Reference ID: 3129601

Table 4.2.1.1 Comparison of Single Dose and Multiple Dose PK Parameters (Study 031)

PK parameter	Treatment group	Gender	N	Point estimate of ratio[1]	95% CI		CV[2] (%)
					Lower[1]	Upper[1]	
AUC	50 mg Young	Female	5	1.03	0.89	1.21	8.95
		Male	4	0.96	0.75	1.24	11.14
		Overall	9	1.00	0.90	1.11	9.67
	100 mg Young	Female	6	1.32	0.97	1.78	20.50
		Male	6	0.86	0.77	0.95	7.12
		Overall	12	1.06	0.88	1.29	21.71
	200 mg Young	Female	6	1.13	0.71	1.80	32.09
		Male	6	1.26	0.82	1.93	29.31
		Overall	12	1.19	0.92	1.55	29.53
	300 mg Young	Female	6	1.36	1.03	1.82	19.42
		Male	6	1.39	1.21	1.61	9.56
		Overall	12	1.38	1.21	1.57	14.58
	50 mg Elderly	Female	3	0.91	0.72	1.15	6.75
		Male	1	1.18	-	-	0.00
		Overall	4	0.97	0.76	1.24	10.77
	200 mg Elderly	Female	6	1.14	0.84	1.55	20.94
		Male	6	1.34	1.13	1.58	11.26
		Overall	12	1.23	1.06	1.44	17.07
C_{max}	50 mg Young	Female	6	1.27	0.97	1.65	17.97
		Male	6	1.39	0.77	2.50	41.28
		Overall	12	1.33	1.02	1.73	30.15
	100 mg Young	Female	6	1.42	0.76	2.66	44.19
		Male	6	1.17	0.93	1.47	15.61
		Overall	12	1.29	0.97	1.71	31.94
	200 mg Young	Female	6	1.16	0.66	2.05	39.50
		Male	6	1.50	0.85	2.64	39.63
		Overall	12	1.32	0.94	1.85	38.92
	300 mg Young	Female	6	1.19	0.79	1.80	28.18
		Male	6	1.39	0.87	2.25	32.97
		Overall	12	1.29	0.99	1.68	29.77
	50 mg Elderly	Female	6	1.20	0.86	1.66	22.55
		Male	6	1.12	0.46	2.70	65.35
		Overall	12	1.15	0.78	1.70	45.06
	200 mg Elderly	Female	6	1.25	0.86	1.84	26.10
		Male	6	1.28	0.87	1.90	26.92
		Overall	12	1.27	1.01	1.59	25.26

[1]. The ratio was calculated as multiple dose/single dose; for AUC, the ratio was calculated as $AUC_{0\text{-}24h}/AUC_{0\text{-}inf}$. Log-transformed results were back-transformed to the original scale.
[2]. Computed as the square root of (exp (MSE)-1).

Reference ID: 3129601

Figure 4.2.1.3 Mean (SD) Cmax of Mirabegron after Oral Administration of Single and Multiple Doses of OCAS-M Tablets (Study 178-CL-031)

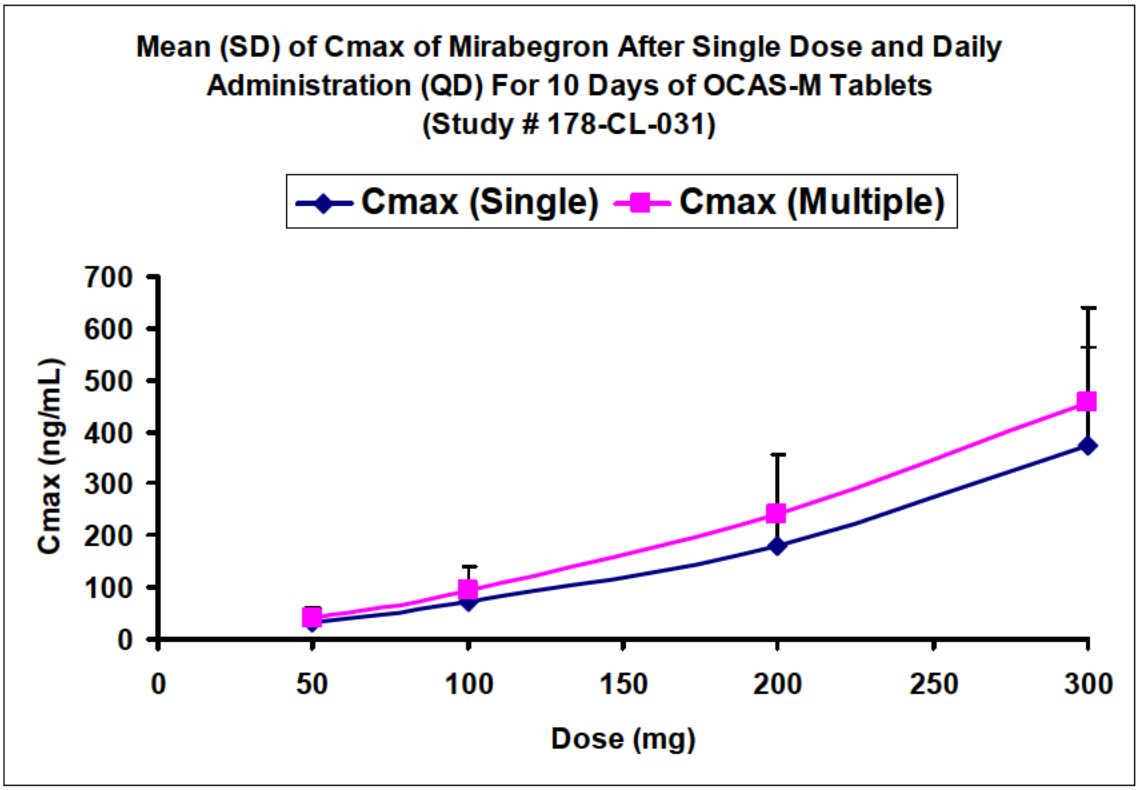
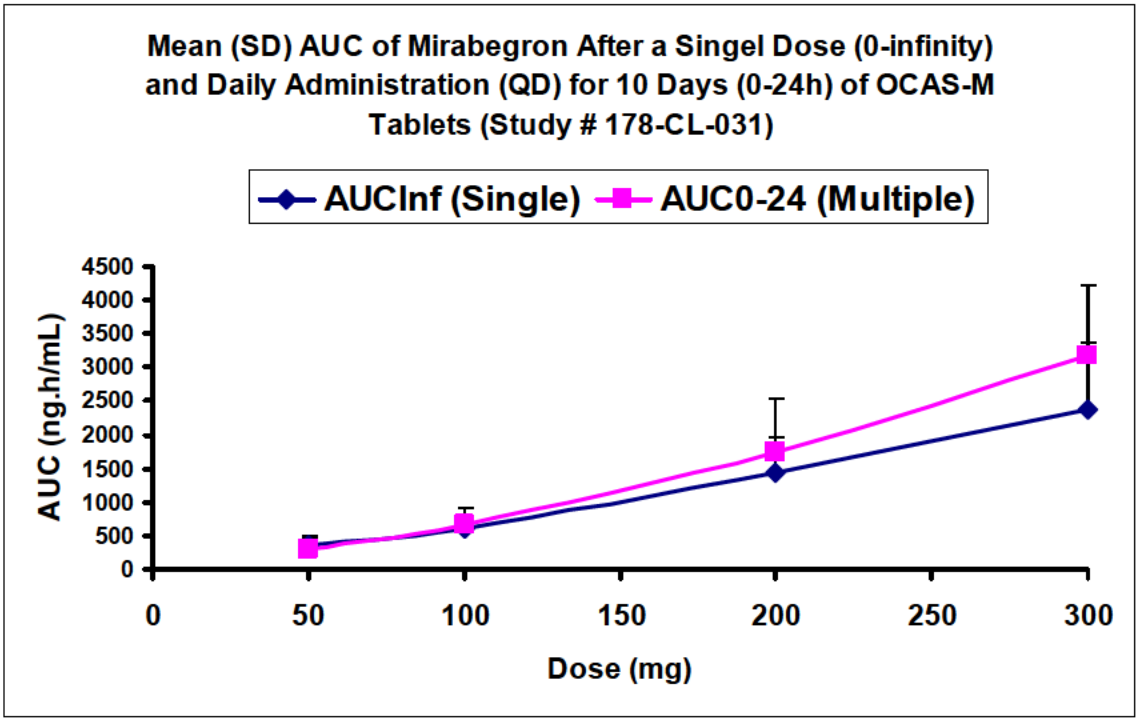


Figure 4.2.1.4 Mean (SD) AUC of Mirabegron After Oral Administration of Single and Multiple Doses of OCAS-M Tablets (Study 178-CL-031)



Reviewer's Comments:

The exposure in females was consistently higher than males at all doses. There was no obvious effect of age on mirabegron PK. There was no obvious accumulation of mirabegron after 10 days daily administration at 50 mg dose, except some at higher doses.

The study clearly shows greater than dose proportionality in exposure in all subjects over the dose range of 50 mg to 300 mg. However, this should not be an issue as the observed deviation from linearly is above the recommended dose of 50 mg.

Reference ID: 3129601

4.2.2 Study 178-CL-034 (Single and Multiple Doses):

Study Title: "Phase I Clinical Study of YM178: Single and Multiple Oral Dose Study of YM178 Sustained-release Tablets"

Objectives:
To assess the safety and PK of mirabegron sustained-release tablets after single and multiple oral dosing in healthy adult male Japanese subjects.

Study Design:
This study was conducted in Japanese subjects as follows:

Part I (single dosing, Steps 1 to 5):
At each step, a single oral dose of mirabegron (50, 100, 200, 300, or 400 mg) or placebo was administered in fasted subjects (n=8 at each dose)

Part II (multiple dosing, Steps 6 to 7)
At each step, a single oral dose of mirabegron (100 mg or 200 mg) or placebo was administered within 30 min to 1 h after breakfast (n=12 at each dose). After a 2-day washout period subjects received multiple doses for 7 days.

Results:

This study shows the exposure of mirabegron over a dose range for 50 mg to 400 mg after single and for 100 mg to 200 mg? multiple doses. There was clear increase in exposure with increasing in dose (**Tables 4.2.2.1-4.2.2.3 and Figures 4.2.2.1-4.2.2.4**).

Table 4.2.2.1 Mean Cmax and AUC of Mirabegron after Single Dose Administration (Study 034)

Parameter	Treatment group	Summary statistics							
		Number of subjects assessed	Mean	SD	Minimum	Maximum	Median	Geometric mean	CV (%)
C_{max} (ng/mL)	50 mg	6	31.01	18.06	9.17	57.40	32.92	25.89	58.25
	100 mg	6	130.67	43.79	88.94	196.27	119.26	124.90	33.52
	200 mg	6	164.51	82.99	43.01	301.77	154.03	142.88	50.45
	300 mg	6	548.52	92.50	374.10	640.81	565.52	540.94	16.86
	400 mg	6	720.14	264.40	380.33	1095.94	712.61	677.64	36.72
AUC_{last} (ng·h/mL)	50 mg	6	223.99	78.96	103.95	335.13	218.71	210.70	35.25
	100 mg	6	773.02	215.55	529.90	1162.36	724.66	750.38	27.88
	200 mg	6	1251.58	417.16	721.66	1908.28	1281.64	1192.91	33.33
	300 mg	6	3053.27	300.18	2484.43	3358.64	3116.28	3039.91	9.83
	400 mg	6	3917.41	694.76	2685.05	4678.42	4073.06	3859.25	17.74
AUC_{inf} (ng·h/mL)	50 mg	6	292.24	76.93	173.44	373.49	298.38	282.81	26.32
	100 mg	6	882.40	234.53	619.57	1308.81	830.59	858.99	26.58
	200 mg	6	1382.68	441.45	853.78	2085.90	1393.07	1324.76	31.93
	300 mg	6	3285.08	333.94	2635.76	3574.22	3370.42	3269.47	10.17
	400 mg	6	4142.50	735.89	2814.32	4868.01	4369.07	4079.85	17.76

Reference ID: 3129601

Table 4.2.2.2 Geometric Mean Ratio (GMR) of Dose-Adjusted Cmax and AUC Between the Steps (Study 034)

Parameter	Comparison	GMR	Lower 95% CI	Upper 95% CI
C_{max}/Dose	100 mg / 50 mg	2.412	1.345	4.328
	200 mg / 50 mg	1.380	0.769	2.475
	300 mg / 50 mg	3.483	1.941	6.248
	400 mg / 50 mg	3.272	1.824	5.870
	200 mg / 100 mg	0.572	0.319	1.026
	300 mg / 100 mg	1.444	0.805	2.590
	400 mg / 100 mg	1.356	0.756	2.433
	300 mg / 200 mg	2.524	1.407	4.528
	400 mg / 200 mg	2.371	1.322	4.254
	400 mg / 300 mg	0.940	0.524	1.686
AUC_{inf}/Dose	100 mg / 50 mg	1.519	1.134	2.034
	200 mg / 50 mg	1.171	0.874	1.568
	300 mg / 50 mg	1.927	1.439	2.580
	400 mg / 50 mg	1.803	1.347	2.415
	200 mg / 100 mg	0.771	0.576	1.033
	300 mg / 100 mg	1.269	0.947	1.699
	400 mg / 100 mg	1.187	0.887	1.590
	300 mg / 200 mg	1.645	1.229	2.203
	400 mg / 200 mg	1.540	1.150	2.062
	400 mg / 300 mg	0.936	0.699	1.253

Table 4.2.2.3 Summary Statistics of PK Parameters after Multiple Dose Administration (Part II) (Study 034)

Parameter	Treatment group	Time of assessment (day)	Summary statistics							
			Number of subjects assessed	Mean	SD	Minimum	Maximum	Median	Geometric mean	CV (%)
C_{max} (ng/mL)	100 mg	1	8	91.23	42.00	43.36	154.97	95.49	82.11	46.04
		10	8	136.14	52.52	63.36	228.18	127.68	127.04	38.58
	200 mg	1	8	313.08	77.57	232.35	451.03	302.81	305.19	24.78
		10	8	290.94	90.64	151.30	397.24	292.31	277.12	31.15
AUC_{24h} (ng·h/mL)	100 mg	1	8	377.16	90.67	228.68	496.12	390.27	366.83	24.04
		10	8	792.75	156.88	481.82	1001.75	814.24	777.07	19.79
	200 mg	1	8	1102.22	284.28	751.58	1550.52	985.29	1071.81	25.79
		10	8	1909.36	366.20	1475.27	2473.70	1795.31	1879.63	19.18
AUC_{last} (ng·h/mL)	100 mg	1	8	536.92	112.36	360.20	705.53	555.74	526.18	20.93
		10	8	1198.22	190.01	787.95	1414.20	1210.18	1182.79	15.86
	200 mg	1	8	1471.14	365.44	1063.26	2102.11	1314.86	1434.48	24.84
		10	8	2663.41	425.67	2138.52	3417.40	2589.87	2634.52	15.98
AUC_{inf} (ng·h/mL)	100 mg	1	8	616.24	111.21	455.84	788.19	630.19	607.28	18.05
		10	8	1402.66	214.51	949.04	1644.45	1427.77	1386.18	15.29
	200 mg	1	8	1631.62	373.35	1215.36	2254.59	1555.53	1596.17	22.88
		10	8	2993.78	451.27	2360.85	3756.26	3019.26	2964.17	15.07
t_{max} (h)	100 mg	1	8	4.8	0.5	4.0	5.0	5.0	4.7	9.75
		10	8	5.0	0.0	5.0	5.0	5.0	5.0	0.00
	200 mg	1	8	5.0	0.0	5.0	5.0	5.0	5.0	0.00
		10	8	5.0	0.5	4.0	6.0	5.0	5.0	10.69
$t_{1/2}$ (h)	100 mg	1	8	28.8	6.8	21.2	37.5	26.3	28.1	23.46
		10	8	30.0	4.4	26.0	38.5	28.1	29.7	14.65
	200 mg	1	8	27.4	7.7	19.2	44.1	25.2	26.5	28.22
		10	8	28.0	1.8	25.4	30.6	28.1	28.0	6.34

Reference ID: 3129601

Figure 4.2.2.1 Mean Cmax (Study 034)

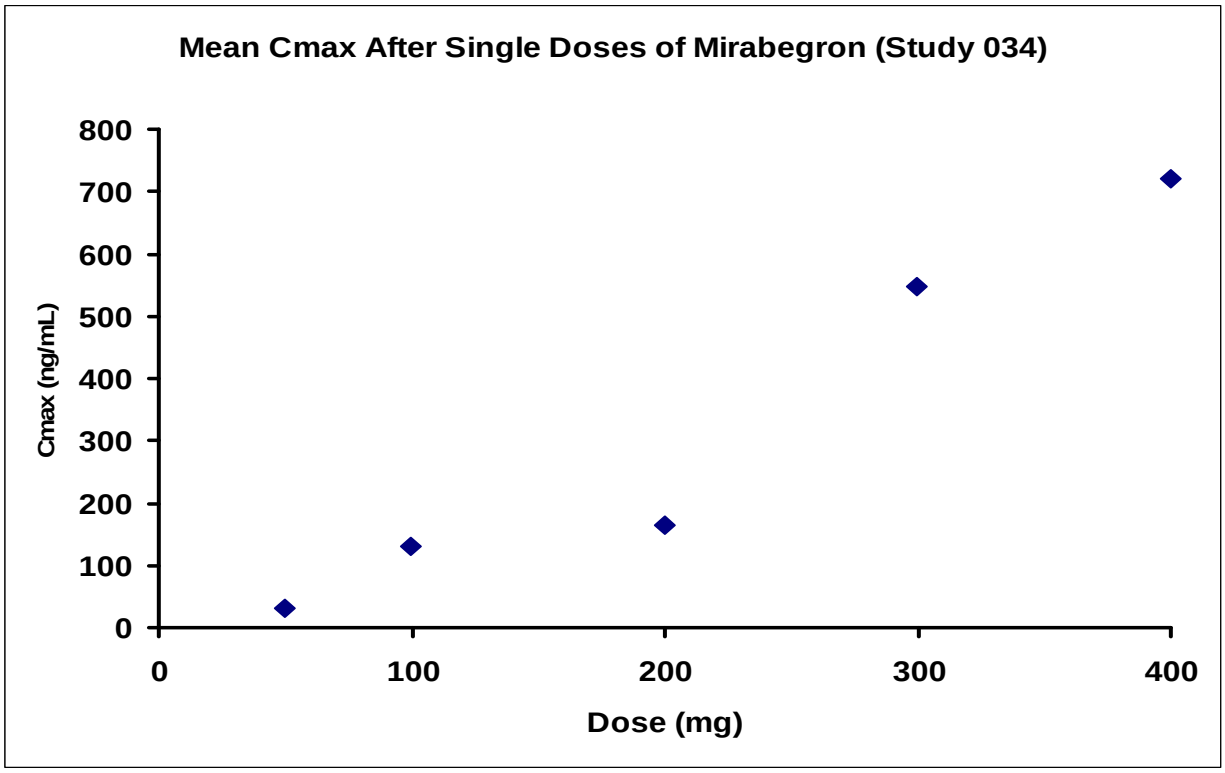
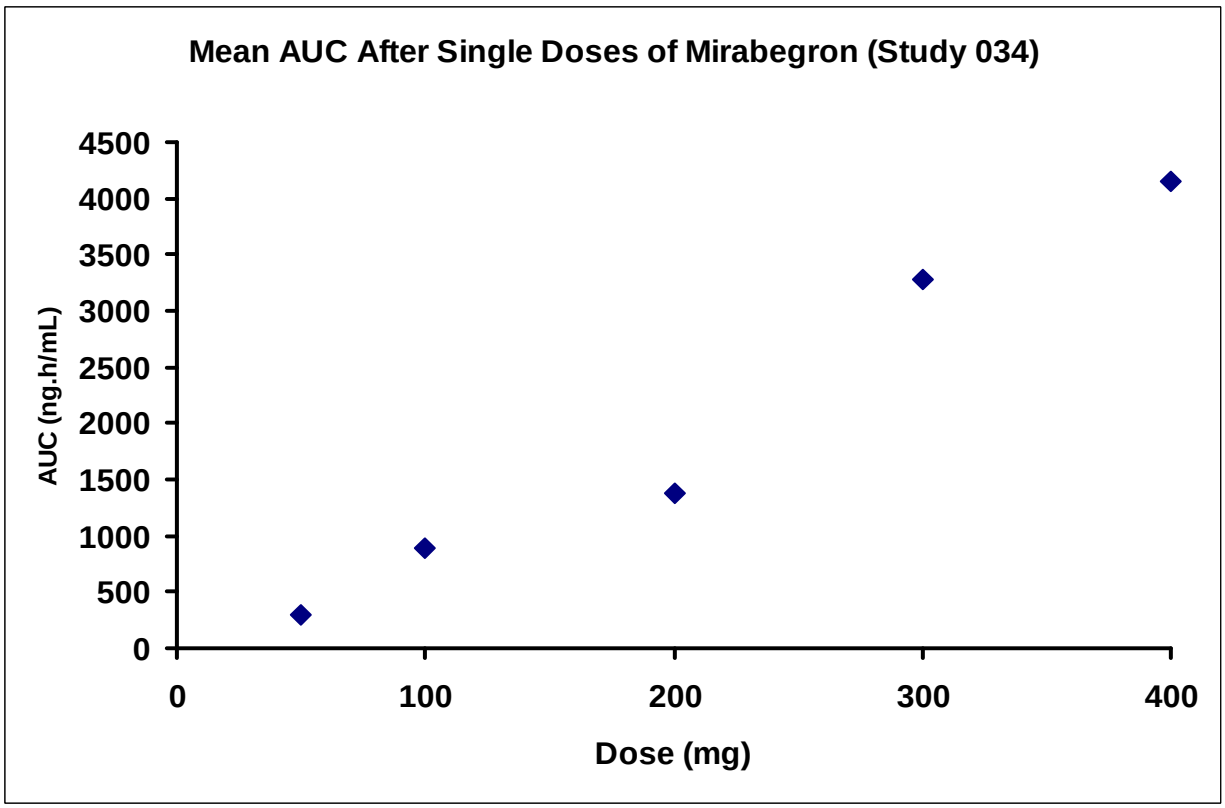


Figure 4.2.2.2 Mean AUC (Study 034)



Reference ID: 3129601

Figure 4.2.2.3 A Linear-Scale of Mean Plasma Concentration-Time Profiles of Mirabegron After Single and Multiple Doses in Healthy Subjects (Study# 178-CL-034).

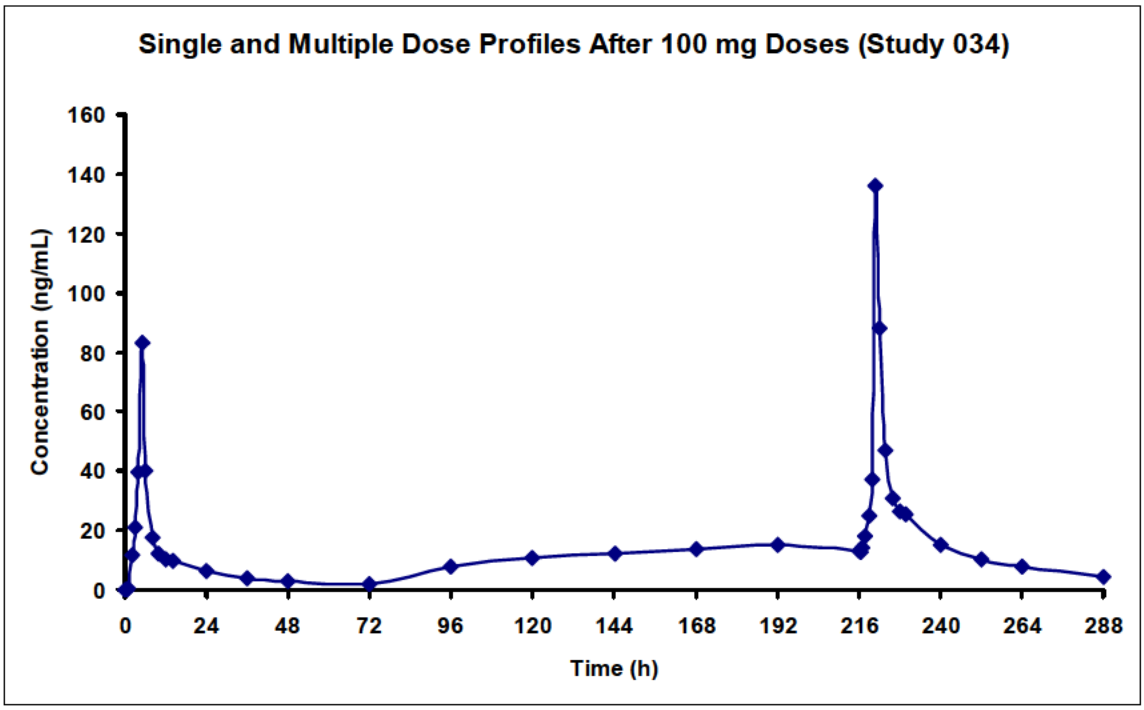
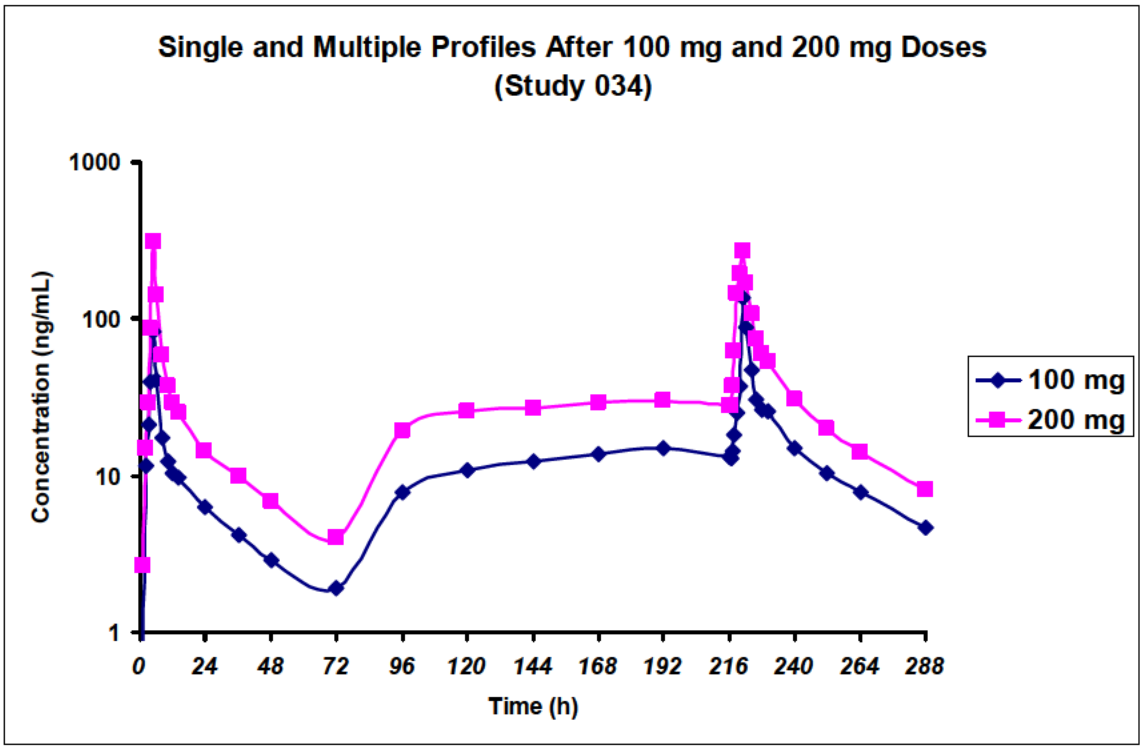


Figure 2.2.2.4. A Semi-Log Scale of Mean Plasma Concentration-Time Profiles of Mirabegron after Single and Multiple Doses in healthy Subjects (Study# 178-CL-034).



Reviewer's Comments:

As shown in study 031, there was minimal accumulation of drug after multiple doses. The steady state was achieved within 7 days. This is a confirmatory study to study 031.

4.2.3 Study 178-CL-072 (Age and Sex):

Study Title: "An Open-Label, Randomized, 2-Way Crossover Study to Evaluate the Pharmacokinetics of Mirabegron and its Metabolites in Healthy Young and Elderly Male and Female Subjects: Mirabegron Age and Gender Pharmacokinetic Study"

Objectives:

Primary:

- To evaluate the steady state PK of mirabegron and its metabolites in healthy subjects.
- To explore the effect of age and gender on the PK of mirabegron and its metabolites.

Secondary:

- To explore the effect of mirabegron on heart rate and cardiac output.

Study Design:

The study was an open-label, randomized, two-way crossover design and comprised 36 young (aged 18 to 45 years) subjects and 39 elderly (aged >55 years) subjects (see Table below for demographic characteristics of the subjects). There was 14 days washout period between treatments. The study was conducted in 75 healthy subjects as follows

Young (18 to 45 years): n=18 females and 18 males
Elderly (>55 years): 21 males and 18 females

Demographic Characteristics (Study 072)

Characteristic	Statistic/ Category	Young Males	Young Females	Elderly ≥55 Males	Elderly ≥55 Females	Elderly ≥65 Males	Elderly ≥65 Females	All subjects n (%)
Number of subjects	n	18	18	21	18	8	9	75
Age † (years)	Mean	28.6	28.7	63.4	65.1	68.5	70.0	47.1
	Std	6.6	6.5	4.8	6.0	2.3	4.2	18.8
	Min	19	19	55	57	65	65	19
	Median	26.5	29.5	62.0	64.5	69.0	70.0	57.0
	Max	45	43	72	77	72	77	77
Sex	Male	18 (100.0%)	0	21 (100.0%)	0	8 (100.0%)	0	39 (52.0%)
	Female	0	18 (100.0%)	0	18 (100.0%)	0	9 (100.0%)	36 (48.0%)
Race	White	14 (77.8%)	14 (77.8%)	19 (90.5%)	18 (100.0%)	7 (87.5%)	9 (100.0%)	65 (86.7%)
	Black	1 (5.6%)	3 (16.7%)	1 (4.8%)	0	0	0	5 (6.7%)
	Asian	0	0	1 (4.8%)	0	1 (12.5%)	0	1 (1.3%)
	Other	3 (16.7%)	1 (5.6%)	0	0	0	0	4 (5.3%)
Weight (kg)	Mean	68.9	58.8	72.6	62.3	70.25	64.61	65.9
	Std	9.6	5.9	8.2	8.5	5.79	9.48	9.7
	Min	54	50	62	48	62.0	48.3	48
	Median	65.2	58.2	70.3	61.5	70.55	64.40	64.6
	Max	84	70	88	83	80.0	82.7	88

† Derived variable. Percentages are based on the number of subjects in each group.
Elderly ≥55, subjects aged 55 and older.
Elderly ≥65, subjects aged 65 and older.

Reference ID: 3129601

Drug Administration:

Only on Day 1, subjects received the assigned oral dose of mirabegron twice, one in the morning and one in the evening. Then, on Day 2 to Day 7 subjects received an oral dose of mirabegron once daily. PK samples were collected over 168 hours after the last dose.

The study was conducted at three doses of 25, 50, and 100 mg as shows in the following scheme:

Treatment sequence	Period 1	Wash-out period	Period 2
A (3 males /3 females)	25 mg mirabegron	X	50 mg mirabegron
B (3 males /3 females)	50 mg mirabegron	X	25 mg mirabegron
C (3 males /3 females)	25 mg mirabegron	X	100 mg mirabegron
D (3 males /3 females)	100 mg mirabegron	X	25 mg mirabegron
E (3 males /3 females)	50 mg mirabegron	X	100 mg mirabegron
F (3 males /3 females)	100 mg mirabegron	X	50 mg mirabegron

Results:

- The PK data from this study is summarized in **Tables 4.2.3.1 to 4.2.3.3 and Figures 4.2.3.1 to 4.2.3.4.**
- As shown in other studies, there was greater than dose proportional increase in Cmax and AUC with increase in dose.
- Across the tested dose range, mean Cmax and AUC were 44% and 38% higher in females compared with males. It appears that this observed difference between males and females was more pronounced in elderly subjects ≥ 55 years of age compared with young subjects (18-45 years of age) (see Figures 4.2.3.3 and 4.2.3.3)
- There were no age-related differences in mean Cmax and AUC of mirabegron.

Reference ID: 3129601

Figure 4.2.3.1 Dose-Cmax in Males and Females (Study 072)

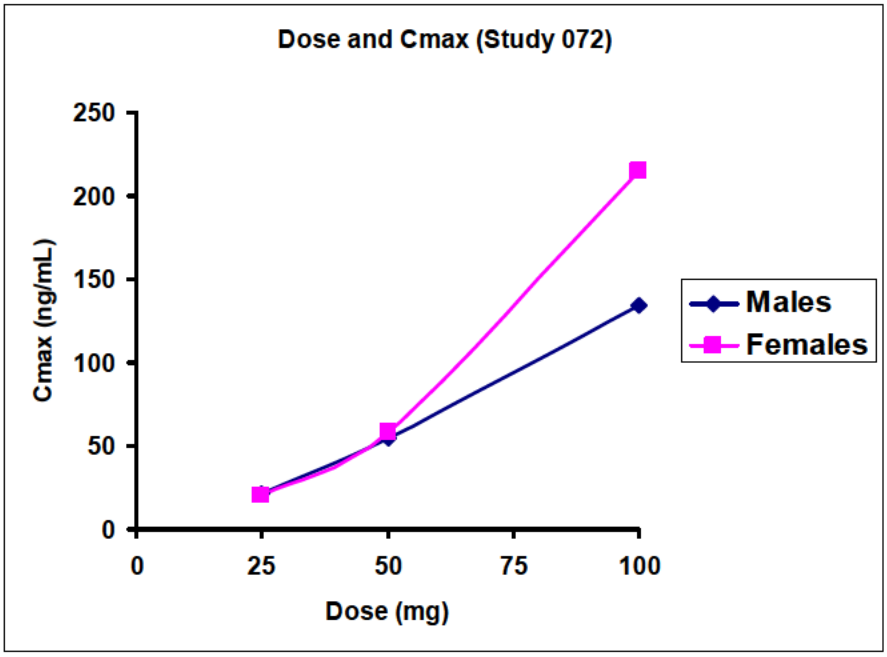
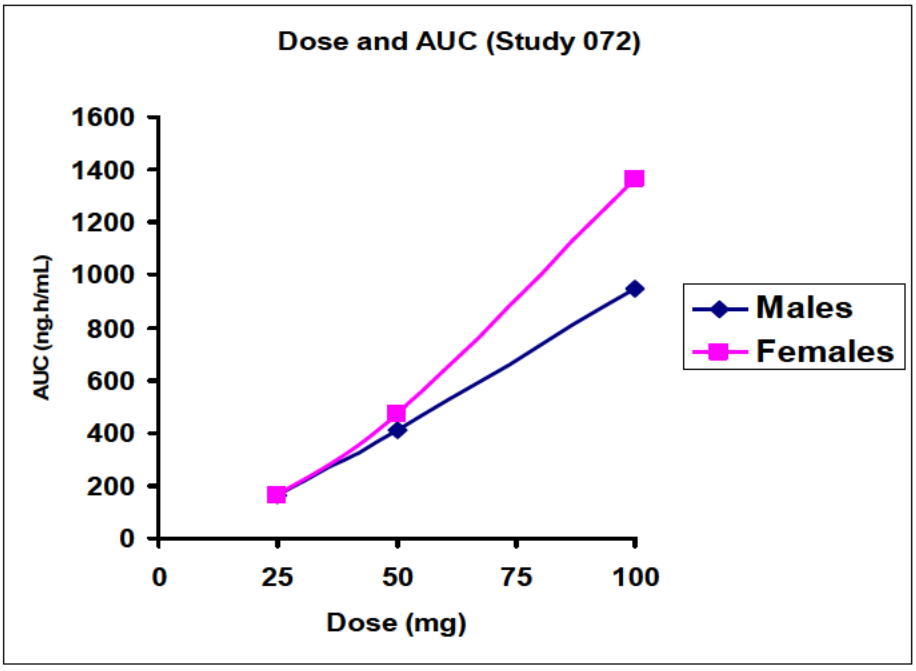


Figure 4.2.3.2 Dose-AUC in Males and Females (Study 072)



Reference ID: 3129601

Figure 4.2.3.3 Mean Mirabegron Plasma-Concentration-Time Profiles in Young Males and Females Following 50 mg Mirabegron Dose (Study 072)

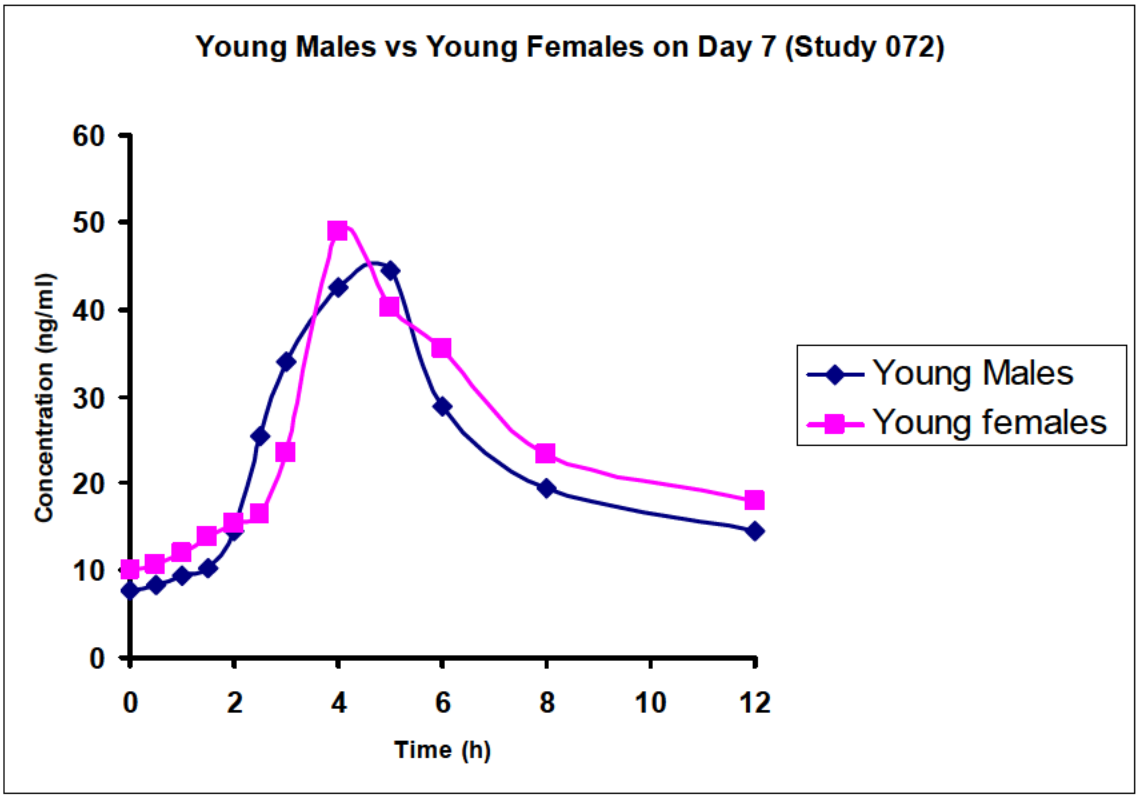


Figure 4.2.3.3 Mean Mirabegron Plasma-Concentration-Time Profiles in Elderly Males and Females Following 50 mg Mirabegron Dose (Study 072)

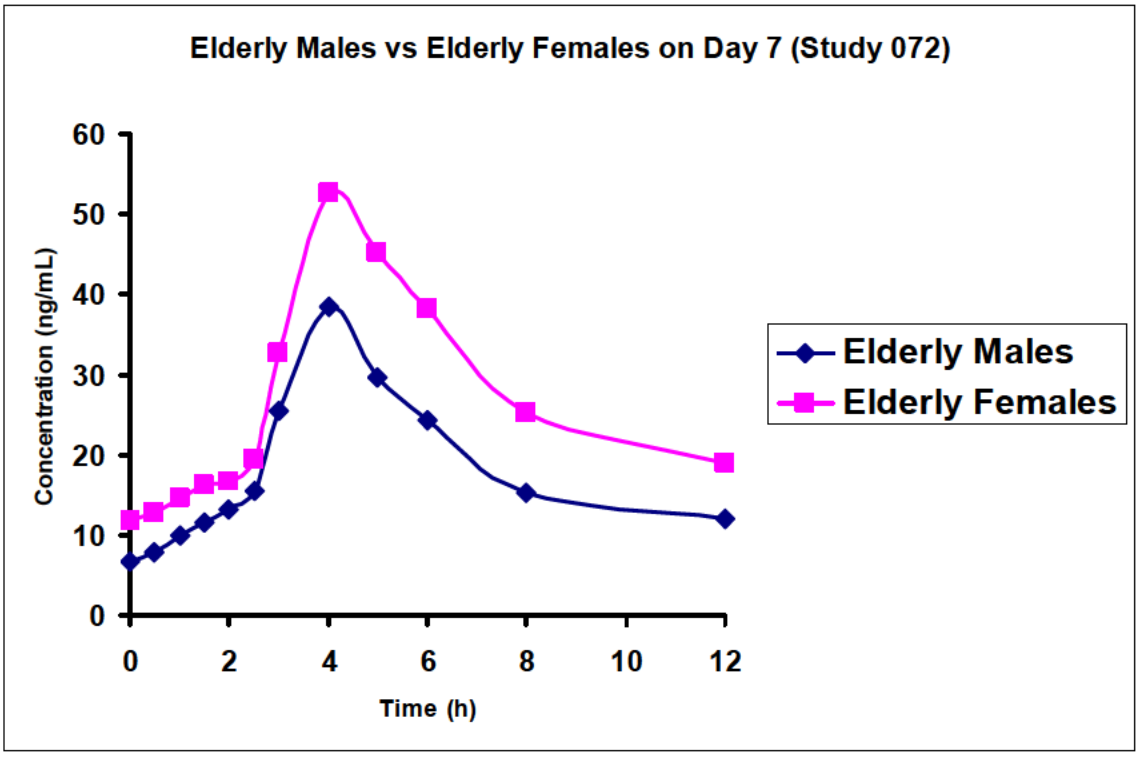


Figure 4.2.3.3 Mean Mirabegron Plasma-Concentration-Time Profiles in Young Males and Elderly Males Following 50 mg Mirabegron Dose (Study 072)

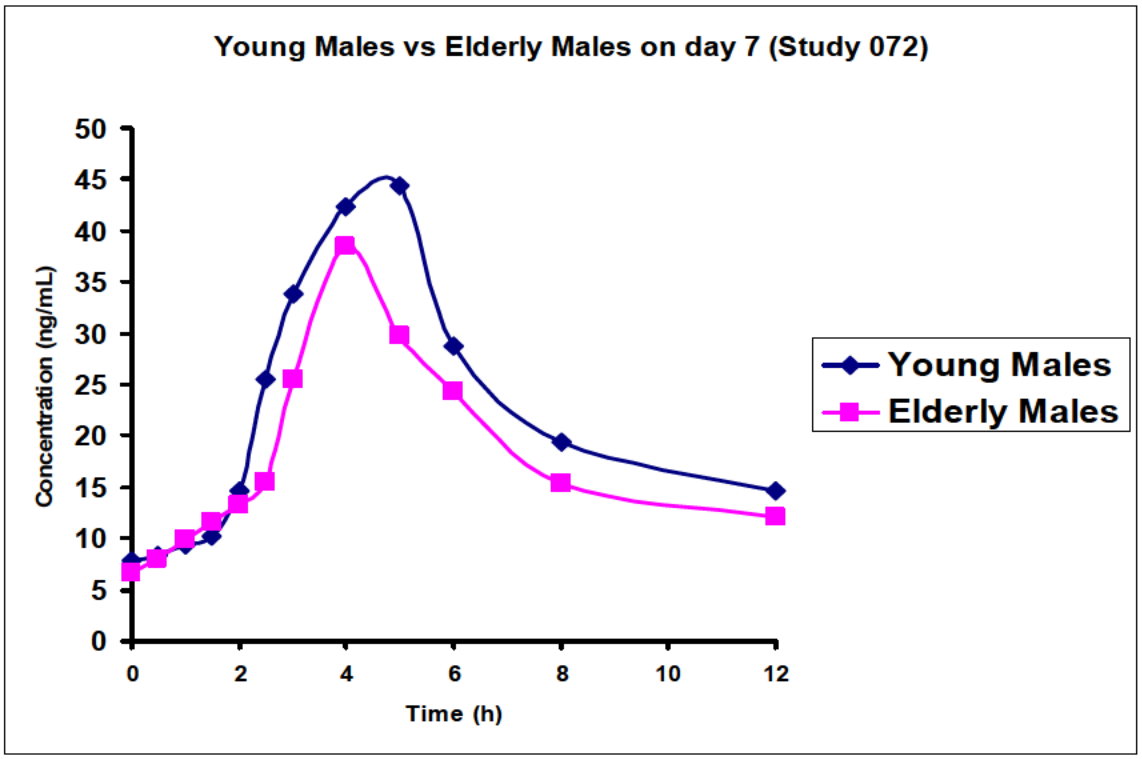


Figure 4.2.3.3 Mean Mirabegron Plasma-Concentration-Time Profiles in Young Females and Elderly Females Following 50 mg Mirabegron Dose (Study 072)

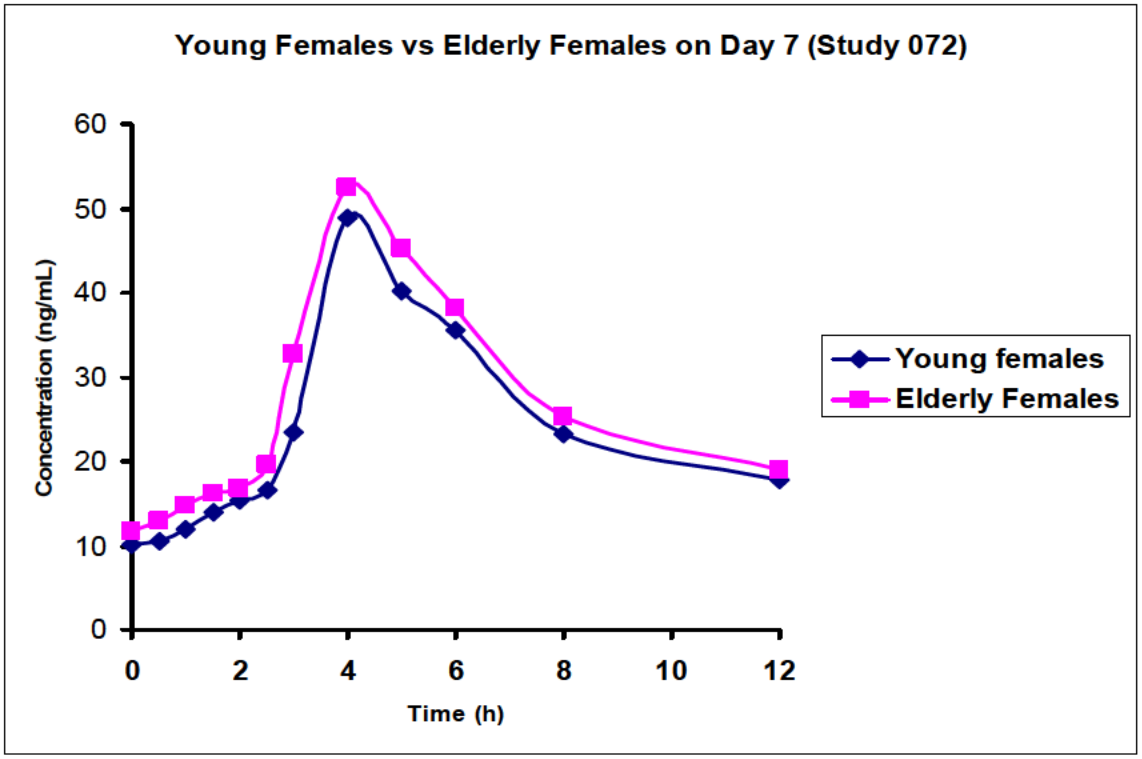


Table 4.2.3.1 Mean Cmax an AUC After 25 mg Dose on Day 7 (Study 072)

		Young		Elderly†	
Parameter	**Statistic**	**Males**	**Females**	**Males**	**Females**
C_{max} (ng/mL)	**n**	11	11	13	12
	Mean	21.6	20.1	11.7	19.7
	(SD, %CV)	(10.5, 49)	(5.6, 28)	(4.6, 39)	(5.6, 29)
	Min-Max	4.8-39	13-27	5.4-20	14-31
	Median	20.3	22.7	10.4	17.3
t_{max} (hr)	**n**	11	11	13	12
	Mean	4.14	3.86	4.70	3.88
	(SD)	(0.84)	(0.78)	(0.85)	(1.13)
	Min-Max	2.5-5.0	2.5-5.0	3.0-6.0	2.0-5.0
	Median	4.00	4.00	5.00	4.00
AUC_{tau} (ng·hr/mL)	**n**	11	11	13	12
	Mean	165	163	113	182
	(SD, %CV)	(65, 39)	(46, 28)	(35, 31)	(56, 31)
	Min-Max	67-293	93-231	69-194	126-307
	Median	141	168	101	165

Table 4.2.3.2 Mean Cmax an AUC After 50 mg Dose on Day 7 (Study 072)

		Young		Elderly†	
Parameter	**Statistic**	**Male**	**Females**	**Males**	**Females**
C_{max} (ng/mL)	**n**	12	12	11	11
	Mean	54.4	58.1	43.5	66.3
	(SD, %CV)	(24.5, 45)	(15.8, 27)	(18.9, 43)	(27.3, 41)
	Min-Max	23-102	31-84	23-71	16-108
	Median	48.6	60.4	34.5	73.0
t_{max} (hr)	**n**	12	12	11	11
	Mean	3.92	4.58	3.86	4.45
	(SD)	(0.87)	(1.00)	(1.31)	(0.82)
	Min-Max	2.5-5.0	3.0-6.0	1.5-6.0	3.0-6.0
	Median	4.00	4.00	4.00	4.00
AUC_{tau} (ng·hr/mL)	**n**	12	12	11	11
	Mean	413	471	341	512
	(SD, %CV)	(148, 36)	(88, 19)	(71, 21)	(178, 35)
	Min-Max	230-716	302-581	212-424	230-739
	Median	392	480	323	568

Reference ID: 3129601

Table 4.2.3.3 Mean Cmax an AUC After 100 mg Dose on Day 7 (Study 072)

		Young		Elderly†	
Parameter	**Statistic**	**Males**	**Females**	**Males**	**Females**
C_{max} (ng/mL)	**n**	12	11	14	11
	Mean	134	215	130	259
	(SD, %CV)	(58, 44)	(60, 28)	(35, 27)	(81.8, 32)
	Min-Max	75-257	108-306	73-197	162-383
	Median	110	213	127	234
t_{max} (hr)	**n**	12	11	14	11
	Mean	3.63	4.00	4.04	4.05
	(SD)	(1.11)	(0.77)	(1.10)	(0.91)
	Min-Max	2.0-5.0	3.0-5.0	2.5-6.0	2.5-5.0
	Median	4.00	4.00	4.00	4.00
AUC_{tau} (ng·hr/mL)	**n**	12	11	14	11
	Mean	947	1366	992	1682
	(SD, %CV)	(228, 24)	(257, 19)	(235, 24)	(352, 21)
	Min-Max	611-1322	875-1805	694-1539	1291-2510
	Median	952	1393	945	1577

† Elderly are subjects aged 55 years and above.

Reviewer's Comments:

This study is a confirmatory to the other studies in terms of:

- Exposure in females compared to males
- Effect of age (i.e., no effect of age on PK of mirabegron)
- Greater-than dose proportionality in exposure with increase in dose

Reference ID: 3129601

4.2.4 Study 178-CL-038 (Effect of Renal Impairment):

Study Title: "A Phase 1, Open-Label, Single-Dose Parallel-Group Study to Assess the Effect of Mild, Moderate and Severe Renal Impairment on the Pharmacokinetics of Mirabegron (YM178)"

Objectives:

- To assess the PK and protein binding of mirabegron administered under fasted conditions to male and female volunteers with mild, moderate or severe renal impairment compared with volunteers with normal renal function.
- To evaluate the safety and tolerability of a single oral 100 mg dose of mirabegron in these patients

Study Design:

This is 100 mg single-dose study in patients with mild, moderate or severe renal impairment (not on dialysis) and healthy subjects with normal renal function (see Table below for demographic Characteristics of the subjects). The renal function was determined based on Estimated Glomerular Filtration Rate (eGFR) as shown below:

- ≥ 90 mL/min/1.73 m^2 (normal renal function)
- 60 to 89 mL/min/1.73 m^2 (mild renal impairment)
- 30 to 59 mL/min/1.73 m^2 (moderate renal impairment)
- 15 to 29 mL/min/1.73 m^2 (severe renal impairment)

A total of 8 volunteers per renal group were enrolled in this study. Subjects received 100 mg single dose after overnight fast. PK samples were collected over 120 hours post dosing.

Demographic Characteristics (Study 038)

		Renal Function Group				
Parameter	Class	Normal (n = 8) †	Mild (n = 8)	Moderate (n = 8) ‡	Severe (n = 9)	Total (n = 33) §
Sex, n (%)	Male	4 (50.0%)	3 (37.5%)	6 (75.0%)	5 (55.6%)	18 (54.5%)
	Female	4 (50.0%)	5 (62.5%)	2 (25.0%)	4 (44.4%)	15 (45.5%)
Race, n (%)	White	5 (62.5%)	6 (75.0%)	8 (100.0%)	7 (77.8%)	26 (78.8%)
	Black or AfAm	2 (25.0%)	0	0	2 (22.2%)	4 (12.1%)
	Asian	1 (12.5%)	0	0	0	1 (3.0%)
	Native Hawaiian-OPI	0	2 (25.0%)	0	0	2 (6.1%)
Ethnicity, n (%)	Hispanic or Latino	6 (75.0%)	4 (50.0%)	6 (75.0%)	6 (66.7%)	22 (66.7%)
	Not Hispanic or Latino	2 (25.0%)	4 (50.0%)	2 (25.0%)	3 (33.3%)	11 (33.3%)
Age (years)	Mean (SD)	60.0 (7.39)	68.5 (8.26)	67.8 (9.65)	64.8 (10.65)	65.2 (9.31)
	Median	62.5	72.5	71.5	68.0	67.0
	Min-Max	50-72	54-76	52-77	42-75	42-77
Weight (kg)	Mean (SD)	74.84 (14.243)	76.36 (24.637)	87.99 (19.514)	73.27 (10.937)	77.97 (18.021)
	Median	75.20	65.85	87.85	73.50	74.70
	Min-Max	49.3-93.0	54.1-118.3	54.3-119.1	53.2-83.2	49.3-119.1
Height (cm)	Mean (SD)	165.08 (6.422)	162.86 (8.005)	171.01 (9.154)	164.48 (4.287)	165.82 (7.452)
	Median	166.50	163.80	172.70	166.00	166.00
	Min-Max	155.0-172.6	148.5-174.0	157.5-182.0	154.9-170.2	148.5-182.0

Reference ID: 3129601

Results:

The data from this study shows increase in Cmax and AUC in severe renal impairment compared to healthy subjects (**Figures 4.2.4.1 and 4.2.4.1, Tables 4.2.4.1 and 4.2.4.2**). However, exposure in mild and moderate was small compared to severe. As a confirmatory data, the cumulative amount excreted in urine was reduced in severe renal impairment compared to healthy subjects (**Figure 4.2.4.3**).

Figure 4.2.4.1. Mean Plasma Concentration-Time Profiles of Mirabegron Over 120 Hours (Study 038)

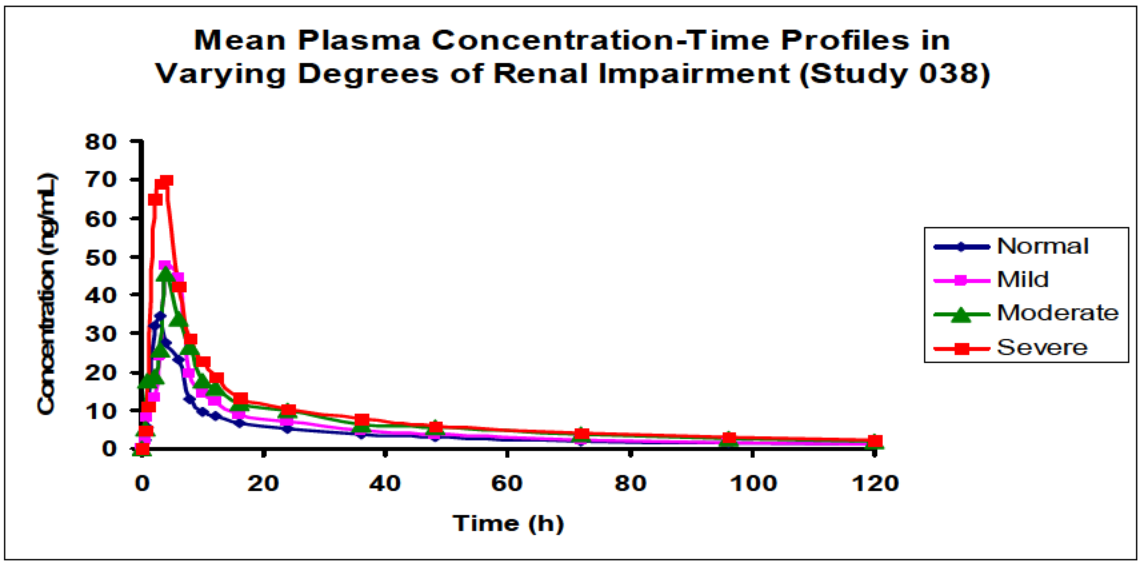
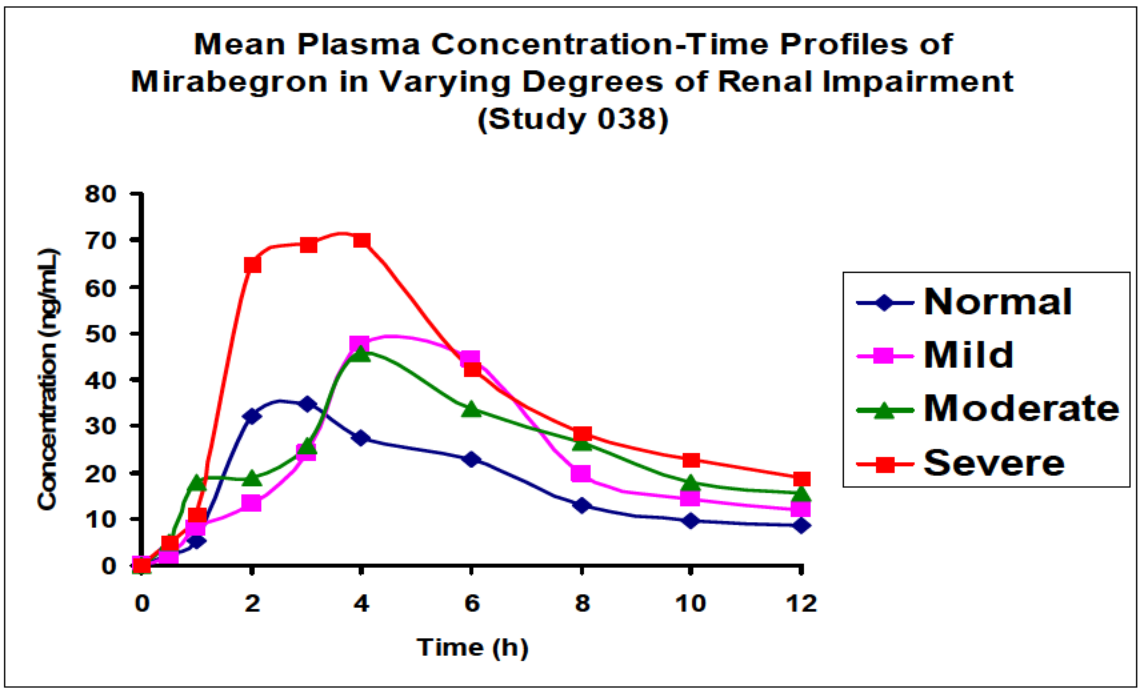


Figure 4.2.4.2. Mean Plasma Concentration-Time Profiles of Mirabegron Over the First 12 Hours (Study 038)



Reference ID: 3129601

Table 4.2.4.1. Summary of Cmax and AUC of Mirabegron (Study 038)

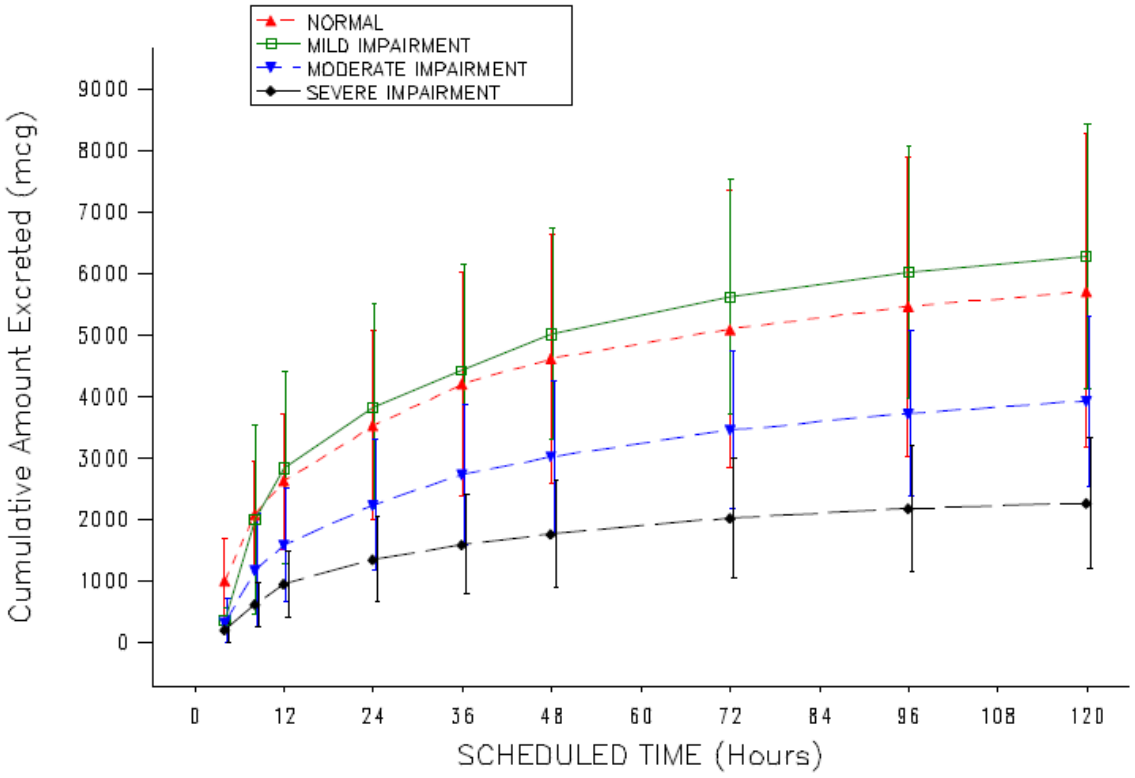
Parameter (Unit)	Statistic	Renal Function Group			
		Normal (n = 8)	Mild (n = 8)	Moderate (n = 8)	Severe (n = 8)
C_{max} (ng/mL)	Mean (SD)	45.2 (26.94)	57.0 (49.99)	60.8 (41.95)	93.8 (70.12)
	% CV	59.5	87.6	69.0	74.8
	Median	41.8	30.5	48.3	72.4
	Min-Max	11.9-99.4	9.8-151.8	8.4-140.5	19.2-231.3
	Geometric mean	38.1	40.4	46.9	73.2
AUC_{last} (hr·ng/mL)	Mean (SD)	497 (216.2)	659 (399.2)	844 (395.8)	1060 (546.8)
	% CV	43.5	60.5	46.9	51.6
	Median	532	550	872	945
	Min-Max	203-788	212-1492	168-1297	377-2115
	Geometric mean	448	567	724	945
AUC_{inf} (hr·ng/mL)	Mean (SD)	558 (249.3)	771 (479.6)	992 (512.0)	1239 (654.2)
	% CV	44.6	62.2	51.6	52.8
	Median	601	645	969	1120
	Min-Max	217-919	227-1768	183-1793	397-2513
	Geometric mean	501	655	833	1093

Table 4.2.4.2. Statistical Analysis of Cmax and AUC of Mirabegron (Study 038)

Parameter (unit)	Test Group/ Reference Group	Test Group		Reference Group		Ratio of Test Group/Reference Group ‡	90% CI for Ratio ‡
		n	Geometric Mean †	n	Geometric Mean †		
AUC_{inf} (hr·ng/mL)	Mild/Normal	8	654.58	8	500.92	130.68	(77.73, 219.69)
	Moderate/Normal	8	832.84	8	500.92	166.26	(98.90, 279.52)
	Severe/Normal	8	1092.77	8	500.92	218.15	(129.76, 366.75)
C_{max} (ng/mL)	Mild/Normal	8	40.39	8	38.12	105.94	(53.36, 210.33)
	Moderate/Normal	8	46.88	8	38.12	122.96	(61.93, 244.12)
	Severe/Normal	8	73.24	8	38.12	192.12	(96.77, 381.43)
AUC_{last} (hr·ng/mL)	Mild/Normal	8	566.76	8	448.40	126.39	(77.09, 207.23)
	Moderate/Normal	8	723.54	8	448.40	161.36	(98.42, 264.56)
	Severe/Normal	8	944.89	8	448.40	210.72	(128.53, 345.49)
CL/F (L/hr)	Mild/Normal	8	152.77	8	199.63	76.53	(45.52, 128.65)
	Moderate/Normal	8	120.07	8	199.63	60.15	(35.78, 101.12)
	Severe/Normal	8	91.51	8	199.63	45.84	(27.27, 77.06)

Reference ID: 3129601

Figure 4.2.4.3. Mean (SD) Cumulative Amounts of Mirabegron Excreted into Urine (Study 038)



Reviewer's Comments:

Since the drug and its metabolites are primarily eliminated by the kidneys, the exposure in renal impairment and in particular in severe condition would be expected to be higher than healthy subjects with normal renal function. Based on this, the sponsor proposed to reduce the dose to 25 mg in patients with severe renal impairment. Mirabegron is not recommended in patients with End Stage Renal Disease (ESRD).

4.2.5 Study 178-CL-039 (Effect of Hepatic Impairment):

Study Title: "An Open Label Single Dose Study to Investigate the Effect of Mild and Moderate Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of Mirabegron (YM178) Compared with Healthy Subjects YM178 Hepatic Impairment"

Objectives:

Primary

- To assess the single dose PK of 100 mg of mirabegron in subjects with mild or moderate hepatic impairment relative to matching healthy subjects.

Secondary

- To evaluate the safety and tolerability of mirabegron in subjects with mild or moderate hepatic impairment.

Study Design:

This was a single 100 mg dose in healthy and hepatically impaired subjects. The determination of the severity of hepatic impairment was based on Child-Pugh scale. The study was conducted in 16 males and females with hepatic impairment, 8 mild, 8 moderate, and 16 healthy (The table below shows the demographic characteristics of the subjects). Subjects received the dose after overnight fast. PK blood samples were collected over 144 hours post dose. Below is the summary of subjects' demographic characteristics.

Reference ID: 3129601

Demographic Characteristics (Study 039)

Characteristic	Statistic/ Category	Subjects with Mild Hepatic Impairment (Group 1A)	Matched Healthy Subjects (Group 1B)	Subjects with Moderate Hepatic Impairment (Group 2A)	Matched Healthy Subjects (Group 2B)	All Healthy Subjects
Age, (years)	n	8	8	8	8	16
	Mean	49.9	48.0	46.8	48.0	48.0
	Std	5.5	6.7	11.7	13.0	10.0
	Min	45	40	28	28	28
	Median	49.0	46.5	50.5	52.0	47.5
	Max	60	58	58	62	62
Sex, n (%)	Male	4 (50.0%)	4 (50.0%)	5 (62.5%)	5 (62.5%)	9 (56.3%)
	Female	4 (50.0%)	4 (50.0%)	3 (37.5%)	3 (37.5%)	7 (43.8%)
Race, n (%)	White	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	16 (100.0%)
	Black	0	0	0	0	0
	Asian	0	0	0	0	0
	Other	0	0	0	0	0
Weight (kg)	n	8	8	8	8	16
	Mean	67.9	69.4	79.9	82.1	75.8
	Std	13.7	15.6	9.0	8.2	13.7
	Min	49	57	60	70	57
	Median	63.5	64.5	82.5	82.5	74.0
	Max	88	106	88	97	106
Height (m)	n	8	8	8	8	16
	Mean	1.708	1.710	1.723	1.748	1.729
	Std	0.101	0.076	0.094	0.088	0.082
	Min	1.57	1.64	1.58	1.63	1.63
	Median	1.715	1.685	1.730	1.755	1.705
	Max	1.82	1.85	1.85	1.86	1.86
BMI (kg/m^2)	n	8	8	8	8	16
	Mean	23.14	23.52	26.97	26.98	25.25
	Std	3.34	3.33	3.08	3.08	3.58
	Min	19.9	20.7	23.7	24.5	20.7
	Median	22.15	22.11	26.03	25.40	24.60
	Max	29.8	31.0	32.0	32.0	32.0

Percentages are based on the number of subjects in each group. Analysis set: SAF

Results:

From this study, the Cmax and AUC were increased in moderate hepatic impairment relative to healthy subjects (**Figure 4.2.5.1 and tables 4.2.5.1 and 4.2.5.2**).

Reference ID: 3129601

Figure 4.2.5.1. Mean Plasma Concentration-Time Profiles of Mirabegron Over The Initial 12 Hours Post Dose (Study 039)

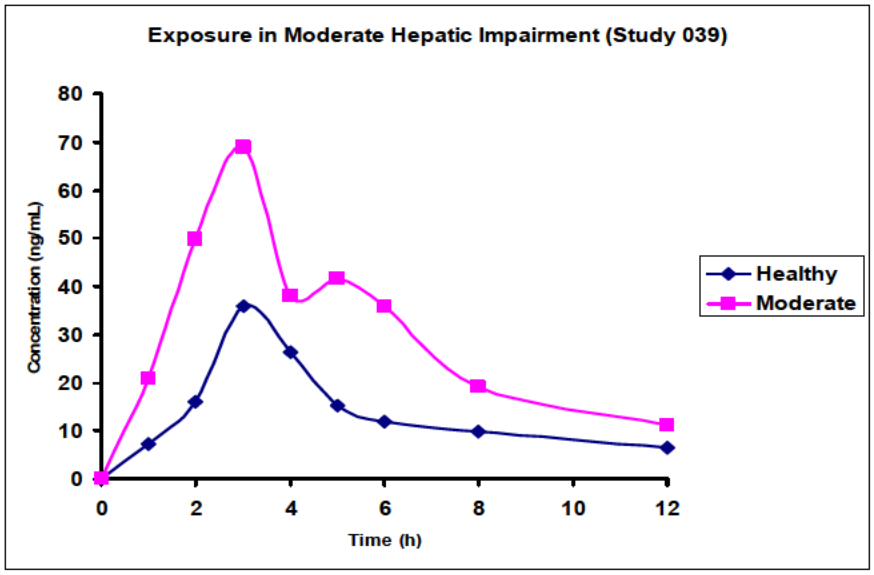


Table 4.2.5.1. Summary of Cmax and AUC of Mirabegron (Study 039)

Parameter	Statistic	Mildly Impaired Subjects (n=8)	Matching Healthy Subjects (n=8)	Moderately Impaired Subjects (n=8)	Matching Healthy Subjects (n=8)
C_{max} (ng/mL)	Mean	71.9	66.9	113	41.5
	(SD, %CV)	(50.5, 70)	(74.4, 111)	(68, 60)	(31.8, 77)
	Min-max	7.2-160	17-242	11-215	11-107
	Median	71.5	38.8	93.0	40.2
t_{max} (hr)	Mean	3.50	2.13	3.63	2.50
	(SD)	(2.07)	(0.83)	(1.51)	(0.93)
	Min-max	1.0-8.0	1.0-3.0	2.0-6.0	1.0-4.0
	Median	3.00	2.00	3.00	2.50
AUC_{last} (ng·hr/mL)	Mean	726	549	749	431
	(SD, %CV)	(369, 51)	(358, 65)	(345, 46)	(226, 52)
	Min-max	130-1291	309-1390	229-1278	123-828
	Median	704	430	663	410
AUC_{inf} (ng·hr/mL)	Mean	770	615	784	486
	(SD, %CV)	(391, 51)	(370, 60)	(363, 46)	(248, 51)
	Min-max	154-1403	348-1482	241-1304	141-883
	Median	723	478	691	461

Reference ID: 3129601

Table 4.2.5.2. Statistical Analysis of Cmax and AUC of Mirabegron (Study 039)

Hepatic Function Group	Parameter	Least Square Means		Ratio Impaired/Healthy Subjects	90% Confidence Interval
		Healthy Subjects	Hepatically Impaired Subjects		
Mild impairment	AUC_{inf} (ng·hr/mL)	550	655	1.19	0.69, 2.05
	AUC_{last} (ng·hr/mL)	482	611	1.27	0.70, 2.28
	C_{max} (ng/mL)	46.6	50.7	1.09	0.42, 2.80
	$t_{1/2}$ (hr)	55.6	66.2	1.19	1.08, 1.32
	CL/F (L/hr)	182	153	0.84	0.49, 1.45
	V_z/F (L)	14587	14582	1.00	0.57, 1.76
	f_u	0.27	0.29	1.09	0.95, 1.25
Moderate impairment	AUC_{inf} (ng·hr/mL)	424	699	1.65	0.95, 2.85
	AUC_{last} (ng·hr/mL)	375	668	1.78	1.01, 3.13
	C_{max} (ng/mL)	31.7	87.1	2.75	1.08, 6.98
	$t_{1/2}$ (hr)	54.5	50.0	0.92	0.77, 1.10
	CL/F (L/hr)	236	143	0.61	0.35, 1.05
	V_z/F (L)	18524	10328	0.56	0.34, 0.92
	f_u	0.30	0.28	0.95	0.83, 1.09

Reviewer's Comments:

Since mirabegron is extensively metabolized drug, it is expected the exposure will be increased as a function of hepatic impairment. Based on this, the sponsor proposed to reduce the dose of mirabegron to 25 mg in patients with moderate renal impairment. Mirabegron is not recommended in patients with severe hepatic impairment.

Reference ID: 3129601

4.2.6 Study 178-CL-005 (CYP2D6 Assessment and DDI with Metoprolol):

Study Title: "An Open-Label, One-Sequence, Parallel Study to Compare the Single Dose Pharmacokinetics of YM178 in Healthy Poor or Extensive Metabolizers for CYP2D6 and to Assess the Effect of Multiple Doses of YM178 on the Metabolism of the Model Substrate Metoprolol"

Objectives:

Part I: To compare the single dose PK profile of mirabegron in poor (PM) and extensive (EM) metabolizers for CYP2D6
Part II: To evaluate the effect of multiple doses of mirabegron on the metabolism of metoprolol; a model substrate of CYP2D6

Study Design:

All subjects were genotyped for CYP2D6 before the study. Genotype expression was confirmed by dextromethorphan phenotyping.

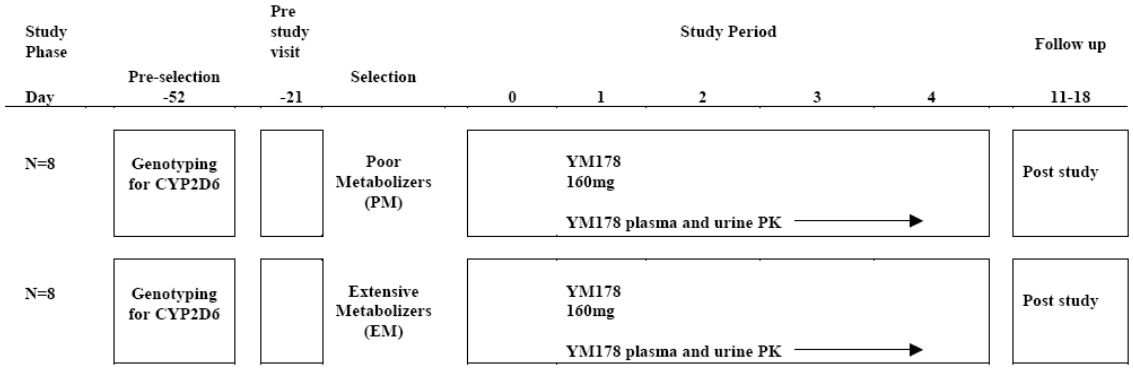
Part I: The PK profile of a single dose of mirabegron was compared in 8 healthy subjects genotyped and phenotyped as PM for CYP2D6 and in 8 healthy subjects genotyped and phenotyped as EM for CYP2D6. Subjects were admitted from the day before dosing until 72 h after dose administration. Plasma and urine samples of mirabegron were collected before dosing and for 72h thereafter.

Part II: The effect of mirabegron on the model substrate of CYP2D6 metoprolol was evaluated, using a cross-over design, in 12 healthy male subjects genotyped and phenotyped as EM for CYP2D6.

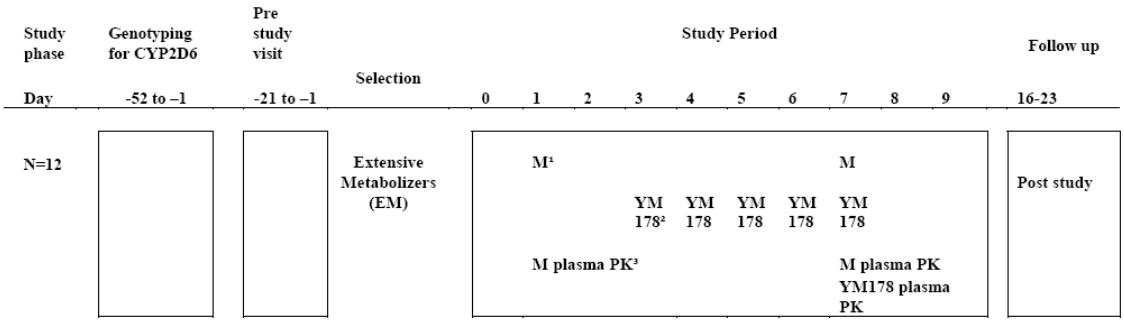
Each subject received a single dose of metoprolol tartrate on the first day of dosing (Day 1). After a 1-day washout mirabegron was given as multiple doses alone for 4 days (Days 3-6) and in combination with metoprolol for 1 day (Day 7). The PK profile of metoprolol was assessed on the first day and on the last day of dosing. Plasma concentrations of mirabegron were measured on the last day of monotherapy and during the combination treatment of mirabegron with metoprolol. Trough levels of mirabegron were assessed throughout dosing of mirabegron. The following scheme shows the overall study design:

Reference ID: 3129601

Schedule of the Overall Study design for Part I



Schedule of the Overall Study design for Part II



¹ M: Metoprolol tartrate 100 mg
² YM178: YM178 160 mg
³ PK: Pharmacokinetic

Subjects:

The study was conducted in male Caucasian subjects with the age ranged from 18 to 55 years. Prior the initiation of the study, 120 subjects were genotyped for CYP2D6 alleles, and 49 of them were screened. Out of these, a total of 28 subjects completed the study as follows:

Part I: 8 EMs and 8 PMs for CYP2D6 were planned, enrolled and completed the study, and were analyzed for the primary endpoints and for safety.
Part II: 12 EMs for CYP2D6 were planned, enrolled and completed the study, and were analyzed for the primary endpoints and for safety.

Dosing and Administration:

Part I: Subjects received a single 160 mg dose of mirabegron as 2 x80 mg capsule after overnight fast. Plasma and urine samples were collected over 72 hours.

Part II:
This part was designed as a crossover study as follows:

Reference ID: 3129601

Metoprolol: Subjects received 2 single doses of 100 mg metoporolol tablets on Day 1 and Day 7.

Mirabegron: Subjects received multiple doses of 160 mg as 2 x 80 mg capsules once daily on Days 3 through Day 7 and metoprolol on Days 1 and 7 (see above). In this case, mirabegron was administered alone for 4 days (Days 3 to 6). Metoprolol was administered alone on Day 1 and in combination with mirabegron on Day 7. Therefore, nothing was administered on Day 2 (washout).

Plasma concentrations of mirabegron were measured on the last day of monotherapy (Day 6) and during the combination treatment of mirabegron with metoprolol (Day 7). Trough levels of mirabegron were assessed throughout (pre-dose on days 3, 4, 5, and 6). Plasma samples for metoprolol PK were collected on Day 1 and Day 7 up to 36 hours post dosing in each day.

Results:

Part I:

There was small difference in the PK data for mirabegron between EM and PM subjects (**Table 4.2.6.1 and Figure 4.2.6.1**). The exposure in PM appears to be slightly higher (~19%) compared to EM. The same trend was also seen for urinary excretion data in PM which was approximately 26% higher than EM (**Table 4.2.6.2**). For detail discussion please see Genomics Group review in **Appendix II**.

Table 4.2.6.1 Mean Mirabegron PK Parameters in PM and EM Subjects (Study 005)

Genotype	Statistic	t_{max}[1] (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	$AUC_{0\text{-}inf}$ (ng.h/ml)	$t_{1/2}$ (h)	CL/F (l/h)	V_z/F (l)
EM	Mean	2.31	230	1173	1253	22.9	129	4268
	(SD, CV)	(0.46)	(53, 23%)	(141, 12%)	(153, 12%)	(2.8, 12%)	(16, 12%)	(661, 15%)
	Range	1.5 – 3.0	149 – 302	998 – 1392	1047 – 1492	20 – 27	107 – 153	3489 – 5538
	Median	2.50	240	1186	1263	22.0	127	4224
PM	Mean	2.13	263	1381	1493	25.0	114	4090
	(SD, CV)	(1.16)	(113, 43%)	(373, 27%)	(394, 26%)	(4.6, 19%)	(30, 26%)	(1367, 33%)
	Range	0.5 – 4.0	128 – 432	929 – 1793	1061 – 1936	15 – 29	83 – 151	2701 – 6317
	Median	2.00	245	1390	1448	26.1	113	3373

Reference ID: 3129601

Figure 4.2.6.1 Mean Plasma Concentration-Time Profiles of Mirabegron in PM and EM Subjects (Study 0005)

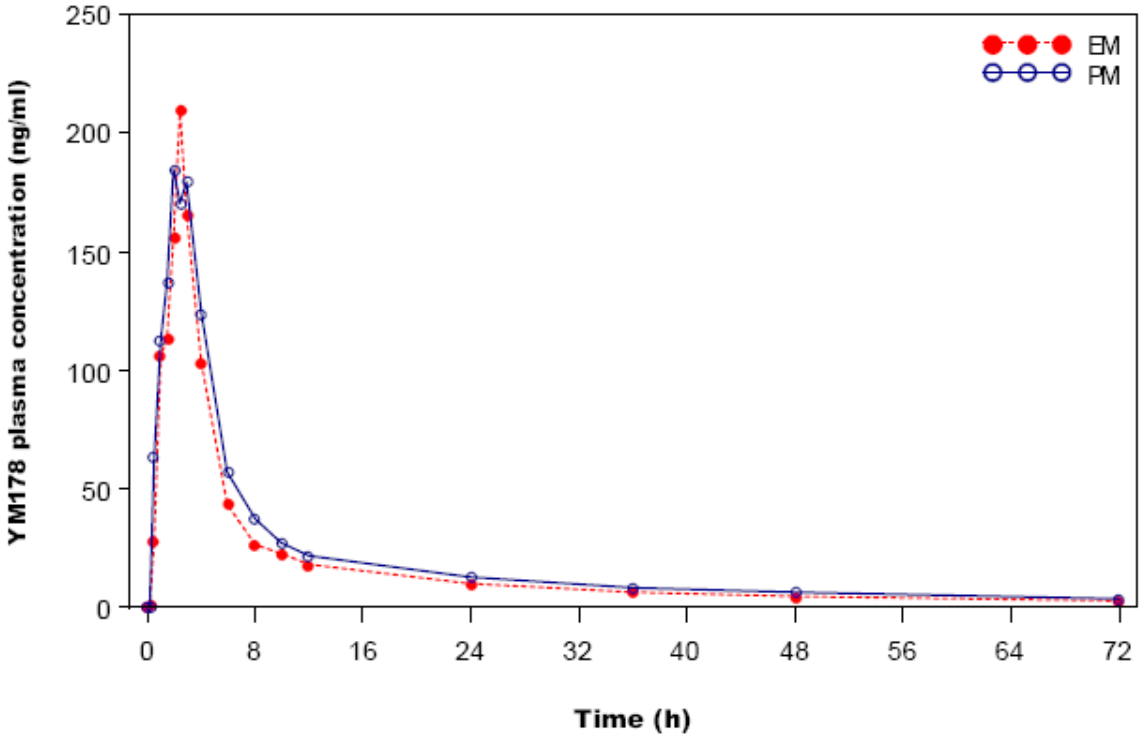


Table 4.2.6.2 Mean Mirabegron Urine PK Parameters in PM and EM Subjects (Study 005)

Genotype	Statistic	$Ae_{0\text{-}72h}$ (mg)	% of the dose excreted (%)	CL_R (l/h)
EM	Arithmetic mean (SD, CV) Range Median	18.7 (4.8, 26%) 8.6 – 24 19.4	11.7 (3.0, 26%) 5.4 – 15 12.1	16.1 (4.0, 25%) 7 – 20 16.3
PM	Arithmetic mean (SD, CV) Range Median	24.6 (6.7, 27%) 15 – 34 25.3	15.4 (4.2, 27%) 9.3 – 21 15.8	18.0 (3.1, 17%) 15 – 25 17.4

Part II:

- The summary data from Part II study is shown in **Figure 4.2.6.2 and Tables 4.2.6.3-4.2.6.5.**
- The mean metoprolol Cmax was increased from 132 ng/mL to 247 ng/mL when co-administered with miraegron. Also, the AUC was increased from 439 ng.h/mL to 1389 ng.h/mL. Metoprolol half-life was also increased from the mean of 2.96 h to 4.11 h.
- As expected, the Cmax and AUC of metoprolol metabolite, α-hydroxymetoprolol, were decreased (Cmax from 81.7 to 33.6 ng/mL and AUC from 540 to 260 ng.h/mL).

Reference ID: 3129601

Figure 4.2.6.2 Mean Plasma Concentration-Time Profiles of Metoprolol With and Without Mirabegron (Study 005)

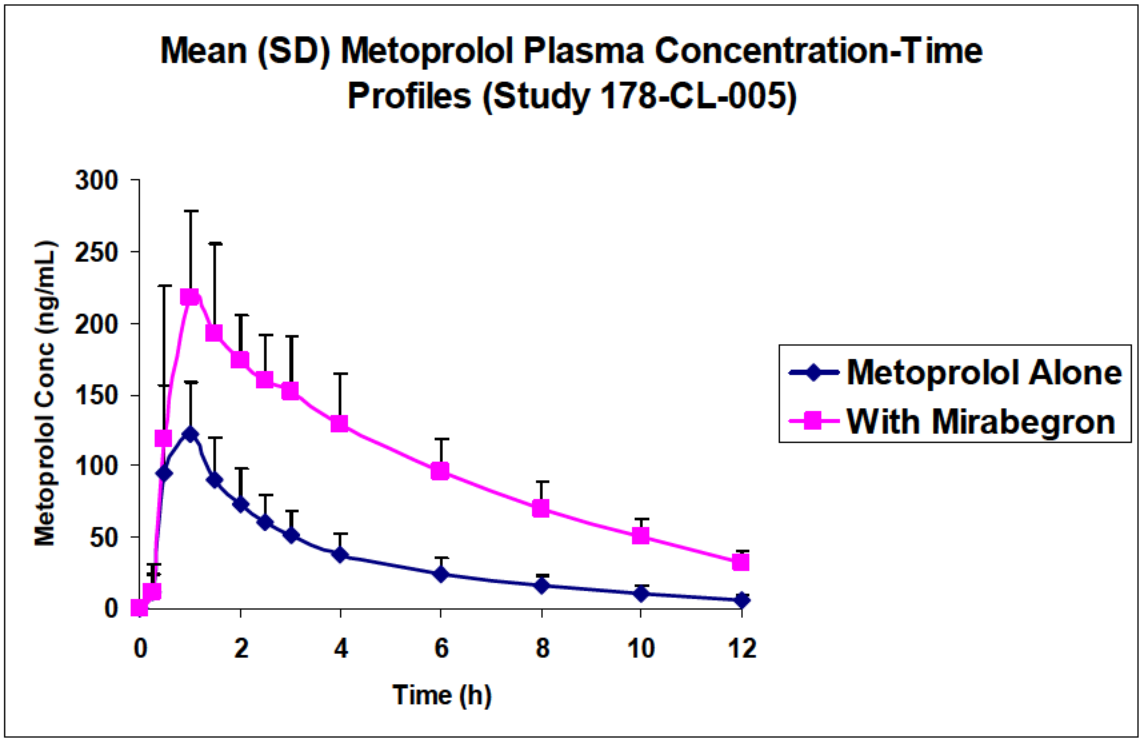


Table 4.2.6.3 Mean PK Parameters of Metoprolol with and Without Mirabegron (Study 005)

Treatment	Statistic	t_{max}[1] (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	$AUC_{0\text{-}inf}$ (ng.h/ml)	$t_{1/2}$ (h)	CL/F (l/h)	V_z/F (l)
Metoprolol	Mean	0.79	132	408	439	2.96	200	844
	(SD, CV)	(0.26)	(41, 31%)	(147, 36%)	(153, 35%)	(0.35, 12%)	(70, 35%)	(288, 34%)
	Range	0.5 – 1.0	64 – 180	212 – 606	240 – 657	2.3 – 3.5	119 – 325	485 – 1271
	Median	1.0	155	377	402	2.93	195	821
Metoprolol and YM178	Mean	1.25	247	1242	1389	4.11	58.6	346
	(SD, CV)	(0.69)	(67, 27%)	(317, 26%)	(286, 21%)	(0.24, 6%)	(13, 22%)	(72, 21%)
	Range	0.5 – 3.0	133 – 352	821 – 1809	986 – 1845	3.6 – 4.4	42 – 79	250 – 470
	Median	1.0	226	1220	1399	4.17	55.9	321

Table 4.2.6.4 Statistical Analysis of Metoprolol PK Parameters with and Without Mirabegron (Study 005)

Analysis Population	Substance	PK parameter	Ratio with/without YM178			Coefficient of variation (%)
			Point estimate	90% Confidence interval		
				Lower	Upper	
PPS	Metoprolol	$AUC_{0\text{-}inf}$	3.285	2.699	3.998	27.3
PPS	Metoprolol	C_{max}	1.897	1.543	2.332	28.7

Table 4.2.6.5 Mean PK Parameters of α-Hydroxymetoprolol With and Without Mirabegron (Study 005)

Treatment	Statistic	t_{max}[1] (h)	C_{max} (ng/ml)	AUC_{last} (ng.h/ml)	$AUC_{0\text{-}inf}$ (ng.h/ml)	$t_{1/2}$ (h)	CL/F (l/h)	V_z/F (l)
Metoprolol	Mean	1.1	81.7	540	665	6.34	128	1167
	(SD, CV)	(0.42)	(23, 28%)	(143, 26%)	(125, 19%)	(1.0, 16%)	(23, 18%)	(272, 23%)
	Range	0.5 – 2.0	55 – 118	343 – 865	501 – 935	4.3 – 8.0	89 – 165	805 – 1703
	Median	1.0	70.2	543	649	6.41	128	1129
Metoprolol and YM178	Mean	1.29	33.6	260	ND	ND	ND	ND
	(SD, CV)	(0.78)	(17, 50%)	(127, 49%)				
	Range	0.5 – 3.0	14 – 68	120 – 513				
	Median	1.0	34.9	238				

Reviewer's Comments:

- The observed increase in Cmax and AUC of mirabegron in the PMs compared to the EMs was minimal (see also Genomics Review in **Appendix II**).
- The increase in metoprolol exposure was expected as mirabegron was found *in vitro* to be a moderate CYP2D6 inhibitor. Therefore, the increase in exposure of metoprolol could be a result of a combination of decrease the clearance of metoprolol by inhibition of its metabolism and increased the bioavailability by decreasing first-pass effect.
- The inhibition of metoprolol metabolism by mirabegron was confirmed by the reduction in the formation its metabolites, α-hydroxymetoprolol.

Reference ID: 3129601

4.2.7 Study 178-CL-038 (Effect of Desipramine):

Study Title: "An Open-Label, One-Sequence Crossover Study to Evaluate the Effect of Multiple Doses YM178 on the Pharmacokinetics of the CYP2D6 Substrate Desipramine in Healthy Subjects: DDI Desipramine

Objectives:

- To determine the effects of steady state mirabegron levels on the PK of a single dose of desipramine
- To evaluate the interaction between mirabegron and desipramine in terms of safety and tolerability
- To evaluate the PK of desipramine after washout of mirabegron

Study Design:

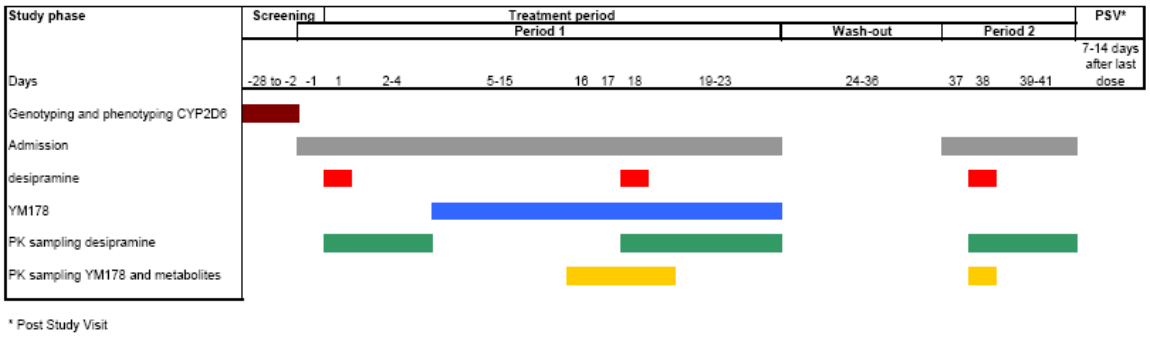
This was one-sequence crossover study of 2 periods as follows:

Period 1:

Subjects received a single oral dose of 50 mg desipramine on Day 1. From Day 5 up to and including Day 23, subjects received daily oral doses of 100 mg mirabegron. A single dose of 50 mg desipramine was given in combination with mirabegron on Day 18 (13 days after the first dose of mirabegron). Blood PK samples for desipramine were collected post dose on Day 18. In addition, from Day 16 up to and including Day 19, blood samples for mirabegron were collected.

Period 2:

After a wash-out period of 13 days, subjects received a single oral dose of 50 mg desipramine on Day 38. The overall design of the study is presented in the Scheme below:



Blood samples for desipramine PK were collected over 120 hours post dose.

Reference ID: 3129601

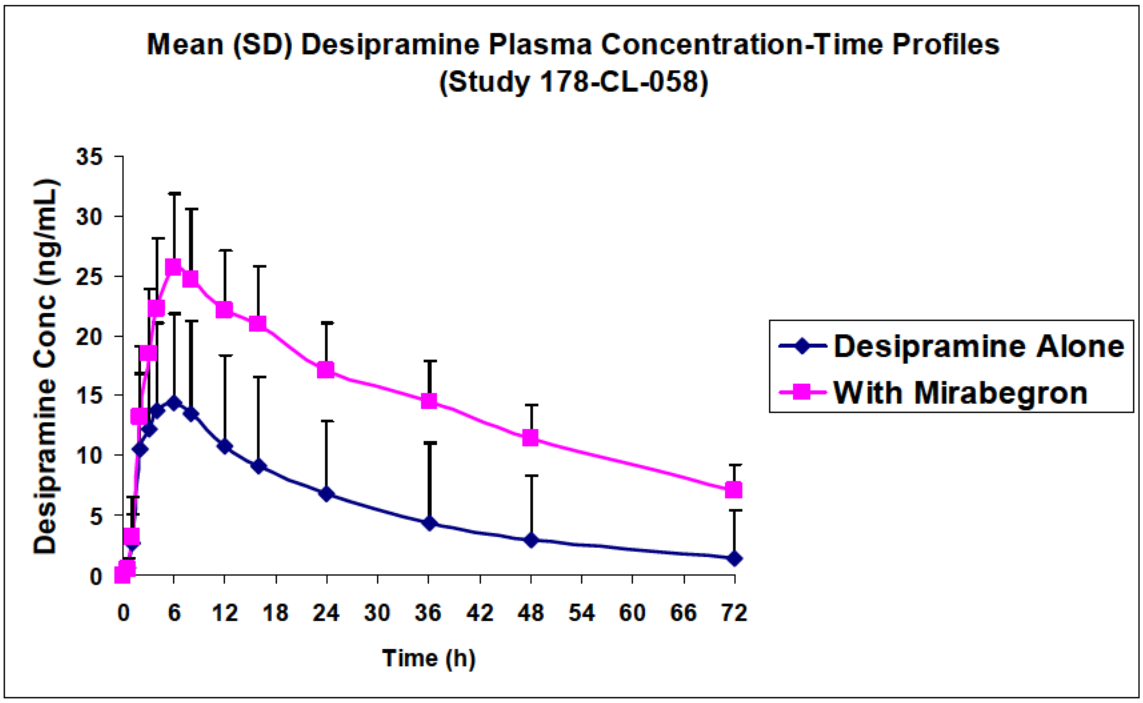
Subjects:

A total of 28 healthy subjects (14 males and 14 females), aged between 18 and 55 years were enrolled in the study.

Results:

- The PK data for desipramine and its metabolites, 2-hydroxydesipramine are shown in **Figures 4.2.7.1-4.2.7.4 and Tables 4.2.7.1-4.2.7.3**.
- As was demonstrated for metoprolol, a similar effect of mirabegron as CYP2D6 inhibitor was observed with desipramine.
- After the 15-day wash-out period, Cmax on Day 38 remained high when compared to baseline (ratio 1.12). The mean ratio of AUC for desipramine in the presence of mirabegron was 3.41 compared to desipramine alone. This increase was observed in all subjects. There was minimal difference between Day 1 and Day 38 when desipramine was given alone.
- It should be noted that throughout the study, exposure to desipramine was generally higher in female subjects than in male subjects.

Figure 4.2.7.1 Mean Plasma Concentration-Time Profiles of Desipramine With and Without Mirabegron (Study 058)



Reference ID: 3129601

Figure 4.2.7.2 Mean (SD) Cmax of Desipramine With and Without Mirabegron (Study 058)

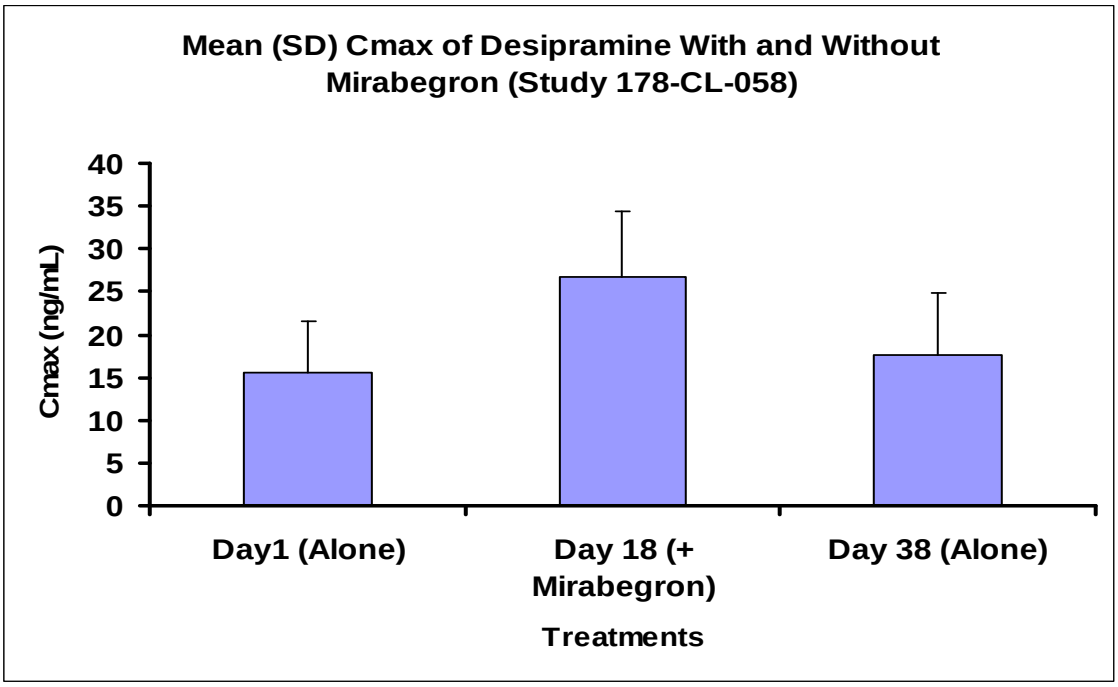
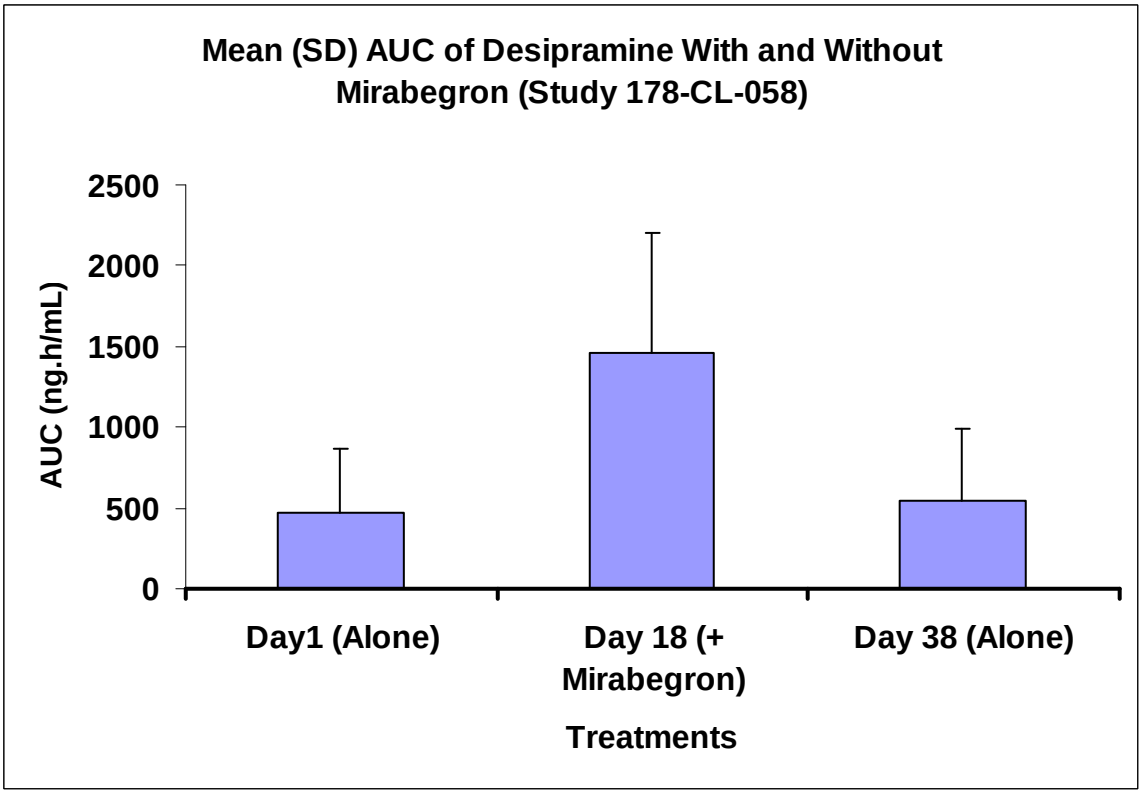


Figure 4.2.7.3 Mean (SD) AUCof Desipramine With and Without Mirabegron (Study 058)



Reference ID: 3129601

Table 4.2.7.1 Mean PK Parameters of Desipramine With and Without Mirabegron (Study 058)

PK parameter	Statistic	Day 1 (desipramine alone) (N=28)	Day 18 (desipramine + YM178) (N=28)	Day 38 (desipramine alone) (N=27)
t_{max} (h)	Mean	5.18	6.39	4.85
	(SD)	(1.93)	(2.18)	(1.81)
	Min – Max	2.0 – 8.0	2.0 - 12	2.0 – 8.0
	Median	6.00	6.00	6.00
C_{max} (ng/mL)	Mean	15.5	26.8	17.6
	(SD, CV)	(6.0, 39%)	(7.7, 29%)	(7.2, 41%)
	Min – Max	5.6 - 30	12 - 40	6.8 - 30
	Median	16.3	28.6	18.6
AUC_{last} (ng.h/mL)	Mean	401	1270	460
	(SD, CV)	(243, 61%)	(542, 43%)	(286, 62%)
	Min – Max	126 - 1259	469 - 2372	119 - 1417
	Median	349	1371	453
AUC_{inf} (ng.h/mL)	Mean	468	1466	540
	(SD, CV)	(397, 85%)	(731, 50%)	(453, 84%)
	Min – Max	137 – 2177	479 - 3326	134 - 2400
	Median	382	1481	482
$t_{1/2}$ (h)	Mean	19.5	35.8	19.6
	(SD, CV)	(8.4, 43%)	(10.5, 29%)	(8.5, 43%)
	Min – Max	13 - 56	21 - 64	11 - 55
	Median	17.5	33.3	17.2
CL/F (L/h)	Mean	138	39.3	125
	(SD, CV)	(77, 56%)	(22.2, 57%)	(79, 63%)
	Min – Max	20 - 321	13 - 92	18 - 329
	Median	116	29.7	91.2
V_z/F (h)	Mean	3437	1783	3044
	(SD, CV)	(1647, 48)	(612, 34%)	(1519, 50%)
	Min – Max	1638 - 7364	1094 - 3375	1444 - 6715
	Median	2710	1527	2353

Table 4.2.7.2 Statistical PK Data of Desipramine with and Without Mirabegron (Study 058)

PK parameter	Mean ratio [90% CI] N	
	Day 18 vs Day 1 (N=28)	Day 38 vs Day 1 (N=27)
AUC_{inf} (ng.h/mL)	3.41 [3.07 – 3.80]	1.13 [1.05 – 1.20]
C_{max} (ng/mL)	1.79 [1.69 – 1.90]	1.12 [1.05 – 1.20]

- As expected, the formation of desipramine metabolite, 2-hydroxydesipramine was reduced by inhibition of its metabolism (**Figure 4.2.7.4 and Table 4.2.7.3**). The mechanism of this reduction is similar to that for metoprolol (i.e., inhibition of CYP2D6 mediated metabolism).
- In the presence of mirabegron, the Cmax of 2-hydroxydesipramine was approximately 50% lower than without mirabegron.
- The mean ratio of AUC for 2-hydroxydesipramine in the presence of mirabegron was approximately 1.3. After the 15-day washout period, the mean AUC was comparable to the value observed at baseline.

Reference ID: 3129601

Figure 4.2.7.4 Mean Plasma Concentration-Time Profiles of Desipramine Metabolite, α-hydroxydesipramine, with and Without Mirabegron (Study 058)

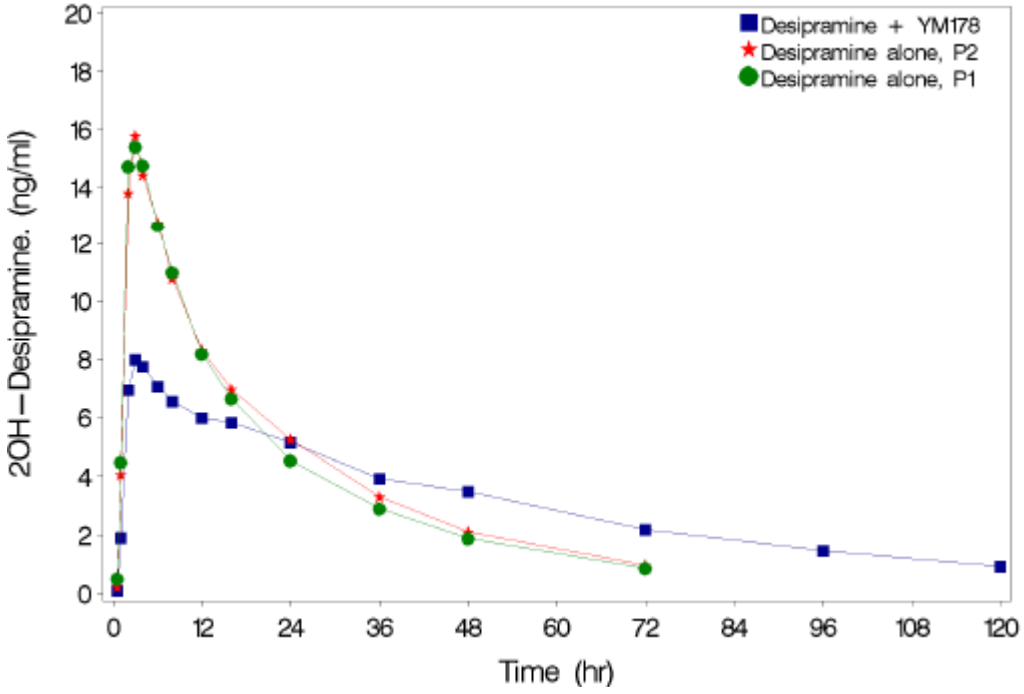


Table 4.2.7.3 Summary of PK Parameters of Desipramine Metabolite, α-hydroxydesipramine, with and Without Mirabegron (Study 058)

PK parameter	Statistic	Day 1 (desipramine alone) (N=28)	Day 18 (desipramine + YM178) (N=28)	Day 38 (desipramine alone) (N=27)
t_{max} (h)	Mean (SD)	3.00 (0.98)	4.46 (2.53)	3.56 (1.42)
	Min – Max	2.0 – 6.0	2.0 - 12	2.0 – 8.0
	Median	3.00	4.00	3.00
C_{max} (ng/mL)	Mean (SD, CV)	16.4 (4.6, 28%)	8.53 (3.45, 40%)	16.5 (5.2, 32%)
	Min – Max	6.8 - 30	3.4 - 18	5.7 - 31
	Median	16.6	8.07	17.3
AUC_{last} (ng.h/mL)	Mean (SD, CV)	307 (73, 24%)	378 (92, 24%)	325 (92, 28%)
	Min – Max	188 - 425	207 - 586	190 - 481
	Median	309	372	318
AUC_{inf} (ng.h/mL)	Mean (SD, CV)	341 (95, 28%)	435 (109, 25%)	359 (107, 30%)
	Min – Max	199 - 576	274 - 656	200 - 545
	Median	329	412	335
$t_{1/2}$ (h)	Mean (SD, CV)	21.0 (9.4, 45%)	38.9 (12, 31%)	20.4 (7.9, 39%)
	Min – Max	13 - 60	22 - 64	12 - 48
	Median	18.4	35.4	17.5
Ratio AUC_{inf} 2OH-Desi / Desi	Mean (SD, CV)	0.942 (0.352, 37%)	0.372 (0.155, 42%)	0.884 (0.351, 40%)
	Min – Max	0.26 – 1.7	0.12 – 0.69	0.17 -1.5
	Median	0.918	0.319	0.810

Reviewer's Comments:

- The administration of mirabegron as a single dose for 19 days resulted in a 3.41-fold (i.e., 241%) increase in desipramine AUC and 1.79-fold (i.e., 79%) increase in Cmax.
- As expected, the formation of desipramine, α-hydroxydesipramine is expected to be reduced. In this case, the Cmax was reduced by 2-fold and AUC by 1.3 fold.
- Desipramine half-life was also increased from approximately 19.5 h to 35.8 h when co-administered with mirabegron.

4.2.8 Study 178-CL-036 (Effect of Ketoconazole):

Study Title: "A Phase 1, Open-Label, Two-Period, One-Sequence Crossover Study to Assess Pharmacokinetic Interaction of Multiple Dose Ketoconazole on Single Dose YM178 Oral Controlled Absorption System (OCAS) in Healthy Male and Female Adult Volunteers"

Objectives:

- The primary objective of this study was to assess the PK interaction of multiple dose ketoconazole on single-dose mirabegron in healthy adult volunteers.

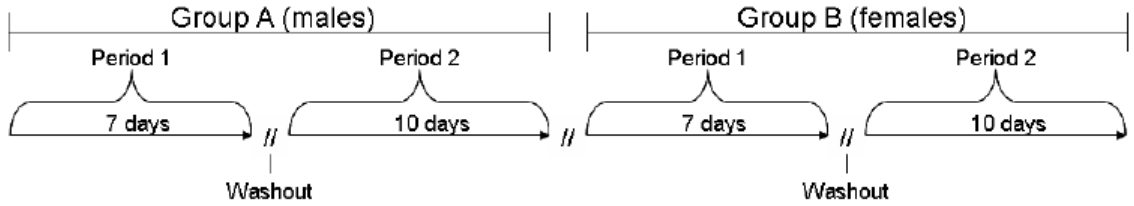
- The secondary objective of this study was to assess the safety and tolerability of mirabegron alone and in combination with ketoconazole in healthy adult volunteers.

Study Design:

This was two-period, one-sequence crossover study in 12 healthy male (Group A) and 12 female (Group B) subjects. There were 2 study periods for each group. A single 100 mg oral dose of mirabegron OCAS tablet was administered on Day 1 of period 1 and on Day 4 of period 2. During period 2, a 400 mg oral dose of ketoconazole was administered once daily on Days 1 through 9.

During period 1, subjects were admitted to the clinical unit on day -1, confined through the morning of day 4, and then released. Subjects returned the mornings of Days 5 through 7 for the collection of PK blood samples.

During period 2, subjects were re-admitted to the clinical unit on Day -1, confined through the morning of Day 7, and then released. Subjects returned the mornings of Days 8 and 9 for ketoconazole dosing, the collection of PK blood samples. Subjects returned on the morning of Day 10 for final study assessments, including the collection of PK blood samples. The following Scheme shows the overall study design:



Period 1*: Mirabegron 100 mg administered on Day 1*
Period 2*: Ketoconazole 400 mg once daily on Days 1 through 9. Mirabegron 100 mg was administered on Day 4 (Concomitant with ketoconazole).*
Washout*: ~ 7 days from day 1 of period 1*

In period 1 and period 2 blood samples for mirabegron PK were collected up to 144 hours post dose of Day 1 (i.e., up to Day 7 in period 1) and post dose on Day 4 (i.e., up to Day 10 in period 2).

Reference ID: 3129601

Results:

- The data from this study is summarized in **Figures 4.2.8.1-4.2.8.3 and Tables 4.2.8.1 and 4.2.8.2.**
- In males, mean Cmax was approximately 1.2-times greater and AUC approximately 1.6-times greater in period 2 compared to period 1. In females, mean Cmax was approximately 1.6-times greater and AUC approximately 2-times greater in period 2 compared to period 1.
- During period 1 (mirabegron alone), mean Cmax and AUC were approximately 1.4-times greater in females compared to males. Also, during period 2 (mirabegron + ketoconazole), mean Cmax and AUC were approximately 1.8-times greater in females compared to males.
- Therefore, overall the effect of ketoconazole was greater in females compared to males.
- Overall, Ketoconazole increased mirabegron Cmax by approximately 45% and AUC by approximately 81% (**Table 4.2.8.2**)

Figure 4.2.8.1 Mean Plasma Concentration-Time Profiles of Mirabegron with and Without Ketoconazole in ALL SUBJECTS (Study 036)

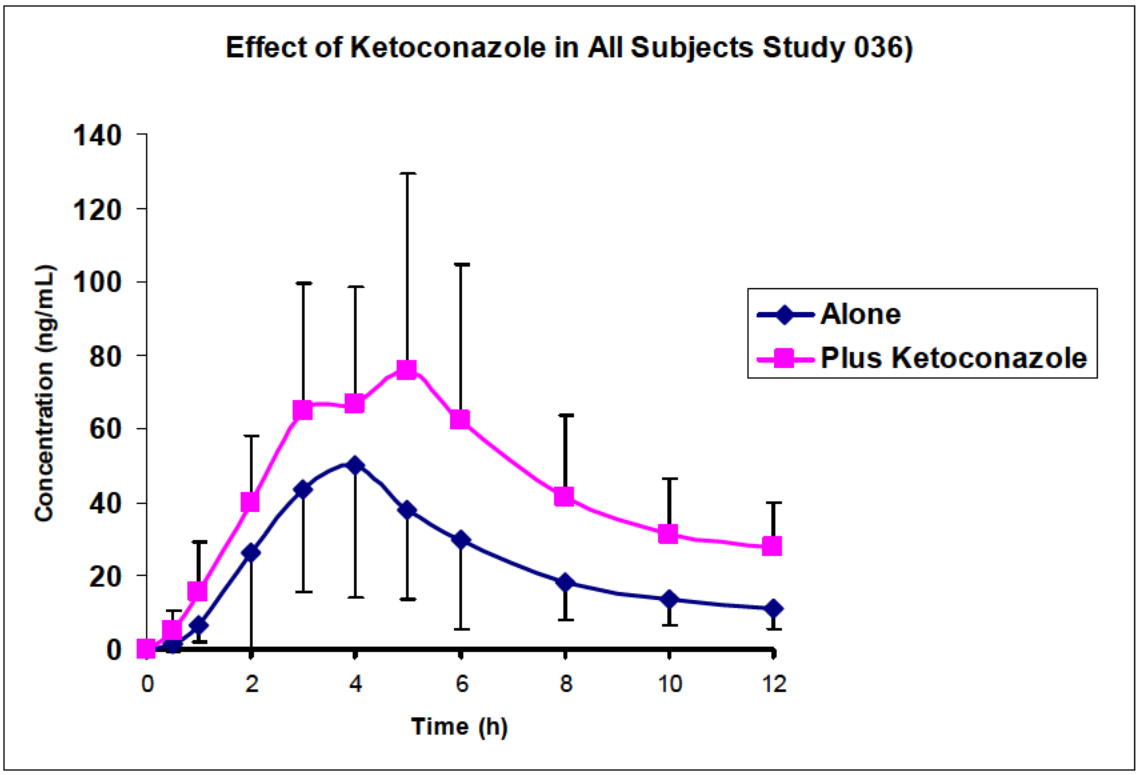


Figure 4.2.8.2 Mean Plasma Concentration-Time Profiles of Mirabegron with and Without Ketoconazole in FEMALES (Study 036)

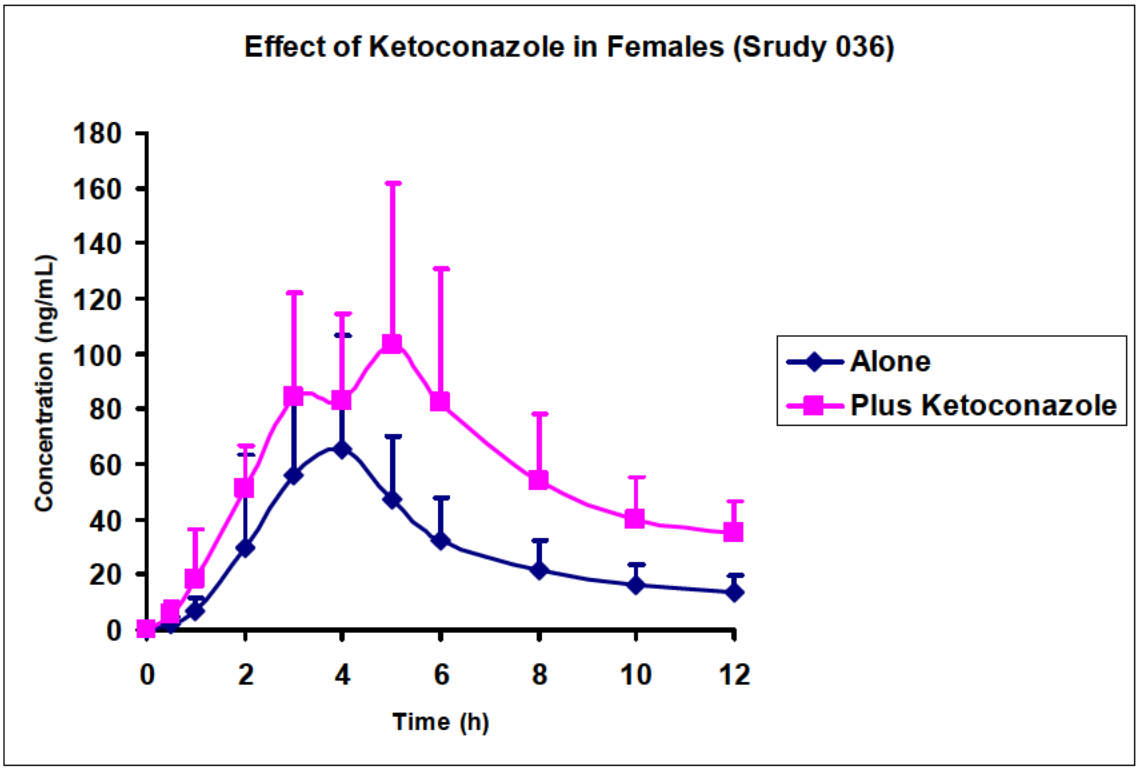


Figure 4.2.8.3 Mean Plasma Concentration-Time Profiles of Mirabegron with and Without Ketoconazole in MALES (Study 036)

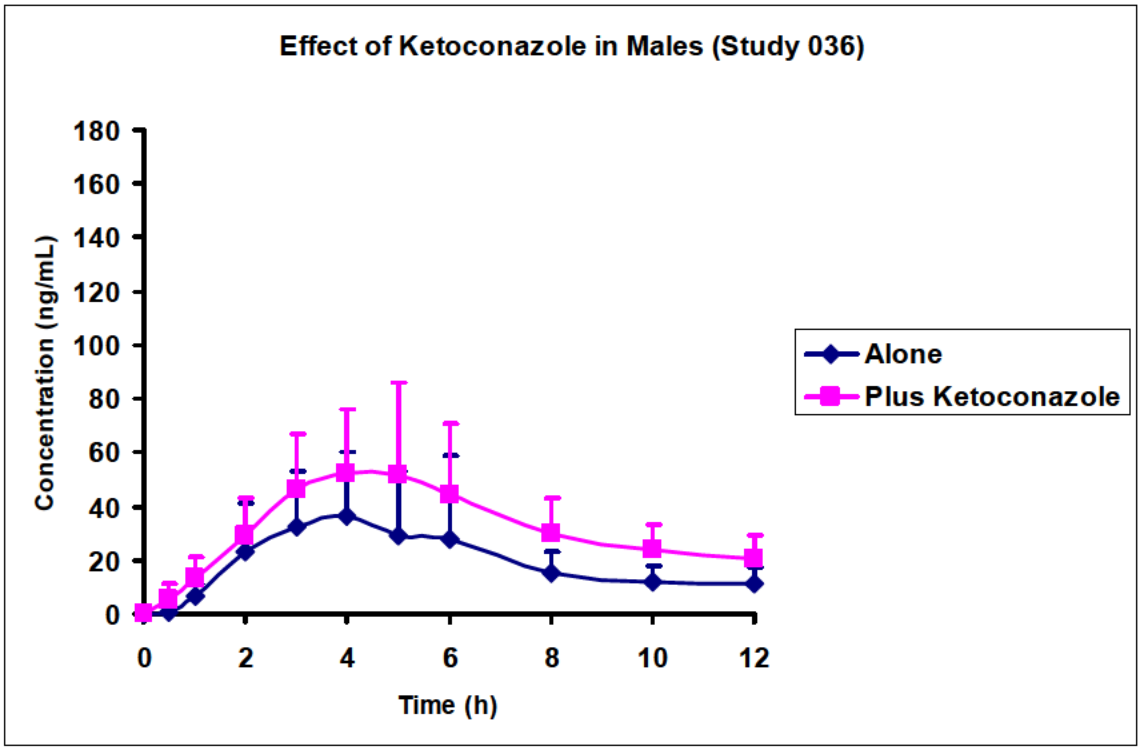


Table 4.2.8.1 Summary of PK Parameters of Mirabegron with and Without Ketoconazole (Study 036)

Parameter		Males (n = 12)	Females (n = 11)	Overall (n = 23)
Period	Statistic			
C_{max} (ng/mL)				
Period 1	Mean ± SD	56.38 ± 31.247	77.30 ± 34.984	66.39 ± 34.039
	Median	45.45	68.54	66.62
	Range	15.5 – 121.4	28.5 – 143.8	15.5 – 143.8
	Geometric Mean	48.51	69.77	57.72
	CV (%)	55.4	45.3	51.3
Period 2	Mean ± SD	68.57 ± 30.423	124.03 ± 48.858	95.09 ± 48.480
	Median	67.59	107.46	85.16
	Range	29.1 – 126.7	53.0 – 215.0	29.1 – 215.0
	Geometric Mean	62.27	115.48	83.67
	CV (%)	44.4	39.4	51.0
t_{max} (hr)				
Period 1	Mean ± SD	3.50 ± 1.000	3.55 ± 1.036	3.52 ± 0.994
	Median	3.00	4.00	4.00
	Range	2.0 – 6.0	2.0 – 5.0	2.0 – 6.0
	Geometric Mean	3.38	3.38	3.38
	CV (%)	28.6	29.2	28.2
Period 2	Mean ± SD	3.75 ± 1.138	3.91 ± 1.446	3.83 ± 1.267
	Median	3.50	4.00	4.00
	Range	2.0 – 6.0	1.0 – 6.0	1.0 – 6.0
	Geometric Mean	3.60	3.57	3.59
	CV (%)	30.4	37.0	33.1
$t_{½}$ (hr)				
Period 1	Mean ± SD	48.62 ± 15.988	53.34 ± 11.569	50.87 ± 13.945
	Median	43.06	52.64	47.63
	Range	28.4 – 80.8	36.6 – 71.7	28.4 – 80.8
	Geometric Mean	46.37	52.21	49.08
	CV (%)	32.9	21.7	27.4
Period 2	Mean ± SD	34.51 ± 7.532	41.02 ± 11.078	37.62 ± 9.756
	Median	32.57	40.73	35.47
	Range	23.4 – 50.6	29.1 – 67.9	23.4 – 67.9
	Geometric Mean	33.80	39.85	36.57
	CV (%)	21.8	27.0	25.9
AUC_{inf} (hr•ng/mL)				
Period 1	Mean ± SD	627.77 ± 263.047	870.78 ± 301.377	743.99 ± 302.140
	Median	595.33	761.58	743.60
	Range	176.7 – 1098.1	476.7 – 1433.9	176.7 – 1433.9
	Geometric Mean	567.34	827.77	679.69
	CV (%)	41.9	34.6	40.6
Period 2	Mean ± SD	1000.95 ± 334.397	1688.57 ± 357.154	1329.82 ± 487.069
	Median	1075.28	1663.07	1297.73
	Range	382.8 – 1495.9	1261.1 – 2323.8	382.3 – 2323.8
	Geometric Mean	936.37	1655.01	1229.55
	CV (%)	33.4	21.2	36.6

Reference ID: 3129601

Table 4.2.8.2 Statistical Analysis of PK Parameters of Mirabegron with and Without Ketoconazole (Study 036

Parameter Gender	LSM† YM178 Alone	LSM† YM178 + Keto	YM178 + Keto/ YM178 Alone‡	90% Confidence Interval‡
AUC_{inf}				
Overall (n = 23)	679.7	1229.6	180.9	[162.6, 201.2]
Females (n = 11)	827.8	1655.0	199.9	[175.2, 228.1]
Males (n = 12)	567.3	936.4	165.0	[139.6, 195.1]
C_{max}				
Overall (n = 23)	57.7	83.7	145.0	[122.5, 171.5]
Females (n = 11)	69.8	115.5	165.5	[128.5, 213.2]
Males (n = 12)	48.5	62.3	128.4	[101.0, 163.1]

Reviewer's Comments:

Since mirabegron is extensively metabolized and it undergoes multiple metabolic pathways, the effect of ketoconazole is considered minimal in this study. If CYP3A4 is the only isoenzyme that is responsible for the metabolism of mirabegron and if involved a single metabolic pathway, the effect of co-administration of ketoconazole would have been much greater (may be several folds) than what was observed in this study.

Reference ID: 3129601

4.2.9 Study 178-CL-077 (TQT Study):

Study Title: "A Phase 1, Randomized, Double-Blind, Placebo and Active Controlled, Parallel Crossover Study to Evaluate the Effect of Repeat Oral Doses of Mirabegron on Cardiac Repolarization in Healthy Male and Female Adult Subjects

Objectives:

- The primary objective of this study was to evaluate the effect of repeat oral dosing of mirabegron (50, 100 and 200 mg QD) on QTcI interval in healthy male and female adult subjects.
- The secondary objectives of the study were:
    - To evaluate the effect of repeat oral doses of mirabegron (50, 100 and 200 mg QD) on QT interval corrected for heart rate using fixed mathematical form optimized for each subject (QTcIf) and QTcF interval in healthy adult subjects.
    - To characterize the PK of mirabegron in healthy adult subjects
    - To evaluate the safety and tolerability of mirabegron.

Study Design:

This was a double-blind, randomized, placebo and active controlled, parallel crossover, phase 1 thorough QT (TQT) study in which each active treatment was investigated in a separate group crossed over with placebo. A randomization of 352 healthy volunteers (176 women and 176 men) was planned for the study. The study consisted of two 10-day treatment periods (Days 1-10) as follows:

Days 1 to 9: Once daily dosing of mirabegron, mirabegron placebo or moxifloxacin placebo
Day 10: Mirabegron, mirabegron placebo, moxifloxacin, or moxifloxacin placebo followed by a 1 day post-treatment period (Day 11).

All drugs were administered under fasted conditions.

Baseline and ECG Measurements: Subjects checked in on Day -4 of each treatment period and had continuous baseline 12-lead ECGs recorded on Days -3 and -1.

Washout: Each treatment period was separated by a washout period of at least 12 days from Day 10 of treatment period 1 to day -4 of treatment period 2.

Randomization and Subjects: Subjects were randomized to 1 of 8 treatment sequences (Sequence 1-8) and randomization was stratified by sex, with 22 women and 22 men assigned to each sequence as shown below:

Reference ID: 3129601

Study Treatment Sequences:

Sequence	n (Men/Women)	Treatment Period 1	Treatment Period 2
1	22/22	Placebo	Mirabegron 200 mg
2	22/22	Mirabegron 200 mg	Placebo
3	22/22	Placebo	Mirabegron 100 mg
4	22/22	Mirabegron 100 mg	Placebo
5	22/22	Placebo	Mirabegron 50 mg
6	22/22	Mirabegron 50 mg	Placebo
7	22/22	Placebo	Moxifloxacin 400 mg
8	22/22	Moxifloxacin 400 mg	Placebo

Dosing and Treatments:

Miraabegron: 50, 100 and 200 mg tablets
Moxifloxacin: 400 mg over-encapsulated tablets with matching placebos.

The following table outlines the treatments:

Study Treatments Administered:

Seq	Study Day	Treatment Period 1 Number of tablets or capsules/day/volunteer						Treatment Period 2 Number of tablets or capsules/day/volunteer					
		50 mg		100 mg		Moxi	Moxi pbo	50 mg		100 mg		Moxi	Moxi pbo
		Mira	PBO	Mira	PBO			Mira	PBO	Mira	PBO		
1	Days 1-9		1		2				1	2			
	Day 10		1		2		1		1	2			1
2	Days 1-9		1	2					1		2		
	Day 10		1	2			1		1		2		1
3	Days 1-9		1		2				1	1	1		
	Day 10		1		2		1		1	1	1		1
4	Days 1-9		1	1	1				1		2		
	Day 10		1	1	1		1		1		2		1
5	Days 1-9		1		2			1			2		
	Day 10		1		2		1	1			2		1
6	Days 1-9	1			2				1		2		
	Day 10	1			2		1		1		2		1
7	Days 1-9		1		2				1		2		
	Day 10		1		2		1		1		2	1	
8	Days 1-9		1		2				1		2		
	Day 10		1		2	1			1		2		1

Days 1 to 9 volunteers received 3 tablets per day; day 10 volunteers received 3 tablets plus one capsule.
Mira: mirabegron; Moxi: moxifloxacin; PBO: Placebo for corresponding dose of mirabegron (Mira) (tablet); pbo: Placebo for moxifloxacin (Moxi) (capsule); Seq: Treatment sequence.

All subjects received the same number of tablets per day (3 tablets on days 1-9; and 3 tablets and one over-encapsulated tablet on Day 10) in each treatment period as either active drug or placebo to maintain the blind.

Subject's Confinement: For each treatment period, subjects were admitted to the study center on day -4 and confined until the mid-day of Day 11. Subjects fasted for a minimum of 8 hours prior to dosing on Days 1 to 10; the same fasting schedule was followed on day -3 and day -1 within each treatment period.

ECG Measurement: On days of continuous ECG monitoring (Days -3, -1, 10 and 11 of each study period), subjects remained in the same comfortable supine positions for at least 10 minutes at prespecified data collection times. During these 10-minute periods, subjects had their whole body supported in a supine position, and were requested to remain as motionless as possible. They were not permitted to speak or to sleep and were strictly kept free of any external disturbance. On Days 1 and 3 of each treatment period, ECG recordings were obtained while the subjects were not required to adopt strict motionless supine positions. However, during these study days, the subjects were required to be in supine position for no less than 20 minutes of each hour in order to obtain noise-free ECG signals of sufficient technical quality.

PK Samples:

Blood samples were collected at the following time points: predose on Day 1 and Day 9, and at predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 14 hours postdose on Day 10 and on Day 11 (24 hours postdose on Day 10).

Results:

For detail discussion of the study design and results please see Pharmacometics group review in **Appendix I** and also QT-IRT review dated January 24, 2012. This review briefly discusses the main results and conclusions from this study.

- The mean difference from placebo in QTcI increased with increasing doses of mirabegron in all treatment groups in both the total population and by sex (**Table 4.2.9.1**)
- Mirabegron did not cause a QTcI prolongation at the proposed therapeutic dose of 50 mg. In the mirabegron 50 mg group the largest treatment effect occurred at 3 to 4 hours with a mean (upper bound of the 1-sided 95% CI) treatment difference of 3.66 (5.16) msec in all subjects, 4.49 (6.81) msec in female volunteers and 2.96 (5.00) msec in male subjects.
- A dose dependent increase in time-matched mean change in baseline-adjusted heart rate (HR) between mirabegron and placebo on Days 10 and 11 was observed after treatment with mirabegron (**Table 4.2.9.2**)

Reference ID: 3129601

Table 4.2.9.1 Summary of Mean Difference Between Mirabegron and Placebo, Baseline Adjusted in Time-Matched QTcI Interval (msec) on Days 10 and 11, by Sex (Study 077)

Hours postdose	Statistic†	Study Treatment					
		Female			Male		
		Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg
Predose	Diff from Plb	2.37	6.25	6.72	1.73	2.53	6.09
	90% CI	(0.72, 4.02)	(4.28, 8.23)	(3.99, 9.46)	(-0.00, 3.46)	(0.48, 4.58)	(4.16, 8.02)
0.5	Diff from Plb	1.85	4.93	8.61	1.79	1.82	5.60
	90% CI	(-0.32, 4.02)	(3.24, 6.63)	(5.96, 11.27)	(0.34, 3.24)	(-0.01, 3.65)	(3.95, 7.25)
1	Diff from Plb	1.96	4.79	6.94	2.36	2.12	5.39
	90% CI	(-0.07, 3.98)	(2.55, 7.04)	(4.04, 9.83)	(0.74, 3.99)	(0.44, 3.80)	(3.38, 7.40)
1.5	Diff from Plb	2.56	4.57	8.59	1.14	2.60	5.66
	90% CI	(0.35, 4.77)	(2.30, 6.83)	(5.52, 11.66)	(-0.55, 2.82)	(0.54, 4.66)	(4.08, 7.24)
2	Diff from Plb	2.34	4.73	8.33	1.86	1.84	6.00
	90% CI	(0.31, 4.36)	(2.49, 6.96)	(5.72, 10.94)	(-0.07, 3.78)	(-0.16, 3.85)	(4.32, 7.68)
2.5	Diff from Plb	2.65	5.56	8.73	2.45	2.86	7.08
	90% CI	(0.59, 4.71)	(3.44, 7.69)	(6.04, 11.41)	(0.64, 4.25)	(0.85, 4.88)	(5.15, 9.00)
3	Diff from Plb	3.52	7.27	8.96	1.90	3.19	7.12
	90% CI	(1.47, 5.57)	(5.08, 9.46)	(6.09, 11.82)	(-0.01, 3.81)	(1.43, 4.95)	(5.07, 9.17)
3.5	Diff from Plb	4.49	7.66	9.33	1.63	3.83	6.88
	90% CI	(2.17, 6.81)	(5.75, 9.57)	(6.65, 12.00)	(-0.25, 3.50)	(2.13, 5.52)	(4.82, 8.93)
4	Diff from Plb	4.00	7.70	7.98	2.96	4.63	7.33
	90% CI	(1.70, 6.29)	(5.68, 9.72)	(4.72, 11.23)	(0.92, 5.00)	(2.81, 6.45)	(5.23, 9.42)
4.5	Diff from Plb	3.97	7.27	9.31	2.57	4.39	6.28
	90% CI	(1.90, 6.04)	(4.94, 9.60)	(6.15, 12.47)	(0.88, 4.27)	(2.65, 6.14)	(4.18, 8.37)
5	Diff from Plb	3.67	6.71	10.42	2.89	3.39	6.02
	90% CI	(1.62, 5.72)	(4.35, 9.07)	(7.40, 13.44)	(0.87, 4.90)	(1.39, 5.40)	(4.06, 7.99)
6	Diff from Plb	2.55	5.11	7.17	2.16	3.98	6.61
	90% CI	(0.29, 4.81)	(2.70, 7.52)	(4.07, 10.28)	(0.58, 3.73)	(2.11, 5.85)	(4.36, 8.86)
7	Diff from Plb	2.49	4.54	4.66	1.48	3.94	5.78
	90% CI	(0.43, 4.56)	(2.68, 6.40)	(1.62, 7.70)	(-0.05, 3.01)	(2.20, 5.67)	(3.86, 7.70)
8	Diff from Plb	2.25	4.27	6.38	1.21	3.89	5.11
	90% CI	(0.31, 4.20)	(2.39, 6.15)	(3.77, 8.99)	(-0.49, 2.91)	(2.18, 5.60)	(3.08, 7.15)
10	Diff from Plb	1.51	5.28	8.08	1.59	1.95	5.33
	90% CI	(-0.82, 3.83)	(3.29, 7.27)	(5.57, 10.59)	(-0.19, 3.37)	(0.14, 3.76)	(3.40, 7.26)
12	Diff from Plb	-1.11	2.01	7.68	1.19	2.06	3.75
	90% CI	(-3.04, 0.81)	(0.06, 3.97)	(5.74, 9.63)	(-0.34, 2.72)	(0.34, 3.78)	(1.80, 5.71)
24	Diff from Plb	2.75	6.64	6.61	0.97	1.23	4.31
	90% CI	(0.77, 4.74)	(4.76, 8.52)	(3.76, 9.45)	(-0.81, 2.75)	(-0.71, 3.17)	(2.36, 6.26)
25	Diff from Plb	2.82	5.13	6.98	2.22	0.97	4.25
	90% CI	(0.80, 4.85)	(2.62, 7.64)	(4.21, 9.74)	(0.61, 3.84)	(-1.02, 2.96)	(2.48, 6.01)

Reference ID: 3129601

Table 4.2.9.2 Summary of Mean Difference Between Mirabegron and Placebo, Baseline Adjusted in Time-Matched HR (bpm) on Days 10 and 11, by Sex (Study 077)

Hours postdose	Statistic†	Study Treatment					
		Female			Male		
		Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg
Predose	Diff from Plb	4.75	10.38	13.75	3.45	7.43	9.61
	90% CI	(3.15, 6.35)	(7.99, 12.77)	(12.17, 15.32)	(1.75, 5.14)	(5.55, 9.30)	(8.21, 11.01)
0.5	Diff from Plb	4.92	7.89	13.56	2.80	7.36	10.59
	90% CI	(3.39, 6.45)	(5.59, 10.18)	(11.82, 15.30)	(1.18, 4.42)	(5.50, 9.22)	(9.05, 12.12)
1	Diff from Plb	5.46	7.86	13.07	3.60	6.98	10.39
	90% CI	(3.87, 7.05)	(5.36, 10.37)	(11.37, 14.78)	(2.09, 5.11)	(5.11, 8.84)	(8.49, 12.29)
1.5	Diff from Plb	6.05	9.70	16.46	3.40	6.94	9.78
	90% CI	(3.87, 8.23)	(7.13, 12.26)	(14.58, 18.34)	(1.98, 4.82)	(4.89, 8.99)	(8.14, 11.43)
2	Diff from Plb	5.28	9.69	16.58	4.06	7.12	10.54
	90% CI	(3.31, 7.25)	(7.51, 11.87)	(14.60, 18.57)	(2.53, 5.60)	(5.55, 8.70)	(8.71, 12.36)
2.5	Diff from Plb	5.31	9.45	17.86	4.93	6.96	10.97
	90% CI	(3.90, 6.72)	(7.29, 11.61)	(15.77, 19.94)	(3.24, 6.61)	(5.04, 8.89)	(8.91, 13.04)
3	Diff from Plb	6.90	10.93	18.57	4.85	6.54	12.28
	90% CI	(5.39, 8.40)	(8.79, 13.07)	(16.24, 20.90)	(3.22, 6.47)	(4.64, 8.44)	(10.22, 14.33)
3.5	Diff from Plb	6.56	11.10	20.19	4.02	8.37	12.77
	90% CI	(5.07, 8.04)	(8.93, 13.28)	(18.21, 22.17)	(2.49, 5.54)	(6.70, 10.03)	(10.55, 14.98)
4	Diff from Plb	8.27	13.63	19.82	5.15	9.01	13.68
	90% CI	(6.72, 9.82)	(11.04, 16.22)	(17.14, 22.49)	(3.64, 6.67)	(7.16, 10.86)	(11.77, 15.59)
4.5	Diff from Plb	8.18	12.65	20.08	5.46	8.98	13.61
	90% CI	(6.57, 9.80)	(10.15, 15.15)	(18.01, 22.14)	(4.27, 6.65)	(7.40, 10.55)	(11.73, 15.49)
5	Diff from Plb	8.53	13.52	20.24	5.28	9.01	14.37
	90% CI	(6.27, 10.78)	(10.64, 16.41)	(18.31, 22.18)	(3.89, 6.68)	(6.99, 11.02)	(12.27, 16.46)
6	Diff from Plb	7.90	13.28	18.80	4.11	9.64	13.84
	90% CI	(5.58, 10.22)	(10.00, 16.57)	(16.35, 21.26)	(2.07, 6.16)	(7.10, 12.19)	(11.54, 16.14)
7	Diff from Plb	7.58	11.42	17.20	3.26	10.36	12.91
	90% CI	(5.52, 9.64)	(8.64, 14.21)	(14.84, 19.57)	(1.36, 5.15)	(8.07, 12.66)	(10.78, 15.03)
8	Diff from Plb	6.46	12.44	17.67	3.64	10.90	13.34
	90% CI	(4.47, 8.44)	(9.68, 15.21)	(15.32, 20.02)	(1.81, 5.47)	(8.68, 13.12)	(11.36, 15.32)
10	Diff from Plb	6.52	11.45	17.46	3.97	7.79	11.41
	90% CI	(3.94, 9.10)	(9.32, 13.58)	(15.50, 19.42)	(2.19, 5.75)	(5.99, 9.59)	(9.30, 13.51)
12	Diff from Plb	6.04	8.75	16.35	3.69	6.90	11.20
	90% CI	(4.15, 7.93)	(6.76, 10.75)	(14.23, 18.47)	(1.57, 5.81)	(4.67, 9.14)	(9.32, 13.08)
24	Diff from Plb	5.27	9.26	13.51	2.72	6.81	9.87
	90% CI	(3.69, 6.86)	(7.07, 11.45)	(11.79, 15.23)	(0.97, 4.48)	(4.96, 8.66)	(8.25, 11.48)
25	Diff from Plb	5.94	8.66	13.41	1.85	6.94	9.02
	90% CI	(4.19, 7.69)	(6.39, 10.92)	(11.50, 15.32)	(0.44, 3.27)	(5.44, 8.44)	(7.30, 10.73)

- Mirabegron exposure increased with increase in dose. As shown in all other studies, the exposure was higher in females compared to males at all doses (**Figures 4.2.9.1-4.2.9.3**).

Reference ID: 3129601

Figure 4.2.9.1 Mean (SD) Plasma Concentration-Time Profiles of Mirabegron in Females and Males after 50 mg Dose (Study 077)

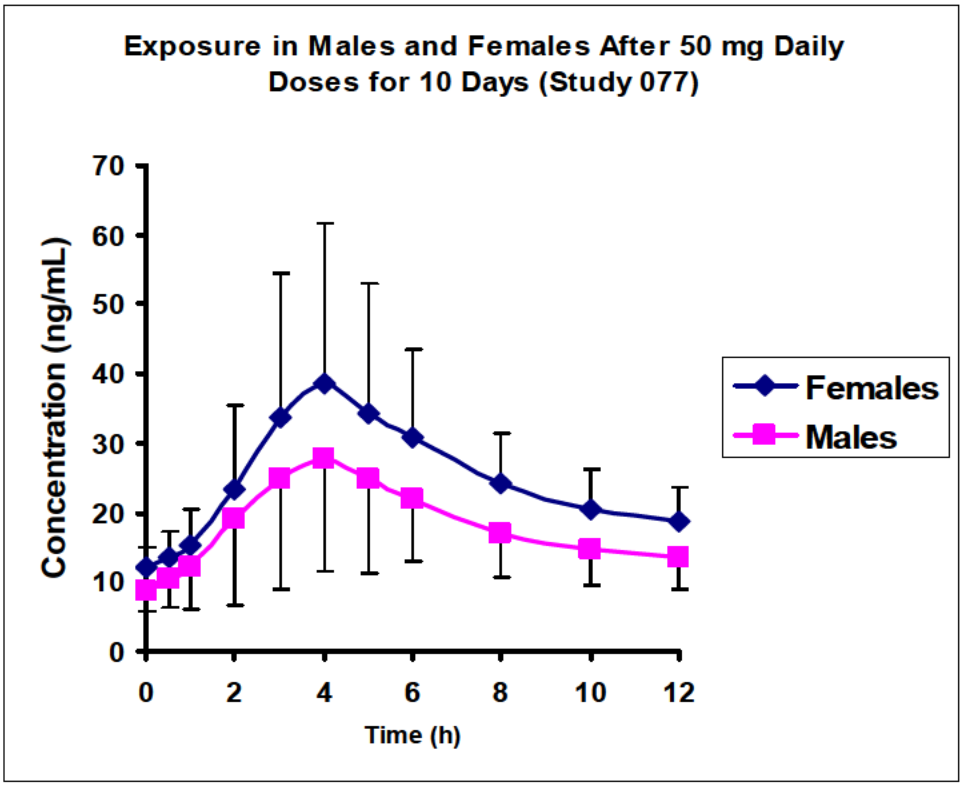
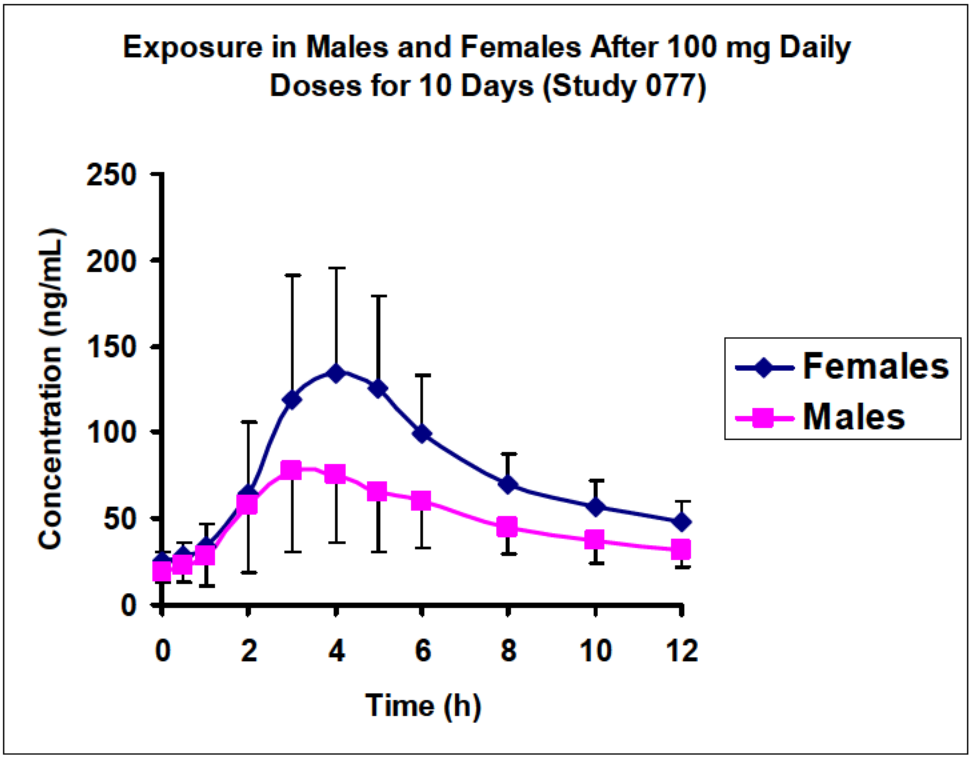
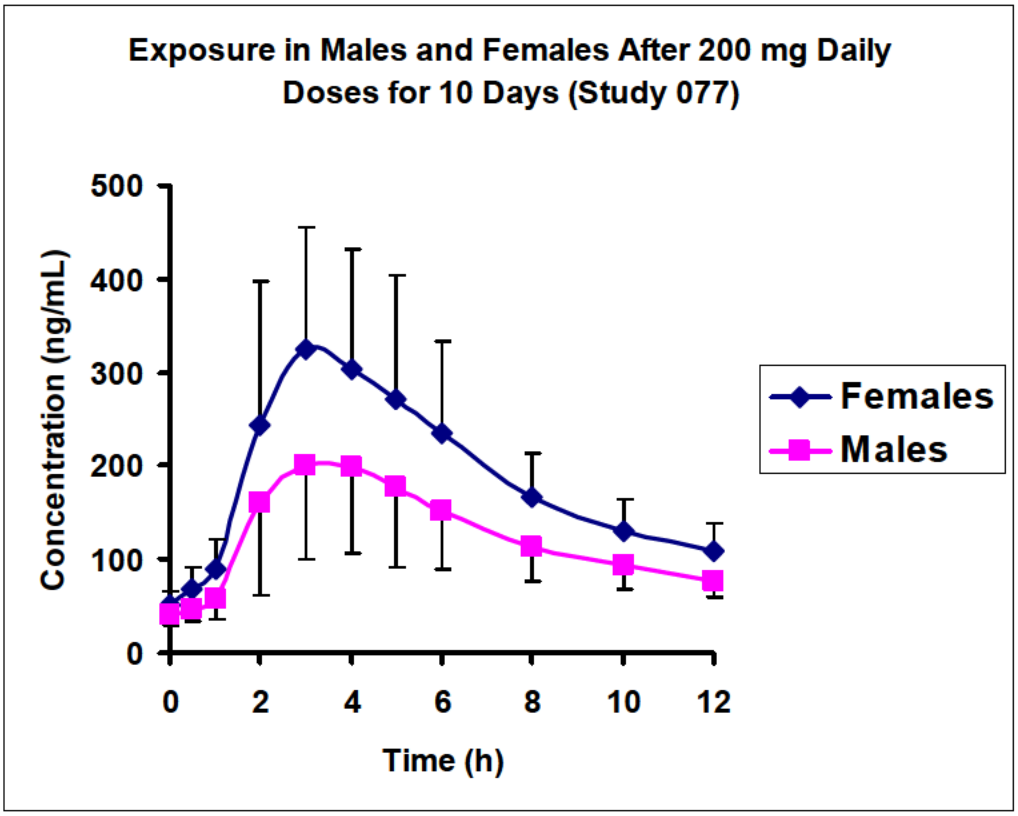


Figure 4.2.9.2 Mean (SD) Plasma Concentration-Time Profiles of Mirabegron in Females and Males after 100 mg Dose (Study 077)



Reference ID: 3129601

Figure 4.2.9.3 Mean (SD) Plasma Concentration-Time Profiles of Mirabegron in Females and Males after 200 mg Dose (Study 077)



Reviewer's Comments:

- Overall, at 50 mg dose there was no signal to suggest that mirabegron causes QT prolongation compared to the positive control, moxifloxicin. This study was reviewed in detail by Pharmacometics Group (**Appendix I**) and by QT-IRT team (Review dated January 24, 2012).

- There was dose and concentration depended effect on blood pressure and heart rate (see Pharmacometrics Group Review, **Appendix I**).

- No new PK information is observed in this study. In summary, there was greater than dose-proportional increase in exposure with increased in dose and females had higher exposure than males at all doses.

4.2.10 Study 178-CL-0041 (Effect of Food, U.S. Study):

Study Title: "A Phase 1, Open-label, Randomized, Single Oral Dose, Three-Way Crossover Study to Assess the Effect of Food on the Pharmacokinetics of Mirabegron:
Phase 1 Food Effect Study"

Objective:

The primary objective of the study was to assess the effect of food on the PK of a single oral dose of the mirabegron OCAS formulation (50 mg or 100 mg) in healthy male and female volunteers.

Study Design:

This was a single-dose, randomized, parallel-dose group, 3-period, 6-sequence crossover study. It was designed to assess the effect of food on the PK of mirabegron (50 mg or 100 mg) administered under fasted and fed conditions. Two fed conditions (high-fat and low-fat breakfasts) were evaluated.

A total of 72 healthy subjects were enrolled in this study as follows:

Group A: 50 mg dose (n=36, 18 men and 18 women) of OCAS tablet
Group B: 100 mg dose (n=36, 18 men and 18 women) of OCAS tablet

Subjects in each dose group were randomized to 1 of 6 sequences of treatment administration. Each subject participated in 3 treatment periods, with washout periods of at least 10 days between consecutive dose administrations.

During the fasted treatment, subjects fasted overnight for at least 10 hours prior to receiving the dose of mirabegron (50 or 100 mg) and continued to fast for at least 4 hours after dosing. During the fed treatments, subjects fasted overnight for at least 10 hours before receiving either a high-fat, high-calorie breakfast (approximately 1000 calories) or low-fat, light-calorie breakfast (approximately 450 calories). Mirabegron (50 or 100 mg) was orally administered 30 minutes after the start of the meal and no additional food was served until 4 hours after dosing. The caloric breakdown of the test breakfasts is shown below:

Reference ID: 3129601

Composition and Caloric Breakdown of Breakfast (Study 041)

Test Breakfast	Menu	Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)
Low-fat breakfast	1 cup Cheerios	110	3	2	20
	8 ounces 2% milk	129	8	5	13
	2 slices wheat bread	162	0	2	36
	1 ounce ham	34.3	4.66	1	1.66
	1 packet ketchup	9	0	0	3
	Total (kcal or g)	444.3	15.7	10.0	73.7
High-fat breakfast	2 large eggs	144	12.58	9.94	0.78
	4 links sausage	328	16	28	2
	2.25 ounces hash brown potato patty	140	2	8	15
	1 cup cantaloupe	60.3	1.3	0.34	14.4
	1 slice wheat bread	80	3	1	17
	4 ounces orange juice	55	0.5	0	13.5
	8 ounces 2% milk	130	8	5	13
	1 pat butter	70	0	8	0
	2 packets ketchup	18	0	0	4.5
	Total (kcal or g)	1025.3	43.4	60.3	70.2

Blood was collected over 96 hours for mirabegron PK.

Results:

From this study, low fat meals showed greater reduction in the bioavailability of mirabegron compared to high fat meals at both 50 mg and 100 mg doses (**Figures 4.2.10.1-4.2.10.3 and Tables 4.2.10.1 and 4.2.10.2**)

Figure 4.2.10.1 Mean Plasma Concentration-Time Profiles of Mirabegron in Fed and Fasted Condition after 50 mg Dose (Study 041)

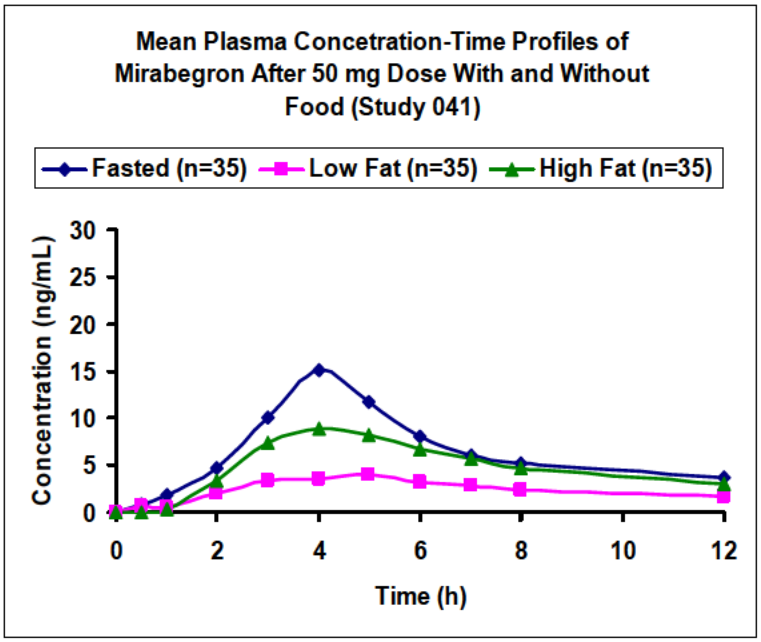


Figure 4.2.10.2 Mean (SD) Cmax of Mirabegron in Fed and Fasted Condition after 50 mg Dose (Study 041)

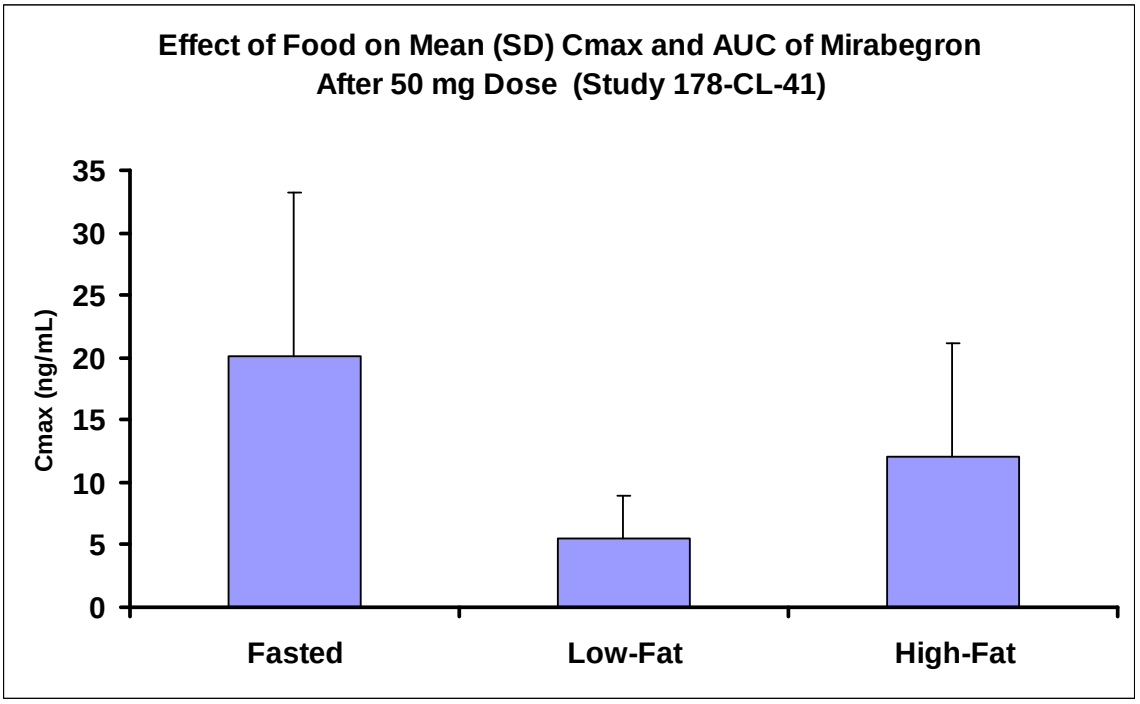
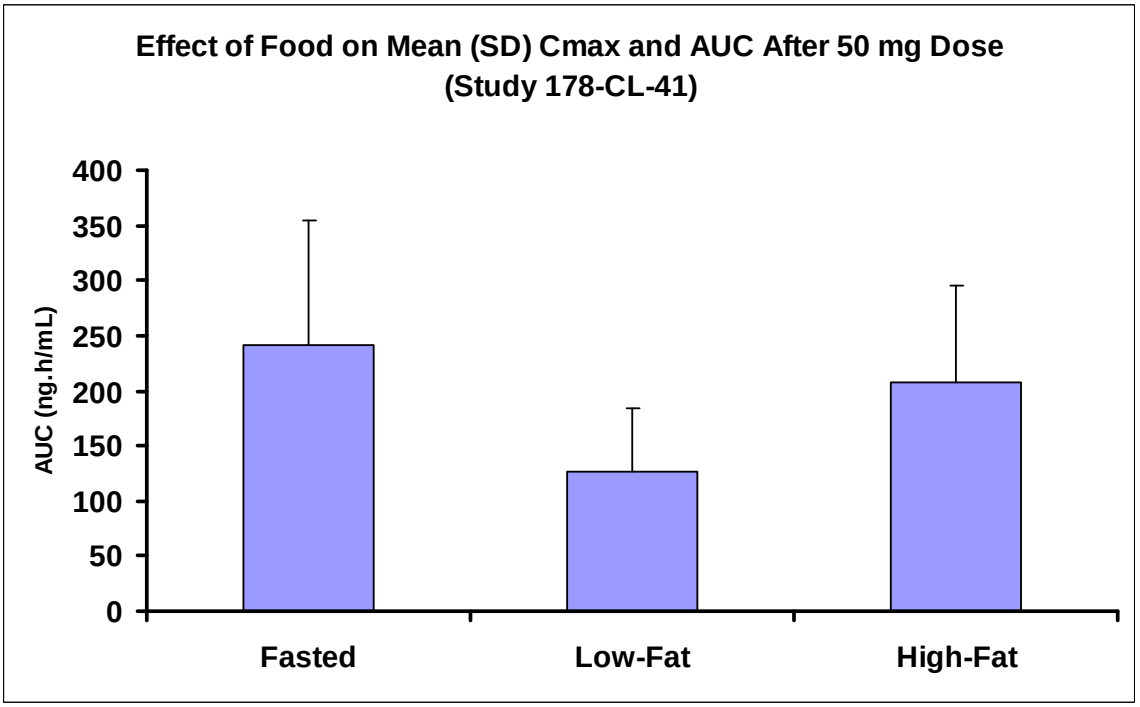


Figure 4.2.10.3 Mean (SD) AUC of Mirabegron in Fed and Fasted Condition after 50 mg Dose (Study 041)



Reference ID: 3129601

Table 4.2.10.1 Summary of Mirabegron PK Parameters in Fed and Fasted Condition after 50 mg Dose (Study 041)

Parameter (unit)	Statistic	Mirabegron 50 mg Under 3 Treatment Conditions		
		Fasted (n=35)	Low-fat Breakfast (n=36)†	High-fat Breakfast (n=36)†
C_{max} (ng/mL)	Mean±SD	20.1±13.07	5.5±3.41	12.1±9.00
	% CV	65.1	62.5	74.5
	Median	16.9	4.1	10.3
	Min-Max	4.1-58.5	1.6-13.7	4.0-53.7
	Geometric Mean	16.6	4.6	10.0
AUC_{last} (hr·ng/mL)	Mean±SD	197.7±85.36	94.8±39.73	166.1±69.56
	% CV	43.2	41.9	41.9
	Median	183.7	85.4	144.0
	Min-Max	47.5-429.3	25.0-198.3	78.8-415.7
	Geometric Mean	179.6	86.2	154.5
AUC_{inf} (hr·ng/mL)	Mean±SD	241.9±112.25	126.5±57.95	207.8±86.87
	% CV	46.4	45.8	41.8
	Median	219.0	107.5	175.9
	Min-Max	60.6-555.1	32.7-298.6	99.8-469.3
	Geometric Mean	218.0	114.1	192.9
t_{lag} (hr)	Mean±SD	0.04±0.142	0.60±0.410	0.59±0.455
	% CV	331.4	68.4	77.5
	Median	0.00	0.50	0.51
	Min-Max	0.00-0.50	0.00-2.00	0.00-2.00
t_{max} (hr)	Mean±SD	3.9±1.08	4.8±1.57	4.8±1.56
	% CV	27.5	32.8	32.7
	Median	4.0	5.0	4.0
	Min-Max	2.0-6.0	2.0-8.0	2.0-8.0
$t_{1/2}$ (hr)	Mean±SD	43.8±9.03	49.8±22.60	45.4±10.72
	% CV	20.6	45.4	23.6
	Median	42.2	43.2	44.5
	Min-Max	27.8-66.8	21.1-154.6	27.9-77.0
CL/F (L/hr)	Mean±SD	257.2±139.95	492.0±268.49	277.2±98.54
	% CV	54.4	54.6	35.6
	Median	228.3	465.1	284.6
	Min-Max	90.1-825.4	167.5-1527.6	106.5-501.1
Rel F	Mean±SD	NA	0.58±0.272	0.99±0.562
	% CV		47.0	56.5
	Median		0.48	0.87
	Min-Max		0.26-1.52	0.35-3.35

Table 4.2.10.2 Statistical Analysis of Mirabegron PK Parameters in Fed and Fasted Condition after 50 mg Dose (Study 041)

Parameter (unit)	Treatment	n	LS Mean†	Comparison	LS Mean Ratio (%)‡	90% CI of Ratio (%)‡
AUC_{inf} (hr·ng/mL)	Fasted	35	227.44	Low-fat/Fasted	48.66	(43.32, 54.67)
	Low-fat	36	110.68	High-fat/Fasted	83.24	(74.16, 93.42)
	High-fat	36	189.31	High-fat/Low-fat	171.05	(152.47, 191.89)
AUC_{last} (hr·ng/mL)	Fasted	35	188.42	Low-fat/Fasted	44.29	(38.90, 50.42)
	Low-fat	36	83.45	High-fat/Fasted	80.32	(70.61, 91.36)
	High-fat	36	151.33	High-fat/Low-fat	181.35	(159.52, 206.17)
C_{max} (ng/mL)	Fasted	35	17.75	Low-fat/Fasted	24.96	(19.89, 31.33)
	Low-fat	36	4.43	High-fat/Fasted	54.76	(43.69, 68.65)
	High-fat	36	9.72	High-fat/Low-fat	219.38	(175.08, 274.89)

Reference ID: 3129601

Reviewer's Comments:

The observed effect of food on mirabegron is associated with delay in absorption as a result of possible physical interaction with food. As BCS Class 3 (high solubility/low permeability) drug the absorption is likely to be rate limited by intestinal membrane permeation (i.e., intestinal influx and efflux plays an important role). The transport mechanism may become saturated in presence of fat. Therefore, meal constituents may compete for mirabegron uptake and efflux.

Anther study was conducted in Japan with similar design as this study (178-CL-078). The effect of food observed in the Japanese study was similar to this study.

It should be noted that Phase 3 studies were conducted irrespective of food. Since there was no major safety concern and the drug shows efficacy in Phase 3, the sponsor proposed that mirabegron can be taken with or without food.

Appendix I

4.3.1 Pharmacometric Review

Office of clinical PHarmacology: Pharmacometric review

Application Number	NDA 202611
Submission Number (Date)	29 Aug 2011
Drug Name	Mirabegron
Formulation:	Extended release tablets
Dose:	50 mg once daily (reduced to 25 mg daily for patients with severe renal or moderate hepatic insufficiency)
Clinical Division	Division of Reproductive and Urologic Products
Primary CP Reviewer	Sayed (Sam) Al Habet, RP.h., Ph.D.
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Myong-Jin Kim, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.
Sponsor	Astellas Pharma Global Development, Inc.

1 Summary of Findings

1.1 Key Review Questions

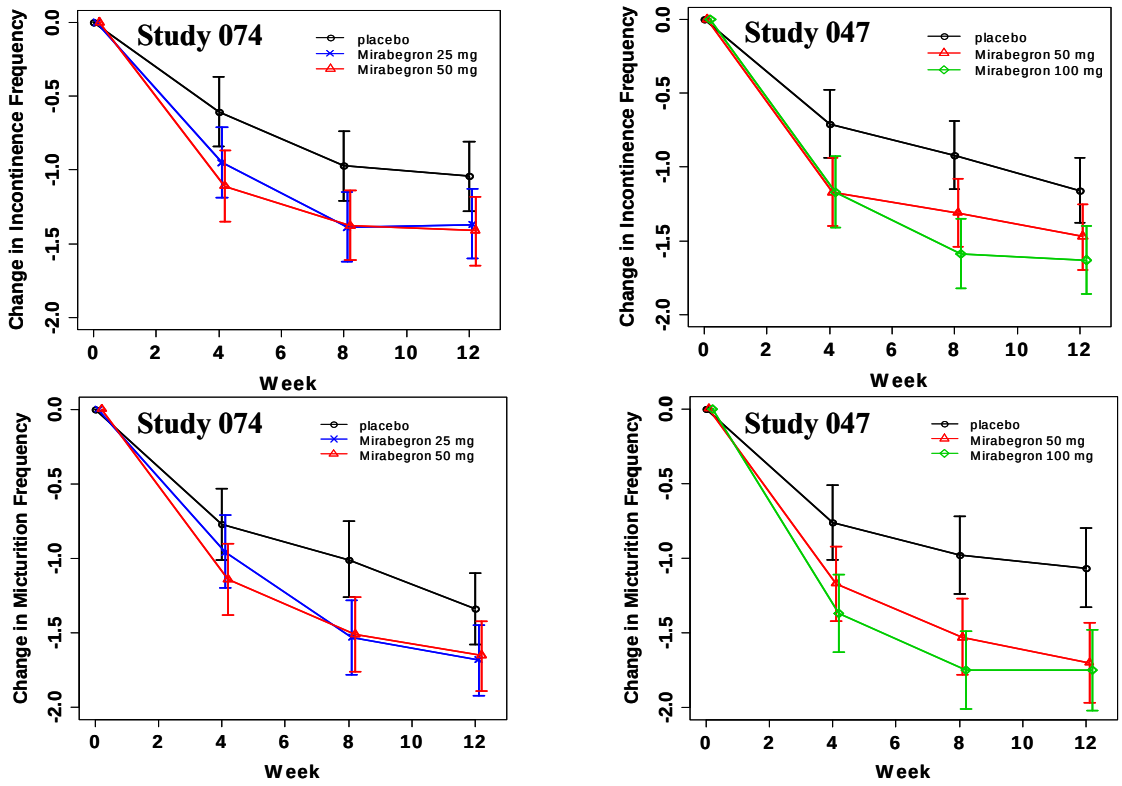
The purpose of this review is to address the following key questions.

1.1.1 Does mirabegron exposure-response for efficacy and safety support the proposed 50 mg QD dose?

For the co-primary efficacy endpoints (i.e., change from baseline to final visit in mean number of incontinence episodes per 24 hours and change from baseline to final visit in mean number of micturitions per 24 hours), the 25, 50, and 100 mg QD mirabegron doses were consistently superior to the placebo in all of the Phase 3 clinical trials. A dose higher than 25 mg does not seem to provide significant further benefit for primary efficacy endpoints (Figure 1). Exposure-response analyses indicate higher mirabegron exposure (AUC_{24_ss}) was associated with larger volume voided and other supportive efficacy endpoints (e.g, better urgency and quality of life outcome). However, doses higher than 50 mg do not seem to offer significant further advantage (Figure 2 and Figure 3). The lack of substantial blood pressure (BP) effect of the 50 mg QD mirabegron in overactive bladder (OAB) patients may not be accurately evaluated from the Phase 3 trials. In healthy subjects stabilized at the 50 mg QD mirabegron dose, an increase of 4 mmHg (1.64, 6.43) in placebo corrected systolic blood pressure (SBP) 3 to 6 hours after dosing was observed (Figure 6). Further investigation of the BP effect of mirabegron in OAB patients should be conducted.

Reference ID: 3129601

Figure 1. The 25, 50, and 100 mg Mirabegron Doses Were Superior to the Placebo in the Pivotal Phase 3 Trials for the Co-Primary Efficacy Endpoints: Change in Incontinence Episodes (Top) and Micturitions (Bottom) Per 24 Hours.



Exposure-response for efficacy:

- For the co-primary efficacy endpoints, the 25, 50, and 100 mg mirabegron doses were all superior to the placebo in the pivotal Phase 3 trials. A dose higher than 25 mg does not seem to provide significant further benefit (Figure 1).
- For the secondary efficacy endpoint (i.e., change from baseline to final visit in mean volume voided per micturition), higher mirabegron exposure (AUC_{24_ss}) was associated with larger volume voided. However, doses higher than 50 mg do not seem to offer significant further advantage (Figure 2 and Figure 3).
- For supportive efficacy endpoints (e.g, change from baseline to final visit in mean number of urgency episodes per 24 hours, change from baseline to final visit in mean level of urgency, and change from baseline to final visit in treatment satisfaction- visual analog scale, TS-VAS), higher mirabegron exposure (AUC_{24_ss}) was also associated with better outcomes. Again, doses higher than 50 mg do not seem to offer significant further advantage (not shown).

Figure 2. Mirabegron Doses Response for Change from Baseline to Final Visit in Mean Volume Voided per Micturition.

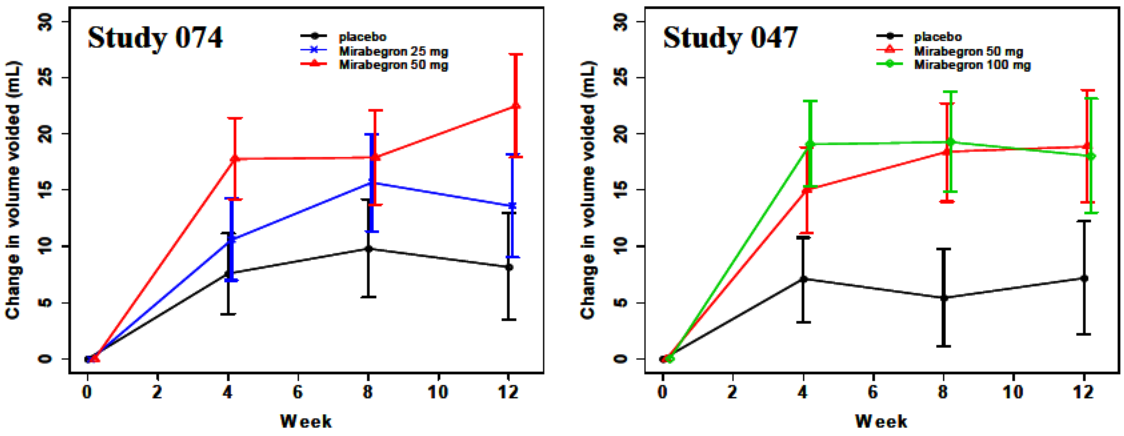
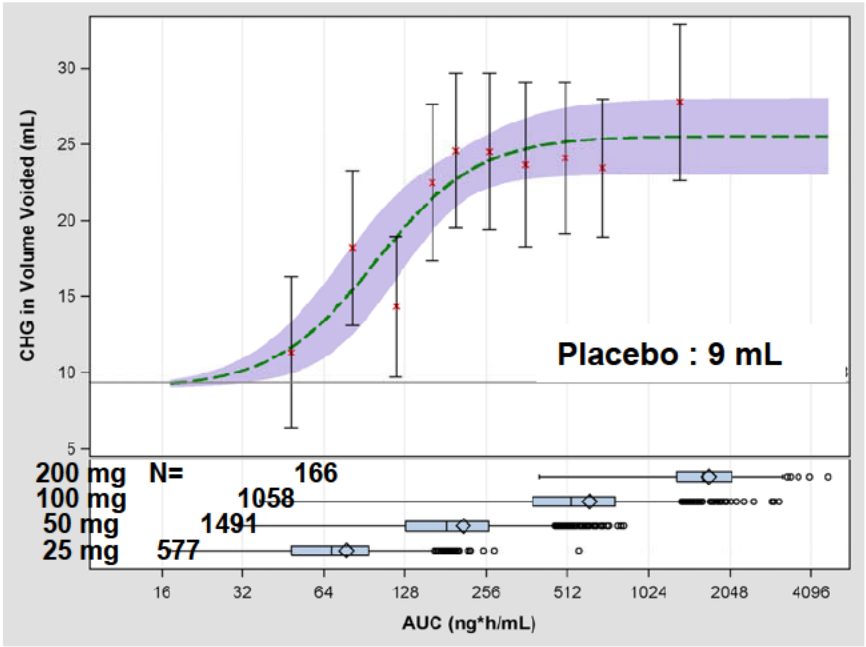


Figure 3. Higher Mirabegron Exposure Was Associated with Larger Volume Voided.



Data were pooled from Study 178-CL-044, 178-CL-046, 178-CL-047, and 178-CL-074 based on the sponsor's population PK/PD dataset. Individual AUC_{24} at the steady state is obtained from the population PK post-hoc estimation.

Exposure-response for safety:

- Higher mirabegron exposure was significantly associated with pulse rate (in OAB patients) and heart rate (in healthy subjects) increases (Figure 4).
- QT prolongation was not observed at the proposed 50 mg dose. However a small signal was observed in females at 200 mg (see IRT-TQT review for mirabegron).

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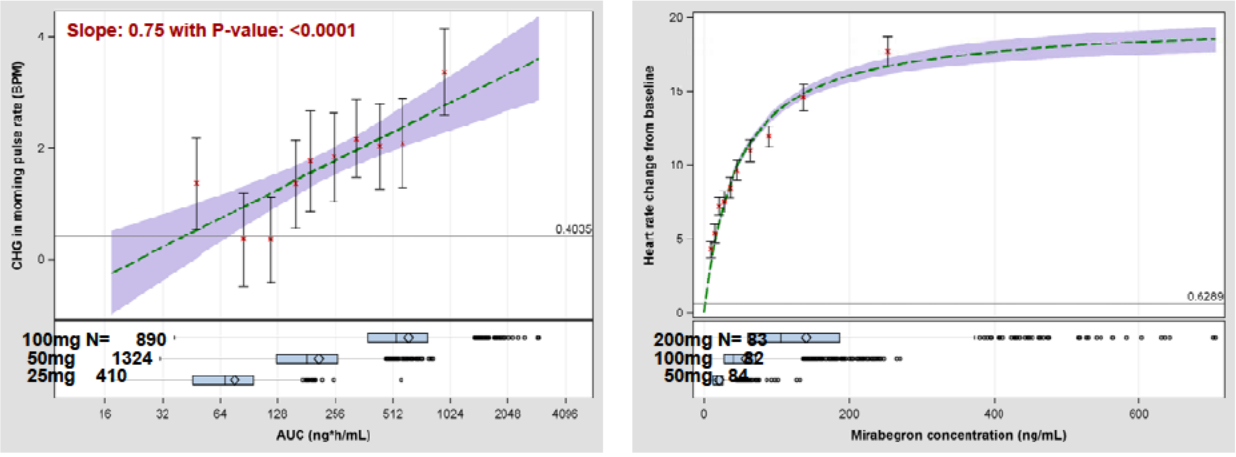
- No substantial exposure-blood pressure (BP) relationship was observed in OAB patients from Phase 3 trials. However, a significant exposure-BP relationship was observed in healthy subjects from Phase 1 studies (Figure 5).
- Dose-BP analyses demonstrated a 4 mmHg (1.64, 6.43) increase in placebo corrected systolic blood pressure (SBP) during 3 to 6 hours after dosing in healthy subjects stabilized at the 50 mg QD mirabegron dose (Figure 6). Moxifloxacin (the active control for the TQT study) did not show any SBP increase as expected.

The potential reasons for observing different exposure-BP relationship between healthy subjects from Phase 1 studies and OAB patients from Phase 2b and 3 studies include:

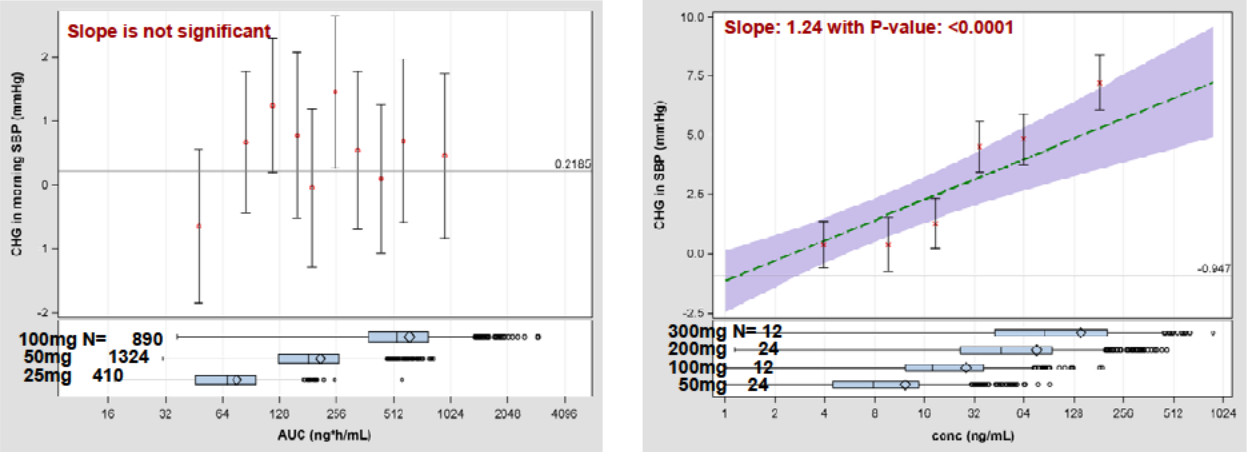
- Difference in population: Healthy subjects from Phase 1 studies are young and have relatively low BP baseline.
- Difference in BP measurement: Self measurement of sitting BP in Phase III versus clinic measurements of supine BP in Phase 1 studies.
- Timing of the blood pressure sampling. In Phase 1 studies, relatively more measurements within the inter-dosing interval allowed for assessment of drug effect at peak and trough. In the Phase III studies, vital signs were collected by the subject during the AM (after waking up in the morning before the morning dose) and PM (between 2 PM and 6 PM) in a 5-day vital sign diary using a self-measurement device. This sampling scheme did not allow for the assessment of the peak effects which generally occurred around 3 – 4.5 hours coinciding with the peak mirabegron concentrations post-dose. However, given the flat SBP-time profile, this may not be that important.

Figure 4. Higher Mirabegron Exposure Was Significantly Associated with Increased Pulse Rate (Left [a]) and Heart Rate (Right [b]).



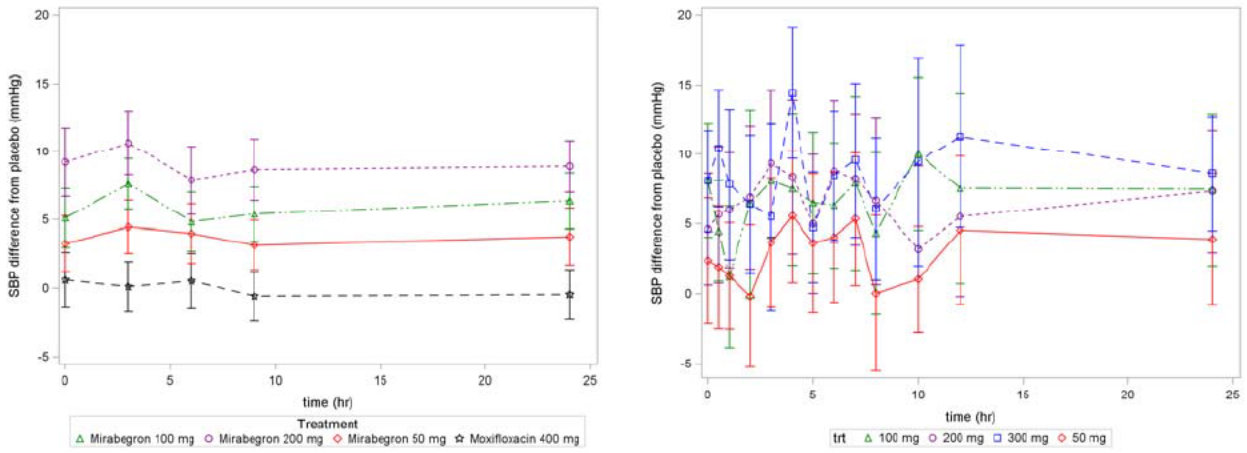
[a] AUC-pulse rate analysis was conducted in the pooled Phase 3 studies.
[b] Concentration-heart rate analysis was conducted in the TQT Study 178-CL-077 on Day 9.

Figure 5. No Substantial Exposure-SBP Relationship Was Observed in OAB Patients From Phase 3 Trials (Left [a]). A Significant Relationship Was Observed in Phase 1 Healthy Subjects (Right [b]).



[a] AUC-SBP analysis was conducted in the pooled Phase 3 studies.
[b] Concentration-SBP analysis was conducted in the Phase 1 Study 178-CL-031.

Figure 6. Significant Dose-Response Relationship for Placebo Corrected SBP Increase Was Observed in Healthy Subjects at the Steady State from the Phase 1 Study 178-CL-077 on Day 9 (Left) and a Trend Was Also Observed in Study 178-CL-031 on Day 14 (Right).



1.2 Recommendations

- Based on the phase 3 pivotal trials, a dose higher than 25 mg does not seem to provide further benefit for the co-primary efficacy endpoints.
- Considering the BP effect of mirabegron from Phase 1 studies and the higher neoplasm event rate at the 100 mg mirabegron dosing (see Dr. Wiederhorn's clinical review), a starting dose of 25 mg with titration up to 50 mg if required based on response seems to balance the benefit and risk better compared to the proposed 50 mg. As shown in Figure 1, the numerical difference between 25 mg and 50 mg dismissed after 8 weeks of treatment. Therefore, titration at 8-week if required based on response is recommended.

Reference ID: 3129601

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2. Pertinent regulatory background

This is the original submission (NDA 202611) that the sponsor is seeking approval of mirabegron 50 mg QD for the treatment of symptoms associated with OAB in adult patients.

Mirabegron is a selective agonist for human beta 3-adrenoceptor (beta 3-AR). It is a new chemical entity, first-in-class compound with a distinct mechanism of action compared with the current standard of care, primarily antimuscarinics, as pharmacotherapy for the above indication. Mirabegron was approved in Japan in 2011.

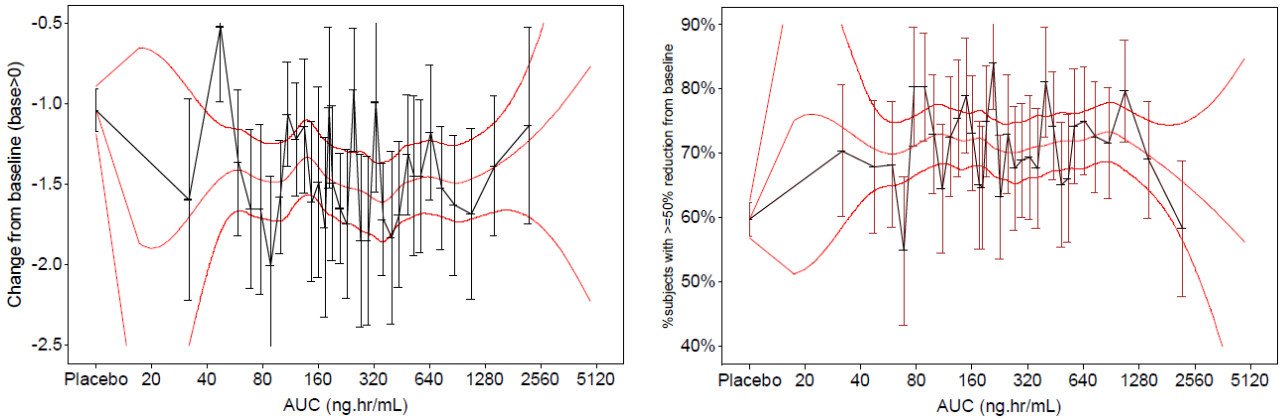
The initial clinical development program examined an indication of type 2 diabetes mellitus and was subsequently discontinued due to the absence of efficacy. A total of 29 Phase 1 studies and 12 Phase 2 and 3 studies (9 in patients with OAB) have been conducted globally over 10 years in 10,552 volunteers, patients with OAB, patients with lower urinary tract symptoms (LUTS)/bladder outlet obstruction (BOO), or patients with type 2 diabetes mellitus. The primary efficacy and safety data comes from 3 Phase 3 studies: 178-CL-046, 178-CL-047, and 178-CL-074. Also the Phase 2b Study 178-CL-044 and the Japanese Phase 3 Study 178-CL-048 and Phase 2b Study 178-CL-045 provide supportive evidence.

3 Results of Sponsor's Analysis

3.1 Explore the exposure-response relationship for efficacy

The exposure-response relationships for micturition frequency, mean volume voided and incontinence frequency have been investigated. The data included were from the Phase 2b Study 178-CL-044 and the 3 pivotal Phase 3 studies. In total, there were 5346 subjects in the analysis, and doses of mirabegron ranging from 25 mg to 200 mg. The exposure-response for incontinent episodes indicated that the exposure response relationship was flat (Figure 7). Exploratory graphical analyses demonstrated higher mirabegron exposure (AUC_{24}) was associated with larger volume voided and more reduction in micturition frequency (Figure 8).

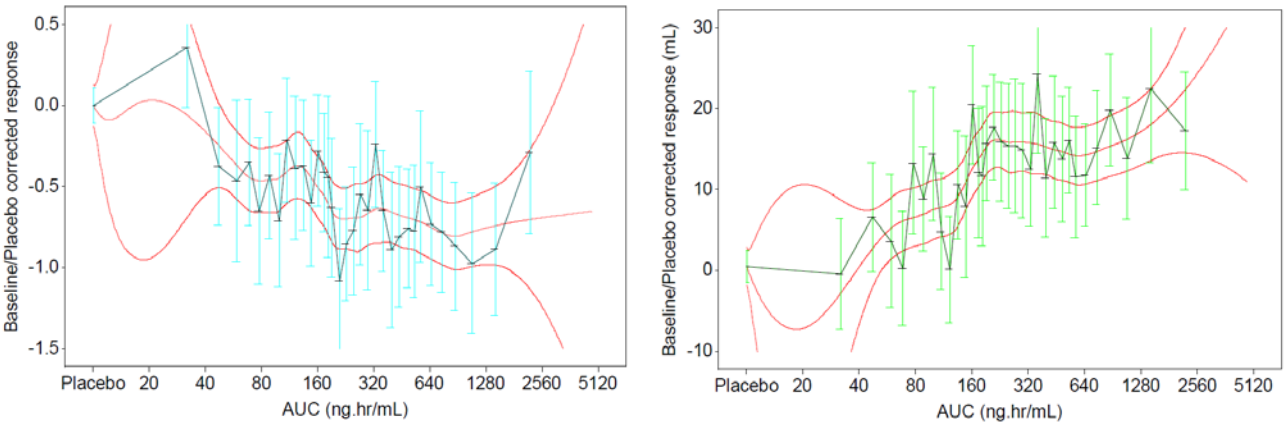
Figure 7. Incontinent Episodes Change from Baseline (Left) and Incontinent Episodes for at Least a 50% Reduction from Baseline (Right) versus Mirabegron AUC_{24}



Comparison of a smooth through the data (red) to the grouped means with 90% CI (by ascending AUC group)

(Source: Sponsor's Study Report: 178-PK-017, Figure 19 and 21)

Figure 8. Placebo Corrected Change from Baseline (Left) in Micturition Frequency and Volume Voided (Right) versus Mirabegron AUC_{24}



Comparison of a smooth through the data (red) to the grouped means with 90% CI (by ascending AUC group)

(Source: Sponsor's Study Report: 178-PK-017, Figure 12)

A joint ANCOVA type model was also developed for Micturition frequency and mean volume voided. The model corrected for baseline, estimated the placebo effect, and used a sigmoidal E_{max} model for mirabegron. It also estimated the tolterodine 4 mg SR effect for both endpoints:

Reference ID: 3129601

$$E_{mic} = B_{mic}.(base_{mic\,i}\text{-}12) + E0_{mic} + \frac{E_{max}.AUC_i^{\gamma}}{AUC_{50}^{\gamma} + AUC_i^{\gamma}} + Tol_{mic} + b_1$$

$$E_{vol} = B_{vol}.(base_{vol\,i}\text{-}160) + E0_{vol} - FACTOR.\frac{.E_{max}.AUC_i^{\gamma}}{AUC_{50}^{\gamma} + AUC_i^{\gamma}} + Tol_{vol} + b_2$$

$$\begin{matrix} b_1 \\ b_2 \end{matrix} \sim N(0,\Sigma),\ \Sigma \sim \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

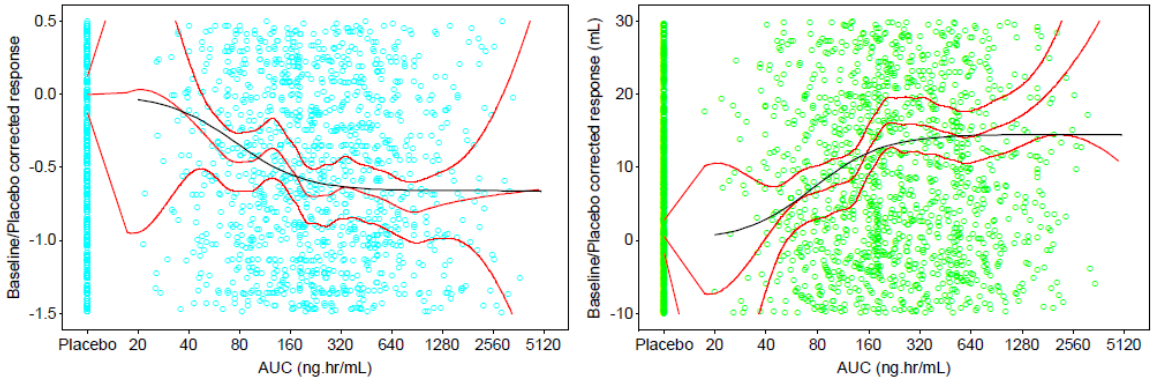
$$E0_{mic} = E0_{mic} \text{ for study 46},\ E0_{mic} = E0_{mic} + E0_{mic\,x} \text{ for x = study 44, 47 and 74}$$

$$E0_{vol} = E0_{vol} \text{ for study 46},\ E0_{vol} = E0_{vol} + E0_{vol\,x} \text{ for x = study 44, 47 and 74}$$

where "E_{mic}" is the observed LOCF change from baseline for micturition frequency, and "E_{vol}" is the observed LOCF change from baseline for mean volume voided. The ANCOVA correction for baseline micturitions for subject i ("$base_{mic\,i}$") and baseline mean volume voided ("$base_{vol\,i}$") is through parameters "B_{mic}" and "B_{vol}", which are centered using 12 micturitions and 160 mL for micturition frequency and mean volume voided respectively. The "E_{max}" is the maximum effect, "AUC_{50}" is the AUC required to give 50% of the maximal response, "AUC_i" is the AUC for subject i, and "γ" is the Hill coefficient. The parameter "FACTOR" scales the "E_{max}" from the micturition frequency to the correct value for mean volume voided. The tolterodine 4 mg SR effects are estimated using parameters "Tol_{mic}" and "Tol_{vol}" for micturition frequency and mean volume voided respectively. The placebo effect is modelled with parameters "$E0_{mic}$" and "$E0_{vol}$". As different studies typically vary in the placebo response, the parameters "$E0_{mic}$" and "$E0_{vol}$" were fitted for a reference study (the largest, Study 46), with offset terms for the other three studies (44, 47, and 74). The residual variances for micturition frequency and mean volume voided are σ_1^2 and σ_2^2 respectively, with ρ the correlation between the two residual variances. The influence of continuous and categorical covariates was also tested for their effect on the placebo response for either micturition frequency ($E0_{mic}$) and/or mean volume voided ($E0_{vol}$) and the mirabegron AUC_{50} parameter. Both the base and the final model offered a reasonable description of the relationship between both micturition frequency and mean volume voided and mirabegron exposure (Figure 9). E_{max} was estimated to be a -0.66 change in micturitions versus placebo (95% CI: -0.49, -0.88). The maximum effect for mean volume voided was about 14.5 mL. AUC_{50} was estimated to be 75 ng*hr/mL (95% CI: 46, 123 ng*hr/mL). No covariates were found to influence AUC_{50}. Simulation predicted 52% and 85% of the estimated maximal response for the 25 and 50 mg mirabegron doses respectively.

Reference ID: 3129601

Figure 9. Placebo Corrected Change from Baseline (Left) in Micturition Frequency and Volume Voided (Right) versus Mirabegron AUC_{24} with Smooth and 95% CI (Red Lines) and the Final Fitted Models Overlaid (Black Line).

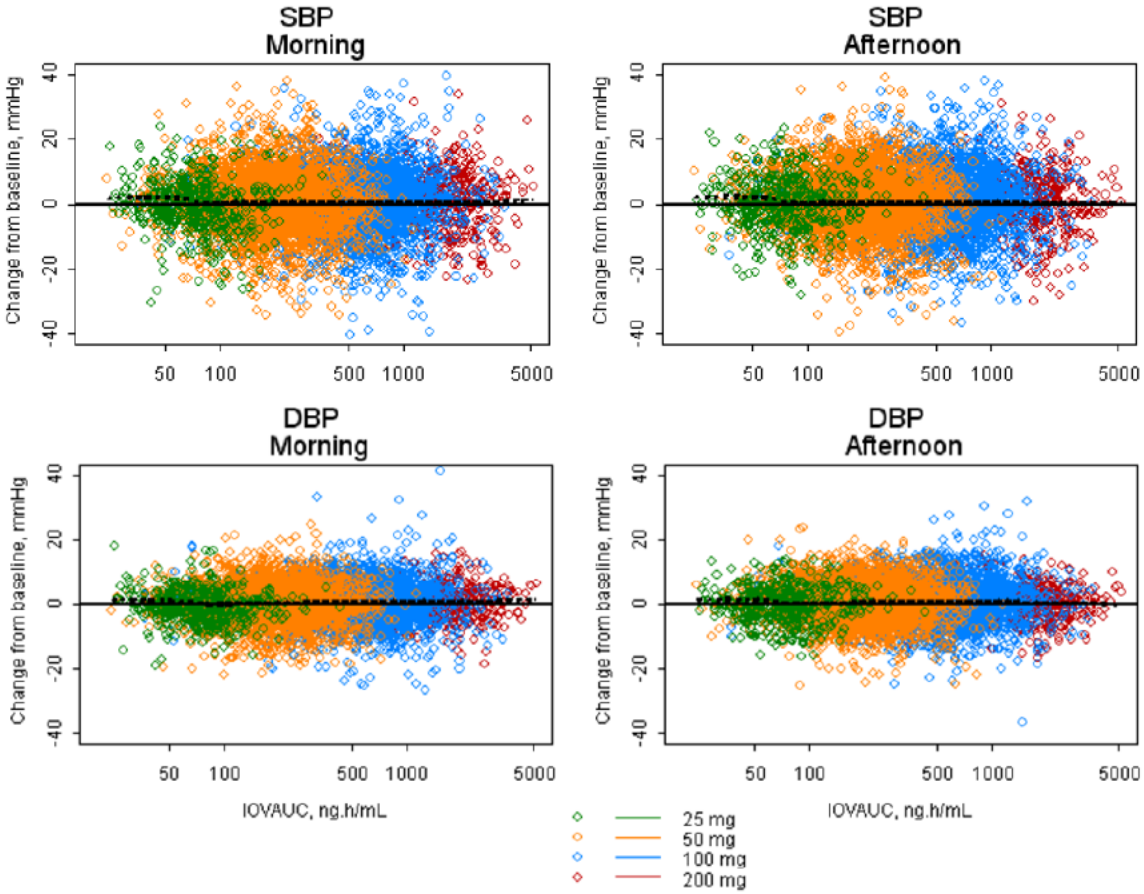


(Source: Sponsor's Study Report: 178-PK-017, Figure 24)

3.2 Explore the exposure-response relationship for safety

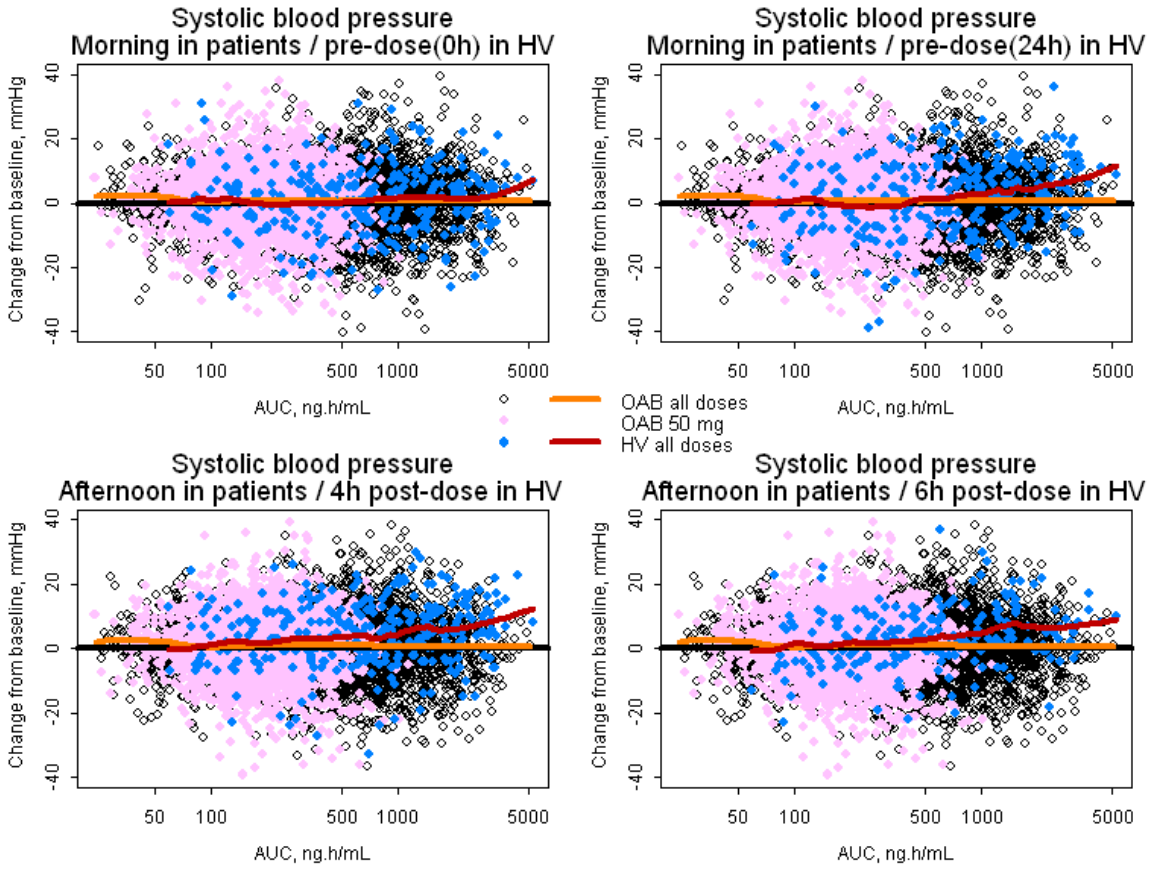
No exposure-response relationships were found for either systolic or diastolic blood pressure in patients with OAB using data from the above 4 studies (Figure 10). In contrast, a graphical analysis of data from 3 separate healthy volunteer studies (178-CL-031, 178-CL-037 and 178-CL-072) revealed an increase in SBP as a function of increase in exposure (Figure 11). Sex had no effect on the SBP response. The increase in SBP as a function of exposure tended to be more marked in younger subjects. Analysis by age subsets revealed that the absence of an effect of exposure on changes in SBP overall was age-dependent. An increase in SBP as a function of exposure was observed in OAB patients younger than 45 (Figure 12).

Figure 10. Individual Morning (Left) And Afternoon (Right) SBP (Top) and DBP (Bottom) Changes from Baseline (Weeks 4, 8 And 12 Combined) as a Function of Mirabegron AUC in Patients with OAB from Studies 178-CL-044, 178-CL-046 and 178-CL-047. The Dashed Black Lines Are Smoothes through the Data.



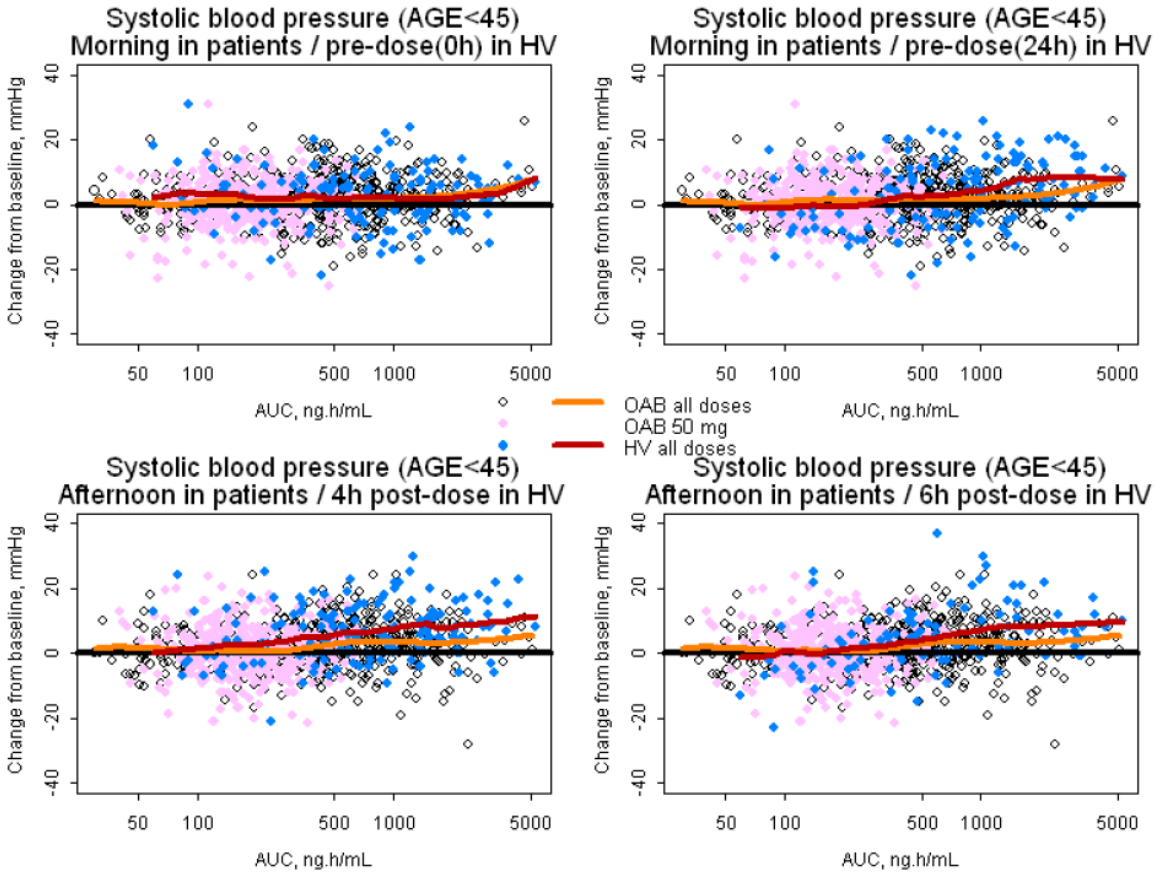
(Source: Sponsor's Study Report: 178-PK-016, Figure 14 and 23)

Figure 11. Comparison of SBP Change from Baseline versus AUC_{24} at the Steady State from Healthy Volunteers and Patients with OAB. Trend Lines for the Healthy Volunteers (Red Lines) and Patients with OAB (Orange Lines) Are Superimposed.



(Source: Sponsor's Study Report: 178-PK-022, Figure 33)

Figure 12. Comparison of SBP Change from Baseline versus AUC_{24} at the Steady State from Healthy Volunteers and Patients with OAB Aged Less Than 45 Years. Trend Lines for the Healthy Volunteers (Red Lines) and Patients with OAB (Orange Lines) Are Superimposed.



(Source: Sponsor's Study Report: 178-PK-022, Figure 33)

The graphical analysis of the exposure-pulse rate relationship in patients with OAB revealed that an apparent pulse rate increase with a higher mirabegron exposure (Figure 13). A population exposure-pulse rate model of mirabegron in OAB patients was also developed. The model has three major components: (1) a 'baseline' model that describes the morning and afternoon pulse rate during the run-in period, (2) a 'placebo' model that describes the placebo effect which is additive to the baseline during the treatment period (only significant in the afternoon: -0.39 ± 0.10 bpm), (3) a 'drug' EMAX model which is additive to both the baseline and placebo models and that describes the mirabegron exposure-related pulse rate increase. The results indicated that the mean maximum increase in pulse rate was 6.97 ± 0.81 bpm and the mean mirabegron exposure that gives 50% of maximum pulse rate increase is 1086 ng.h/mL (with 95%CI: 721 – 1635 ng.h/mL) in the typical subject (60 years with morning pulse rate baseline of 70 bpm and no co-medication with beta-blockers). The covariate analysis found the mean log(AUC50) of 6.99 ± 0.21 increased with increasing age (+0.31 ± 0.06 per 10 years), morning baseline (+0.55 ± 0.098 per 10 bpm) and co-treatment with beta-blockers (+0.73 ± 0.22) indicating that the pulse rate increase induced by mirabegron diminishes with age, with increased baseline pulse rate and when beta-blockers are co-administered. The impact of period of the day, body mass index, sex, studies, race, diabetes, cardiac heart failure, hypertension, beta2-agonists and diuretics on drug

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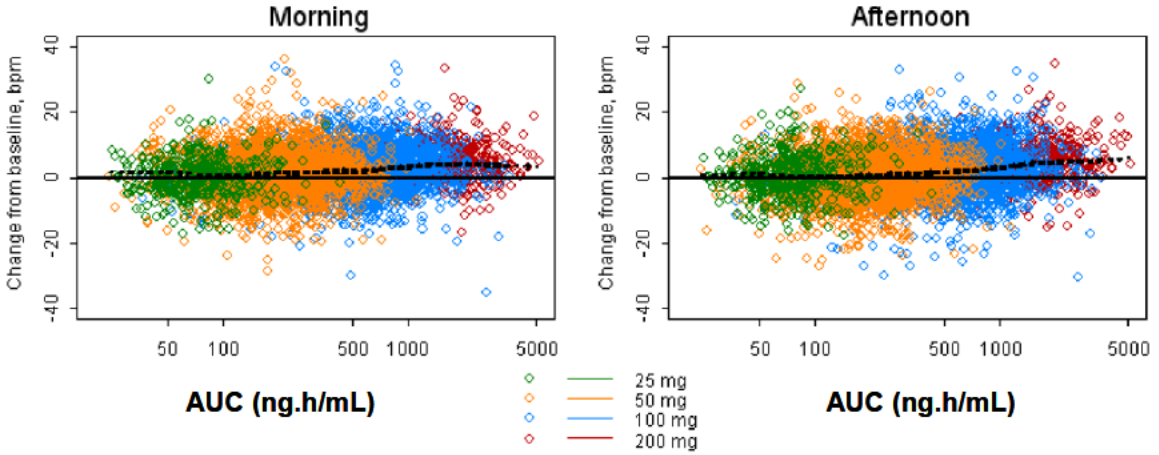
effect (AUC50) was tested, but were not found to be statistically significant. Comparison of the relationship between change in pulse rate and degree of exposure in healthy volunteers and in patients with OAB revealed that while the relationship held in both groups, the magnitude of the pulse rate change as a function of increasing exposure was greater in healthy subjects overall compared to patients with OAB. This differential response between the 2 groups was more marked in younger subjects whether considered as younger than 45 years or younger than 65 years.

Figure 13. Individual Morning (Left) and Afternoon (Right) Pulse Rate Changes from Baseline (Weeks 4, 8 And 12 Combined) as a Function of Mirabegron AUC in Patients with OAB from Studies 178-CL-044, 178-CL-046 and 178-CL-047. The Dashed Black Lines Are Smoothes through the Data.



(Source: Sponsor's Study Report: 178-PK-016, Figure 5)

Reviewer's comments: The reviewer performed independent analyses and the results were consistent with those from the sponsor:

- *More micturition reduction seems to associate with higher mirabegron exposure. However, the relationship was not supported by the dose-response within trial comparison from Study 178-CL-074. The dose-response from the Phase 2b study 178-CL-044 indicated the additional benefit in micturition from the 50 mg is small compared to the 25 mg (-0.64 vs. -0.45 in change from placebo respectively). For incontinence, the 25 mg provided significant benefit compared to placebo in the Phase 2b study 178-CL-044 (Table 1 and Table 2).*
- *In healthy subjects stabilized at the 50 mg QD mirabegron, an increase of 4 mmHg (1.64, 6.43) in placebo corrected systolic blood pressure (SBP) 3 to 6 hours after dosing was observed (Figure 6). Further investigation of the BP effect of mirabegron in OAB patients should be conducted.*

A starting dose of 25 mg with titration up to 50 mg if required based on response seems to balance the benefit and risk better compared to the proposed 50 mg.

Table 1. ANCOVA Modeling Results: Change from Baseline at Endpoint in Mean Number of Micturitions per 24 Hours (FAS)

	Placebo	YM178 OCAS 25 mg qd	YM178 OCAS 50 mg qd	YM178 OCAS 100 mg qd	YM178 OCAS 200 mg qd
N	166	167	167	168	166
Adjusted mean CFB	-1.44	-1.88	-2.08	-2.12	-2.24
Estimated difference from placebo		-0.45	-0.64	-0.68	-0.80
95% CI		-0.99; 0.10	-1.19; -0.10	-1.22; -0.13	-1.34; -0.25
P-value		0.1083	0.0205*	0.0152*	0.0041*

(Source: Sponsor's Study Report: 178-PK-044, Table 13)

Table 2. ANCOVA Modeling Results: Change from Baseline at Endpoint in Mean Number of Incontinence Episodes per 24 Hours (FAS)

	Placebo	YM178 OCAS 25 mg qd	YM178 OCAS 50 mg qd	YM178 OCAS 100 mg qd	YM178 OCAS 200 mg qd
N	106	99	108	111	110
Adjusted mean CFB	-0.53	-1.36	-1.15	-1.06	-1.10
Estimated difference from placebo		-0.84	-0.62	-0.53	-0.58
95% CI		-1.45; -0.23	-1.22; -0.02	-1.12; 0.06	-1.16; 0.01
P-value		0.0072*	0.0416*	0.0758	0.0551

(Source: Sponsor's Study Report: 178-PK-044, Table 21)

4 Reviewer's Analysis

4.1 Introduction

This is the original submission of mirabegron, a first-in-class of a selective agonist for human beta 3-adrenoceptor (beta 3-AR). The sponsor is seeking approval of mirabegron for the treatment of symptoms associated with OAB in adult patients. The proposed dose of mirabegron is 50 mg orally once daily (QD) with or without food in the general population and 25 mg QD in renal and hepatic impairment patients. A thorough review of the dosing strategy and exposure-response relationships for efficacy and safety is performed.

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4.2 Objectives

Analysis objective is to assess the proposed 50 mg QD dose based on the exposure-response relationship for efficacy and safety.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 3

Table 3 Table 3

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
178-pk-017	input01.xpt (incontinent)	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\178-pk-017\analysis\datasets\input01.xpt
178-pk-017	input02.xpt (Micturition and Volume Voided)	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\178-pk-017\analysis\datasets\input02.xpt
integrated-analysis-of-efficacy	admd.xpt	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\integrated-analysis-of-efficacy\analysis\datasets\admd.xpt
integrated-analysis-of-efficacy	admd2.xpt	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\integrated-analysis-of-efficacy\analysis\datasets\admd2.xpt
integrated-analysis-of-safety-p2-3	advsoor.xpt	\\cdsesub5\EVSPROD\NDA202611\0014\m5\datasets\integrated-analysis-of-safety-p2-3-datasets\analysis\datasets\advsoor.xpt'
178-cl-031	vs_os.xpt	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\178-cl-031\analysis\datasets\vs_os.xpt'
178-cl-031	D_PK.xpt	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\178-cl-031\analysis\datasets\D PK.xpt'
178-cl-077	advs.xpt	\\cdsesub5\EVSPROD\NDA202611\0000\m5\datasets\178-cl-077\analysis\datasets\advs.xpt'

4.3.2 Software

SAS, R, and NONMEM were used for the reviewer's analyses.

4.3.3 Models and Results

4.3.3.1 Exposure-Response relationship for efficacy

The exposure-response analyses for efficacy mainly focused on the non-Japanese trials for patients with OAB. The data were pooled from the Phase 2b study 178-CL-044 and the three pivotal Phase 3 studies 178-CL-046, 178-CL-047, and 178-CL-074. The exposure was the

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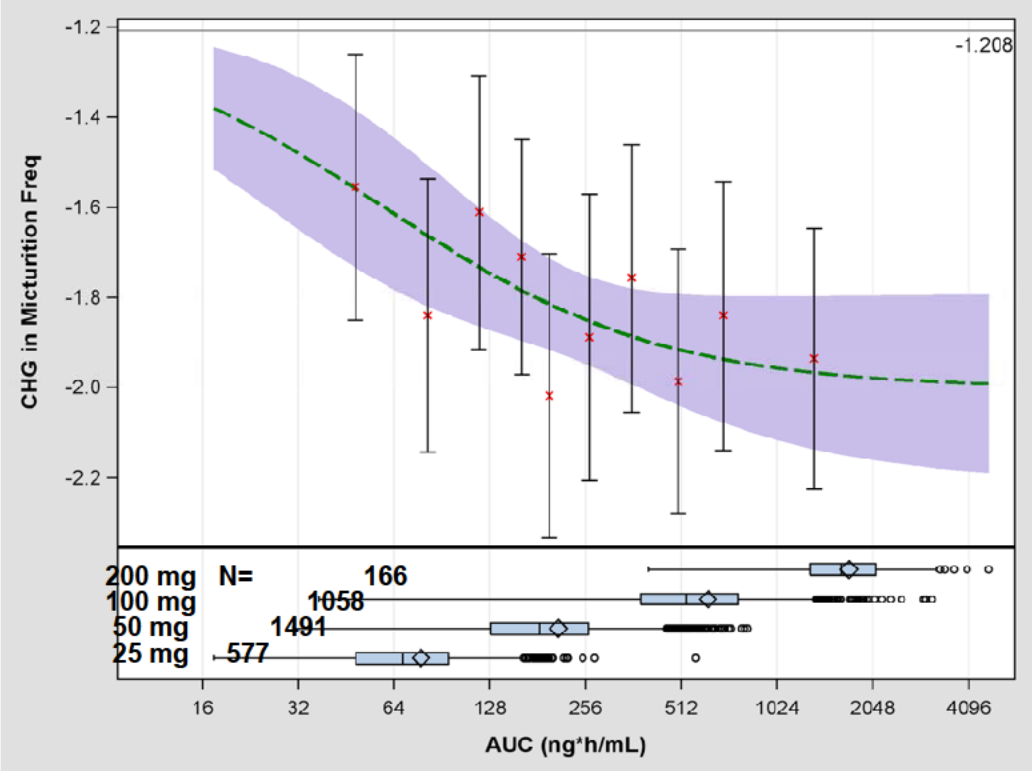
individual AUC_{24} at the steady state obtained from the population PK post-hoc estimation. Graphical visualization and non-linear regression modeling were used to explore the effects of drug exposures and baseline characteristics on the clinical outcomes. Unlike the sponsor's approach which modeled the micturition frequency and mean volume voided jointly, we were exploring the exposure-response relationship for each efficacy endpoint independently. Our analysis results are consistent with the sponsor's findings: (1) The exposure-response relationship for incontinent episodes was relatively flat. (2) More micturition reduction seems to be associated with higher mirabegron exposure and the exposure-response relationship can be characterized by an E_{max} model (Figure 14). A dose higher than 50 mg does not seem to offer further advantage. (3) Higher mirabegron exposure was significantly associated with larger volume voided per micturition and the exposure-response relationship can be characterized by a sigmoid E_{max} model. A dose higher than 50 mg does not seem to offer further advantage (Figure 3). In addition to the primary and secondary efficacy endpoints, we also explored the exposure-response relationship for some supportive efficacy endpoints recommended by the medical reviewers (e.g, change from baseline to final visit in mean number of urgency episodes per 24 hours, change from baseline to final visit in mean level of urgency, and change from baseline to final visit in treatment satisfaction- visual analog scale, TS-VAS). Higher mirabegron exposure was also significantly associated with better outcomes of those supportive efficacy endpoints. Consistently, a dose higher than 50 mg does not seem to offer further advantage.

Figure 14. More Micturition Reduction Seems to Be Associated with Higher Mirabegron Exposure



Data were pooled from Study 178-CL-044, 178-CL-046, 178-CL-047, and 178-CL-074 based on the sponsor's population PK/PD dataset. Individual AUC_{24} at the steady state is obtained from the population PK post-hoc estimation.

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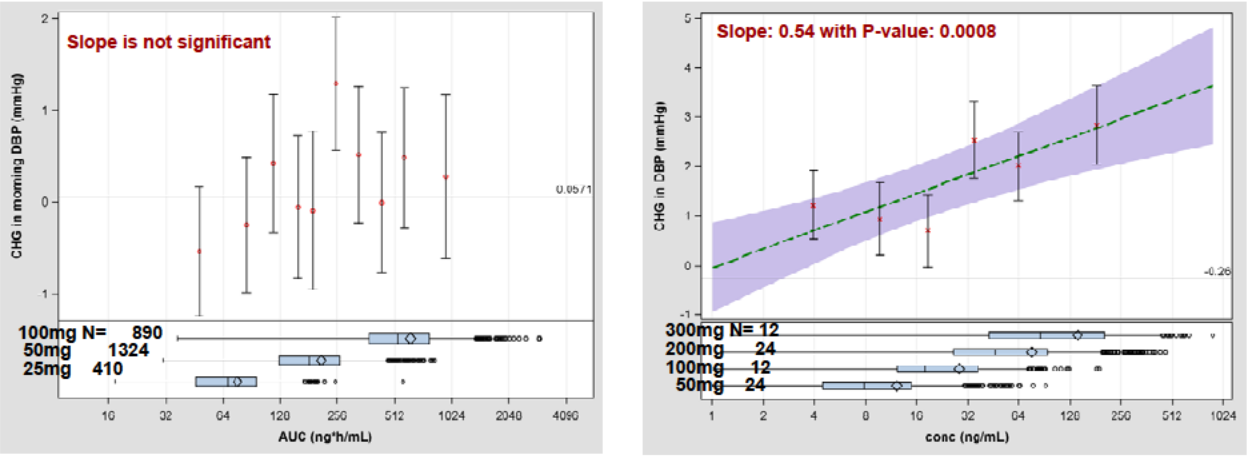
4.3.3.2 Exposure-Response relationship for safety

The exposure-response analyses for safety mainly focused on the cardiovascular effects of mirabegron. The data of patients with OAB were from the pooled 3 pivotal Phase 3 studies. Phase 1 studies 178-CL-077 and 178-CL-031 were also reviewed. The exposure in the OAB patients from the Phase 3 studies was the individual AUC_{24} at the steady state obtained from the population PK post-hoc estimation. The exposure in the healthy subjects from the Phase 1 studies was the observed mirabegron plasma concentration sampled at the same time that safety endpoints were measured. Graphical visualization and linear regression modeling were used to explore the effects of drug exposures and baseline characteristics on the safety endpoints. Our analysis results are consistent with the sponsor's findings: (1) Higher mirabegron exposure was significantly associated with pulse rate and heart rate increases. The exposure-response relationship for heart rate in healthy subjects measured in the well-controlled Phase 1 study is much stronger than that for pulse rate in OAB patients in the Phase 3 setting (Figure 4). (2) QT prolongation was not observed at the proposed 50 mg dose. However a small signal was observed in females at 200 mg (see IRT-TQT review for mirabegron). (3) No substantial exposure-BP relationship was observed in OAB patients from Phase 3 trials. However, a significant exposure-BP relationship was observed in healthy subjects from Phase 1 studies (Figure 5 and Figure 15). Additionally, our dose-BP analyses demonstrated a 4 mmHg increase in placebo corrected SBP during 3 to 6 hours after dosing in healthy subjects stabilized at the 50 mg QD mirabegron dose (Figure 6). The age effect on SBP was also explored in healthy subjects from Study 178-CL-031. It seems the SBP increase from baseline is more pronounce in young subject compared that in the elderly subjects. However, it seems there is no substantial difference in the placebo corrected SBP change from baseline between young and elderly subjects (Figure 16).

Figure 15. No Significant Exposure-DBP Relationship Was Observed in OAB Patients From Phase 3 Trials (Left [a]). However, A Significant Relationship Was Observed in Phase 1 Healthy Subjects (Right [b]).



[a] AUC-DBP analysis was conducted in the pooled Phase 3 studies.
[b] Concentration-DBP analysis was conducted in the Phase 1 Study 178-CL-031.

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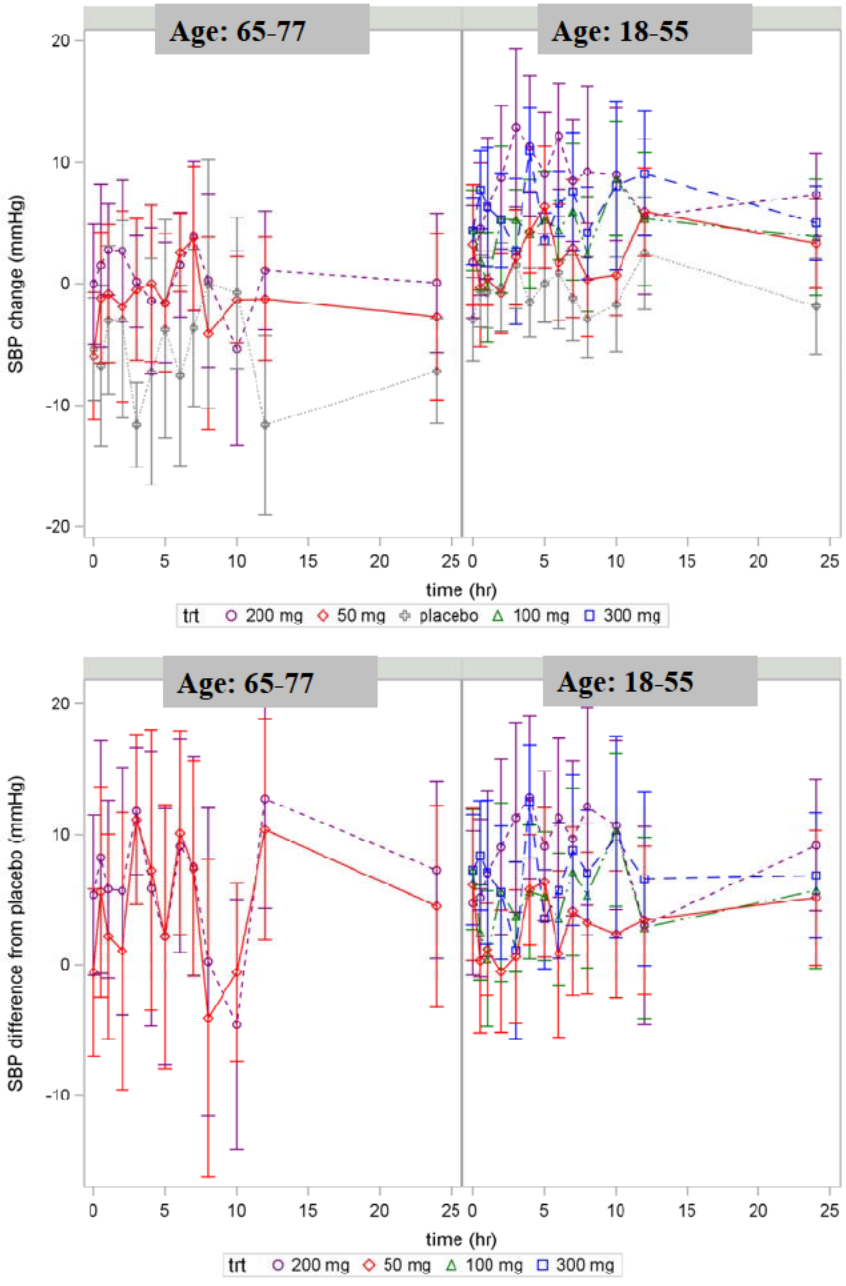
Figure 16. SBP Increase from Baseline Seems More Pronounce in Young Subjects (Top). However, Placebo Corrected SBP Increase Seems to Be Comparable Between Young and Elderly Subjects (Bottom).



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5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
ER_efficacySafety.sas	ER analysis in OAB patients	\Mirabegron_NDA202611_JL\ER_Analyses\
BP_S31.sas	ER analysis for BP in healthy subjects	\Mirabegron_NDA202611_JL\ER_Analyses\
quartilePlot_sigEmax.sas	ER plotting	\Mirabegron_NDA202611_JL\ER_Analyses\
quartilePlot_loglinearMix.sas	ER plotting	\Mirabegron_NDA202611_JL\ER_Analyses\
S047_incontinenceTimeCourse.r	Dose-response time course	\Mirabegron_NDA202611_JL\ER_Analyses\
S077_BPTimeCourse.r	Dose-response time course for BP	\Mirabegron_NDA202611_JL\ER_Analyses\

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Appendix - Population PK Analyses of Mirabegron

6 Summary of Findings

The final population PK model for orally administered mirabegron was a three compartment model with sequential zero- and first-order absorption processes. Mirabegron exposure was influenced by covariates:

- weight and sex on CL and central volume of distribution
- dose on F1.

Other covariate influences affecting the exposure were age, co-administration of proton pump inhibitors, co-administration of weak to moderate CYP3A4 inhibitors, creatinine clearance and food conditions. Important effects based on simulations were found for the following covariates:

- Dose: AUC_{tau} for doses of 25 to 200 mg increased by a factor 20 while the dose increased only by a factor of 8.
- Body weight: AUC_{tau} increased with decreasing body weight. From a body weight of 70 kg, AUC_{tau} increased by 52.8 % for a body weight of 30 kg and decreased by 16.5% for a body weight of 100 kg.
- Sex: AUC_{tau} was 27.5% lower for male compared to female.
- Creatinine clearance: AUC_{tau} increased with decreasing creatinine clearance. From a creatinine clearance of 92 mL/min, AUCtau increased by 39.9 % for a creatinine clearance of 25 mL/min and decreased by 10.6 % for a creatinine clearance of 142 mL/min.
- Age: AUC_{tau} increased with increasing age. From a patient aged 60 years, AUC_{tau} decreased by 23.9 % for a patient aged 20 years and increased by 10.6 % for a patient aged 90 years.

7 Results of Sponsor's Analysis

The sponsor conducted a population pharmacokinetic analysis to:

1. Characterize the pharmacokinetics of mirabegron in OAB patients
2. Evaluate the effects of covariates on mirabegron exposure
3. Obtain individual post-hoc estimates of mirabegron exposure for exposure-response analysis

The dataset consisted of plasma concentrations in OAB patients from 2 Phase 2 studies (178-CL-044, 178-CL-045) and four Phase 3 studies (178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074). In all studies, mirabegron was administered in OCAS formulation. Due to very sparse information in these above 6 studies and in order to well characterize the disposition Phases of mirabegron, a population structural PK model was first developed using only intravenous data from Studies 178-CL-033 and 178-CL-076 in healthy subjects. Records for which concentrations were missing or below the limit of quantification (BLQ) were removed from the database. Further details of the dataset are provided in Table 4-Table 6.

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Table 4. Summary of Data Included in the Population Pharmacokinetic Analysis

Study	033	076	044	045	046	047	048	074
Number of subjects	12	89	626	586	925	778	358	808
Number of PK samples	202	1670	3292	1675	3421	2723	1020	2975
Mirabegron formulation	IV	IV	OCAS	OCAS	OCAS	OCAS	OCAS	OCAS
Single/Multiple dose	Single	Single	Multiple	Multiple	Multiple	Multiple	Multiple	Multiple
Dose levels	15 and 50 mg	7.5, 15 and 30 mg	25, 50, 100 and 200 mg	25, 50 and 100 mg	50 and 100 mg	50 and 100 mg	50 mg	25 and 50 mg
No. samples/subject	18 post-dose	19 post-dose	5 to 6 samples: 2 to 3 samples per visit (WK 4, 8, 12)	3 samples: 1 samples per visit (WK 4, 8, 12)	4 samples: 1, 2 or 3 samples per visit (WK 4, 8, 12)	4 samples: 1, 2 or 3 samples per visit (WK 4, 8, 12)	3 samples: 1 samples per visit (WK 4, 8, 12)	4 samples: 1, 2 or 3 samples per visit (WK 4, 8, 12)
LOQ	1 ng/mL	0.2 ng/mL	1 ng/mL	1 ng/mL	0.2 ng/mL	0.2 ng/mL	1 ng/mL	0.2 ng/mL

Table 5. Summary of Continuous Covariates for the Subjects Included in the Oral Phase II and III Analysis

Study	Statistic	Age (years)	BMI (Kg/m^2)	Scr (µM/L)	CrCL (mL/min)	GFR ($mL/min/1.73m^2$)	Weight (kg)
044 n=626	Mean	57	27	73	92	82	74
	Median	58	27	71	88	81	72
	Min	18	16	32	31	34	40
	Max	91	51	176	239	195	129
045 n=586	Mean	56	23	55	97	111	57
	Median	58	22	53	93	110	55
	Min	20	16	19	30	34	33
	Max	80	42	137	262	290	106
046 n=925	Mean	59	28	72	98	88	77
	Median	60	27	70	94	88	76
	Min	19	17	24	27	24	42
	Max	90	50	236	224	259	132
047 n=778	Mean	60	30	77	98	81	84
	Median	61	29	74	91	80	81
	Min	21	17	37	33	34	43
	Max	87	63	147	258	177	172

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048	Mean	59	22	58	86	103	55
n=358	Median	60	22	55	83	101	53
	Min	22	15	34	28	40	34
	Max	89	38	124	195	177	90
049	Mean	60	29	77	97	83	82
n=808	Median	61	28	75	92	82	80
	Min	21	16	46	35	31	41
	Max	87	58	187	241	137	168
Total	**Mean**	**59**	**27**	**70**	**96**	**89**	**74**
n=4081	**Median**	**60**	**26**	**69**	**91**	**87**	**72**
	Min	**18**	**15**	**19**	**27**	**24**	**33**
	Max	**91**	**63**	**236**	**262**	**290**	**172**

(Source: Sponsor's Study Report: 178-PK-015, Table 7)

Table 6. Summary of Categorical Covariates for the Subjects Included in the Oral Phase II and III Analysis

Study[1]	**Sex**		**Race**		**Study[2]**	**Food[4]**	
044	Male	61	Caucasian	615	**3**	Fasting	0
n=626	Female	565	Black	2	**n=3292**	Fed	3292
			Asian	2	**CL-044**		
			Japanese	0			
			Other[3]	7			
045	Male	102	Caucasian	0	**4**	Fasting	0
n=586	Female	484	Black	0	**n=1675**	Fed	1675
			Asian	0	**CL-045**		
			Japanese	586			
			Other	0			
046	Male	263	Caucasian	916	**5**	Fasting	1672
n=925	Female	662	Black	2	**n=3421**	Fed	1749
			Asian	4	**CL-046**		
			Japanese	0			
			Other	3			
047	Male	206	Caucasian	697	**6**	Fasting	1012
n=778	Female	572	Black	53	**n=2723**	Fed	1711
			Asian	15	**CL-047**		
			Japanese	0			
			Other	13			
048	Male	58	Caucasian	0	**7**	Fasting	2
n=358	Female	300	Black	0	**n=1020**	Fed	1018
			Asian	0	**CL-048**		
			Japanese	358			
			Other	0			
049	Male	261	Caucasian	741	**8**	Fasting	1461
n=808	Female	547	Black	57	**n=2975**	Fed	1514
			Asian	7	**CL-074**		
			Japanese	0			
			Other	3			

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Total n=4081	**Male**	**951**	**Caucasian**	**2969**	**Total n=15106**	Fasting	4147
	Female	**3130**	**Black**	**114**		Fed	10959
			Asian	**28**			
			Japanese	**944**			
			Other	**26**			

[1]: n corresponds to the number of subjects
[2]: n corresponds to the number of mirabegron concentrations
[3]: missing RACE information was re-coded to race 'Other'
[4]: missing FOOD information was re-coded to Fed conditions
(Source: Sponsor's Study Report: 178-PK-015, Table 9)

7.1 Pharmacokinetics Model

A three compartment structural model was first selected based on the IV data. The parameter estimates for the final IV pharmacokinetic model are presented in Table 7. Based on goodness-of-fit plots (Figure 17), the model describes the data well. Inter-individual variability was fairly low, being approximately 14% for both CL and central volume of distribution (V1). Covariates entered the model in a way, as is illustrated in $PAR_i = \theta_1 \bullet \left(\frac{COVAR_i}{TV_{COVAR}} \right)^{\theta_2}$ for continuous covariates and in $PAR_i = \theta_1 \bullet (1 + \theta_2 \bullet COVAR_i)$ for categorical covariates. Both total CL and V1 increased with increasing Weight, 10% change in Weight leads to around 5% change in parameters, and both parameters were higher in males (+14.2%).

Table 7. Estimated Population Pharmacokinetic Parameters of Mirabegron from the Final Pharmacokinetic Model after IV Administration

Parameter	Estimate	SE[1] (CV %)	IIV (%)
CL L/h	50.5	2.2	14.5
V1 L	19.8	3.9	14.1
K12 1/h	2.39	4.3	/
K21 1/h	0.0399	2.1	/
K13 1/h	3.15	3.2	/
K31 1/h	0.374	2.4	/
Weight effect	0.50 FIX	/	/
Males effect	+ 0.142	22	/
Correlation (CL/V1)	0.539	/	/
Residual error (%)	14.3	4.2	/

(Source: Sponsor's Study Report: 178-PK-015, Table 20)

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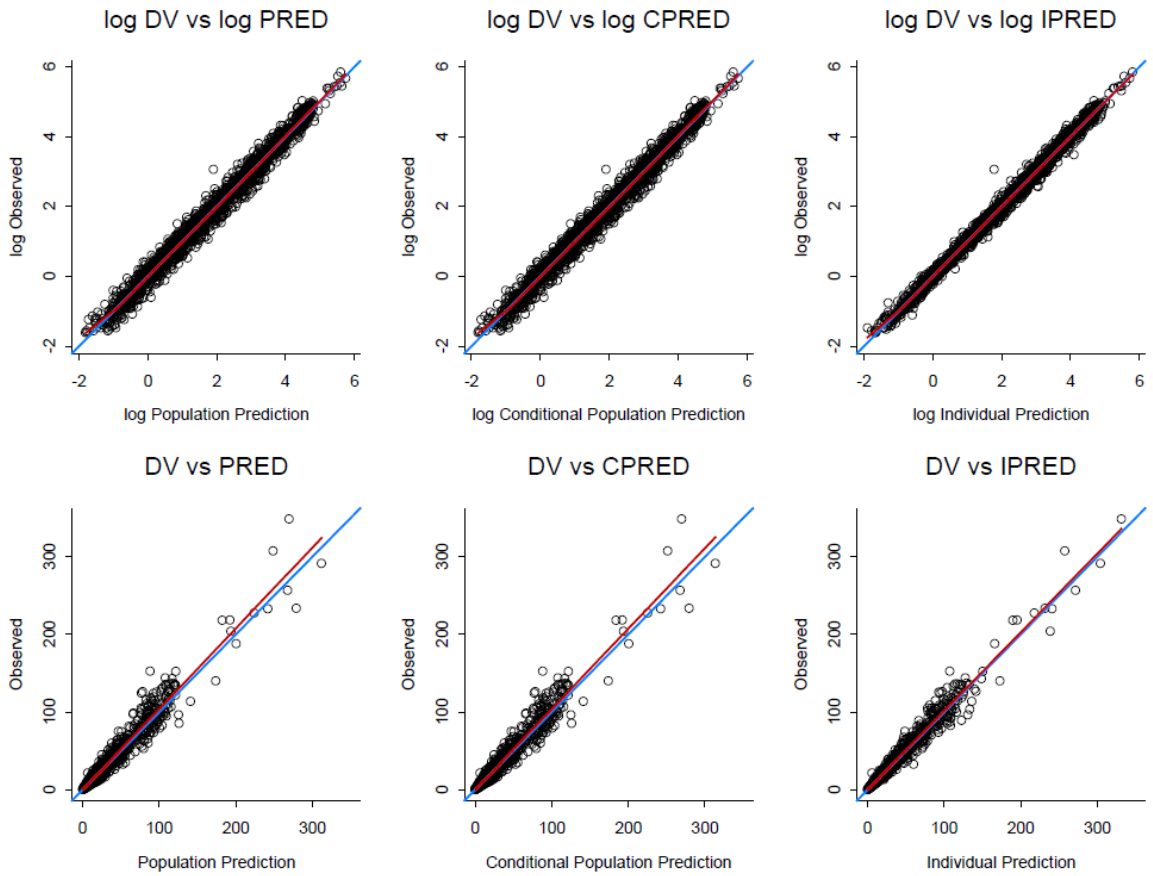
Figure 17. Mirabegron Goodness-of-Fit Plots for the Final Three Compartment Model with Covariate Influences after IV Administration of Mirabegron. The Red Lines Show the Observed Trend Which Overlaid With the Identity Line (Blue Lines).



(Source: Sponsor's Study Report: 178-PK-015, Figure 13)

For the oral data, a combination of zero-order and first order absorption model was chosen. The disposition parameter values as obtained in the IV model were applied in the oral model. A power model was selected to take into account the dose-dependency on F1. The parameter estimates for the final oral pharmacokinetic model are presented inTable 7. Based on goodness-of-fit plots (Figure 18 - Figure 19), the model fitted well the data at the population level (PRED and CWRES), but some minor trends could be observed at the individual level (IPRED). There was no trend when looking at residuals as function of period (Week 4, 8 and 12). The influence of the different covariates on the typical concentration-time profiles after oral administration in OAB patients is illustrated in Figure 20. Some covariates (e.g. co-administration of Proton Pump inhibitors on total clearance, and Food condition and co-administration of Weak to Moderate CYP3A4 inhibitors on central volume of distribution), in spite their statistical significance, have little impact on the concentration-time profile of mirabegron and the exposure.

Table 8. Estimated Population Pharmacokinetic Parameters of Mirabegron from the Final Pharmacokinetic Model after Oral Administration

Parameter	Estimate	SE (CV %)	IIV (%)	IOV (%)

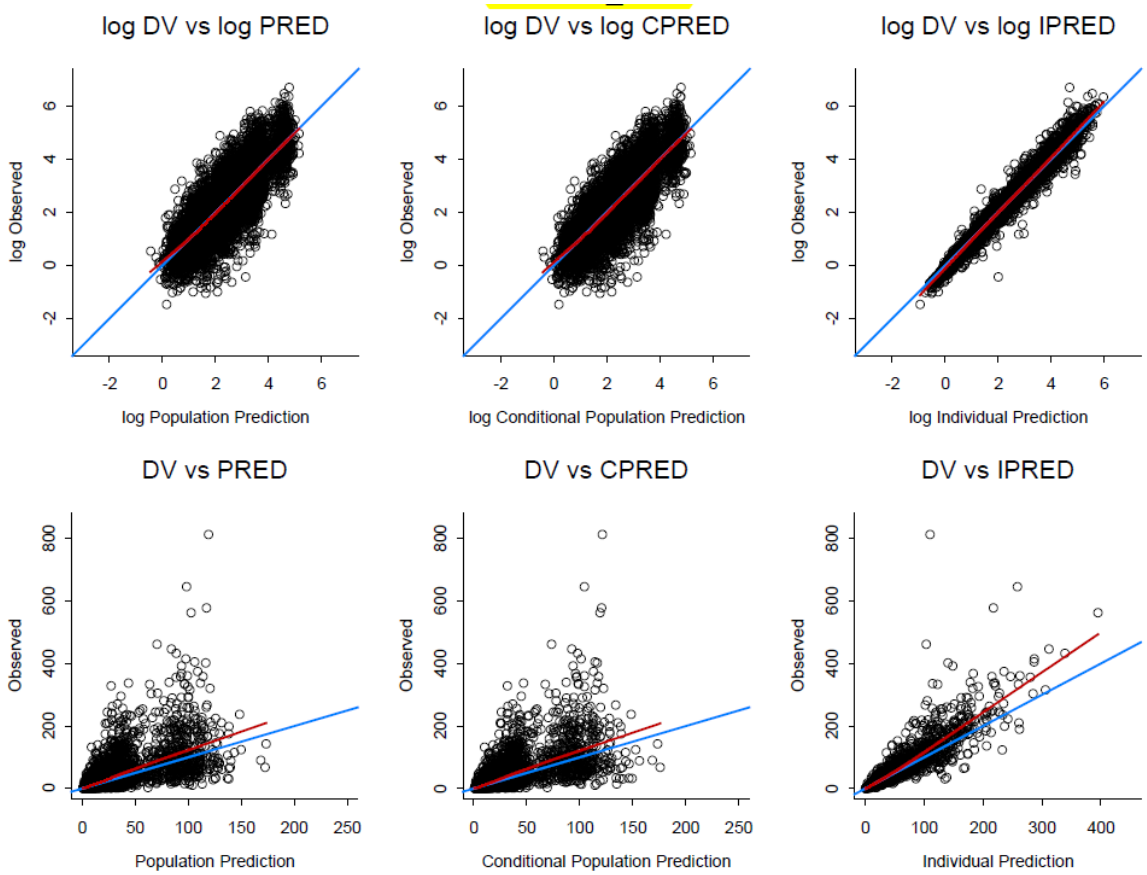
Reference ID: 3129601

CL L/h	50.5 Fixed	/	41	/
V2 (V1) L	19.8 Fixed	/	106	/
K23 1/h	2.39 Fixed	/	/	/
K32 1/h	0.0399 Fixed	/	/	/
K24 1/h	3.15 Fixed	/	/	/
K42 1/h	0.374 Fixed	/	/	/
Ka 1/h	0.109	4.0	/	/
D1 h	2.79	6.4	/	/
F1 50 mg	0.220	1.3	21[1]	32[1]
Gamma_CL,V2_Weight	+0.50 Fixed	/	/	/
CL,V2_Male	+0.142 Fixed	/	/	/
CL_Proton_Pump_Inh	-0.0919	20	/	/
CL_Proton_Pump_Inh missing	+0.102	23	/	/
Gamma_V2_Dose	-0.453	9.3	/	/
V2_Weak_CYP3A4	+0.426	15	/	/
V2_Weak_CYP3A4 missing	+0.690	21	/	/
V2_Food_non_Japanese	+0.187	16	/	/
Gamma_F1_Dose	+0.443	3.7	/	/
F1_Male	-0.170	9.7	/	/
Gamma_F1_Age	+0.245	17	/	/
Gamma_F1_CrCL	-0.258	12	/	/
Correlation (CL/V2)	+0.775	/	/	/
Residual error (%)	26.1	3.5	/	/

[2] IIV/IOV calculation: 100*(F1 50 mg)*(1-F1 50 mg)*sqrt(ETA)/(F1 50 mg)

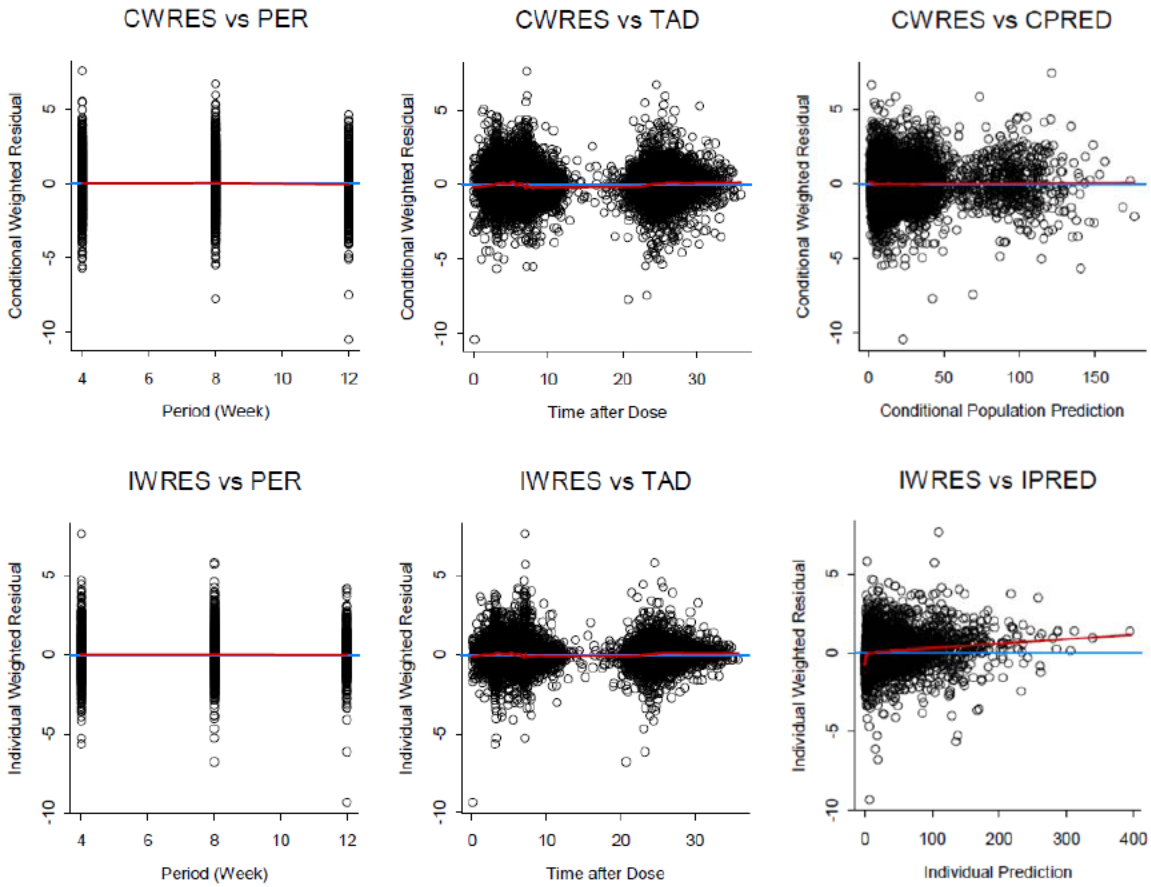
(Source: Sponsor's Study Report: 178-PK-015, Table 27)

Figure 18. Mirabegron Goodness-of-Fit Plots for the Final Model with Covariate Influences after Oral Administration of Mirabegron. The Red Lines Show the Observed Trend Which Overlaid with the Identity Line (Blue Lines).



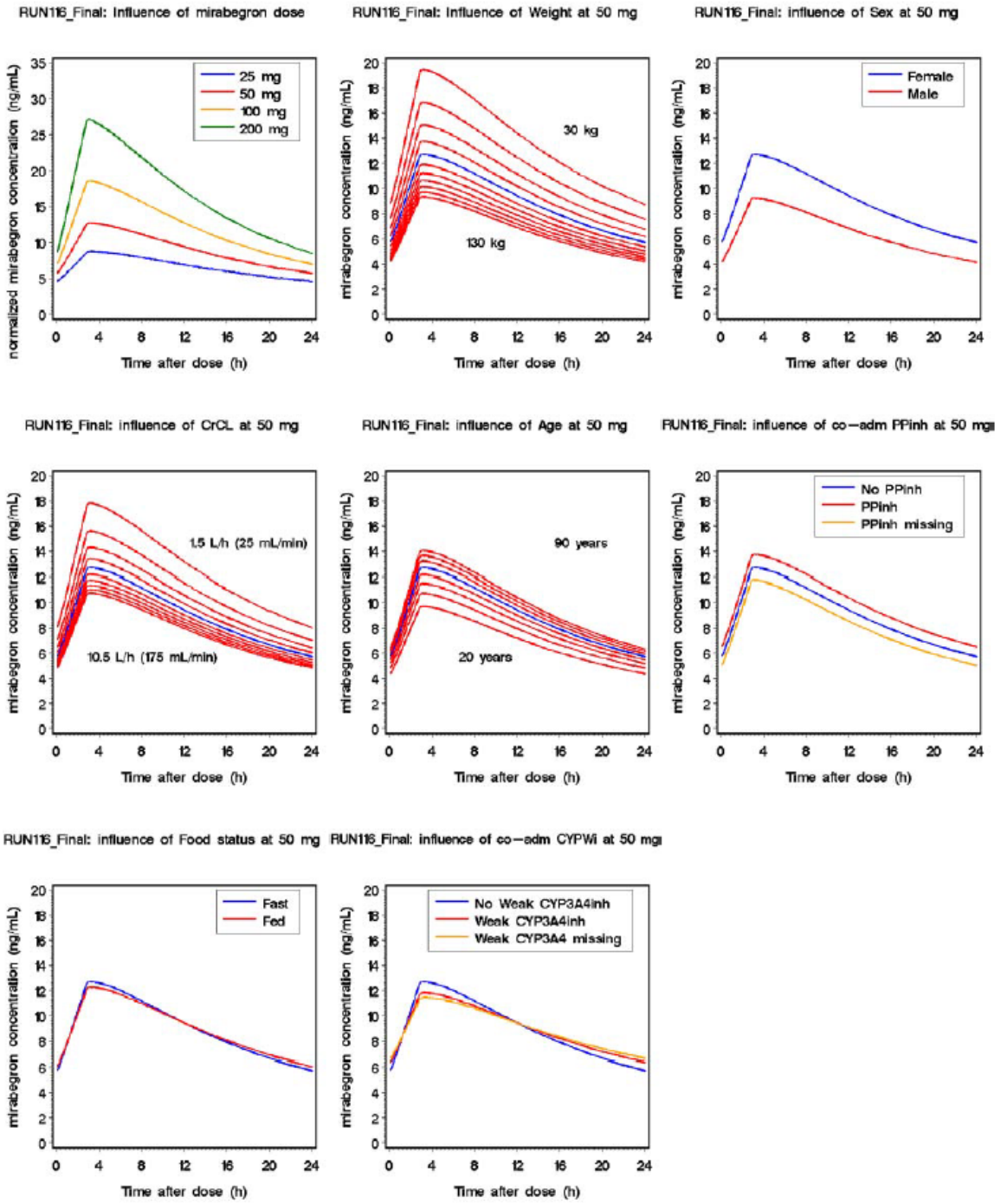
(Source: Sponsor's Study Report: 178-PK-015, Figure 26)

Figure 19. Plots of Mirabegron Conditional Population Residuals (Top) and Individual Residuals (Bottom) for the Final Population PK Model after Oral Administration. The Red Lines Show the Observed Trend and the Blue Lines Show the Zero Reference Line.



(Source: Sponsor's Study Report: 178-PK-015, Figure 27 and 28)

Figure 20. Simulated Effects of Covariates on Population Concentration-Time Profiles after Oral Administration of Mirabegron at the Steady-State.



(Source: Sponsor's Study Report: 178-PK-015, Figure 30)

Reviewer's Comment: The population PK model based on the IV data characterized the disposition Phase of mirabegron reasonably well. Due to the sparse information in the oral datasets, precisely characterizing the absorption PK profile of the oral formulation was

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challenging and the outcome from evaluating the influence of covariates should be interpreted only as evaluating the influence of covariates on the exposure of mirabegron and not on specific parameters. The food conditions had no or little impact on mirabegron exposure based on the population PK oral model, however this result was likely to be confounded by other factors (e.g., food effect can only be assessed in the non-Japanese studies). The clinical significance of the effect of weight, sex, age, and food on mirabegron exposure has also been evaluated with specific studies (see Dr. Al Habet's review).

Appendix II

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202611
Submission Date	08/29/11
Applicant Name	Astellas
Generic Name	Mirabegron
Proposed Indication	Treatment of overactive bladder
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Mike Pacanowski, Pharm.D. M.P.H.

1 Background

Mirabegron is a beta-3 adrenergic agonist that is proposed for use in the treatment of overactive bladder. Mirabegron is metabolized by the polymorphic CYP2D6 based on in vitro studies. The sponsor assessed mirabegron exposure among different CYP2D6 phenotypes in several single- and multiple-dose studies using either the immediate release (IR) or the to-be-marketed orally-controlled absorption system (OCAS) formulation. According to the sponsor's analysis, no differences in exposure were seen among the various CYP2D6 phenotypes, regardless of formulation and dosing regimen (i.e. single-dose vs. multiple-dose). In the label, the sponsor has proposed language stating that CYP2D6 does not impact mirabegron exposure (b) (4) The purpose of this review is to assess the magnitude of the CYP2D6 genotype effect on mirabegron exposure in the multiple-dose scenario and whether these results are appropriate to include in labeling.

2 Submission Contents Related to Genomics

The sponsor provided subject level CYP2D6 phenotype and genotype data from three Phase 1 multiple-dose clinical studies in which the OCAS formulation was administered (Table 1). Dextromethorphan phenotype data were available for one multiple-dose study (study 178-CL-072).

Table 1: Studies with subject-level CYP2D6 phenotype and genotype data.

Study	Population	Design	Objective	Genotypes assessed	Dose/ regimen	DNA sampling rate
178-CL-037	Healthy	R, DB, 4-way crossover	QT	*3, *4, *5, *6, xN, *17 (unknown if other alleles were assessed)	100mg, 200mg, qd	46/49 (94%)
178-CL-072	Healthy	R, OL, 2-way crossover	PK	*3,*4, *5, *6, xN	25mg, 50mg, 100mg; qd	71/75 (95%)
178-CL-077	Healthy	R, DB, 2-way crossover	QT	*2, *3, *4,*5, *6, *7, *9, *10, *14, *17, *29, *41, *45/46, xN	50mg, 100mg, 200mg; qd	249/352 (71%)

R: randomized; DB: double-blind; OL: open-label

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Subjects were categorized based on their genotype-derived phenotype in studies 178-CL-037 and -077 (using a validated real-time PCR assay), and based on dextromethorphan phenotype in study 178-CL-072 (metabolic ratios >0.3 were classified as poor metabolizers). Genotype-inferred phenotype designations were inconsistent across studies. Although CYP2D6 *3, *4, *5, and *6 were assessed in all three studies, other CYP2D6 alleles were not assessed in all three studies. Generally, subjects were predicted as poor metabolizers (PMs) if they carried two non-functional alleles (*3, *4, *5, *6), intermediate metabolizers (IMs) if they carried 1 non-functional and 1 functional or 1 allele with reduced function or 2 alleles with reduced function. Extensive metabolizers (EMs) carried 2 functional alleles or 1 functional allele and 1 allele with reduced activity. Ultrarapid metabolizers (UMs) carried gene duplications. The intermediate metabolizer category was not assigned in studies 178-CL-037 and 178-CL-072, and the ultra-rapid metabolizer category was not assigned in study 178-CL-072.

The sponsor evaluated doses of 25mg, 50mg, 100mg, and 200mg. The effect of CYP2D6 genotype was also determined following 242 single-dose exposures to 50 or 100 mg of mirabegron. The proposed labeling is based on this single-dose PK data and is summarized in section 5.2. Only the sponsor's assessment of the multiple dose studies will be reviewed here and reanalyzed below, as this represents the more relevant clinical scenario.

3 Key Questions and Summary of Findings

3.1 Does CYP2D6 genotype affect mirabegron PK?

Sponsor's analysis:

In study 178-CL-072, the sponsor determined CYP2D6 phenotype based on dextromethorphan/ dextrorphan ratio in urine at screening (genotype was assessed in this study as well but not used for phenotype classification). In contrast, in studies 178-CL-037 and -077, phenotypes were assigned based on genotypes. Based on the sponsor's analysis, no clinically relevant differences between assessed CYP2D6 phenotypes were observed (Tables 2, 3). The sponsor concluded that CYP2D6 phenotype does not impact mirabegron exposure as indicated in section 12.3 of the proposed labeling. The reviewer confirmed the sponsor's analyses presented below.

Table 2: Mirabegron PK parameters by predicted CYP2D6 phenotype after multiple-dose administration of mirabegron in study 178-CL-077

Dose	PK parameter	Predicted CYP2D6 Phenotype				
		UM	EM	IM	PM	INC
50 mg qd	n	5	56	18	3	2
	C_{max} (ng/mL)	30.0 (5.07)	43.0 (26.4)	39.9 (9.87)	43.8 (20.0)	59.0 (17.4)
	AUC_{tau} (ng·hr/mL)	306 (91.7)	438 (167)	417 (89.3)	475 (83.5)	587 (85.1)
	CL/F (L/hr)	182 (77.7)	147 (141)	126 (29.4)	108 (21.0)	86.1 (12.5)
100 mg qd	n	5	43	22	10	2
	C_{max} (ng/mL)	74.4 (48.7)	141 (58.9)	149 (58.1)	147 (63.0)	88.0 (26.3)
	AUC_{tau} (ng·hr/mL)	667 (307)	1170 (375)	1170 (415)	1310 (353)	820 (223)
	CL/F (L/hr)	184 (95.6)	95.4 (37.1)	101 (60.2)	84.0 (33.3)	127 (34.5)
200 mg qd	n	3	62	16	0	2
	C_{max} (ng/mL)	348 (117)	334 (142)	344 (138)	-	274 (37.3)
	AUC_{tau} (ng·hr/mL)	2510 (910)	2760 (949)	2800 (612)	-	1840 (102)
	CL/F (L/hr)	89.5 (40.2)	81.1 (27.2)	75.5 (20.1)	-	109 (6.07)

Values of PK parameters are mean (SD). EM: extensive metabolizer; IM: intermediate metabolizer; INC: inconclusive; PM: poor metabolizer; UM: ultrarapid metabolizer. - : no data.

Source: 178-CL-077 Table 12.4.3.4.

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Table 3: Mirabegron PK parameters by predicted CYP2D6 phenotype after single- and multiple-dose administration of mirabegron

Dose	PK parameter	Predicted CYP2D6 Phenotype			
		UM	EM	IM	PM
Single Dose					
50 mg	n	6	84	17	2
	C_{max} (ng/mL)	18.9 (7.11)	34.0 (41.9)	36.8 (35.7)	18.4 (9.24)
	AUC_{inf} (ng·hr/mL)	219 (95.3)	360 (278)	426 (216)	319 (184)
	CL/F (L/hr)	267 (115)	200 (116)	147 (48.6)	188 (106)
100 mg	n	1	118	6	8
	C_{max} (ng/mL)	47.2	78.9 (49.8)	91.1 (36.6)	96.5 (46.8)
	AUC_{inf} (ng·hr/mL)	474	788 (346)	936 (281)	1020 (376)
	CL/F (L/hr)	211	156 (88.5)	115 (32.9)	114 (51.9)
Multiple Dose					
25 mg qd	n	0	44	0	3
	C_{max} (ng/mL)	-	17.6 (7.60)	-	23.7 (9.24)
	AUC_{tau} (ng·hr/mL)	-	151 (55.7)	-	206 (40.9)
	CL/F (L/hr)	-	188 (69.4)	-	125 (25.7)
50 mg qd	n	0	44	0	2
	C_{max} (ng/mL)	-	54.7 (22.8)	-	75.7 (11.7)
	AUC_{tau} (ng·hr/mL)	-	427 (136)	-	605 (157)
	CL/F (L/hr)	-	130 (43.8)	-	85.6 (22.2)
100 mg qd	n	1	88	0	5
	C_{max} (ng/mL)	123	144 (82.8)	-	198 (30.6)
	AUC_{tau} (ng·hr/mL)	1130	1030 (434)	-	1330 (194)
	CL/F (L/hr)	88.3	118 (60.2)	-	77.1 (13.8)

Values of PK parameters are mean (SD). EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer. -: no data. Pooled data from Studies 178-CL-033, 178-CL-036 (mirabegron alone), 178-CL-037, 178-CL-039 (healthy subjects only), 178-CL-041 (fasted only), 178-CL-072, 178-CL-076 (target OCAS formulation), 178-CL-078 (fasted only).

Source: Appendix Table 2.7.2.8.9 and 2.7.2.8.11

Reviewer's analysis:

To assess the effect of CYP2D6 phenotype on mirabegron exposure (AUCtau and Cmax), the reviewer's analysis pooled subject-level data from three multiple dose studies (178-CL-037, -072, -077) in which the proposed commercialized formulation OCAS was administered. Phenotypes of individuals were assigned based on genotype as described in Table 4.

Table 4: Assignment of CYP2D6 phenotype based on predicted CYP2D6 activity

CYP2D6 allele	*3,*4,*4xN,*5,*6,*7, *16,*36,*40,*42,*56B	*9,*10,*17,*29,*41, *45,*46	*1,*2,*35,*43, *45xN	*1xN,*2xN, *35xN
Predicted CYP2D6 activity	Poor activity (PA)	Intermediate activity (IA)	Extensive activity (EA)	Ultra-rapid activity (UA)
Assigned CYP2D6 Phenotype	Poor metabolizer: PA+PA	Intermediate metabolizer: PA+IA; PA+EA; IA+IA	Extensive metabolizer IA+EA, EA+EA, PA+UA	Ultra-Rapid metabolizer UA+UA, UA+EA

As shown in Figure 1 and Table 5, the reviewer's evaluation identified a graded effect of CYP2D6 genotype on mirabegron PK. However, the effect was not large or statistically significant and is not likely to be clinically meaningful across all doses assessed. When looking at dose normalized exposure differences between phenotypes, a statistical significant difference between mirabegron AUCtau in PMs and EMs was observed. AUCtau in PMs is 17% higher

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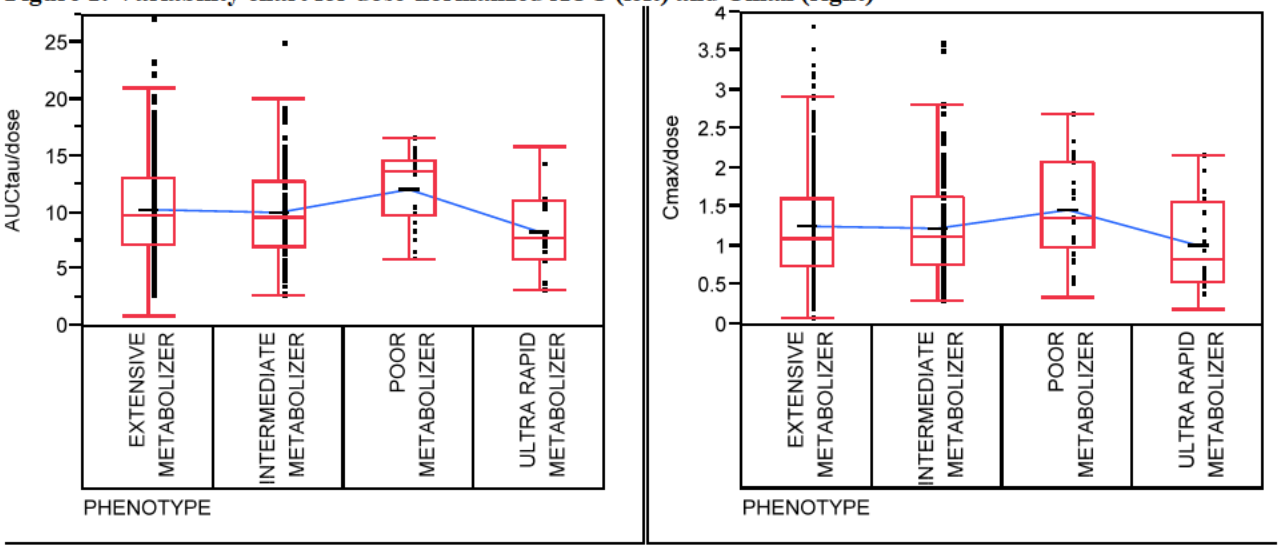
compared to EMs. Dose-normalized mirabegron Cmax is increased by 16% in PMs compared to EMs but the difference is not significant (Table 5, Figure 1).

Table 5: Exposure parameter based on phenotypes

Dose (mg)	Parameter	Phenotype				p-value*
		UM	EM	IM	PM	
	N (total)	15	229	94	23	
25	N	0	28	16	3	
	Cmax	n/a	17.4 (8.36)	18.1 (6.3)	23.7 (9.2)	0.39
	AUCtau	n/a	148.1 (10.5)	155.9 (13.9)	206.0 (32.1)	0.18
50	N	5	78	38	5	
	Cmax	30.0 (5.1)	45.5 (24.2)	49.8 (23.5)	56.5 (23.2)	0.15
	AUCtau	305.7 (91.7)	425.0 (153.9)	441.9 (125.2)	527.1 (121.0)	0.08
100	N	6	101	51	15	
	Cmax	82.5 (47.8)	143.4 (74.3)	144.3 (72.3)	164.1 (58.6)	0.08
	AUCtau	744.5 (334.2)	1089.0 (399.8)	1106.8 (461.4)	1316.3 (301.6)	0.03*
200	N	5	91	27	2	
	Cmax	341.7 (83.6)	318.9 (133.8)	310.8 (127.2)	407.0 (189.0)	0.71
	AUCtau	2382.9 (665.7)	2566.3 (915.1)	2521.6 (744.5)	2976.0 (82.8)	0.83
Dose-normalized	N	16	298	132	25	
	Cmax	1.0 (0.6)	1.3 (0.7)	1.3 (0.7)	1.5 (0.6)	0.11
	AUCtau	8.4 (3.7)	10.4 (4.4)	10.2 (4.1)	12.2 (3.2)	0.02*

Phenotype was not determined from N=9 patients due to inconclusive genotype.
Data are presented as mean (SD)
* Based on Kruskal-Wallis test; Dunn's post hoc test (with control: EM) was performed and result was non-significant adjusted for multiple comparison (EM-PM difference was largest with p=0.09).

Figure 1: Variability chart for dose-normalized AUC (left) and Cmax (right)



4 Summary and Conclusions

The reviewer concurs with the sponsor's assessment that CYP2D6 phenotype does not affect steady-state mirabegron exposure to a clinically relevant extent at any of the doses evaluated (i.e., 25, 50, 100, 200mg).

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While higher concentrations were observed in subjects with lower CYP2D6 activity, the effect is small (dose-normalized Cmax and AUCtau are only increased by approximately 16-17% in PMs compared to EMs). For individual 25-200 mg dose levels, Cmax and AUCtau are increased 14-36% and 16%-39%, respectively. These findings are consistent with previous reports that multiple metabolic pathways are involved in mirabegron metabolism (see Clinical Pharmacology review). Results for proposed doses (25mg and 50mg) should be interpreted with caution due to small subject numbers, particularly in the PM group (N≤5).

No dose adjustments based on CYP2D6 genotype/phenotype are recommended. Additional studies with CYP2D6 inhibitors do not appear to be indicated on the basis of these data.

5 Recommendations

The submission is acceptable from a Genomics Group perspective. The labeling should be modified to reflect the multiple-dose scenario with the to-be-marketed formulation.

5.1 Post-marketing studies

None

5.2 Label Recommendations

Recommended label additions are noted in underlined blue text, deletions are noted in ~~red strikethrough~~ text.

12.3 Pharmacokinetics

Metabolism

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-mirabegron. Two major metabolites were observed in human plasma and are phase 2 glucuronides representing (b) (4) and 11% of total exposure, respectively. These metabolites are not pharmacologically active. Although in vitro studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, in vivo results indicate that these isozymes play a limited role in the overall elimination. In healthy subjects who are genotypically poor metabolizers of CYP2D6 substrates, mean Cmax and AUCtau were 16% and 17% (b) (4) higher than in extensive metabolizers, (b) (4) n vitro and ex vivo studies have shown the involvement of butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

4.4 Filing Memo

FINAL
(November 8, 2011)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	20-2611	Brand Name	NA
OCP Division (I, II, III, IV, V)	III	Generic Name	Mirabegron
Medical Division	DRUP	Drug Class	Beta 3-adrenoceptor (AR) agonist
OCP Reviewer	Sayed (Sam,) Al Habet, R.Ph., Ph.D.	Indication(s)	Overactive Bladder
OCP Secondary Reviewer/Signer	E. Dennis Bashaw, Pharm.D.	Dosage Form	25 mg and 50 mg ER tablets
Pharmacometrics Reviewer	N/A	Dosing Regimen	50 mg QD or 25 mg QD in special population
Date of Submission	August 26, 20111 (cover letter)	Route of Administration	Oral
Estimated Due Date of OCP Review	April 2012	Sponsor	Astellas, Deertfield, IL
Medical Division Due Date	June 2012	Priority Classification	Standard
PDUFA Due Date	June 25, 2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE		**X**		
Table of Contents present and sufficient to locate reports, tables, data, etc.		**X**		

Reference ID: 3129601

Tabular Listing of All Human Studies		**X**		
HPK Summary		**X**		
Labeling		**X**		
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	**X**			
Mass balance:	**X**			
Isozyme characterization:	**X**			
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -	**X**	**29**		
Healthy Volunteers-				
single dose:		**19**		Studies: SCO-5432, 1034-PHII, OXBTN/2006/223, SCO 5486, SCO 5488, SCO 5487, and OXPK2)
multiple dose:		**10**		42 mg, 60 mg, and 84 mg/da x 20 days (Study # 1034-PhII), n=48 healthy subjects And Pilot study x 7 days (#OXPK2)
Patients-				
single dose:		-		
multiple dose:		**3**		
Dose proportionality -				
fasting / non-fasting single dose:		**3**		Dose escalation (Study # 1034-PhII)
fasting / non-fasting multiple dose:				Dose escalation (Study # 1034-PhII)
Drug-drug interaction studies -				
In-vivo effects on primary drug:		**8**		
In-vivo effects of primary drug:		**2**		
In-vitro:	**X**	**1**		

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Subpopulation studies -				Across study comparison between efficacy and safety data from Study # 20070060 and data available in literature for marketed Oxytrol-TDS® and Gelnique®) in special population
ethnicity:	X	1		+ Pop PK
gender:	X	1		+ Pop PK
pediatrics:	-	-		-
geriatrics:	X	1		+ Pop PK
renal impairment:	X	1		
hepatic impairment:	X	1		
PD -				
Phase 2:	X	6		
Phase 3:	x	6		
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	5		
Phase 3 clinical trial:	x	6		
Population Analyses -				
Data rich:	x			
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability	x	1		
Relative bioavailability -	x	2		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				

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***In vitro* Penetration Studies**		**3**		3 ex vivo penetration studies with pig, human cadaver, and fresh human skin (Studies # AP-1034, 368/03, and 932/09)
Genotype/phenotype studies	**X**	**2**		
Chronopharmacokinetics				
Pediatric development plan				**Requested waiver for WAIVER for <5 years of age for OAB (b) (4) and DEFERRAL for 5 to <18 years of age for OAB**
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA	waiver and deferral

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					requests
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			N/A	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes_

Executive Filing Summary:

This is original NDA for a new molecular entity (NME), mirabegron (YM178) tablets. Pharmacologically, the drug is a beta 3-adrenoceptor (AR) agonist for the treatment of overactive bladder.

The sponsor conducted 41 studies consisting of 29 Phase I and II safety and efficacy (Phase II/III) studies (**Appendix I)**. The Phase I studies 6 biopharmaceutics studies and 23 human PK studies including extensive PK/PD modeling and simulation (**Appendix I, Sections A and B**). The efficacy was evaluated in 6 global, 12 week Phase 2b and 3 studies. The following are the three pivotal efficacy studies in patients with over active bladder (OAB) that were conducted in North America and Europe: 178-CL-046, 178-CL-047, and 178-CL-074 (**Appendix I, Section C**).

In addition to the standard clinical pharmacology studies, the sponsor conducted two thorough QT (TQT) studies (# 178-CL-037 and 178-CL-077).

What are the Primary Clinical Pharmacology Characteristics of the Drug from the NDA?

Pharmacology:

- Beta 3- adrenoceptor (beta 3-AR) agonist
- First-in-class NME
- Beta 3-AR dominant in the human detrusor muscle. Therefore, activation of Beta 3-AR in the bladder facilities urine storage (in contrast to stimulation of muscarinic receptors which facilitates urine voiding)

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Basic PK Information:

Chemistry:

- Mirabegron has a chiral center (R and S). However, it is developed as R-enantiomer
- No chiral inversion

Absorption, Effect of Food and Alcohol:

- Tmax = 3-4 h
- Based on the Biopharmaceutics Classification System (BCS) mirabegron is a Class 3 (High solubility and Low permeability).
- Absolute bioavailability is 29% at 25 mg dose and 35% at 50 mg dose (i.e., dose dependent).
- Absolute bioavailability appears to be higher in females than males.
- Dose disproportional PK (i.e., more than dose proportional increase in exposure)
- Saturation of efflux transport mechanism (P-glycoprotein, P-gP)
- Solution exhibits higher bioavailability (~40%) than tablets (Modified Release Tablet with Intermediate Dissolution Rate, OCAS-M).
- **Food decrease exposure**:
    - Overall food decreases exposure:
        - High-fat meals: reduces Cmax and AUC by 45% and 17%, respectively
        - Low-fat meals: reduces Cmax and AUC by 75% and 51%, respectively
- **Alcohol:** 4% ethanol has no effect on in-vitro dissolution profiles. However, 40% ethanol delays dissolution profiles.

Systemic PK:

Distribution:

- Protein binding: 71% (albumin and alpha-1 acid glycoprotein)
- Erythrocytes concentration is 2-fold higher than in the plasma (*in-vitro* data)
- Large volume of distribution (approximately 1670 L)

Elimination:

- Terminal half life = ~50 hours (effective half life = ~19 h)
- Excretion: primary renal and secondary biliary
- Renal clearance (CLr) appears to be independent of dose
- Primary excretion occurs via active tubular secretion and glomerular filtration

Metabolism:

- 10 metabolites (none appears to be active in reference to 3-AR activity)
- Extensively metabolized: ~6% to 9% unchanged in urine (dose-dependent).
- Approximately 55% of radioactivity (^{14}C) recovered in urine and 34% in feces
- **Pathways:** Dealkylation, oxidation, and glucuronidation, and amid hydrolysis

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- **Enzymes and isoenzymes**: butyrylcholinesterase, uridine diphospho-glucuronosyltransferase (UGT), CYP3A4, and CYP2D6, and alcohol dehydrogenase. However, CYP3A4 is the primary responsible isoenzyme.
- Metabolites-to-parent AUC ratios were relatively constant over 25 to 200 mg (i.e,, metabolism appears **not** to be saturable)

Dose-Exposure (Dose-Proportionality):

- Greater than dose-proportional increase in Cmax and AUC after oral administration (e.g., 2-fold increase in dose results in 2.9- and 2.6-fold increase in Cmax and AUC, respectively).
- Dose proportional after IV
- **Steady-state**: Reached within 7 days after once daily (QD) dosing
- **Variability:** There is considerable inter-subject variability with estimated %CV of approximately 40% to 52% for Cmax and 39% to 45% for AUC. However, the intra-subject variability is lower than inter-subject (%CV = 33% to 45% for Cmax and 19% to 31% for AUC)

Special Population:

- **Age:** No apparent difference in PK in relation to age
- **Gender:** Cmax and AUC were approximately 40% to 50% higher in females compared to males.
- **Race:** No apparent difference
- **Body Weight:** Based on Pop PK analysis the AUC appears to be approximately 53% **higher** in subjects with small body weight of approximately 30 Kg compared to 70 kg. By contrast, the AUC is approximately 17% **lower** in subject with body weight of 100 kg compared to subjects with body weight of 70 kg. The reasons for these discrepancies are not clear at this time (pending review and re-analysis).
- **Renal Impairment:**
    - **Mild** renal impairment: Cmax and AUC increased by 6% and 31% compared to healthy subjects, respectively.
    - **Moderate** renal impairment: Cmax and AUC increased by 23% and 66% compared to healthy subjects, respectively.
    - **Severe** renal impairment: Cmax and AUC increased by 92% and 118% compared to healthy subjects, respectively.
    - **ESRD:** The sponsor recommends reduction in dose to 25 mg QD in severe renal impairment and is **not recommended** in End Stage Renal Disease (ESRD). However, no dose adjustment in mild and moderate.
- **Hepatic Impairment**:
    - **Mild** (Child-Pugh Class A): Cmax and AUC increased by 9% and 19% compared to healthy subjects, respectively.
    - **Moderate** (Child-Pugh Class B): Cmax and AUC increased by 175% and 65% compared to healthy subjects, respectively.
    - **Severe** (Child-Pugh Class C): Not studied.
    - **Sponsor's recommendation**: No dose adjustment in mild. Reduction in dose to 25 mg QD in moderate hepatic impairment. It is **not recommended** in severe hepatic impairment (child-Pugh C).

- **Patients with Over Active Bladder (OAB):** The AUC appears to be 20% to 50% lower in patients with OAB compared to healthy subjects. It should be noted that in Phase IIb and Phase III studies the drug was given irrespective of food. Therefore, it appears that the low exposure in OAB patients could be contributed by the effect of food.
- **Genetic Polymorphism:** No apparent difference in exposure between CYP2D6 poor metabolizers and extensive metabolizers.
- **Drug Interaction Data:**
    - **Effect of Other Drugs on Mirabegron PK:**
        - **Ketoconazole:** 45% increase in Cmax and 81% increase in AUC
        - **Rifampin:** 35% and 44% reduction in Cmax and AUC, respectively.
        - **CYP2D6 inhibitors**: No study was conducted with CYP2D6 inhibitors as there was no difference in exposure in CYP2D6 poor and extensive metabolizsers. Therefore, the sponsor recommends no dose adjustment is needed when the drug is co-administered with CYP2D6 inhibitors or patients who are CYP2D6 poor metabolizers.
        - **Others:** metformin, solifenacin, tamsulosin had no effect. Therefore, the sponsor recommends no dose adjustment.
- **Effect of Mirabegron on Other Drugs**
    - *In vitro* data shows that mirabegron is moderate inhibitor of CYP2D6 and weak inhibitor of CYP3A4.
    - Based on *in-vitro* data mirabegron is unlikely to inhibits the metabolism of of co-administered drugs metabolized by the following CYP enzymes; CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2E1. Also, based on *in-vitro* data no effect on **glibenclamide** (a CYP3A4 substrate), **tolbutamide** (a CYP2C9 substrate), **warfarin** (CYP2C9) and **metformin**.
    - CYP2D6 substrate (**metoprolol**): Cmax and AUC of metoprolol increased by **90% and 229%,** respectively.
    - CYP2D6 substrate (**desipramine**): Cmax and AUC of desipramine increased by **79% and 241%**, respectively. Sponsor's recommendation no dose adjustment when mirabegron is co-administered with CYP2D6 substrates, unless the drug has a narrow therapeutic index. (b) (4)
    - **Steroids** (Ethinyl estradiol and levovorgesttrel) or solifenacin (CYP3A4 substrates): no apparent difference.
    - **Tamsulosin** (CYP2D6 and CYP3A4 substrate): 60% increase in tamsulosin exposure
    - **Warfarin** (probe substrate for CYO2C9): no effect on R- or S-warfarin or prothrombin time (PT).
    - **Metformin**: no change in metformin exposure
    - **Digoxin:** Cmax and AUC of digoxin increased by 29% and 27%, respectively. The sponsor recommends the lowest digoxin dose as initial therapy followed by monitoring and titration.

- **Effect on Cardiovascular Parameters:**
    - There is apparent dose-dependent increase in heart rate with mirabegron. Overall, there is increase from the average of 6.7 beats per minutes (bpm) to 17.3 bpm as the dose increase from 50 mg to 200 mg.

- QT prolongation is also apparent with a mean increase of approximately 10 msc (pending review).

- **Exposure-Response and Efficacy:**
  - Based on Emax model, it appears there is a dose separation in micturation frequency and mean volume voided across the dose range of 25mg, 50 mg, and 100 mg that achieving 52%, 85%, and 98% of the Emax (maximum efficacy), respectively.
  - However, the exposure-response relationship for incontinence episodes per 24 hours was flat across the 25 to 100 mg doses range. All doses were associated with approximately 26% reduction in the rate of incontinence compared to placebo.
  - It appears the modeling and simulation data for exposure-efficacy analyses appears to complement the data observed in Phase II studies.
  - PK/PD modeling showed that heart rate increased with increasing mirabegron plasma exposure. However, no apparent relationship with respect to systolic blood pressure (SBP) or diastolic blood pressure (DBP) and exposure in patients with OAB.

- **Phase III Studies:**

  - Primary clinical trials are 178-CL-046, -047, and -074
  - The majority of population in Phase III studies was females (~725)
  - Primary efficacy end-points:
    - Urge urinary incontinence
    - Urgency
    - Urinary frequency
  - Phase III Doses: 25 mg, 50 mg, and 100 mg QD x 12 weeks
  - Overall there is apparent superiority compared to placebo in reference to incontinence episodes per 24 hours and micturitions per 24 hours at 50 mg and 100 mg doses, but **not** at 25 mg dose.
  - No separation in efficacy between 25 mg and placebo.
  - Also no separation in efficacy between 50 mg and 100 mg.
  - **Dose Selection**: As stated earlier, there was some separation across the dose range of 25 mg, 50 mg, and 100 mg that acehiving 52%, 85%, and 98% of Emax for micturition and volume voiding, respectively. However, the difference between 50 mg and 100 mg is small (85% and 98%).
  - Collectively, based on the primary and secondary endpoints, the data support the use of 50 mg QD dose over 100 mg dose which is associated with higher adverse events than 50 mg dose and 25 mg dose which exhibits narrow difference in efficacy compared to placebo. However, 25 mg dose is only recommended in patients with severe renal impairment and moderate hepatic impairment.

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Formulation Development:

Synopsis:
The proposed mirabegron 25 mg and 50 mg commercial formulations are identical to the tablets used in the Phase III stage, except that the commercial product will be debossed (i.e., imprinted with the number 325 or 355 and logo). Therefore, no bioequivalence study is necessary. The 25 mg tablet color is brown and the 50 mg table is yellow. The composition of the final formulations is shown in the table below:

Components	Reference Quality Standard	Function	Quantity (mg/tablet)	
			Mirabegron OCAS tablets 25 mg	Mirabegron OCAS tablets 50 mg
Mirabegron	In house	Active Ingredient	25.0	50.0
Polyethylene Oxide (b) (4)	NF/In house	(b) (4)		
Polyethylene Glycol (b) (4)	NF			
Hydroxypropyl Cellulose (b) (4)	NF			
	USP			
Butylated Hydroxytoluene	NF			
Magnesium Stearate (b) (4)	NF			
	In house			
	In house			
	USP			
Total tablet weight (mg)			257.5	257.5

(b) (4) The total weight of each tablet is the same (257.5 mg).

Process of Formulation Development:

At glance, it appears that the Biopharmaceutical Classification System (BCS) of mirabegron is a Class 3 (i.e., high solubility and low permeability). The sponsor developed various dosage forms and formulations at different stages of clinical development. The early clinical studies were conducted with immediate release (IR) capsules and tablets. An aqueous solution was used in the mass balance study. Since the IR formulations showed a considerable decrease in plasma exposure with food and high peak-to-trough fluctuations in plasma concentrations with once daily dosing, a modified release tablet was developed utilizing Oral Control Absorption System (OCAS) technology. The same technology was modified further intermediate dissolving rate known as OCAS with intermediate dissolving rate (OCAS-M). These modified release formulations are also referred to as extended-release or prolonged-release formulations. Several

OCAS formulations, with differing dissolution profiles, were screened to select the formulation for development and eventual commercialization (Study 178-CL-030). An OCAS tablet with an intermediate dissolution rate (OCAS-M) was selected for further development.

The release rate of mirabegron from this OCAS formulation resulted in a pharmacokinetic (PK) profile with a slower rate of absorption than the IR tablet, an attenuated food effect with a high-fat meal and reduced fluctuations in plasma concentrations compared with once daily mirabegron IR.

The OCAS-M tablet was used in the phase II and III efficacy studies and all clinical pharmacology studies, except the study related CYP2D6 genotyping and DDI study with metoprolol (Study 178-CL-005), DDI study with metformin (Study 178-CL-006), and the mass balance study (Study 178-CL-007).

Pediatric Waiver and Deferral:

The sponsor is requesting waiver from studies in pediatric patients <5 years of age for OAB indication. The primary rationale of the sponsor request is that OAB is not a condition that seen in children <5 years of age who are not yet bladder trained.

In addition, the sponsor is requesting deferral of conducting studies in children between 5 to <18 years of age for OAB indication and (b) (4) for Neurogenic Detrusor Overactivity. The sponsor requesting deferral until the initial NDA is approved in adults first. This deferral request was accepted by the Agency at the End-of-Phase II meeting held on November 14, 2007. It should be noted, however, that the (b) (4)

Reviewer's Comments:

The sponsor conducted adequate studies to satisfy the clinical pharmacology program. (b) (4) The 25 mg tablet is designated to be used only in patients with renal and hepatic impairment. However, the presence of the 25 mg tablet may be misleading if the prescribe or the pharmacist may substituted the 2x25 mg for 50 mg table if the 50mg tablet is out of stock. Therefore, the sponsor is required to provide justification for dosage strength equivalence (i.e., 2 x 25 mg is equivalent to 50 mg tablet).

The approvability of the NDA will be based on overall assessment of the PK data as well as the safety and efficacy data. From the clinical pharmacology perspective, the NDA can be filed.

Comments for the 74-Day Letter:

- (b) (4) please provide justification for dosage strength equivalency between the 25 mg tablet and 50 mg tablet (i.e., 2 x25 mg tablets are equivalent to 50 mg tablet).

Recommendation:

The NDA can be filed from the clinical pharmacology perspective.

Sayed (Sam) Al Habet, RP.h., Ph.D.

Reviewing Clinical Pharmacologist Date

E. Dennis Bashaw, Pharm.D.

Secondary Reviewer/Supervisor Date

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Appendix 1: Synopsis of Individual Studies (Biopharmaceutics, PK, and Clinical Studies)

A: Biopharmaceutics Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Biopharmaceutic Studies								
BA	178-CL-033 Netherlands	Absolute BA (iv vs OCAS tablet)	Phase 1, open label, randomized, 2-way crossover	Mirabegron OCAS 50 mg or 150 mg tablet po, 15 or 50 mg iv over 2 hours; fasted	12	Healthy volunteers	Single dose	Complete; Full
BA/BE	178-CL-030 Netherlands	PK, 3 OCAS formulations vs IR	Phase 1, open-label, 3-way crossover	Mirabegron OCAS-F 200 mg qd (fed and fasted), OCAS-S 200 mg qd (fed and fasted), OCAS-M 200 mg qd (fed and fasted); tablet po Mirabegron IR 100 mg bid (fasted); tablet po	36	Healthy volunteers	8 days each treatment (OCAS fasted, OCAS fed, IR fasted), washout of ≥7-days between treatments	Complete; Full
BA	178-CL-041 United States	Effect of food on PK of mirabegron	Phase 1, randomized open-label, 3-way crossover	Mirabegron OCAS 50 or 100 mg tablet po; single dose administered fasted, with high-fat breakfast or with low-fat breakfast	76	Healthy volunteers	Single dose on day 1 of each of 3 periods; washout of ≥10 days between periods	Complete; Full
BA	178-CL-064 Japan	Effect of food on PK of mirabegron	Phase 1 randomized, open-label, 2-way crossover	Mirabegron OCAS 50 mg tablet po; single dose administered fasted or with high-fat breakfast	24	Healthy male volunteers	Single dose on day 1 of each of 2 periods; washout of ≥12 days between periods	Complete; Full
BA	178-CL-078 Japan	Effect of food on PK of mirabegron	Phase 1, randomized open-label, 3-way crossover	Mirabegron OCAS 50 or 100 mg tablet po; single dose administered fasted, with high-fat breakfast or with normal (i.e., low-fat) breakfast	72	Healthy volunteers	Single dose on day 1 of each of 3 periods; washout of ≥12 days between treatments	Complete; Full
BA	178-CL-076 United States	PK, iv and 3 OCAS formulations	Phase 1, open-label, 5-way crossover, with 3 of the treatments given in random order	Mirabegron iv 7.5, 15 or 30 mg iv over 120 minutes and mirabegron OCAS 25, 50 mg or 100 mg tablet po (fast-release, target-release, slow-release and other target release); fasted	91	Healthy volunteers	Single dose on day 1 of each of 5 periods; washout of ≥10 days between treatments	Complete; Full

B: Human PK Studies

PK	178-CL-001 United Kingdom	PK, safety, tolerability, food effect	Part I Phase 1, placebo-controlled, randomized, double-blind, dose-escalation study	Placebo or mirabegron IR 0.1, 0.3, 1, 3, 10, 30, 100, 160, 240, or 340 mg po; fasted	85	Healthy male volunteers	Single dose	Complete; Full
			Part II Phase 1, open-label, randomized, 3-way crossover	Mirabegron IR 160 mg capsule (two 80 mg capsules) po; fed (with high-fat breakfast), semi-fed (30 min before high-fat breakfast), and fasted	12		Single dose, 7 day washout between doses	

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PK	178-CL-002 United Kingdom	PK, safety, tolerability, PD	Phase 1, placebo-controlled, double-blind, randomized, dose-escalation study	Mirabegron IR 40, 80, 160, 240 mg capsule (20 and 80 mg capsules) po; once daily fasted Mirabegron IR 240 mg capsule (80 mg capsules) po; once daily fed (high-fat breakfast days 1 and 9; standard breakfast days 2-8)	40	Healthy male volunteers	Single dose on day 1 followed by once daily dosing for 7 days (days 3-9)	Complete; Full
PK	178-CL-007 Netherlands	PK/mass balance	Phase 1, open-label study	^{14}C-mirabegron 160 mg drinking solution; fasted	4	Healthy male volunteers	Single dose	Complete; Full
PK	178-CL-031 Netherlands	PK, safety, tolerability of OCAS-M formulation, explore PK in elderly and young	Phase 1, double-blind, randomized, placebo-controlled, dose-escalating study	Mirabegron OCAS-M 50, 100, 200, 300 mg po; fasted on PK days, otherwise standard breakfast was served	96	Healthy volunteers	Single dose OCAS-M on day 2 followed by qd dosing for 10 days (days 5-14)	Complete; Full
PK	178-CL-066 Japan	Dose-proportionality of mirabegron	Phase 1 open-label, 3-period, dose escalation	Mirabegron OCAS 25, 50, and 100 mg tablet po; fasted	12	Healthy non-elderly male volunteers	Single dose on day 1 of each of 3 periods; washout of ≥12 days between treatments	Complete; Full
PK	178-CL-034 Japan	PK of mirabegron after single and repeated dosing	Phase 1, single-blind, placebo-controlled, single-dose and repeated-dose study	Single dose: Mirabegron OCAS 0 (placebo), 50, 100, 200, 300, or 400 mg; tablets po; fasted	40	Healthy male volunteers	Single dose	Complete; Full
				Repeated dose: Mirabegron OCAS 0 (placebo), 100, or 200 mg tablet po; 30 min to 1 hour after breakfast	24		Single dose followed by 2-day washout, followed by 7 days	
PK	178-CL-072 France	PK, safety, tolerability, age and gender effects	Phase 1, open-label, randomized, 2-way crossover	Mirabegron OCAS 25, 50 and 100 mg tablet po; 30 minutes after breakfast and dinner on day 1, 30 minutes after breakfast on days 2-5, fasted on days 6 and 7	75	Healthy volunteers	Two 7-day treatment periods; morning and evening dose on day 1, single morning doses on days 2-7; washout of ≥14 days between treatments Treatment sequences included (Period 1 to Period 2): 25 to 50 mg; 50 to 25 mg, 25 to 100 mg; 100 to 25 mg; 50 to 100 mg; 100 to 50 mg	Complete; Full
PK	178-CL-038 United States	PK, safety, tolerability, renal impairment	Phase 1 open-label	Mirabegron OCAS 100 mg tablet po; fasted	33	Healthy volunteers/ volunteers with mild to severe renal impairment	Single dose	Complete; Full
PK	178-CL-039 Slovakia	PK, safety, tolerability, hepatic impairment	Phase 1 open-label	Mirabegron OCAS 100 mg tablet po; fasted	32	Healthy volunteers/ volunteers with mild or moderate hepatic impairment	Single dose	Complete; Full
PK/DDI	178-CL-005 Netherlands	Part 1: PK in poor and extensive CYP2D6 metabolizers	Phase 1, open-label, 1-sequence, parallel study	Mirabegron IR 160 mg capsules (two 80 mg capsules) po; fasted	16	Healthy male volunteers (extensive and poor CYP2D6 metabolizers	Single dose	Complete; Full
		Part 2: DDI of mirabegron and metoprolol (CYP2D6 substrate)	Phase 1, open-label, cross-over	Mirabegron IR 160 mg capsules (two 80 mg capsules) once daily po; fasted metoprolol tartrate 100 mg tablet; fasted	12	Healthy male volunteers (extensive CYP2D6 metabolizers)	7 days total single dose metoprolol on days 1 and 7, mirabegron on days 3-7	
PK/ DDI	178-CL-006 Netherlands	DDI of mirabegron and metformin	Phase 1, one-sequence crossover	Mirabegron IR 160 mg tablets (one 100 mg tablet and two 30 mg tablets) po; once daily fasted <u>Seq A</u>: metformin 500 mg tablets; twice daily on days 12-15, single morning dose on day 16, fasted (morning dose only) <u>Seq B</u>: metformin 500 mg tablets; twice daily on days 1-4 and 6-15, single morning dose on day 5 and 16, fasted (morning dose only)	32	Healthy male volunteers	Sequence A: mirabegron days 1-11 and mirabegron+ metformin or placebo days 12-16 Sequence B: metformin days 1-5 and metformin +mirabegron or placebo days 6-16	Complete; Full

PK/ DDI	178-CL-036 United States	PK interaction of multiple dose ketoconazole on single dose mirabegron	Phase 1, open-label, 2-period, 1-sequence crossover	Mirabegron OCAS 100 mg tablet po; ketoconazole 400 mg po (2x 200 mg tablet); once daily fasted	24	Healthy volunteers	Period 1: Single dose mirabegron on day 1 followed by ≥7 day washout; Period 2: ketoconazole days 1-9 and single dose mirabegron on day 4	Complete; Full
PK/DDI	178-CL-070 United States	Effect of repeat doses of rifampin on PK of single dose mirabegron	Phase 1, open-label	Mirabegron OCAS 100 mg tablet po, fasted; Rifampin 600 mg capsule po, once daily 1 hour before breakfast except fasted on day 12	24	Healthy volunteers	Mirabegron 100 mg single dose day 1, rifampin 600 mg day 5 to day 15, mirabegron 100 mg single dose in combination with rifampin dose on day 12	Complete; Full
PK/DDI	178-CL-058 France	Effect of steady state mirabegron on PK of single dose desipramine	Phase 1, open-label, 1-sequence crossover study	Mirabegron OCAS 100 mg tablet po, only daily fasted; Desipramine 50 mg tablets (as two 25 mg tablets) po, fasted	28	Healthy volunteers	Period 1: desipramine 50 mg single dose on day 1; mirabegron 100 mg qd (day 5 to 23); desipramine 50 mg single dose in combination with mirabegron on day 18 (washout period 13 days) Period 2: desipramine 50 mg single dose on day 38	Complete; Full
PK/DDI	178-CL-068 France	Effect of multiple doses of mirabegron on the PK of a COC	Phase 1, double-blind, 2-sequence crossover study	Mirabegron OCAS 100 mg or matching placebo tablet po; once daily fasted Combined oral contraceptive (COC) (ethinyl estradiol 30 mcg + levonorgestrel 150 mcg) tablet po; once daily fasted	30	Healthy female volunteers	Dosed according to menstrual cycle Period 1: COC qd day 1 to day 21; stop for 7 days; start mirabegron 100 mg or matching placebo qd day 12 for 10 days (washout period 19 days) Period 2: COC qd day 1 to day 21; start mirabegron 100 mg or matching placebo qd (opposite of period 1) day 12 for 10 days	Complete; Full
PK/DDI	178-CL-059 France	Effect of steady state mirabegron on PK of single dose digoxin	Phase 1, open-label, 1-sequence crossover study	Mirabegron OCAS 100 mg tablet po, only daily fasted; Digoxin 0.250 mg tablet po; fasted	25	Healthy volunteers	Digoxin 0.250 mg single dose on day 1; mirabegron 100 mg qd (day 10 to day 23); digoxin 0.250 mg single dose in combination with mirabegron dose on day 18	Complete; Full
PK/DDI	178-CL-040 France	Effect of mirabegron at steady state on the PK of single dose of warfarin	Phase 1, open-label, 1-sequence crossover	Mirabegron OCAS 100 mg po; once daily fasted Warfarin 25 mg tablet (as five 5 mg tablets) po; once daily fasted	24	Healthy volunteers	Warfarin 25 mg single dose on day 1 washout period of 14 days mirabegron 100 mg qd for 16 consecutive days (day 15 to day 30) warfarin 25 mg single dose on day 23	Complete; Full

PK/DDI	178-CL-069 France	Effect of steady state mirabegron on PK of single dose solifenacin and effect of steady state solifenacin on PK of single dose mirabegron	Phase 1, open-label, 1-sequence, 2-arm study	Mirabegron OCAS 100 mg tablet po, once daily fasted Solifenacin 10 mg tablet po; once daily fasted	41	Healthy volunteers	Treatment arm 1: solifenacin 10 mg single dose day 1 (washout 14 days); mirabegron 100 mg qd day 15 to 38; solifenacin 10 mg single dose in combination with mirabegron dose on day 23 Treatment arm 2: mirabegron 100 mg single dose day 1 (washout 6 days); solifenacin 10 mg qd day 7 to 20; mirabegron 100 mg single dose in combination with solifenacin dose on day 16	Complete; Full
PD/PK	178-CL-080 France	Cardiovascular interactions between mirabegron and tamsulosin	Phase 1, open-label, 2-arm, 2-sequence crossover	Mirabegron OCAS 100 mg po; once daily fasted Tamsulosin 0.4 mg capsule po; once daily fasted	48	Healthy volunteers	Arm 1, Sequence 1: tamsulosin 0.4 mg on day 2 (washout 22 days), mirabegron 100 mg days 27 to 39, tamsulosin 0.4 mg single dose on day 35 Arm 1, Sequence 2: mirabegron 100 mg days 2-14, tamsulosin 0.4 mg single dose on day 10 (washout 10 days); tamsulosin 0.4 mg single dose on day 27 Arm 2, Sequence 1: mirabegron 100 mg on day 2 (washout 18 days) tamsulosin 0.4 mg days 23-35, mirabegron 100 mg single dose on day 27 Arm 2, Sequence 2: tamsulosin 0.4 mg days 2-14, mirabegron 100 mg single dose on day 6 (washout 6 days); mirabegron 100 single dose on day 23	Complete; Full
PD/PK	178-CL-037 United States	Thorough QT	Phase 1, randomized, double-blind, placebo- and active-controlled, 4-way crossover	Mirabegron OCAS 100 and 200 mg tablet; moxifloxacin 400 mg capsule; matching placebo tablet (mirabegron) and capsule (moxifloxacin) po; once daily fasted	49	Healthy volunteers	Four 7-day treatment periods; washout of ≥10 days between treatments Mirabegron/ matching placebo: 7 days Moxifloxacin: placebo to match mirabegron days 1-6, moxifloxacin/ matching placebo on day 7	Complete; Full
PD/PK	178-CL-077 United States	Thorough QT	Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group, 2-way crossover	Mirabegron OCAS 50, 100 or 200 mg tablet or moxifloxacin 400 mg capsule po; and matching placebo; once daily fasted	352	Healthy volunteers	Two 10-day treatment periods; washout of ≥10 days between treatments	Complete; Full

PD/PK	178-CL-053 France	Cardiovascular mechanistic study	Phase 1, randomized, single-blind, 2-arm, 3-way crossover design	Mirabegron OCAS 200 mg tablets (2x 100 mg) po; matching placebo; fasted Propranolol 160 mg capsule (prolonged release, overencapsulated) po, Bisoprolol 10 mg tablet po (overencapsulated); or matching placebo; fasted	12	Healthy male volunteers	Day 1: Propranolol, bisoprolol or placebo followed by mirabegron placebo; Day 5: Propranolol, bisoprolol or placebo followed by mirabegron 200 mg; minimum of 14 days between each dose of mirabegron	Complete; Full
PD	178-CL-081 United States	Ocular Safety	Phase 1b, randomized, double-masked, 2-arm, parallel group	Mirabegron OCAS 100 mg tablets po; matching placebo; once daily fasted	321	Research subjects (Healthy volunteers or adults with overactive bladder)	56 days	Complete; Full

C: Efficacy and Safety Studies

E/S	178-CL-044 Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, United Kingdom	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2b, randomized, double-blind, parallel group, placebo- and active-controlled, dose ranging	Treatment groups: placebo, mirabegron 25, 50, 100 or 200 mg, or tolterodine SR 4 mg Mirabegron OCAS 25, 50, 100, 200 mg tablet or matching placebo po; once daily fed (after breakfast) tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily fed (after breakfast)	928†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S PK	178-CL-045 Japan	Dose-response efficacy; safety and tolerability of mirabegron	Phase 2, randomized, double-blind, placebo-controlled, parallel group	Treatment groups: placebo, mirabegron 25, 50, or 100 mg Mirabegron OCAS 25, 50, 100 mg qd or matching placebo tablet po; once daily fed (after breakfast)	842†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-046 Europe‡ and Australia	Efficacy and safety of mirabegron compared to placebo and tolterodine SR	Phase 3, randomized, double-blind, placebo-controlled and active-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg, or tolterodine SR 4 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	1987†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-047 Canada United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 50 or 100 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food	1329†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full

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E/S	178-CL-048 Japan	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo- and active-controlled	Treatment groups: placebo, mirabegron 50 mg, or tolterodine SR 4 mg Mirabegron OCAS 50 mg tablet or matching placebo po; once daily with food (after breakfast) tolterodine SR 4 mg capsule (overencapsulated) or matching placebo po; once daily with food (after breakfast)	1139†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-074 Canada, Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, Sweden, United States	Efficacy and safety of mirabegron compared to placebo	Phase 3, randomized, double-blind, placebo-controlled	Treatment groups: placebo, mirabegron 25 or 50 mg Mirabegron OCAS 25 or 50 mg tablet or matching placebo po; once daily with or without food	1306†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12-week double-blind treatment period	Complete; Full
E/S	178-CL-049 Europe§ Canada United States Australia New Zealand South Africa	Long term safety	Phase 3, randomized, double-blind, active-controlled	Treatment groups: Mirabegron 50 or 100 mg, or tolterodine ER mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily with or without food tolterodine ER 4 mg capsule (overencapsulated) or matching placebo po; once daily with or without food	2452†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 12 month double-blind treatment period	Complete; Full
E/S	178-CL-051 Japan	Long term safety	Phase 3, open-label	Treatment group: Mirabegron (titration) Mirabegron OCAS 50 mg po, dose escalation to 100 mg allowed after 8 weeks (improve efficacy); once daily fed (after breakfast)	204 enrolled	Adults with overactive bladder	52 weeks	Complete; Full
E/S POC	178-CL-008 Belgium, Czech Republic, Denmark, Germany, Spain, Sweden, United Kingdom	Efficacy, safety, tolerability, population PK; proof of concept	Phase 2a, randomized, double-blind, parallel group, placebo-controlled and active-controlled	Treatment groups: placebo, mirabegron IR 100 or 150 mg bid, or tolterodine MR 4 mg Mirabegron IR 100 mg or 150 mg tablet po (total daily doses of 200 or 300 mg); twice daily with food (after breakfast and after dinner) tolterodine MR 4 mg capsule (overencapsulated) po; once daily in the morning with food (after breakfast)	262†	Adults with overactive bladder	2-week single-blind placebo run-in followed by 4-week double-blind treatment period	Complete; Full
E/S	178-CL-060 Canada United States	Urodynamic safety in male patients with LUTS and BOO	Phase 2, randomized, double-blind, placebo controlled, multicenter	Treatment groups: placebo, mirabegron 50 or 100 mg Mirabegron OCAS 50 or 100 mg tablet or matching placebo po; once daily fed (after breakfast)	200†	Men with LUTS and BOO	12-week DB treatment period	Complete; Full
E/S PD/PK	178-CL-003 Poland	PD, safety, tolerability, PK	Phase 2a, placebo-controlled, dose titration study	Treatment groups: placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast	59†	Adults with type 2 diabetes (on dietary and exercise measures)	4-week single-blind placebo run-in followed by 12-week double-blind treatment period: Mirabegron 60 mg 1 week, 130 mg 1 week, 200 mg 10 weeks	Complete; Full

Reference ID: 3129601

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of Efficacy and Safety Studies *continued*								
E/S PD/PK	178-CL-004 Poland	PD, safety, tolerability, PK	Phase 2a, placebo-controlled, dose titration study	Treatment groups: placebo or mirabegron (titration) Mirabegron IR 60, 130, 200 mg tablet (using 30 and 100 mg tablets) or matching placebo po; once daily after breakfast Metformin 500 and 850 mg tablets po; stable dose throughout treatment period	60†	Adults with type 2 diabetes on metformin monotherapy (stable doses)	4-week single-blind placebo run-in followed by 12-week double-blind treatment period: Mirabegron 60 mg 1 week, 130 mg 1 week, 200 mg 10 weeks	Complete; Full

POC: proof of concept; IR: immediate release; OAB: overactive bladder; E/S: efficacy and safety; PD: pharmacodynamic; PK: pharmacokinetics; LUTS: lower urinary tract symptoms; BOO: bladder outlet obstruction; OCAS: oral-controlled absorption system (-F [fast], -M [medium], -S [slow]); BP: biopharmaceutics; DDI: drug-drug interaction; BA: bioavailability; COC: combined oral contraceptive (ethinyl estradiol and levonorgestrel); SR: slow release.

† randomized into the double-blind treatment period

‡Europe: Austria, Belarus, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Romania, Russian Federation, Slovakia, Spain, Sweden, Switzerland and United Kingdom

¶ Europe: Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Portugal, Slovakia, Spain, and Sweden

§ Europe: Austria, Belgium, Bulgaria, Belarus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, Spain, Sweden, Switzerland, Ukraine, and United Kingdom

Reference ID: 3129601

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/s/

SAYED AL HABET
05/11/2012

MICHAEL A PACANOWSKI on behalf of CHRISTIAN GRIMSTEIN
05/11/2012

MICHAEL A PACANOWSKI
05/11/2012

JIANG LIU
05/11/2012

YANING WANG
05/11/2012

MYONG JIN KIM
05/11/2012

EDWARD D BASHAW
05/22/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**202-611**
Submission Date:	08/26/2011
Drug Name:	Mirabegron
Formulation:	Extended Release Tablets
Strength:	25 and 50 mg
Applicant:	Astellas
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

SYNOPSIS:

Submission: In NDA 202-611 the Applicant is seeking approval of Mirabegron ER Tablets. Mirabegron is a New Molecular Entity, which is a selective agonist for human beta 3-adrenoceptor (beta 3-AR) that is proposed to be indicated for the treatment of overactive bladder.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed IVIVC model linking the effects of manufacturing parameters on clinical performance. The submission includes IVIVC and the DoE studies investigating the effect of manufacturing parameters on dissolution.

Based on the evaluation of the overall data, ONDQA-Biopharmaceutics has the following summary comments:

COMMENTS

1. The following proposed dissolution method and acceptance criteria are acceptable.

USP Apparatus	Speed	Medium/ Temperature	Volume	Assay	Acceptance Criteria % Mirabegron Dissolved	
					25 mg	**50 mg**
1 (basket) (40 mesh screen)	100 rpm	USP pH 6.8 phosphate buffer/ 37±0.5 °C	900 mL	HPLC/ UV at 250 nm	3 hr: (b) (4) 5 hr: (b) (4) 8.5 hr: (b) (4)	3 hr: (b) (4) 5 hr: (b) (4) 8.5 hr: (b) (4)

2. The results from the in vitro alcohol dose dumping study showed that Mirabegron ER Tablets do not have a potential for dose dumping in the presence of alcohol.

3. The provided data support the approval of a "Level C" IVIVC for Mirabegron ER Tablets.

4. The results from the multivariate design of experiment (DoE) using dissolution as an endpoint and linking it with IVIVC to evaluate the clinical relevance of the manufacturing attributes, showed that the proposed attribute ranges (see the black box in the figure below) are well within the bioequivalence range compared to the

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references (with the median values of material attributes). Therefore, the proposed material attribute ranges are acceptable.

RECOMMENDATION

NDA 202-611 for Mirabegron ER Tablets is recommended for approval from the Biopharmaceutics perspective.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
ONDQA Acting Biopharmaceutics Supervisory Lead

cc: NDA 202611/DARRTS

Reference ID: 3121195

BIOPHARMACEUTICS EVALUATION

APPENDIX 1.

➔ **The Reviewer's analyses on the formulation development**

1. The formulation development of Mirabegron used a QbD-like approach. Dissolution was defined as a CQA.

The figure below shows an Ishikawa diagram which represents the relationship between raw material attributes and final product quality. Based on the results of the Ishikawa diagram analysis and prior knowledge including whole experimental results obtained from the early development stage, a risk assessment on material attributes using Failure Mode Effects Analysis (FMEA) was performed.

(b) (4)

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APPENDIX 2.

➔ **Summary of the biopharmaceutics related information in the submission**

1. The composition of the formulations for the proposed drug product Mirabegron extended release tablets

Components	Reference Quality Standard	Function	Quantity (mg/tablet)	
			Mirabegron OCAS tablets 25 mg	Mirabegron OCAS tablets 50 mg
Mirabegron	In house	Active Ingredient	25.0	50.0
Polyethylene Oxide (b) (4)	NF/In-house			(b) (4)
Polyethylene Glycol (b) (4)	NF			
Hydroxypropyl Cellulose	NF			
(b) (4)	USP			
Butylated Hydroxytoluene	NF			
Magnesium Stearate	NF			
(b) (4)	In house			
	In house			
	USP			
Total tablet weight (mg)			257.5	257.5

USP: United States Pharmacopeia, NF: National Formulary

(b) (4)

2. The proposed dissolution method and acceptance criteria

The proposed dissolution method:
Apparatus: USP 1 (40 mesh screen)
Rotation: 100 rpm
Medium: USP pH 6.8 phosphate buffer
Volume: 900 mL
Temperature: 37±0.5 °C
Assay: HPLC

The proposed acceptance criteria are (b) (4) shown below.

25 mg:
3 hours:
5 hours:
8.5 hours:

(b) (4)

50 mg:
3 hours:
5 hours:
8.5 hours:

The HPLC conditions are shown below.

Parameter	Description
Detector	An ultraviolet absorption photometer (wavelength: 250 nm)
Column	Octadecyl silica column, particle size: 3 μm, 4.6 mm i.d. × 150 mm (e.g. Develosil ODS-HG-3, Nomura Chemical Co.,Ltd or equivalent)
Column temperature	40°C
Mobile phase	A mixture of perchloric acid solution (pH 2.0)/acetonitrile (7:3)
Flow rate	Adjust the flow rate to elute mirabegron at about 4 minutes
Injection volume	10 μL

The following table shows the validation summary for dissolution of the 25 mg strength.

Validation Parameter	Study Design	Results
Specificity	(b) (4)	No interfering peaks with mirabegron.
Linearity		(Standard solution) Y = 8977x + 2459, R = 1.00, Y-intercept: 0.3% (Spiked excipient solution) Y = 10114x + 1784, R = 1.00, Y-intercept: 0.2%
Accuracy		Concentration — Mean Recovery 10% — 99.9% 30% — 101.1% 50% — 100.0% 80% — 102.0% 120% — 100.2% 150% — 100.8% All conc. — 100.7%
Precision Repeatability		Concentration — RSD 10% — 0.3% 30% — 0.4% 50% — 0.5% 80% — 0.4% 120% — 0.3% 150% — 0.3% All conc. — 0.8%
Precision Intermediate Precision		(30%-level) Experiment # — Recovery — RSD 1 — 102.3% 2 — 101.5% 3 — 102.7% — 1.0% 4 — 100.1% 5 — 100.7% 6 — 101.8% (50%-level) Experiment # — Recovery — RSD 1 — 102.9% 2 — 100.1% 3 — 102.2% — 1.1% 4 — 100.4% 5 — 100.4% 6 — 101.7% (80%-level) Experiment # — Recovery — RSD 1 — 100.7% 2 — 100.5% 3 — 101.3% — 0.5% 4 — 99.9% 5 — 100.4% 6 — 101.1%
Range		From 10% to 150%
Robustness		Acceptance criteria for specificity and system suitability were satisfied in all conditions.
Stability of Solution		Standard and spiked excipient solutions were stable for two days under both conditions.

Reference ID: 3121195

The following table shows the validation summary for dissolution of the 50 mg strength.

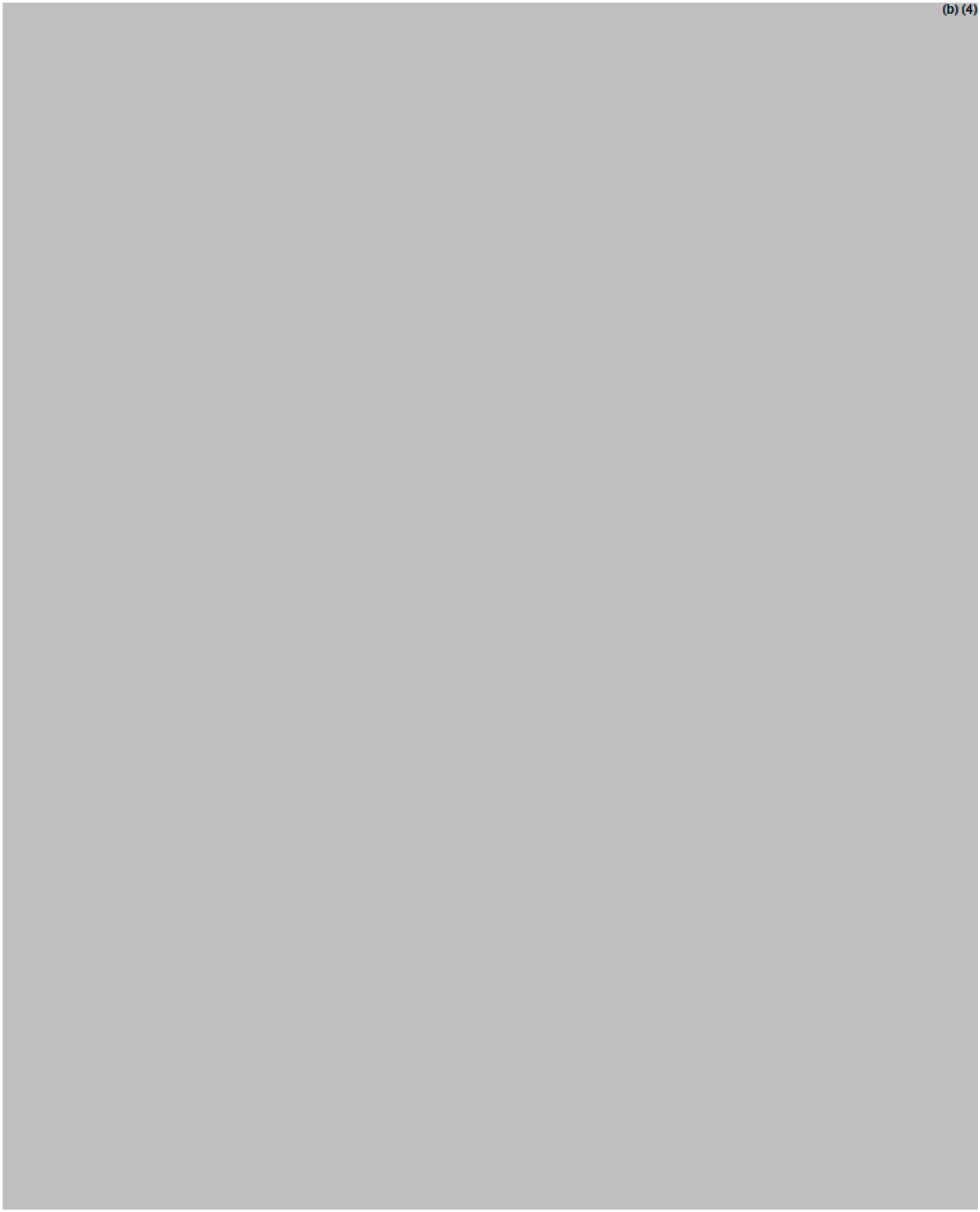
Validation Parameter	Study Design	Results
Specificity	(b) (4)	No interfering peaks with mirabegron.
Linearity		(Standard solution) Y = 18356x + 2552, R = 1.00, Y-intercept: 0.1% (Spiked excipient solution) Y = 20453x + 3180, R = 1.00, Y-intercept: 0.2%
Accuracy		Concentration — Mean Recovery 10% — 99.9% 30% — 100.4% 50% — 100.2% 80% — 100.4% 120% — 100.5% 150% — 99.8% All Conc. — 100.2%
Precision Repeatability		Concentration — RSD 10% — 0.5% 30% — 0.5% 50% — 0.5% 80% — 0.5% 120% — 0.4% 150% — 0.9% All Conc. — 0.6%
Precision Intermediate Precision		(30%-level) Experiment # — Recovery — RSD 1 — 100.4 2 — 102.0 3 — 100.7 — 0.9% 4 — 100.3 5 — 101.2 6 — 99.3 (50%-level) Experiment # — Recovery — RSD 1 — 100.3 2 — 101.0 3 — 101.4 — 0.8% 4 — 100.1 5 — 101.3 6 — 99.3 (80%-level) Experiment # — Recovery — RSD 1 — 100.3 2 — 100.5 3 — 100.5 — 0.5% 4 — 100.3 5 — 101.3 6 — 99.9
Robustness		Acceptance criteria for specificity and system suitability were satisfied in all conditions.
Stability of Solution		Standard and spiked excipient solutions were stable for two days under both conditions.

Reference ID: 3121195

Reviewer's Comments:
The proposed dissolution method with a mild 100 rpm condition is acceptable. In addition, an IVIVC has been established using the proposed dissolution method.

3. Dissolution method development

(b) (4)



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4. Justification for proposed acceptance criteria

Dissolution data of the commercial representative batches, which include the bio-batches used for the phase 3 clinical studies (178-CL-046, 047 and 074) and the IVIVC study (178- CL-076) are summarized in the following tables.

Table P.5.6-9 Basket Dissolution Data of Representative Commercial Batches from IVIVC Study

Dose		25 mg		50 mg	
Batch number		E0800025	F0800460	K0700248	L0700018
Batch used for		IVIVC (validation) / Primary stability	P-3 study / IVIVC (target) / Primary stability	P-3 study / IVIVC (validation) / Primary stability	IVIVC (target) / Primary stability
Dissolution test [1), 2)]	0.5 h	4.2% (b) (4)	4.2% (b) (4)	3.4% (b) (4)	3.6% (b) (4)
	1 h	8.7%	8.6%	7.2%	7.5%
	2 h	18.9%	18.7%	16.5%	16.9%
	3 h	31.0%	30.8%	27.9%	28.4%
	4 h	44.7%	44.9%	40.6%	41.6%
	5 h	59.6%	59.0%	54.4%	55.7%
	6 h	74.1%	73.6%	68.5%	69.4%
	7 h	87.4%	87.3%	81.9%	82.2%
	8 h	97.7%	97.9%	92.9%	93.3%
	8.5 h	100.6%	101.1%	97.4%	97.7%
	9 h	101.6%	102.1%	100.4%	101.0%
	10 h	101.5%	102.1%	101.8%	102.6%
	11 h	101.4%	102.1%	101.8%	102.8%
	12 h	101.3%	102.1%	101.8%	102.8%

[1)] Dissolution results from 12 vessels with the basket method at 100 rpm rotation, Mean (min. – max.)
[2)] The proposed acceptance criteria time points are underlined.

Table P.5.6-10 Basket Dissolution Data of Representative Commercial Batches from PQ Studies

Dose		25 mg		50 mg		
Batch number		H0900008	H0900009	G0900435	G0900436	G0900437
Batch used for		PQ study		PQ study		
Dissolution test [1), 2)]	1 h	8.4% (b) (4)	8.2% (b) (4)	6.6% (b) (4)	6.8% (b) (4)	6.5% (b) (4)
	3 h	29.3%	30.5%	26.8%	26.2%	27.0%
	5 h	54.1%	58.5%	53.0%	50.4%	52.8%
	7 h	79.8%	84.8%	78.7%	76.3%	78.2%
	8.5 h	96.6%	99.9%	94.1%	92.4%	94.3%
	10 h	101.9%	102.9%	101.2%	101.0%	101.2%

[1)] Dissolution results from 6 vessels with the basket method at 100 rpm rotation, Mean (min. – max.)
[2)] The proposed acceptance criteria time points are underlined.

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Table P.5.6-11 Basket Dissolution Data of Representative Commercial Batches from PV Studies (25 mg Tablets)

Dose		25 mg			
Batch number		K1000056	K1000057	K1000058	M1000086
Batch used for		PV study for EU and US markets			
Dissolution test [1), 2)]	1 h	8.1% (b) (4)	8.1% (b) (4)	7.8% (b) (4)	8.1% (b) (4)
	3 h	30.3%	30.5%	29.0%	30.7%
	5 h	57.4%	57.9%	55.3%	58.0%
	7 h	84.5%	84.7%	80.5%	84.8%
	8.5 h	97.8%	97.8%	96.3%	98.3%
	10 h	100.7%	100.1%	100.4%	101.0%

[1)] Dissolution results from 6 vessels with the basket method at 100 rpm rotation, Mean (min. – max.)
[2)] The proposed acceptance criteria time points are underlined.

Table P.5.6-11 (Continued)

Dose		25 mg		
Batch number		G1000069	G1000070	G1000071
Batch used for		PV study for Japanese market		
Dissolution test [1), 2)]	1 h	8.5% (b) (4)	8.5% (b) (4)	8.5% (b) (4)
	3 h	29.7%	29.4%	29.8%
	5 h	57.3%	57.3%	57.2%
	7 h	85.0%	84.3%	85.3%
	8.5 h	98.8%	98.8%	99.0%
	10 h	100.1%	100.5%	100.1%

[1)] Dissolution results from 6 vessels with the basket method at 100 rpm rotation, Mean (min. – max.)
[2)] The proposed acceptance criteria time points are underlined.

Table P.5.6-12 Basket Dissolution Data of Representative Commercial Batches from PV Studies (50 mg Tablets)

Dose		50 mg					
Batch number		C1000023	C1000024	C1000025	G1000078	G1000079	G1000080
Batch used for		PV study for EU and US markets			PV study for Japanese market		
Dissolution test [1), 2)]	1 h	7.4% (b) (4)	7.5% (b) (4)	7.3% (b) (4)	7.3% (b) (4)	7.4% (b) (4)	7.2% (b) (4)
	3 h	28.1%	28.0%	27.8%	27.2%	28.1%	27.4%
	5 h	53.3%	54.1%	53.5%	54.1%	56.1%	54.5%
	7 h	78.8%	78.6%	79.6%	80.5%	82.5%	81.5%
	8.5 h	92.6%	93.2%	94.0%	96.3%	97.6%	97.5%
	10 h	100.5%	101.3%	100.2%	100.4%	101.0%	101.6%

[1)] Dissolution results from 6 vessels with the basket method at 100 rpm rotation, Mean (min. – max.)
[2)] The proposed acceptance criteria time points are underlined.

Table P.5.6-13 Basket Dissolution Data of Representative Commercial Batches from Primary Stability Study

Dose		25 mg			50 mg		
Batch number		E0800025	F0800460	F0800461	K0700248	L0700018	A0800039
Dissolution test [1)]	3 h	32.1% (b) (4)	32.8% (b) (4)	30.9% (b) (4)	28.6% (b) (4)	28.1% (b) (4)	27.9% (b) (4)
	5 h	60.5%	60.9%	59.4%	54.9%	54.0%	54.8%
	8.5 h	100.0%	100.9%	100.1%	95.5%	96.5%	95.2%

[1)] Dissolution results at time-zero point in the primary stability study in Section [3.2.P.8.3]. Results from 6 vessels with the basket method at 100 rpm rotation, Mean (min. – max.)

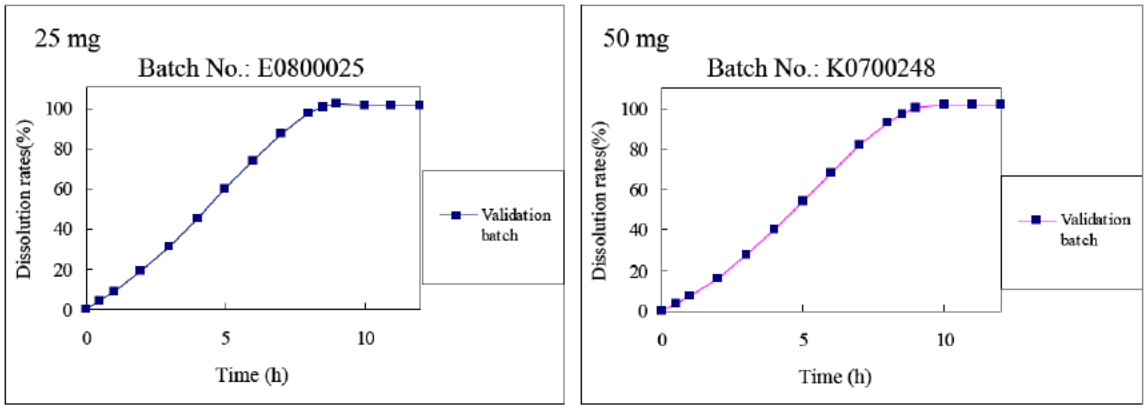
Representative dissolution profiles of mirabegron OCAS tablets 25 mg and 50 mg using the basket method are also shown in the following Figure. According to the recommendation from the Division during the Pre-NDA meeting, the dissolution data from multiple sampling points were considered in proposing the appropriate time points for dissolution specification of mirabegron OCAS tablets. Based on the requirements in USP <1092>, three time points at 3 hours, 5 hours and 8.5 hours were selected to cover the early, intermediate and final stage of the dissolution. As shown in the following Table, the mean dissolution values at each sampling point from all available basket data show the following target dissolution for each strength of mirabegron OCAS tablets.

25 mg	**50 mg**
3 h: (b) (4) 5 h: (b) (4) 8.5 h: More than (b) (4)	3 h: (b) (4) 5 h: (b) (4) 8.5 h: More than (b) (4)

Table P.5.6-14 Basket Dissolution Data Summary of Representative Commercial Batches

Dose		25 mg	50 mg
Number of dissolution data for calculation		14	14
Mean rates (min. – max.) from all batches (%)	3 h	30.5 (b) (4)	27.7 (b) (4)
	5 h	58.0	54.0
	8.5 h	99.0	95.3

Figure P.5.6-4 Representative Dissolution Profiles with Basket Method at 100 rpm



The established IVIVC model indicates that in vitro dissolution changes of mirabegron OCAS tablets give a considerable effect on in vivo performance, therefore, the criteria of a (b) (4) range from the target dissolution and (b) (4) for the last time point are considered appropriate.

Since the target dissolution for each strength are supported by the commercial representative batch data and the allowable range is set considering an effect of the dissolution on in vivo performance, the proposed dissolution criteria are considered appropriate to control the dissolution of mirabegron OCAS tablets during the commercial production.

Reviewer's comment:
The proposed acceptance criteria are acceptable.

4. In Vitro Alcohol dose dumping study

The effects of alcohol on the dissolution properties of mirabegron OCAS tablets in 0.1 N HCl, pH 4.5, and pH 6.8 media containing ethanol were evaluated. The dissolution profiles of 25 mg and 200 mg tablets in USP phosphate buffer (pH 6.8) containing ethanol are presented in the figures below. The results indicated that ethanol addition into the dissolution medium decreased the dissolution rates, slightly with 4% addition and markedly with 40%. The trends were the same in two different strengths, the lowest (25 mg) and the highest (200 mg).

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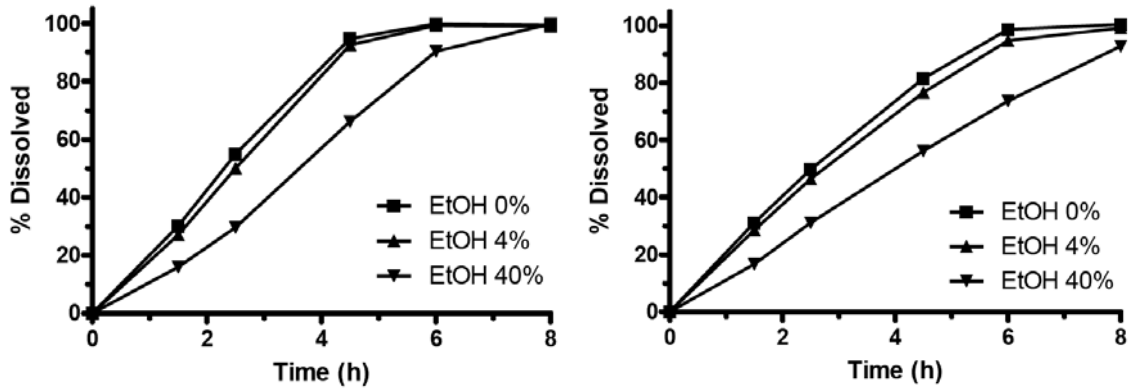

Reviewer's Comments:
The drug burst release from mirabegron OCAS tablet does not occur by addition of alcohol in vitro dissolution media.

APPENDIX 3.

➔ The In Vivo-In Vitro Correlation (IVIVC) study

1. The formulations used in IVIVC study

The formulations of mirabegron OCAS tablets to be used for the IVIVC analysis are listed in Table 1 to Table 3. MR-M is the formulation which represents the target dissolution profile.

Table 1 Formulations of Mirabegron OCAS Tablets 25 mg, 50 mg and 100 mg (MR-M)

Component	Reference to standards	Quantity (mg/tablet)		
		YM178 OCAS tablet 25 mg	YM178 OCAS tablet 50 mg	YM178 OCAS tablet 100 mg
YM178	In house	25.0	50.0	100.0
Polyethylene Oxide (b) (4)	NF	(b) (4)		
Polyethylene Glycol (b) (4)	NF			
Hydroxypropyl Cellulose	NF			
Butylated Hydroxytoluene	NF			
Magnesium Stearate	NF			
(b) (4)	In house			
	In house			
	In house			
Total				

Table 2 Formulations of Mirabegron OCAS Tablets 25 mg, 50 mg and 100 mg (MR-H)

Component	Reference to standards	Quantity (mg/tablet)		
		YM178 OCAS tablet MR-H 25 mg	YM178 OCAS tablet MR-H 50 mg	YM178 OCAS tablet MR-H 100 mg
YM178	In house	25.0	50.0	100.0
Polyethylene Oxide (b) (4)	NF	(b) (4)		
Polyethylene Glycol (b) (4)	NF			
Hydroxypropyl Cellulose	NF			
Butylated Hydroxytoluene	NF			
Magnesium Stearate	NF			
(b) (4)	In house			
	In house			
	In house			
Total				

Table 3 Formulations of Mirabegron OCAS Tablets 25 mg, 50 mg and 100 mg (MR-L)

Component	Reference to Standards	Quantity (mg/tablet)		
		YM178 OCAS tablet MR-L 25 mg	YM178 OCAS tablet MR-L 50 mg	YM178 OCAS tablet MR-L 100 mg
YM178	In house	25.0	50.0	100.0
Polyethylene Oxide (b) (4)	NF	(b) (4)		
Polyethylene Glycol (b) (4)	NF			
Hydroxypropyl Cellulose	NF			
Butylated Hydroxytoluene	NF			
Magnesium Stearate	NF			
(b) (4)	In house			
	In house			
	In house			
Total				

Reference ID: 3121195

2. In vitro dissolution

The dissolution data from the development of an IVIVC were collected (Study No.: PCAR0902770). The dissolution test of 12 individual tablets of each formulation were performed under four conditions listed in Table 4, which were believed to be predictive of in vivo performance. The mean data for the batches under condition II are shown in Table 9 to Table 11.

Table 4 Dissolution Test Method for Mirabegron OCAS Tablets

	Dissolution medium	Method	Rotation speed (rpm)
Condition I	pH 6.8 USP phosphate buffer	(b) (4)	(b) (4)
Condition II		40 mesh baskets	100
Condition III		(b) (4)	(b) (4)
Condition IV	(b) (4)		

Table 9 Dissolution Results of 25 mg Tablet for IVIVC Establishment (Condition II)

25 mg tablets	Mean dissolution rates (%) [1]										
	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	8.5 h	9 h
MR-H (08174)	4.7	10.4	24.5	40.1	57.3	75.1	90.4	100.2	101.4	101.4	101.6
MR-M (F0800460)	4.2	8.6	18.7	30.8	44.9	59.0	73.6	87.3	97.9	101.1	102.1
MR-L (08175)	3.7	7.3	15.3	24.7	35.6	47.3	59.7	72.1	83.7	89.1	93.9
	10 h	11 h	12 h								
MR-H (08174)	101.5	101.5	101.4								
MR-M (F0800460)	102.1	102.1	102.1								
MR-L (08175)	100.2	101.5	101.6								

[1] Mean values from 12 individual dissolution rates.

Table 10 Dissolution Results of 50 mg Tablet for IVIVC Establishment (Condition II)

50 mg tablets	Mean dissolution rates (%) [1]										
	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	8.5 h	9 h
MR-H (08176)	4.1	9.5	23.6	39.3	56.2	73.5	88.2	98.6	101.1	101.0	100.9
MR-M (L0700018)	3.6	7.5	16.9	28.4	41.6	55.7	69.4	82.2	93.3	97.7	101.0
MR-L (08177)	3.0	6.2	13.5	22.3	32.5	43.5	55.5	66.7	77.6	83.1	88.0
	10 h	11 h	12 h								
MR-H (08176)	101.0	101.1	100.9								
MR-M (L0700018)	102.6	102.8	102.8								
MR-L (08177)	96.0	100.5	100.7								

[1] Mean values from 12 individual dissolution rates.

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Table 11 Dissolution Results of 100 mg Tablet for IVIVC Establishment (Condition II)

100 mg tablets	Mean dissolution rates (%) [1)]										
	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	8.5 h	9 h
MR-H (08178)	3.6	9.3	24.2	39.8	55.2	70.7	85.2	95.5	101.3	101.5	101.4
MR-M (L0700011)	3.0	7.0	17.0	29.1	41.8	55.0	68.4	81.8	92.2	96.2	99.5
MR-L (08179)	2.6	5.6	13.4	22.8	33.2	44.5	56.1	67.5	78.0	82.8	87.2
	10 h	11 h	12 h								
MR-H (08178)	101.5	101.5	101.6								
MR-M (L0700011)	102.0	102.1	102.0								
MR-L (08179)	94.5	100.0	101.8								

[1)] Mean values from 12 individual dissolution rates.

3. In vivo pharmacokinetics

The PK data from the Phase 1 study No. 178-CL-076 were used for the development of the IVIVC model. The study consisted of three parallel single dose, randomized, open-label three-way, six-sequence crossover studies involving 90 healthy male and female volunteers. Three different mirabegron OCAS tablet formulations with different release rates [target release rate (MR-M), slow release rate (MR-L), fast release rate (MR-H)] in addition to the target release rate formulation obtained from another batch/lot (for external predictability validation) and an IV formulation (for reference) were administered at each of three dose levels.

Each subject was randomized to one of the three oral mirabegron doses (25, 50 or 100 mg), then further randomized to a treatment sequence (1, 2, 3, 4, 5 or 6) as shown in Table 20. Each subject participated in five-treatment periods separated by washout periods of at least 10 days between dose administrations.

Table 20 Study Design for Phase 1 Study of Mirabegron OCAS(n=30 Planned for Each Dose)

		Treatment Period (Randomized for Periods 2 to 4)					
Treatment Sequence	**N**	**1**	**2**	**3**	**4**	**5 (For IVIVC External Validation)**	**Condition**
1	5	A	B	D	C	E	Fasted
2	5	A	C	B	D	E	Fasted
3	5	A	D	C	B	E	Fasted
4	5	A	C	D	B	E	Fasted
5	5	A	D	B	C	E	Fasted
6	5	A	B	C	D	E	Fasted

A: single 120 minute IV infusion

B: MR-H

C: MR-M (Phase III CTM)

D: MR-L

E: MR-M obtained from another batch/lot

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Subjects fasted for at least 10 hours prior to the morning dosing of mirabegron on Day 1 of each period.

The IV treatment (A) was a reference and was administered in the first period of each sequence for all dose levels. Each subject received a single IV infusion of 7.5 mg over 120 minutes if randomized to the 25 mg oral dose group, 15 mg over 120 minutes if randomized to the 50 mg dose group or 30 mg over 120 minutes if randomized to the 100 mg dose group.

During each of Periods 2-4, the subject received one of three mirabegron OCAS tablet formulations (B=fast release, C=target release, D=slow release) in random order. The additional batch at the target release rate (Formulation E) was not be randomized within each sequence but was administered in the fifth period of each sequence for all doses.

Serial blood samples were taken pre-dose and up to 96 hours post-dose after each dose for the determination of plasma mirabegron concentrations.

The mean PK parameters of mirabegron after a single oral dose of OCAS formulations are attached in Table 23 to Table 25. For the internal validation of IVIVC model, the PK data (Cmax and AUCinf) of Periods 2-4 were used. For the external validation, the PK data of Period 5 were used.

Table 23 Summary of Plasma Pharmacokinetic Parameters Following Oral Administration of 25 mg Mirabegron OCAS

Parameter (unit)	MR-H (n=29)	MR-M (n=29)	MR-L (n=29)	MR-M-Val. (n=26)
C_{max} (ng/mL)	11.3±5.29	9.8±5.11	6.9±4.19	10.0±4.80
AUC_{inf} (ng· h/mL)	149.0±58.95	130.8±58.75	105.8±43.11	143.4±57.75
t_{max} (h)	3.7±0.96	4.0±1.34	4.4±1.42	3.8±1.06

Values are represented as the mean ± SD.

Table 24 Summary of Plasma Pharmacokinetic Parameters Following Oral Administration of 50 mg Mirabegron OCAS

Parameter (unit)	MR-H (n=29)	MR-M (n=26)	MR-L (n=28)	MR-M-Val. (n=25)
C_{max} (ng/mL)	34.5±15.33	22.9±9.24	19.2±11.77	24.2±8.96
AUC_{inf} (ng· h/mL)	412.5±152.84	336.0±130.80	287.4±125.11	347.6±117.91
t_{max} (h)	4.0±1.35	4.3±1.46	4.3±1.52	4.2±1.23

Values are represented as the mean ± SD.

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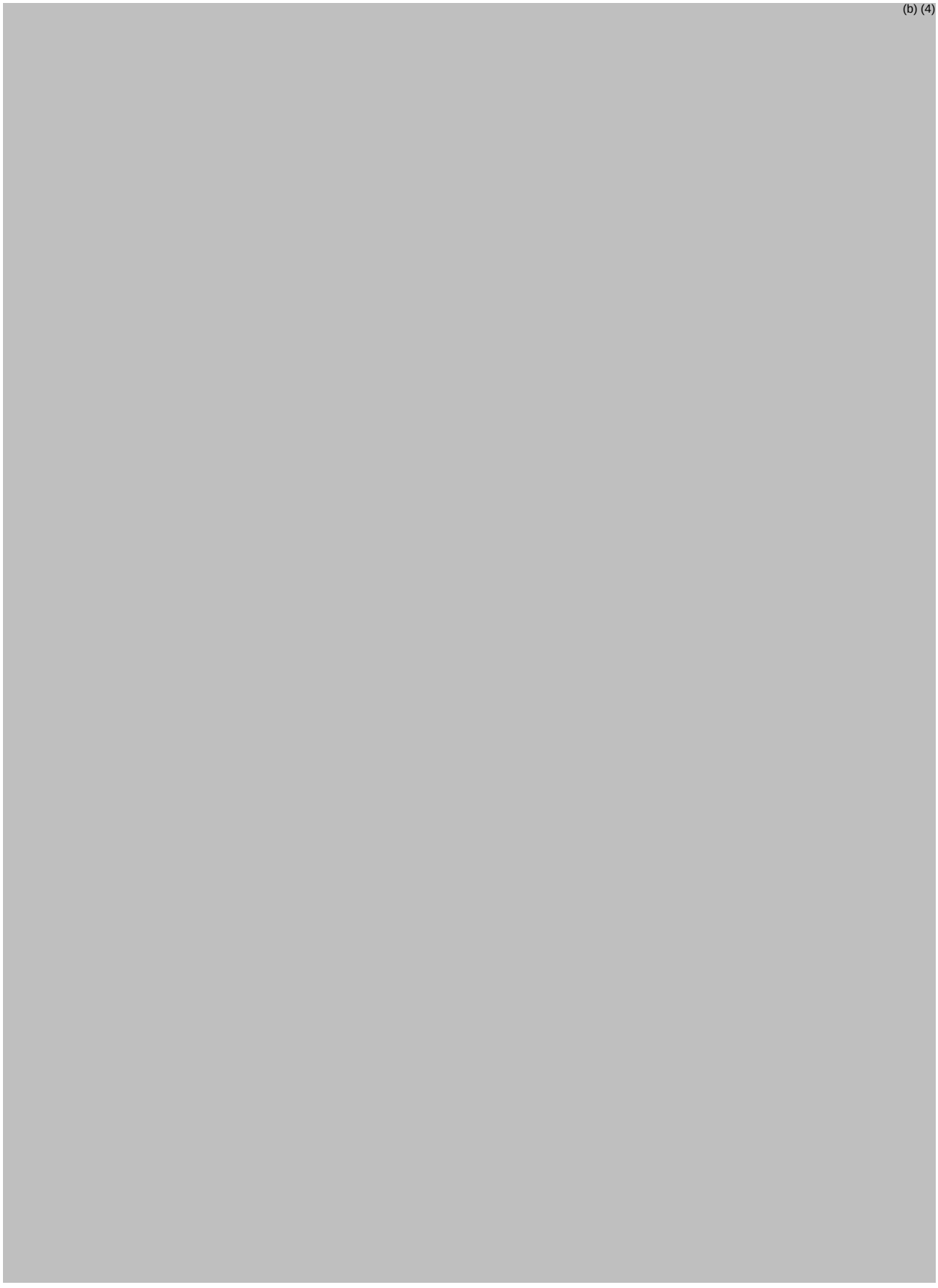
Table 25 Summary of Plasma Pharmacokinetic Parameters Following Oral Administration of 100 mg Mirabegron OCAS

Parameter (unit)	MR-H (n=26)	MR-M (n=27)	MR-L (n=27)	MR-M-Val. (n=24)
C_{max} (ng/mL)	103.5±47.59	77.4±37.28	65.3±38.21	84.3±35.39
AUC_{inf} (ng· h/mL)	983.9±399.28	857.6±378.64	744.1±309.07	826.3±258.78
t_{max} (h)	3.8±1.08	4.0±0.73	3.9±1.24	3.7±1.05

Values are represented as the mean ± SD.

4. The development of "Level A" IVIVC

(b) (4)


(b) (4)

(b) (4)

Therefore, the "Level A" IVIVC model was not established.

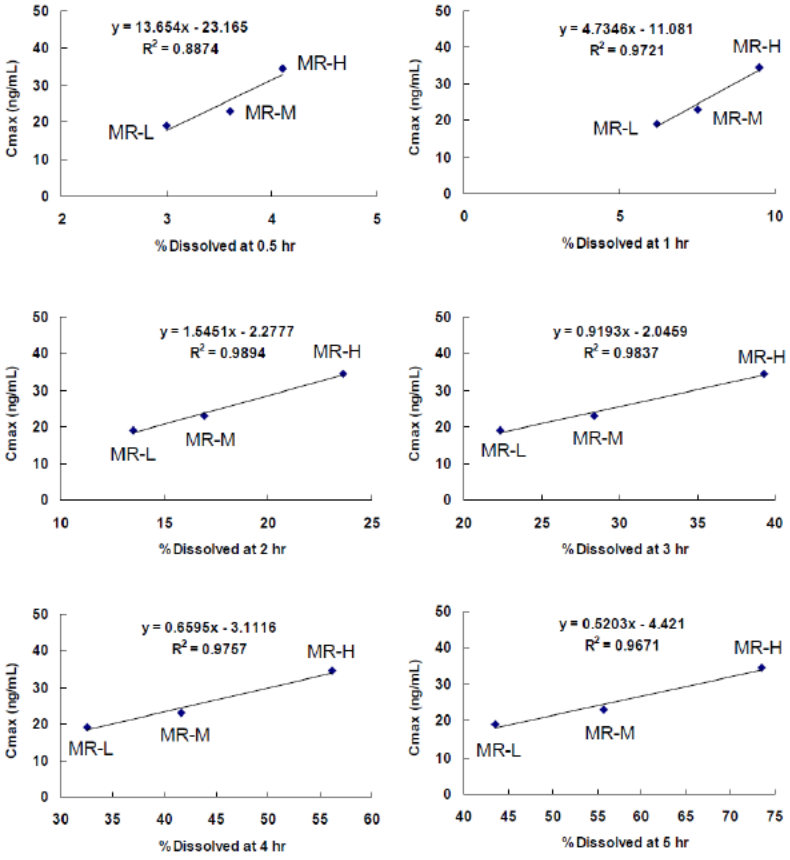
(b) (4)

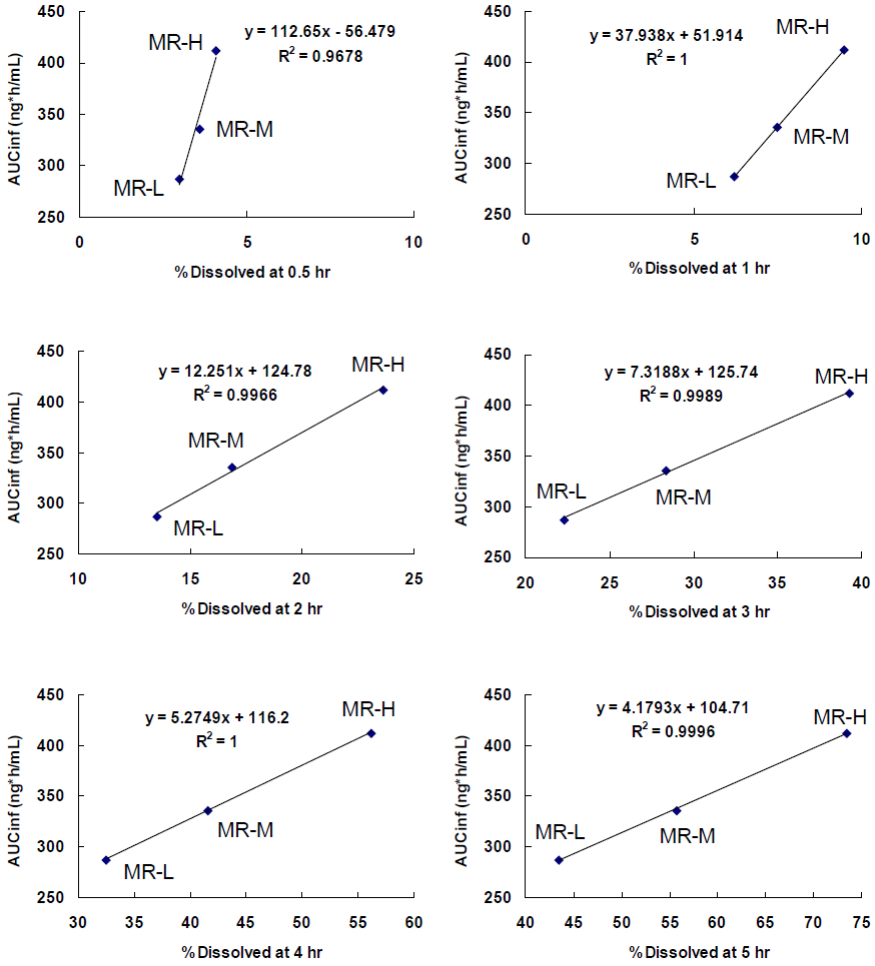
Fraction Dissolved

5. The development of multiple "Level C" IVIVC

For the development of a multiple "Level C" IVIVC, AUCinf and Cmax were selected as PK parameters and the percent dissolved at several time points were selected as dissolution parameters.

The graphical representations of the results on the linear regression analysis between in vivo PK parameters and in vitro dissolution at some time points for Cmax and AUC of 50 mg strength using dissolution condition II are shown below.





The criteria for internal predictability of the IVIVC are that the absolute %PE for each formulation should not exceed 15% and the MAPPE should not exceed 10% for Cmax and AUCinf. The criteria for external predictability of the IVIVC as acceptable are that the absolute %PE for external formulation should not exceed 10% for Cmax and AUCinf.

The predicted Cmax and AUCinf values were obtained as in the internal validation. As the observed Cmax and AUCinf values, the PK data of Phase 1 study (178-CL-076) were used directly. The percent prediction error was estimated for each treatment as listed in the reviewer's analyses section (see pages 9-14 of this review).

In conclusion, a multiple "Level C" IVIVC was established, which is considered to be as useful as the "Level A" IVIVC.

Reviewer's Comment:
Although, the proposed "Level A" IVIVC model could not be validated, a "Level C" IVIVC was established for mirabegron ER Tablets.

Reference ID: 3121195

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/s/

JOHN Z DUAN
04/24/2012

ANGELICA DORANTES
04/24/2012

Review of Analysis Plan for the 10-year CVD Risk Estimates

NDA:	202611
Drug name:	mirabegron
Sponsor:	Astellas Pharma US, Inc
Consult requesting division:	Division of Reproductive and Urologic Products
Type of document reviewed:	Synopsis of Analysis Plan
Consult request date:	February 21, 2012
Review date:	February 22, 2012
Primary Clinical Pharmacology Reviewer:	Rajanikanth Madabushi, Ph.D.
Primary Medical Reviewer	Preston Dunnmon, MD
Secondary Reviewer:	Norman Stockbridge, MD, Ph.D.

BACKGROUND

The Division of Reproductive and Urologic Products (DRUP) consulted us to review the sponsor's Analysis Plan for the 10-year Cardiovascular Disease (CVD) Risk Estimates. A copy of the Analysis Plan can be found at the following link: *\\cdsesub1\EVSPROD\NDA202611\\0019\m1\us\cover-20120217-0019.pdf.*

COMMENTS:

1. **Derivation of General CVD Risk:** We recommend you use the continuous risk function using the Cox model estimates instead of the using the score sheet provided by D'Agostino et al, 2008 for computing. Specifically we recommend that you use the following general formula provided in the appendix of the publication by D'Agostino et al, 2008:

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)}$$

Table 2. Regression Coefficients and Hazard Ratios

Variable	β^*	P	Hazard Ratio	95% CI
Women [So(10)=0.95012]				
Log of age	2.32888	<0.0001	10.27	(5.65–18.64)
Log of total cholesterol	1.20904	<0.0001	3.35	(2.00–5.62)
Log of HDL cholesterol	−0.70833	<0.0001	0.49	(0.35–0.69)
Log of SBP if not treated	2.76157	<0.0001	15.82	(7.86–31.87)
Log of SBP if treated	2.82263	<0.0001	16.82	(8.46–33.46)
Smoking	0.52873	<0.0001	1.70	(1.40–2.06)
Diabetes	0.69154	<0.0001	2.00	(1.49–2.67)
Men [So(10)=0.88936]				
Log of age	3.06117	<0.0001	21.35	(14.03–32.48)
Log of total cholesterol	1.12370	<0.0001	3.08	(2.05–4.62)
Log of HDL cholesterol	−0.93263	<0.0001	0.39	(0.30–0.52)
Log of SBP if not treated	1.93303	<0.0001	6.91	(3.91–12.20)
Log of SBP if treated	1.99881	<0.0001	7.38	(4.22–12.92)
Smoking	0.65451	<0.0001	1.92	(1.65–2.24)
Diabetes	0.57367	<0.0001	1.78	(1.43–2.20)

So(10) indicates 10-year baseline survival; SBP, systolic blood pressure.
*Estimated regression coefficient

Reference ID: 3093452

2. **Total cholesterol and HDL at baseline and final visit:** Your proposal to impute the baseline total cholesterol and HDL based on Carroll et al, 2005 is acceptable. If possible consider utilizing the NHANES data over the duration of 2008 to 2010 to represent the duration of the trials 178-CL-046, 178-CL-047 and 178-CL-074.

3. **Systolic Blood Pressure (SBP) at baseline and final visit:** In addition to the sponsor proposal, we recommend that you conduct independent analyses of incremental cardiovascular risk using the mean AM SBP as well as mean PM SBP separately. Both the sponsor proposed analysis and the analysis of AM SBP and PM SBP should then be conducted using maximal observed as opposed to mean SBPs.

   In study 046, the definition of "Final Visit" is as follows: "In last observation carried forward (LOCF) analyses at the Final Visit, the week 12 measurement was used. If no week 12 measurement was available, the last available earlier postbaseline measurement within the post-dosing window was used." Please confirm that all data used for these calculations for final visit blood pressures were obtained while the patients were actually taking study drug (as opposed to being allowed to discontinue medication and then return to the site for a final visit).

4. **Anti-hypertensive medication use at the time of the measurement for SBP:** Your definition is acceptable.

5. **Smoking Status at baseline and final visit:** It is not clear as to why you choose to average the percent of the current cigarette smokers in 2005 and 2010. We recommend you to consider derive the smoking status over the duration comparable to the time-frame of the conduct of your studies.

6. **Diabetes Status at baseline and final visit:** Your proposed definition is reasonable.

7. **Analysis of the General CVD Risk Estimates: In addition to your proposal, we recommend you to provide:**
   a. Descriptive statistics for age, total cholesterol, HDL, SBP, proportion of patients on antihypertensive medications, proportion of smokers, proportion of diabetics, and the 10-year CVD risk at baseline and the final visit by dose.
   b. The above request by dose (including tolterodine) and study.
   c. Please provide the cumulative distribution function (CDF) plots for change in the 10-year CVD risk for the final visit from baseline by dose (please show the placebo arm also). Also provide the CDF plots by quartiles of baseline risk for all the doses (please show the placebo arm also).
   d. To identify whether or not a subgroup of subjects who might be at an increased risk of developing CVD after treatment of mirabegron compared to the placebo, we recommend you to perform the following analyses:
      1. Calculate and compare proportion of subjects with ≥ 5% increase in estimated CVD risk from baseline to final visit by treatment groups
      2. Calculate and compare proportion of subjects with ≥ 10% increase in estimated CVD risk from baseline to final visit by treatment groups
      3. If sufficient numbers of patients are predicted to be at the higher risk group (≥ 5% or ≥ 10% increase in CVD risk), conduct subgroup analyses to identify potential characteristics of subjects associated with the high risk group.

Reference ID: 3093452

e. Perform a sensitivity analysis for all of the above excluding the Open label Study 178-CL-049
f. We request you to provide the datasets supporting the analysis with the report.

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/s/

RAJANIKANTH MADABUSHI
02/27/2012

PRESTON M DUNNMON
02/27/2012

NORMAN L STOCKBRIDGE
02/28/2012