

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202611Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA # 202611
Product Name: Myrbetriq (mirabegron)

PMR/PMC Description: A long-term observational study in electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using Myrbetriq (mirabegron). An interview based prospective cohort study would follow, if the study in electronic healthcare data is unsuccessful.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	March 2013
	Study/Trial Completion:	July 2018
	Final Report Submission:	June 2019
	Other: Assessment and Summary Report Submission:	March 2015
	Interim Study Completion:	June 2017
	Interim Analysis Report:	June 2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

An increased incidence of serious adverse events in the Neoplasm category (and new malignant events) was observed in the mirabegron 100 mg dose group compared to the mirabegron 50 mg dose group and compared to the active control in a 52-week clinical trial. The neoplasms were of no single type and represented the most common neoplasms in the target population. The clinical trial databases for mirabegron were insufficient to determine valid, adjusted, and stable incidence rates of new malignant events because of the wide variety of potential confounders and the rarity of the reported events. This epidemiology study will be able to evaluate the rates of these events in users of mirabegron and comparator medications using multiple electronic healthcare databases. Studies in these databases will be able to estimate and compare the risk of new malignant events and also control for confounders using multiple regression analyses.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is a preapproval PMR that was designed to evaluate a finding of new malignant events identified from clinical trials at the 100 mg dose of mirabegron.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The findings will be evaluated using an observational epidemiologic study.

Required

- ☒ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

MEREDITH ALPERT
06/28/2012

CHRISTINE P NGUYEN
06/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA # 202611
Product Name: Myrbetriq (mirabegron)

PMR/PMC Description: A long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients administered Myrbetriq (mirabegron).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	March 2013
	Study/Trial Completion:	July 2018
	Final Report Submission:	June 2019
	Other: Assessment and Summary Report Submission:	March 2015
	Interim Study Completion:	June 2017
	Interim Analysis Report:	June 2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Mirabegron was shown to modestly increase blood pressure. The clinical trial databases for mirabegron were too small to determine the effect of the small blood pressure increase on incidence rates of major cardiovascular outcomes. This epidemiology study will be able to evaluate the rates of major cardiovascular adverse events in users of mirabegron and comparator medications using multiple electronic healthcare databases. Studies in these databases will be able to estimate and compare the risk of cardiovascular outcomes and also control for confounders using multivariate analyses.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is a preapproval PMR that was designed to evaluate a finding of increased mean blood pressure in phase 1 and 3 clinical trials of mirabegron with regard to an increase in cardiovascular events.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The findings will be evaluated using an observational epidemiologic study.

Required

- ☒ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

MEREDITH ALPERT
06/28/2012

CHRISTINE P NGUYEN
06/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA #	202611
Product Name:	Myrbetriq (mirabegron)
PMR/PMC Description:	Open label, baseline-controlled, multicenter, sequential dose titration study followed by a fixed dose observation period to evaluate pharmacokinetics, safety and efficacy of mirabegron modified release microgranule-based suspension in children from 5 to less than 18 years of age with NDO.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	January 2018
	Study/Trial Completion:	June 2023
	Final Report Submission:	June 2024
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Drug is ready to be approved for use in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To evaluate safety and efficacy in the pediatric population with neurogenic detrusor overactivity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pediatric population from 5 to less than 18 years of age.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☒ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
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PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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06/28/2012

CHRISTINE P NGUYEN
06/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA #	202611
Product Name:	Myrbetriq (mirabegron)
PMR/PMC Description:	Open label, multicenter single ascending dose study to evaluate pharmacokinetics, safety and tolerability of mirabegron modified release microgranule-based suspension in children from 5 to less than 18 years of age with neurogenic detrusor overactivity (NDO) or overactive bladder (OAB).
PMR/PMC Schedule Milestones:	Final Protocol Submission: <u>January 2016</u>
	Study/Trial Completion: <u>September 2017</u>
	Final Report Submission: <u>September 2018</u>
	Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Drug is ready to be approved for use in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To evaluate safety and efficacy in the pediatric population with neurogenic detrusor overactivity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pediatric population from 5 to less than 18 years of age.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☒ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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MEREDITH ALPERT
06/28/2012

CHRISTINE P NGUYEN
06/28/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	Myrbetriq (mirabegron) extended release tablets, for oral use
Applicant	Astellas Pharma Global Development Inc.
Application/Supplement Number	NDA 202611
Type of Application	Original NDA
Indication	Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.
Established Pharmacologic Class ¹	Beta-3 adrenergic agonist
Office/Division	Office of Drug Evaluation III/Division of Reproductive and Urologic Products
Division Project Manager	Nenita Crisostomo
Receipt Date	August 29 th , 2011
PDUFA Goal Date	June 29 th , 2012
SEALD Review Date	June 27 th , 2012
SEALD Labeling Reviewer	Abimbola Adebawale
SEALD Labeling Team Leader	Eric Brodsky
SEALD Division Director	Laurie Burke

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information (SRPI)

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information (SRPI) Revised

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **“These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”**

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word **“WARNING”** (even if more than one Warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the Warning (e.g., **“WARNING: SERIOUS INFECTIONS”**).

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information (SRPI) Revised

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Selected Requirements of Prescribing Information (SRPI) Revised

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

Selected Requirements of Prescribing Information (SRPI) Revised

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment: For Section 6.2 (Postmarketing Experience), the cross-reference should be to Section 5.2 for the urinary retention warning as shown below:

Urologic: urinary retention [see **Warnings and Precautions (5.2)** (b) (4)]

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information (SRPI) Revised

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: We defer to DRUP on the final wording of this statement so this is not a SRPI deficiency. However, below are recommendations. For Section 6.2 (**Postmarketing Experience**) the applicant’s proposed modification of the verbatim statement is the following:

(b) (4)

(b) (4)

We recommend the following modification or another appropriate modification that will keep as much of the standard language as possible:

6.2 Postmarketing Experience

(b) (4)

Selected Requirements of Prescribing Information (SRPI) Revised

Patient Counseling Information

NO

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: Remove quotation marks from this statement at the beginning of Section 17.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABIMBOLA O ADEBOWALE
06/27/2012

ERIC R BRODSKY
06/27/2012
I agree.

ANN M TRENTACOSTI
06/27/2012
Signing for Laurie Burke

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology Memo: Comments on Mirabegron PMR studies

Date: 6-26-2012

Reviewer(s): CDR David Moeny, R.Ph., MPH
Division of Epidemiology II

Associate Director of Science Rita Ouellet-Hellstrom, Ph.D. M.P.H.
Division of Epidemiology II

Director Judy Staffa, Ph.D., R.Ph.
Division of Epidemiology II

Drug Name(s): Myrbetriq (Mirabegron)

Subject Post Marketing studies for assessment of cardiovascular and
neoplasm safety signals

Application Type/Number: NDA 202611

Applicant/sponsor: Astellas Pharma

OSE RCM #: 2012-1115

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EXECUTIVE SUMMARY

NDA 202611, mirabegron, is a new marketing application indicated for overactive bladder. Mirabegron is a new molecular entity, first in its class (beta-3 adrenoceptor agonist) with a PDUFA goal date of June 29, 2012. During review of the application, two safety signals were noted:

1. Increases in systolic blood pressure (BP) of 1 mmHg in the 1-year phase 3 trial, and 3 mmHg in the phase 1 trials. No increases in cardiovascular events were seen in the clinical program.
2. A disproportionately high rate of malignancy in the mirabegron 100mg study arm for the 1-year phase 3 trial.

On April 5, 2012, the application was presented to an advisory committee and advice sought regarding the approval of mirabegron in light of the potential safety risks. The committee voted for approval while expressing some concern about the long term effect of mirabegron on blood pressure and cancer outcomes and recommended monitoring and further evaluation of the risk through an epidemiologic study.

The sponsor has provided FDA the protocol outlines for post marketing studies to examine these safety signals. On May 7th 2012, the Division of Reproductive and Urologic Products (DRUP) requested that OSE review the cardiovascular safety study protocol outline, and provide comments regarding the feasibility and proposed designs. Since the preponderance of the available BP information references mirabegron 50 mg and the malignancy risk appeared only in the 100mg dose arms, based upon an agreement with Sponsor, the recommended starting dose will be mirabegron 25 mg with titration to 50 mg if greater efficacy is required.

The Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) has reviewed the Sponsor's PMR proposed study outlines, and has serious concerns with the sponsor's proposed study design for studying the outcomes of malignancy and, to a lesser extent, cardiovascular outcomes in electronic healthcare databases. OSE/DEPI's primary concerns are as follows:

- Case ascertainment of stroke and especially cancer will be very difficult in many or most of the currently available electronic healthcare databases.
- Potentially important covariates influencing cancer and/or cardiovascular risk such as smoking status, alcohol use, and body mass Index (BMI) are inadequately captured in electronic healthcare databases.
- While the dose recommendations are for 25mg with an increase to 50mg if needed, physicians may choose to increase the dose to 100mg per day. This may be particularly important given that this product does not have the limiting side effects (such as dry mouth) seen with the currently available drugs. Since this product will likely be used in patients who have failed previous therapy, in the absence of a warning against prescribing at a 100mg dose, it is not unreasonable to suspect that some physicians will choose to escalate patients to a 100mg dose.

OSE/DEPI has conducted an initial review of the sponsor's proposed study outlines, and believes that the sponsor will face substantial challenges in their development of a post-marketing safety study to assess cancer outcomes with a reasonably high sensitivity and specificity. Therefore, OSE/DEPI supports conducting a post marketing safety study strategy utilizing electronic databases linked to both cancer and death registries. Should the

sponsor be unable to propose and conduct a study which will adequately assess the identified safety risks as determined by OSE/DEPI, OSE/DEPI recommends that a survey-based cohort study (e.g. primary data collection) be conducted using a design which obtains personal and family history, baseline clinical information, and a thorough adverse event assessment during follow-up. OSE/DEPI provides a bulleted list with comments and recommendations to the sponsor regarding their protocol outlines.

1 INTRODUCTION

NDA 202611, mirabegron, is a new marketing application indicated for overactive bladder. Mirabegron is a new molecular entity, first in its class (beta-3 adrenoceptor agonist) with a PDUFA goal date of June 29, 2012. During review of the application, two safety signals were noted in the mirabegron treated study arms: 1) increases in blood pressure (BP) and heart rate (HR), and 2) an increase in the occurrence of malignancies.

1 Increases in systolic BP of 1 mmHg in the phase 3 trial, and 3 mmHg in the phase 1 trial.

No increases in cardiovascular events were seen in the clinical program. In Phase 3 studies (where BP was not measured at the time of peak plasma drug levels (Tmax)), mirabegron increased the group mean BP by 0.5-1.0 mmHg and the HR by 1 beat per minute (BPM). Mirabegron-related increases from baseline in BP and HR were larger in Phase 1 studies where these measurements were taken at Tmax (e.g., approximately 3 mmHg at the 50 mg dose) compared to Phase 3 studies. Additionally, the increase in BP and HR appeared to be dose related for doses of 25 mg, 50 mg, 100 mg and 200 mg. The reason for differences between BP and HR changes in Phase 3 and Phase 1 studies remains unclear.

2 A disproportionately high rate of malignancy.

In the combined population of six 12 week trials, and in the 1 year phase 3 study, the following malignancies were reported: breast cancer (2 cases), prostate cancer (2 cases), endometrial cancer (2 cases), malignant lung neoplasm (2 cases) and 1 case each of pancreatic cancer, transitional cell carcinoma, thyroid neoplasm, and fibroma of the hypopharynx. The combined estimated relative risk of malignancy for mirabegron compared to tolterodine was 1.5 (95% CI 0.45-6.38). Not all of the clinical trials showed an increase in cancer risk. Of the six 12-week studies, there was an imbalance of adjudicated new malignancies in one: Study 178-CL-047: 4 cases in 442 subjects (0.90%) mirabegron 50 mg; 2 cases in 433 subjects (0.46%) mirabegron 100 mg, 0/453 (0%) placebo). An increase in cancer risk and a possible dose response was seen in the 1 year study: Study 178-CL-049: 3/812 (0.37%) mirabegron 50 mg; 9/820 (1.10%) mirabegron 100 mg; 4/812 (0.49%) tolterodine 4 mg).

A consultation from the Cardiovascular and Renal (CR) Division was obtained on January 20, 2012. The CR consultant confirmed that the increase in BP with 50 mg mirabegron in the Phase 3 clinical trials was small. The consultant did not agree, however, with the Sponsor's assertion that small increases in BP have not been associated with cardiovascular risk. The consultant stated that increasing risks for cardiovascular events with increasing levels of BP are on a continuum, i.e., these risk curves do not demonstrate risk thresholds as a function blood pressure, but increase continuously. The consultant expressed concern with regard to patients with higher baseline blood pressures arguing that the absolute risk associated with increasing systolic BP from 169 to 170 mmHg is worse than increasing from 119 to 120 mmHg. The consultant also cautioned that superimposed on this phenomenon are the adverse effects of other risk modifiers such as smoking status and diabetes.

On April 5, 2012, the application was presented to an advisory committee and advice sought regarding the approval of mirabegron in light of the potential safety risks. At this meeting, the sponsor presented an outline for a post-marketing safety study for cardiovascular risks associated with mirabegron. The committee voted for approval while expressing some concern about the long term effect of mirabegron on BP, and recommended monitoring and further evaluation of the risk through a registry or an epidemiologic study.

Given that the preponderance of the available BP potential risk relates to use of the mirabegron 50 mg dose, and the potential malignancy risk appeared with the 100mg dose, an agreement was made with the Sponsor on May 3, 2012 that the recommended starting dose will be mirabegron 25 mg with titration to the 50 mg if greater efficacy is required. On May 3, 2012 in a meeting with the review division, the Sponsor agreed to provide a proposal for a safety study of malignancies. A protocol outline was received on May 15, 2012.

On May 7th 2012, the Division of Reproductive and Urologic Products (DRUP) requested that OSE/DEPI review the cardiovascular safety study protocol outline, and provide comments regarding the feasibility and potential design of a study to evaluate malignancy. After discussions between DRUP and OSE/DEPI, DRUP requested that OSE/DEPI provide a bulleted list of suggestions and recommendations for a post-marketing safety study program to provide to the sponsor.

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS REVIEWED

Two proposal outlines were reviewed

-
-

(b) (4)

2.2 CRITERIA APPLIED TO REVIEW

The materials were reviewed with the objective of 1) providing feedback to DRUP concerning the feasibility of conducting a post marketing study for the identified risks using the sponsor's suggested approach, 2) to provide a brief assessment and feedback to the sponsor, and 3) to provide guidance to DRUP for the general formulation of appropriate post marketing requirements for the assessment of these specific risks.

3 REVIEW RESULTS

The focus of the proposed mirabegron post-marketing safety studies is to confirm and further evaluate the safety signals seen in the clinical trials (cancer, and the risk of cardiovascular events resulting from increases in BP and HR), in the context of real-world use.

Mirabegron is expected to attain a large share of the OAB market, and there is a potential that a large number of patients would be exposed to mirabegron in the years following approval.

Studies in currently existing electronic databases, as proposed by the sponsor, have the advantage of facilitating the relatively rapid completion of post marketing studies, allowing

for the assessment of safety signals while minimizing the number of patients who are exposed to a drug product in the meantime. However, post-marketing epidemiologic safety studies are subject to a number of pitfalls, which may impact both the successful completion and ultimate ability of these studies to appropriately assess the signals of concern. These include but are not limited to the availability of appropriate data resources with required linkages, and unexpectedly low market share (due to labeling restrictions, publicized and/or unexpected safety concerns, cost, insurance restrictions and physician perceptions of potential benefit and risk). OSE/DEPI believes that the sponsor will face substantial challenges in their development of a post-marketing safety study for an increase in cancer risk. These include the ability to identify and confirm cancer outcomes with a reasonably high sensitivity and specificity, assessing potentially confounding covariates, and identifying a data resource with appropriate linkages to cancer and death registries. While a study for cardiovascular risk arguably presents fewer obstacles in case ascertainment, depending on the data resource chosen, several of the outcomes of interest may require substantial effort to obtain adequate sensitivity and specificity.

Despite these challenges, OSE/DEPI acknowledges that a post marketing safety study using currently existing electronic healthcare data (as proposed by the sponsor) may provide some useful information about the potential risks. However, these studies do require a substantial period of time to design, to obtain an adequate number of subjects (due to the new approval status of mirabegron) and to conduct the analyses. While these studies may still require years to complete, if successful, this approach will likely provide a more timely assessment of whether increased rates of cancer and cardiovascular events occur in mirabegron users. However, should the sponsor's proposed studies be determined by OSE/DEPI to be unsuccessful, OSE/DEPI recommends that a cohort study using primary data collection be conducted using a design which obtains personal and family history, baseline clinical information, and a thorough adverse event assessment during follow-up. This study design will have the advantage that it may better assess covariates of interest (body mass index, blood pressure at baseline, etc.), may be able to follow patients over a longer period of time, and be highly sensitive for the occurrence of the outcomes of interest. A bulleted list which provides comments and recommendations to the sponsor on their protocol outlines is provided below.

3.1 ELECTRONIC DATABASE STUDY

Use of an electronic database(s) to conduct a safety study allows an assessment of the cardiovascular safety signal and death. In developing such a study, the sponsor needs to address the following limitations in the current proposal.

The database resource should

-  (b) (4)

 (b) (4)

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

Outcomes and validation

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

Exposure

- [REDACTED] (b) (4)

[REDACTED] (b) (4)

- [REDACTED] (b) (4)
- [REDACTED]

Covariate Selection

- [REDACTED] (b) (4)

Power Calculations

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.2 PROSPECTIVE SURVEY BASED COHORT STUDY

A prospective multi-year survey-based (e.g. primary data collection) cohort study allows for a more in-depth assessment of baseline cardiovascular and cancer risk factors as well as a more complete capture of adverse events and death over the course of the study albeit in a smaller, selected sample of users. In developing such a study, the sponsor would need to address the following limitations in the current proposal:

-
-
-
-
-
-
-
-
-

4 RECOMMENDATIONS

OSE/DEPI believes that the sponsor will face substantial challenges in their development of a post-marketing safety study evaluating cardiovascular and cancer outcomes using the proposed electronic healthcare databases. While a study for cardiovascular risk arguably presents fewer obstacles in case ascertainment, depending on the data resource chosen, several of the outcomes of interest require substantial effort to obtain adequate sensitivity and specificity. Nonetheless, OSE/DEPI supports the sponsor's general approach of using currently existing electronic healthcare data to conduct a post marketing safety. This approach, if successful, will provide an assessment of whether increased rates of cancer and cardiovascular events occur at higher levels than expected in mirabegron users. However, should the sponsor's proposed studies be unsuccessful or not possible, as determined by OSE/DEPI, then OSE/DEPI recommends that a multi-year survey-based cohort study be conducted using a design which obtains personal and family history, baseline clinical information, and a thorough adverse event assessment during follow-up (e.g. primary data collection).

5 REFERENCES

1. Prevalence of stroke - United States, 2006-2010. MMWR Morb Mortal Wkly Rep 2012;61:379-82.

2. Centers for Disease Control- National Center for Health Statistics Highlights section and Detailed Tables for the National Vital Statistics Report (NVSr) "*Deaths: Final Data for 2009.*" . 2012.
3. Friedlin J, Overhage M, Al-Haddad MA, et al. Comparing methods for identifying pancreatic cancer patients using electronic data sources. AMIA Annu Symp Proc 2010;2010:237-41.
4. Leone MA, Capponi A, Varrasi C, et al. Accuracy of the ICD-9 codes for identifying TIA and stroke in an Italian automated database. Neurol Sci 2004;25:281-8.
5. Walker AM. Identification of esophageal cancer in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2011;20:1159-67.
6. Williams GR. Incidence and characteristics of total stroke in the United States. BMC Neurol 2001;1:2.

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/s/

DAVID G MOENY
06/26/2012

RITA P OUELLET-HELLSTROM
06/26/2012

JUDY A STAFFA
06/26/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 202611	NDA Supplement #:S-
Efficacy Supplement Type SE-	
Proprietary Name: Myrbetriq Established/Proper Name: mirabegron Dosage Form: extended release tablets Strengths: 25 mg	
Applicant: Astellas Pharma Global Development, Inc. Agent for Applicant (if applicable):	
Date of Application: August 25, 2011 Date of Receipt: August 29, 2011 Date clock started after UN:	
PDUFA Goal Date: June 29, 2012	Action Goal Date (if different):
Filing Date: October 28, 2011	Date of Filing Meeting: October 21, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1	
Proposed indication(s)/Proposed change(s): Treatment of overactive bladder, with symptoms of urge urinary incontinence, urgency, and urinary frequency.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 69416				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		✓		
If yes, explain in comment column.			✓	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			✓	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			✓		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm			✓		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm			✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			✓	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <u>3 years</u> <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			✓	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?		✓		Included in the Quality section of the NDA
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			✓	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>		✓		
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	✓			PeRC Meeting: May 30, 2012

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		✓		
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?	✓			
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?	✓			
<i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		✓		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	✓			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		✓		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			✓	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	☐ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	✓			DSI: 11/3/11 IRT-QT: 9/16/11 Ophth: 9/15/11 Cardio-Renal:11/9/11

				Oncology:12/28/11 PMR protocol synopsies for neoplasms & CV: 5/4/12
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 11/14/07	✓			
<i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): CMC: 3/1/10 Clinical, Statistics, & Format: 11/2/10 <i>If yes, distribute minutes before filing meeting</i>	✓			
Any Special Protocol Assessments (SPAs)? Date(s): Clinical: 2/5/08, IND 69416 Carcinogenicity: 8/20/04, IND 69416 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	✓			

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 21, 2012

NDA: 202611

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: mirabegron extended release tablets

DOSAGE FORM/STRENGTH: 25 mg and 50 mg

APPLICANT: Astellas Pharma Global Development, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of overactive bladder, with symptoms of urge urinary incontinence, urgency, and urinary frequency.

BACKGROUND: Mirabegron is a human beta 3 adrenoceptor agonist indicated for the treatment of overactive bladder, with symptoms of urge urinary incontinence, urgency, and urinary frequency. It is a new molecular entity, and thus far, there are no drugs in its class that has been approved. This NDA is planned for discussion at an Advisory Committee Meeting on April 5, 2012, with special attention to cardiac safety. The related IND is 069416. The clinical development program consists of 41 studies comprising of 10,552 subjects.

An NDA application for mirabegron is simultaneously submitted to the European Medicines Agency for the Centralised Procedure, sharing common safety and efficacy data package as with US FDA, per Sponsor.

Proprietary name is planned for submission to DMEPA in October 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nenita Crisosotmo, R.N.	Y
	CPMS:	Jennifer Mercier	Y
Cross-Discipline Team Leader (CDTL)	Mark S. Hirsch, M.D.		Y
Clinical	Reviewer:	Roger Wiederhorn, M.D.	Y
	TL:	Mark S. Hirsch, M.D.	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sayed Al-Habet, R.Ph., Ph.D.	Y
	TL:	Myong-Jin Kim, Pharm.D.	Y
Biostatistics	Reviewer:	Jia Guo, Ph.D.	Y
	TL:	Maboob Sobhan, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eric Andreasen, Ph.D.	Y
	TL:	Lynnda Reid, Ph.D.	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka, Ph.D.	Y
	CMC Lead:	Donna Christner, Ph.D.	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Vipul Dholakia, Ph.D.	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Teresa McMillan	Y
	TL:	Zachary Oleszczuk	N
DMPP	Reviewer:	Sharon Williams	Y
	TL:	LaShawn Griffiths	N
OC/OSI	Reviewer:	Roy Blay, Ph.D.	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues? If yes, list issues:		☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:		☒ YES ☐ NO
Electronic Submission comments List comments: Datasets are too large. It takes a long time to open the files.		☐ Not Applicable
CLINICAL Comments:		☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:		☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i>		☒ YES Date if known: ☐ NO ☐ To be determined Reason:

○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Office of Drug Evaluation III 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments: Milestones Listing is posted in the eRoom for everyone's access.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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/s/

NENITA I CRISOSTOMO
06/20/2012

JENNIFER L MERCIER
06/21/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 21, 2012

TO: Memo to File

THROUGH:

FROM: Nenita Crisostomo, R.N. – Regulatory Health Project Manager
Division of Reproductive and Urologic Products

SUBJECT: Cardiovascular and Neoplasms PMR Activities – Goals and Milestones

APPLICATION/DRUG: NDA 202611 Myrbetriq (mirabegron), 25 mg and 50 mg extended
release tablets

Background: On June 21, 2012, a teleconference was held between the Division of Reproductive and Urologic Products (DRUP) and Astellas Pharma Global Development, Inc. to discuss the June 15, 2012, comments and recommendations to the protocols for the cardiovascular and neoplasms post-marketing requirement (PMR) activities. During the teleconference, the Sponsor expressed their understanding and agreement to the recommendations. With this agreement, the Division stated that suggested statements of specific goals and milestones of the PMRs will be emailed to them as soon as possible. This is to document the email communication to Astellas Pharma Global Development, Inc.

From: Crisostomo, Nenita
Sent: Thursday, June 21, 2012 2:02 PM
To: 'Kannenberg, Judy'
Subject: NDA 202611 Myrbetriq (mirabegron) - PMRs

<< File: PMRs.6.21.12.doc >>

Dear Judy,

Attached are the PMR goals and milestones as we discussed in today's teleconference. For our immediate review, please email to me your agreement in writing as soon as possible, or within the next 48 hours, while enroute for official submission to the Electronic Document Room. Because emailed documents are generally not accepted as official, please include in your cover letter a statement confirming that your emailed response is similar to what is being officially submitted. This is for purposes of allowing us to immediately utilize your emailed response in the official documents for the Action.

If you have any questions, please feel free to contact me.

Thank you so much,
Nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

FOOD AND DRUG ADMINISTRATION

**CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS**

June 21, 2012

**NDA 202611 Myrbetriq (mirabegron) 25 mg and 50 mg extended release tablets
Postmarketing Requirements**

Reference is made to our teleconference June 21, 2012, to discuss our recommendations regarding the two post-marketing requirements and our request for your acknowledgement of the two study descriptions and agreement to the proposed milestones outlined below.

PMR #1:

Description:

A long-term observational study using electronic healthcare databases with appropriate linkages conducted in United States and European databases to evaluate the incidence of serious cardiovascular outcomes (both individual and composite outcomes) in patients administered Myrbetriq (mirabegron).

Proposed Milestones:

Final Protocol Submission:	March 2013
Study Completion:	March 2017
Final Report Submission:	March 2018

PMR #2:

Description:

A long-term observational study in electronic healthcare databases with appropriate linkages to prospectively evaluate the incidence of new malignant events (excluding non-melanoma skin cancer) in patients using Myrbetriq (mirabegron).

Proposed Milestones:

Final Protocol Submission:	March 2013
Study Completion:	March 2017
Final Report Submission:	March 2018

- **We remind you that if either of these post-marketing epidemiologic safety studies are not successful, an interview (or survey) -based, prospective cohort study of the safety signal would follow.**
- **We also request that you officially acknowledge the PMR descriptions and submit your agreement to the proposed milestones in writing.**

Please contact Nenita Cristostomo, R.N., at 301-796-0875 with any outstanding questions.

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/s/

NENITA I CRISOSTOMO
06/21/2012

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS**

June 15, 2012

NDA 202611 Myrbetriq (mirabegron) 25 mg extended release tablets

Postmarketing Requirement Recommendations

Reference is made to protocol outlines submitted on May 4, 2012, and May 15, 2012, for postmarketing safety studies to evaluate cardiovascular events and new malignant events, respectively, in users of mirabegron.

We have completed our preliminary review of the protocol outlines and in collaboration with the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE), have the following comments and recommendations:

I. Recommendations and comments regarding your proposed protocol synopses:

1. Regarding electronic databases

Use of an electronic database(s) to conduct a safety study allows a more rapid assessment of the cardiovascular safety signal and death. In developing such a study, you need to address the following limitations in the current proposal.

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(b) (4)

2. Regarding outcomes and validation

(b) (4)

(b) (4)



3. Regarding exposure

-
-
-

(b) (4)



4. Regarding covariate selection

(b) (4)



5. Regarding power calculations

(b) (4)



II. **Additional recommendations regarding determination that the studies are inadequate to assess their proposed outcomes:**

We remind you that post-marketing epidemiologic safety studies are subject to a number of pitfalls which may impact completion and utility of these studies to assess the signals of concern. These include the availability of appropriate data resources, unexpectedly low market share, or the inability to adequately assess important covariates due to data source restrictions. If the studies proposed in electronic healthcare data are not successful, an interview (or survey)-based, prospective cohort study would follow. Herein, we outline a survey-based cohort study that would provide personal and family history, baseline clinical information, and a more thorough adverse event assessment during follow-up.

Prospective survey based cohort study

A prospective survey-based cohort study allows for a more in-depth assessment of baseline cardiovascular and cancer risk factors as well as a more complete capture of adverse events and death over the course of the study albeit in a smaller, selected sample of users. In developing such a study, you should consider the following:

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References

1. Prevalence of stroke - United States, 2006-2010. MMWR Morb Mortal Wkly Rep 2012;61:379-82.
2. Centers for Disease Control- National Center for Health Statistics Highlights section and Detailed Tables for the National Vital Statistics Report (NVSr) "*Deaths: Final Data for 2009.*" . 2012.
3. Friedlin J, Overhage M, Al-Haddad MA, et al. Comparing methods for identifying pancreatic cancer patients using electronic data sources. AMIA Annu Symp Proc 2010;2010:237-41.
4. Leone MA, Capponi A, Varrasi C, et al. Accuracy of the ICD-9 codes for identifying TIA and stroke in an Italian automated database. Neurol Sci 2004;25:281-8.
5. Walker AM. Identification of esophageal cancer in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2011;20:1159-67.
6. Williams GR. Incidence and characteristics of total stroke in the United States. BMC Neurol 2001;1:2.

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/s/

NENITA I CRISOSTOMO
06/15/2012

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: June 13, 2012

To: Nenita Crisostomo
Regulatory Health Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Jina Kwak, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
OPDP

Subject: NDA 202611
OPDP labeling comments for MYRBETRIQ (mirabegron)

OPDP has reviewed the draft product labeling (PI) for MYRBETRIQ (mirabegron) tablets as requested in the consult from DRUP dated September 7, 2011.

OPDP's comments on the full prescribing information, which are based on the substantially complete version of the draft PI emailed by Nenita Crisostomo on June 6, 2012, are provided below. Please note that the Division of Medical Policy Programs (DMPP) provided comments on the MYRBETRIQ Patient Package Insert (PPI) on June 8, 2012 and DCDP has no additional comments on this version of the PPI.

If you have any questions, please contact:

Jessica Cleck Derenick: 301-796-0390; Jessica.Cleck-Derenick@fda.hhs.gov

Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

JESSICA N CLECK DERENICK
06/13/2012

JINA KWAK
06/13/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **June 8, 2012**

To: Scott Monroe, MD,
Director
Division of Reproductive and Urologic Products (DRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, RN, BSN, MSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): MYRBETRIQ (mirabegron)

Dosage Form and Route: Extended Release Tablets

Application Type/Number: NDA 202611

Applicant: Astellas Pharma Global Development, Inc.

1 INTRODUCTION

On August 26, 2011 Astellas Pharma Global Development, Inc. submitted an original New Drug Application (NDA) indicated for the treatment of overactive bladder (OAB), with symptoms of urge urinary incontinence, urgency, and urinary frequency.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for MYRBETRIQ (mirabegron) Extended Release Tablets.

2 MATERIAL REVIEWED

- Draft MYRBETRIQ (mirabegron) PPI received on August 26, 2011 and received by DMPP on June 6, 2012
- Draft (mirabegron) Prescribing Information (PI) received August 26, 2011 revised throughout the review cycle and received by DMPP on June 6, 2012
- Approved VesiCare comparator labeling dated January 17, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the PPI is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
06/08/2012

MELISSA I HULETT
06/08/2012

LASHAWN M GRIFFITHS
06/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: May 31, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Drug Name: Myrbetriq (Mirabegron) Extended-release Tablets
25 mg and 50

Application Type/Number: NDA 202611

Applicant: Astellas Pharma, Inc.

OSE RCM #: 2012-398-2

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Myrbetriq (Mirabegron) Extended-release Tablets, 25 mg and 50 mg, submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant in OSE Review #2012-398-1, dated May 15, 2012.

2 MATERIALS REVIEWED

The revised container labels and carton labeling submitted to the FDA on May 18, 2012 (See Appendix A) and OSE Review #2012-398-1, dated May 15, 2012, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling address all of DMEPA's concerns. Thus, we find the revised container labels and carton labeling acceptable and have no additional comments to the Applicant at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Shawnetta Jackson at 301-796-4952.

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/s/

MANIZHEH SIAHPOUSHAN
05/31/2012

ZACHARY A OLESZCZUK
05/31/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: May 15, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Drug Name(s): Myrbetriq (Mirabegron) Extended-release Tablets
25 mg and 50 mg

Application Type/Number: NDA 202611

Applicant: Astellas Pharma, Inc.

OSE RCM #: 2012-398-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Myrbetriq (Mirabegron) 25 mg and 50 mg Tablets submitted on May 11, 2012. DMEPA previously reviewed the proposed labels and labeling under OSE Review #2012-398 dated March 19, 2012.

2 MATERIALS REVIEWED

DMEPA reviewed the revised container labels and carton labeling submitted on May 11, 2012 (see Appendix A). We compared the revised labels and labeling against the recommendations contained in OSE review #2012-398 dated March 19, 2012 to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling address some of DMEPA's previous concerns, however, there are still areas of the revised container labels and carton labeling that can introduce vulnerability to medication errors. The 'Once-Daily' and 'Swallow tablet whole. Do not cut, crush, or chew tablet.' statements do not appear on the carton labeling of the 7-count (25 mg and 50 mg) and 30-count (25 mg) sample carton labeling. Additionally, the 'Swallow tablet whole. Do not cut, crush, or chew tablet.' statement on the container labels (25 mg and 50 mg) lacks prominence.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Shawnetta Jackson at 301-796-4952.

4 COMMENTS TO THE APPLICANT

A. Trade Container Labels, 25 mg and 50 mg (30-count and 90-count) and Sample Container Label, 25 mg (30-count)

Increase the prominence of the 'Swallow tablet whole. Do not cut, crush, or chew tablet.' statement on the side panel of the 25 mg and 50 mg container labels (30-count and 90-count) by bolding the statement. As currently presented, the statement lacks prominence and can be overlooked.

B. Trade Carton Labeling, 25 mg and 50 mg (30-count, 90-count, and 100-count) and Sample Carton Labeling, 25 mg (30-count)

1. Relocate the 'Each tablet contains 25 mg (or 50 mg) of mirabegron' statement which appears on the principal display panel of the carton labeling of the 25 mg and 50 mg Myrbetriq Tablets (30-count, 90-count, and 100-count) to the side panel to reduce clutter on the label. This information is repetitive because the product strength appears under the dosage form. Additionally, other important information such as 'Once-Daily' can be placed in this area (see comment #2 below).
2. Repeat the statement 'Once-Daily' on the principal display panel after relocating 'Each tablet contains 25 mg (or 50 mg) of mirabegron' to the side

panel. Additionally, the Dosage statement which is currently presented in bold letters on the side panel of the carton labeling of the 25 mg and 50 mg trade carton labeling can be unbolded to provide space for the 'Each tablet contains 25 mg (or 50 mg) of mirabegron' statement.

3. Increase the prominence of the 'Swallow tablet whole. Do not cut, crush, or chew tablet.' on the principal display panel of the 25 mg and 50 mg, 100-count carton labeling (containing blister cards) by using a larger font size or some other means. As currently presented, this information lacks prominence.

C. Sample Carton Labeling (including the Tray), 25 mg and 50 mg (7-count)

1. See comment B1 above.
2. Include the 'Once-Daily' and 'Swallow tablet whole. Do not cut, crush, or chew tablet.' statements to the principal display panel. As currently presented, these statements do not appear on the principal display panel.

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/s/

MANIZHEH SIAHPOUSHAN
05/15/2012

ZACHARY A OLESZCZUK
05/15/2012

Medical Officer's Consultative Review of NDA 202-611
Ophthalmology

Submission date: August 30, 2011
Review date: May 4, 2012
Sponsor: Astellas Pharma
Product: Mirabegron
Pharmacologic Class: Selective beta 3-adrenoreceptor agonist
Proposed Indication: Treatment of overactive bladder

Requested: This new NDA 20211 was received on August 29, 2011, and it is fully electronic in EDR at: \\CDSESUB5\EVSPROD\NDA202611\0000. The related IND is 69,416. The PDUFA Goal Date is June 29, 2011.

Mirabegron is a beta-3 adrenergic agonist which has been developed for the treatment of overactive bladder. It is a new molecular entity, and to our knowledge, no currently approved product has this mechanism of action. Several adverse events of glaucoma were reported during the Phase 3 development program for mirabegron, and this prompted extensive discussions between sponsor and FDA, including consultation with Dr. Chambers in the Division of Transplant and Ophthalmologic Products. In order to address the Agency's concerns regarding glaucoma, Astellas conducted a systematic evaluation of glaucoma-type AE in all completed clinical studies within the global mirabegron clinical development program which included 8752 patients (5863 mirabegron-treated patients) and 1000 mirabegron-treated healthy volunteers. For subjects with a treatment-emergent adverse event (TEAE) in the glaucoma standardized MedDRA query (SMQ) (narrow search), a Targeted Glaucoma Questionnaire was sent to the investigators to elicit consistent information on the reported event as well as any additional ocular history available for these subjects. An external expert panel established case definitions and reviewed subject data packages on all available data, including treatment assignment, to classify the reported events.

Twelve cases were retrieved using the glaucoma SMQ (narrow search) in the mirabegron clinical development program. The external expert panel assessed the cases as follows: 5 cases were classified within the category of glaucoma: 4 of these cases had sufficient documentation to confirm an event of glaucoma:

- 1 patient with acute narrow angle glaucoma
- 1 patient with open angle glaucoma
- 1 patient with glaucoma suspect
- 1 patient with chronic narrow angle glaucoma
- 1 patient had insufficient information to confirm or refute glaucoma and is included conservatively as glaucoma
- 1 case was classified as non-glaucoma, ocular hypertension (ocular hypertension, by definition, is not glaucoma):
- 1 patient with ocular hypertension

6 patients were classified as not having a treatment emergent adverse event since additional data ascertainment revealed a medical history of a preexisting condition with no evidence of worsening of the underlying condition while on study treatment. Eleven of the 12 retrieved cases were in patients who received mirabegron. The case of chronic narrow angle glaucoma occurred in a patient who received tolterodine. Following meetings with the Division and after consultation with DTOP, the sponsor agreed to conduct a randomized, double-blind, placebo-controlled, non-inferiority study to assess the effect of mirabegron on IOP. The study used a supratherapeutic dose of mirabegron (100 mg) administered orally once daily for 8 weeks in healthy research subjects on intra-ocular pressure (IOP). The study results, in the sponsor's opinion, were that 100 mg of mirabegron administered once daily was non-inferior to placebo for the primary endpoint of change from baseline to day 56 in subject average IOP, based on the non-inferiority limit of 1.5 mm Hg. The sponsor concluded that these results and additional eye assessments in other phase 1 studies, as well as the program-wide evaluation of reported ocular events do not suggest an association of mirabegron and glaucoma or other ocular safety issues.

Questions for DTOP

1. Was the non-inferiority study conducted in accordance with DTOP recommendations?
2. Does DTOP agree with the interpretation of the study result by the Sponsor?
3. Does DTOP agree that mirabegron is not associated with increased IOP as evaluated in the study?
4. Does DTOP agree with the sponsor's conclusion that the available data does not suggest an association of mirabegron and glaucoma?
5. Does DTOP have any further recommendations in regard to mirabegron and glaucoma?
6. Are any other ocular safety issues noted by DTOP?

Clinical Study for Ocular Safety

A Phase 1b, Randomized, Double-Masked, Parallel Group, Placebo Controlled Study to Assess Intraocular Pressure and Ocular Safety of the Beta-3 Agonist Mirabegron in Research Subjects

Study Design: This was a double-masked, randomized, parallel group, placebo-controlled, phase 1b study. Approximately 320 subjects were planned for randomization to target 240 subjects to complete the study. Subjects were consented and screened to confirm inclusion/exclusion criteria including normal (≥ 10 mm Hg and ≤ 21 mm Hg) single-eye IOP in each eye.

The study consisted of 4 visits:

- Visit 1: screening (day -28 to day -4)
- Visit 2: baseline (day 1)
- Visit 3: day 10 (+ 2 days)
- Visit 4: day 56/end of treatment (EOT) (+ 3 days)

Each subject was randomized on a 1:1 basis to mirabegron or matching placebo and participated in a 56-day treatment period during which once daily dosing of mirabegron 100 mg or placebo occurred. This dose is 2-4 times the dose recommended for the treatment of hyperactive bladder.

Subjects were admitted to the study center the night prior to visits at baseline, day 10 and day 56. Subjects reported to the clinical research unit prior to 7 PM on the day before study visit 2 baseline day 1, visit 3 day 10 and visit 4 day 56/EOT. Subjects remained confined to the clinic until all study procedures were completed for each visit.

IOP was measured in both eyes using a Goldmann applanation tonometer at screening, baseline and at treatment days 10 and 56. At each site, all IOP measurements for each subject were performed by the same board-certified ophthalmologist using the same Goldmann applanation tonometer throughout the study. The Goldmann applanation tonometer was fully calibrated for accuracy within 1 month prior to screening the first subject and monthly during the conduct of the study. The fluorescein and anesthetic agents used for the tonometry were to be documented and were to remain consistent throughout the study.

IOP was to be measured in duplicate in each eye between the hours of 9 AM and 11 AM at each study visit. A third IOP measurement was to be taken if the difference between the first and second IOP measurement was ≥ 2 mm Hg for an eye.

The primary variable for determination of non-inferiority of mirabegron 100 mg once daily to placebo was the change from baseline to day 56 in subject-average IOP.

Schedule of Assessments for Ophthalmic Procedures

Assessments	Screening †	Study Visit		
	Day -28 to Day -4	Baseline Day 1	Day 10 (+ 2 days)	Day 56/EOT ‡, (± 3 days)
	Visit 1	Visit 2	Visit 3	Visit 4
Visual Acuity (ETDRS Method) §	X	X	X	X
Automated Static Visual fields §	X			
Biomicroscopy ¶, ††	X	X	X	X
Intraocular Pressure ¶, ‡‡	X	X	X	X
Pachymetry §	X			
Ophthalmoscopy (dilated) ¶, §§	X			

ETDRS: early treatment of diabetic retinopathy study, charts for visual acuity; EOT: end of treatment; IOP: intraocular pressure.

† Screening procedures could either be performed all in one visit or may have been split and completed in multiple visits.

‡ Day 56/EOT procedures were to be completed for all subjects early terminating from the study. It is preferable to have the subject in overnight confinement prior to study visit and the IOP must still be completed within the 9 AM to 11 AM window.

§ A licensed ophthalmologist, optometrist or a certified ophthalmic assistant/technician was to perform this evaluation.

¶ A licensed ophthalmologist was to perform this evaluation. A nurse or certified ophthalmic assistant/technician may have administered the fluorescein, anesthetic or dilating agents as appropriate.

†† Included documentation of iris pigmentation color at screening.

‡‡ IOP was measured in duplicate in each eye between the hours of 9 AM and 11 AM at each study visit by the same ophthalmology reader using the same Goldmann applanation tonometer for each study subject.

Approximately 320 subjects were planned to target 240 subjects (120 subjects per treatment group) to complete 56 days of study drug, allowing for a 25% dropout rate. Based on standard deviation of subject-average IOP of 3.0 mm Hg, a 1-sided significant level of 0.025, an expected true difference between the 2 treatment groups of 0 mm Hg, 120 subjects per treatment group would provide 97% power to demonstrate non-inferiority. Non-inferiority was to be accepted if the upper limit of 2-sided 95% CI for the difference in mean change from baseline to day 56 in subject-average IOP between mirabegron and placebo was less than the non-inferiority margin of 1.5 mm Hg.

In a 2-treatment equivalency study of 332 glaucoma patients, [Mundorf et al, 2004] indicated standard deviations of unadjusted IOP from 2.6 to 3.2 mm Hg at various time points, and standard deviations for change from baseline from 2.6 to 3.0 mm Hg at various time points. Subjects in this current study were to be within the range of 10 to 21 mm Hg at baseline, and few subjects were expected to have IOPs ≥ 17 mm Hg. Based on this information, it could be expected that the standard deviation of the baseline IOP would be 3.0 mm Hg or less. Values for standard deviation for change from baseline in IOP between 2.5 and 3.0 mm Hg were plausible, assuming that baseline IOP and day 56 subject-average IOP were moderately correlated. Calculation of sample size was performed using nQuery Advisor version 6.01.

Reviewer's Comments: *The trial was appropriately designed to address the question of whether or not mirabegron causes an increase in intraocular pressure.*

Demographic and Other Baseline Characteristics

Parameter	Study Treatment		
	Placebo n = 159	Mirabegron 100 mg n = 161	Total n = 320
Gender			
Male	87 (54.7%)	91 (56.5%)	178 (55.6%)
Female	72 (45.3%)	70 (43.5%)	142 (44.4%)
Ethnicity			
Hispanic or Latino	66 (41.5%)	74 (46.0%)	140 (43.8%)
Not Hispanic or Latino	93 (58.5%)	87 (54.0%)	180 (56.3%)
Race			
White	145 (91.2%)	148 (91.9%)	293 (91.6%)
Black or African American	8 (5.0%)	10 (6.2%)	18 (5.6%)
Asian	3 (1.9%)	0	3 (0.9%)
American Indian or Alaska Native	3 (1.9%)	2 (1.2%)	5 (1.6%)
Naïve Hawaiian or Other Pacific Islander	0	1 (0.6%)	1 (0.3%)
Age (Years)			
Mean (SD)	35.7 (12.14)	34.4 (11.02)	35.0 (11.59)
Median	34.0	33.0	34.0
Min – Max	19 - 75	18 - 70	18 - 75
Age Group (Years)			
18-24	33 (20.8%)	37 (23.0%)	70 (21.9%)
25-34	52 (32.7%)	48 (29.8%)	100 (31.3%)
35-44	40 (25.2%)	43 (26.7%)	83 (25.9%)
45-54	23 (14.5%)	26 (16.1%)	49 (15.3%)
55-64	6 (3.8%)	5 (3.1%)	11 (3.4%)
≥ 65	5 (3.1%)	2 (1.2%)	7 (2.2%)
Iris pigmentation color			
Blue	36 (23%)	30 (19%)	66 (21%)
Brown	87 (55%)	99 (62%)	186 (58%)
Green	12 (7%)	13 (8%)	25 (8%)
Grey	1 (1%)	0	1 (1%)
Hazel	23 (15%)	19 (12%)	42 (13%)
Central corneal thickness (microns) †			
Mean (SD)	547 (25)	550 (26)	548 (26)
Median	547	549	548
Min - Max	500 - 600	501 - 600	500 - 600
Mean deviation from static visual fields (dB) †			
Mean (SD)	-0.6 (1.2)	-0.7 (1.4)	-0.6 (1.3)
Median	-0.46	-0.45	-0.46
Min - Max	-7.7 – 2.1	-12.9 - 1.5	-12.9 - 2.1
Subject-average intraocular pressure (mm Hg)†			
Mean (SD)	15.4 (2.0)	15.3 (2.0)	15.4 (2.0)
Median	15.5	15.5	15.5
Min - Max	10.3 - 20.5	10.3 – 20.3	10.3 - 20.5
Visual acuity (logMAR)†			
Mean (SD)	-0.086 (0.078)	-0.082 (0.084)	-0.084 (0.081)
Median	-0.09	-0.08	-0.08
Min - Max	-0.24 - 0.15	-0.29 - 0.17	-0.29 - 0.17

Reviewer's Comments: *The population was balanced between groups.*

Change from Baseline in Subject-Average Intraocular Pressure (mm Hg)

Day 10

Statistic	Study Treatment	
	Placebo n = 158	Mirabegron 100 mg n = 159
Baseline, mean (SE)	15.4 (0.16)	15.3 (0.16)
Day 10, mean (SE)	15.1 (0.18)	15.0 (0.15)
Mean change from baseline (SE)	-0.3 (0.13)	-0.3 (0.11)
Adjusted mean (SE) change from baseline	-0.3 (0.11)	-0.3 (0.11)
95% 2-sided CI for adjusted change	(-0.5, -0.1)	(-0.5, -0.1)
Mean (SE) difference vs. placebo		0.0 (0.16)
95% 2-sided CI for difference		(-0.3, 0.3)

Day 56

	Placebo n = 156	Mirabegron 100 mg n = 154
Baseline, mean (SE)	15.4 (0.16)	15.3 (0.16)
Day 56, mean (SE)	15.2 (0.17)	15.0 (0.16)
Mean change from baseline (SE)	-0.2 (0.13)	-0.2 (0.12)
Adjusted mean (SE) change from baseline	-0.2 (0.12)	-0.3 (0.12)
95% 2-sided CI for adjusted change	(-0.4, 0.0)	(-0.5, -0.0)
Mean (SE) difference vs. placebo		-0.1 (0.17)
95% 2-sided CI for difference		(-0.4, 0.3)
Achieve non-inferiority criteria (yes or no)?		yes

All subjects who received study drug, provided a baseline and post-baseline subject-average IOP and met one of the following criteria: completed the study and had a day 56 subject-average IOP measurement; or did not complete the study, but had a subject-average IOP measurement taken within the window for the day 56 visit specified in the schedule of assessments (day 53 to day 59); or, discontinued study drug because of an elevated IOP (full analysis set [FAS]). For subjects who discontinued due to elevated intraocular pressure the day 56 values were values taken at time of discontinuation.

Descriptive statistics for adjusted change from baseline were generated from an ANCOVA model with treatment group as a fixed factor and baseline as a covariate.

ANCOVA: analysis of covariance; IOP: intraocular pressure

Reviewer's Comments: *The 95% confidence interval is well within the ± 1 mmHg limit, and therefore mirabegron is considered to be equivalent to placebo in its likelihood of raising intraocular pressure.*

Visual Acuity

Number and Percent of Subjects with Losses from Baseline in Visual Acuity at Any Visit

Parameter	Study	
	Placebo n = 159	Mirabegron 100 mg n = 161
≥ 0.1 logMAR worsening from baseline	47/159 (29.6%)	44/160 (27.5%)
≥ 0.2 logMAR worsening from baseline	5/159 (3.1%)	4/160 (2.5%)
≥ 0.3 logMAR worsening from baseline	1/159 (0.6%)	1/160 (0.6%)

All subjects who received at least 1 dose of study drug (Safety Analysis Set [SAF]).

Decrease in visual acuity for the worse eye was defined as loss of visual acuity from baseline in the eye with the greater loss.

Reviewer's Comments: *There were no significant differences between groups.*

Biomicroscopy of the Anterior Segment

Reviewer's Comments: *There were no significant anterior segment findings in either group.*

Responses to Questions

1. Was the non-inferiority study conducted in accordance with DTOP recommendations?

Reviewer's Response: Yes.

2. Does DTOP agree with the interpretation of the study result by the Sponsor?

Reviewer's Response: Yes. *Mirabegron in doses up to 100 mg daily does not appear to raise intraocular pressure.*

3. Does DTOP agree that mirabegron is not associated with increased IOP as evaluated in the study?

Reviewer's Response: Yes.

4. Does DTOP agree with the sponsor's conclusion that the available data does not suggest an association of mirabegron and glaucoma?

Reviewer's Response: Yes.

5. Does DTOP have any further recommendations in regard to mirabegron and glaucoma?

Reviewer's Response: *No further recommendations at this time.*

6. Are any other ocular safety issues noted by DTOP?

Reviewer's Response: *No ocular safety issues have been noted.*

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
05/10/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 7, 2012

TO: Nenita Crisostomo, Regulatory Project Manager
Roger Wiederhorn, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202611

APPLICANT: Astellas Pharma Global Development, Inc.

DRUG: Mirabegron (YMI78)

NME: Yes

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of overactive bladder (OAB)

CONSULTATION REQUEST DATE: October 28, 2011
CLINICAL INSPECTION SUMMARY DATE: May 8, 2012
DIVISION ACTION GOAL DATE: June 29, 2012
PDUFA DATE: June 29, 2012

I. BACKGROUND:

The Applicant submitted this NDA to support the use of mirabegron (YMI78) for the indication of treatment of overactive bladder (OAB).

The following three pivotal studies were submitted and inspected in support of the indication:

Protocol 178-CL-046, entitled "A Randomized, Double-blind, Parallel Group, Placebo and Active Controlled, Multi-center Study to Assess the Efficacy and Safety of the Beta-3 Agonist YM178 (50 mg qd and 100 mg qd) in Subjects with Symptoms of Overactive Bladder" (SCORPIO), and

Protocol 178-CL-047, entitled "A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of the Beta-3 Agonist YM178 in Subjects with Symptoms of Overactive Bladder" (ARIES), and

Protocol 178-CL-074, entitled "A Phase III, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Multicenter Study to Assess the Efficacy and Safety of the Beta-3 Agonist YM178 (25 mg qd and 50 mg qd) in Subjects with Symptoms of Overactive Bladder" (CAPRICORN).

The sites below were selected for inspection for the following reasons:

Site #1624 was selected for Protocol 178-CL-047 because it was a negative efficacy driver and for Protocol 178-CL-074 because of its large enrollment. Also, the clinical investigator, Dr. W. Koltun, is associated with a large number of IND studies.

Site #1617 was selected for Protocol 178-CL-047 because it was a negative efficacy driver and there were a large number of protocol violations, in addition to a death in the 100 mg arm of the study.

Site #3225 was selected for Protocol 178-CL-046 because of high enrollment, pronounced efficacy, and a higher than average number of non-serious adverse events. The same site was selected for Protocol 178-CL-074 because of high enrollment and pronounced efficacy.

The sponsor was inspected because its application to FDA requested approval for a drug that is a new molecular entity.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
William D. Koltun, M.D. Medical Center for Clinical Research 9040 Friars Road San Diego, CA 92108	178-CL-047/ Site #1624/ 29 subjects and 178-CL-074/ Site #1624/ 50 subjects	17-24 Feb 2012	Pending (Preliminary Classification VAI)
Evan R. Goldfischer, M.D. Hudson Valley Urology, P.C. 1 Columbia St Poughkeepsie, NY 12601	178-CL-047/ Site #1617/ 29 subjects	5-13 Jan 2012	NAI
Kjetil Høy, M.D. Medi 3 Innlandet AS Parkgaten 12 2317 Hamar, Norway	178-CL-046/ Site #3225/ 50 subjects and 178-CL-074/ Site #3225/ 46 subjects	30 Jan-3 Feb 2012	Pending (Preliminary Classification NAI)
Astellas Pharma Global Development, Inc. Three Parkway North Deerfield, IL 60015 Regulatory Contact: Judy Kannenberg, MBA, RAC	178-CL-047/ 178- CL-046/ 178-CL-074	9 Jan-5 Mar 2012	Pending (Preliminary Classification VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. William D. Koltun, M.D.
Medical Center for Clinical Research
9040 Friars Road
San Diego, CA 92108

- a. **What was inspected:** At this site, for Protocols 178-CL-047 and 178-CL-074, records reviewed included, but were not necessarily limited to, informed consent forms, training records, IRB and monitoring communications, case report forms (CRFs), diaries, financial disclosure forms, source documentation, financial disclosure documents, test article accountability, adverse events, protocol violations, subject discontinuations, and primary efficacy endpoints.

- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Review of the records noted above revealed the following deficiencies in the conduct of Protocol 178-CL-047: (1) Two subjects did not record their blood pressures and pulse rates in the six days prior to Visit 2 nor did they record micturition data and vital signs concurrently as specified by protocol; (2) Three subjects did not record OAB or symptoms of OAB in their medical histories, a requirement for study inclusion; (3) One male subject was identified under multiple study numbers and was subsequently identified as a female on two laboratory reports; and (4) 64 kits of used and unused investigational drug were found in the drug storage room by sponsor representatives preparing for the current FDA inspection which occurred after the monitor's confirmation with the study coordinator that all investigational drug had been returned to the sponsor.

Deficiencies in the conduct of Protocol 178-CL-074 included: (1) One subject enrolled in the study despite having been enrolled in a previous study using the test article (YM178), a protocol-specified exclusion criterion; and (2) One subject did not have a protocol-specified ECG at Visit 5 and which was not documented as having been reported to the IRB.

For both protocols above, shipping records for laboratory samples were not available for review during the inspection, and the timely shipment of these samples could not be verified. According to Dr. Koltun's written response, these records were located after the conclusion of the inspection.

- c. Assessment of data integrity:** Dr. Koltun responded adequately to the inspection findings in a letter dated March 19, 2012, in which he committed to the implementation of additional training, record review, and SOPs to avoid the recurrence of similar observations. The observations noted above appear to be of isolated occurrences with minimal, if any, significance in the evaluation of safety and/or efficacy. Notwithstanding these inspectional observations, the studies appear to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

Note: The observations noted above for Dr. Koltun's site are based on a review of a draft of the Establishment Inspection Report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. Evan R. Goldfischer, M.D.
Hudson Valley Urology, P.C.
1 Columbia St
Poughkeepsie, NY 12601

- a. What was inspected:** At this site, for Protocol 178-CL-047, 43 subjects were screened and 29 subjects were enrolled. An audit of 15 enrolled subjects' records was conducted. Signed informed consent forms were present for all screened subjects. Records reviewed included, but were not limited to, source document worksheets, inclusion/exclusion criteria, randomization, discontinuations, laboratory records,

ECGs, bladder scans, adverse events, test article accountability, and IRB communications.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Kjetil Høye, M.D.
Medi 3 Innlandet AS
Parkgaten 12
2317 Hamar, Norway

- a. What was inspected:** This inspection was a collaborative effort between FDA and the European Medicines Authority (EMA). FDA and EMA inspected Protocol 178-CL-074 together while FDA inspected Protocol 178-CL-046. For Protocol 178-CL-074, 71 subjects were screened, 46 subjects were randomized, and 42 subjects completed the study. FDA and EMA audited approximately 45 subjects' records for Protocol 178-CL-074. EMA noted no major discrepancies for the approximately 30 subject files that they reviewed. Informed consent forms were signed by all subjects prior to study enrollment. Records reviewed included, but were not necessarily limited to, inclusion/exclusion criteria, medical histories, OAB treatment histories, visit schedules, protocol deviations, source document worksheets, laboratory findings, micturition diaries, and primary efficacy data.

For Protocol 178-CL-046, 101 subjects were screened, 61 subjects were randomized, and 50 subjects completed the study. FDA audited approximately 21 subjects' records for protocol 178-CL-046. Records reviewed included, but were not necessarily limited to, informed consent forms, inclusion/exclusion criteria, cough provocation tests, laboratory values, medical histories, demographics, OAB treatment histories, ECGs, bladder scans, and primary efficacy data.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The observations noted above for Dr. Høye's site are based on a review of a draft of the Establishment Inspection Report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. Astellas Pharma Global Development, Inc.
Three Parkway North
Deerfield, IL 60015

- a. What was inspected:** This sponsor inspection focused on the following clinical investigators and associated protocols: Dr. Kjetil Høy (Site #3225, Protocols 178-CL-046 and 178-CL-074); Dr. Evan Goldfischer (Site #1617, Protocol 178-CL-047); and Dr. William Koltun (Site #1624, Protocols 178-CL-047 and 178-CL-074). Records reviewed during the inspection included, but were not necessarily limited to, eCRFs, subjects' diaries and questionnaires, reports of protocol deviations and violations, SOPs describing the investigator selection process, adverse events, informed consent forms, correspondence between investigators and IRBs, monitoring procedures, and test article accountability.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. The observations included the lack of a signed Statement of Investigator Form FDA 1572 from Dr. Kjetil Høy; 12 subjects at Site #3225 in Protocol 178-CL-074 received prohibited concomitant medications; nine subjects in Protocol 178-CL-074 were randomized to two mirabegron studies; one subject at Site #1624 for Protocol 178-CL-047 was enrolled though not practicing a highly reliable form of birth control; one subject at Site #3225 in Protocol 178-CL-046 and two subjects at Site #1617 in Protocol 178-CL-047 were enrolled despite an average daily urine output that met exclusion criteria. These observations were adequately addressed in the sponsor's written response dated March 20, 2012, and supported by the review of the EIR and associated exhibits. Specifically, a Signed Investigator Statement was unavailable because of a conflict with national law and the remaining observations were previously detected and appropriately documented by the sponsor.

OSI Reviewer Note:

For Protocol 178-L-074, Subjects 70824, 70839, 70845, 70897, 70899, 70918, 70956, 70960, 70986, 70992, 71173, and 71266 at Site 3225 were identified as having received prohibited concomitant medications between Visit 5 (End of Treatment) and Visit 6 (Follow-up Visit).

Section 5.1.3.1 of the protocol summarizes prohibited and restricted concomitant medications for this study. Among the prohibited medications are those intended for the treatment of overactive bladder (OAB). The above subjects were administered either solifenacin, fesoterodine, or darifenacin for treatment of OAB. The period of the study during which these medications are prohibited or restricted is "...during the placebo run-in period and double-blind treatment period..." This same period of time is reiterated in the explanation of Code P59 in Listing 7.3 entitled "Protocol Violations and Corresponding Descriptions/Summarized Analysis Set". The double-blind study period for this study ends with Visit 5. The protocol itself refers to Visit 5 as "End of Treatment" (See Synopsis, Section V). Furthermore, Visit 5 coincides with the end of 12 weeks of double-blind treatment which is consistently referenced throughout the protocol (for example, see the Synopsis, Section IV). Given that the period of time during which specified concomitant medications are either prohibited or restricted is clearly and repeatedly stated in the protocol, it is unclear why the

administration of medications for treatment of OAB to 12 subjects between Visits 5 and 6 was considered a protocol violation. According to the sponsor's written response of March 20, 2012, these "violations" were detailed in Section 6.2.4 of the Clinical Study Report dated February 1, 2011. The data collected between Visits 5 and 6 were safety assessments, not efficacy assessments, and a sensitivity analysis conducted by the sponsor determined that these "violations" did not affect the safety data collected during the study.

The following nine subjects in Protocol 178-CL-074 were randomized to two mirabegron studies:

Subject No.	1st Protocol No.	Site No.	Subject No.	2 nd Protocol No.	Site No.
0100	178-CL-049	3034	71120	178-CL-074	3034
71697	178-CL-047	1600	7439	178-CL-074	1720
1213	178-CL-046	3225	71476	178-CL-074	3225
8326	178-CL-049	1529	71162	178-CL-074	1624
6030	178-CL-047	1624	71228	178-CL-074	1943
70449	178-CL-074	1943	70634	178-CL-074	1624
6173	178-CL-049	1624	70203	178-CL-074	1943
194P	178-CL-008	32	70837	178-CL-074	3024
1877	178-CL-046	3089	71108	178-CL-074	3089

Per the sponsor's written response of March 20, 2012, these duplicated subjects were documented in the Clinical Study Report, Section 6.2.4. To prevent duplicate enrollment in future studies, the sponsor committed to providing an enhanced definition of the term "participation" as used as an exclusion criterion, to addressing the potential of duplicate enrollment within the informed consent form, and implementing a check on key subject identifiers to detect potential duplicate enrollers.

- c. **Assessment of data integrity:** The observations on the Form FDA 483 had been previously detected and addressed by the sponsor. For those subjects completing the study despite meeting the exclusion criterion of excessive daily urine output, their data was excluded from the Per Protocol Analysis Set but included in the Safety Analysis Set. The remaining observations appear to be isolated in nature and were addressed and corrected and/or documented in the course of the studies; thus, these issues would not appear to have a significant effect on the analyses of safety and/or efficacy. The studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication.

Note: The observations noted above for Astellas are pending a final review of the Establishment Inspection Report (EIR) and sign-off on the letter to Astellas. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Koltun, Goldfischer, and Hoyer's clinical investigator sites were inspected in support of this NDA. The sponsor, Astellas Pharma Global Development, Inc., was also inspected. Drs. Goldfischer and Hoyer were not issued Form FDA 483s. Dr. Koltun and Astellas were issued Form FDA 483s. The observations from the inspections of Dr. Koltun and Astellas were discussed with Drs. Mark Hirsch and Roger Weiderhorn of DRUP in a telephone conference on May 7, 2012. They agreed that the observations which included subjects receiving prohibited concomitant medications and subjects enrolling in two studies would not have a significant effect upon efficacy and/or safety evaluations. Drs. Hirsch and Weiderhorn noted that the extremely large number of subjects in Protocols 046, 047, and 074 (approximately 1200 to 1500 subjects each) and the blinded design of the studies would minimize or obviate any effect on overall data analysis resulting from the enrollment of a small number of otherwise ineligible study subjects. Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

Note: The observations noted above for Drs. Koltun and Hoyer and Astellas are based on reviews of draft Establishment Inspection Reports (EIRs). An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROY A BLAY
05/07/2012

JANICE K POHLMAN
05/08/2012

LAUREN C IACONO-CONNORS
05/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: March 19, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4) (Mirabegron) Extended-release Tablets
25 mg and 50 mg

Application Type/Number: NDA 202611

Applicant: Astellas Pharma Global Development, Inc

OSE RCM #: 2012-398

***** This document contains proprietary and confidential information that should not be released to the public.*****

1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for (b) (4) (Mirabegron) Extended-release Tablets, 25 mg and 50 mg (NDA 202611), submitted by Astellas Pharma Global Development on February 9, 2012, for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

DMEPA reviewed the initial proposed labels and labeling for this product in OSE Review # 2011-3355, dated November 8, 2011. At that time, the proposed proprietary name, (b) (4) appeared on the container labels and carton labeling, however, DMEPA found this name unacceptable in OSE Review #2011-3947, dated December 16, 2011. The Applicant submitted the proposed proprietary name, (b) (4) on February 9, 2012 for review by DMEPA, and the revised container labels and carton labeling with the new proposed proprietary name, (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principals of Human Factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Revised container Labels and Carton Labeling submitted on February 9, 2012 (See Appendices A through C for images)

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels and carton labeling find that the Applicant implemented the majority of DMEPA's recommendations under OSE review #2011-3355. However, the 'Rx Only' statement on all container labels and carton labeling appears too prominent and the presence of the product strengths in the lower left hand side of all the panels of carton labeling is duplicative. Therefore we recommend the following revisions:

- A. General Comments (All container labels and carton labeling)
 - a. Minimize the prominence of the 'Rx Only' statement further, by unbolding the statement. As currently presented, 'Rx Only' competes in prominence with the product strength.
 - b. In accordance with 21 CFR 201.10(g)(2), ensure the dosage form has the same prominence (i.e. font size and type) as the established name.

*** This document contains proprietary and confidential information that should not be released to the public.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Carton Labeling (25 mg and 50 mg trade)

- a. Remove the product strengths located in the lower left hand side of all the panels of carton labeling, where they appear. This information is duplicative because the product strengths appear below the dosage form on the label. Additionally, the space can be utilized for the quantity statements as recommended below.
- b. Relocate the quantity statements (i.e. 30 tablets, 90 tablets, and 100 tablets-single unit package (10 per blister card)) to the lower left hand side of the carton labeling, after removing the product strength. As currently presented, the area where the quantity statements appear, is too crowded which can detract from important warning statement, 'Swallow tablet whole. Do not cut, crush, or chew tablet.'

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

REFERENCE

OSE Review # 2011-3355, (b) (4) (Mirabegron) Extended-release Tablets, 25 mg & 50 mg Label and Labeling Review; McMillan, T. November, 8, 2011.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MANIZHEH SIAHPOUSHAN
03/16/2012

ZACHARY A OLESZCZUK
03/19/2012

CAROL A HOLQUIST
03/20/2012

Addendum to Memorandum of Consultation

Division of Oncology Products 1 (DOP 1) Office of Hematology and Oncology Products (OHOP)

NDA #	202611
Request	Adverse event reports of a variety of solid tumors
Product	Mirabegron, 25 mg and 50 mg extended release tablets
NDA Sponsor	Astellas Pharma Global Development, Inc.
Primary Reviewer	Y Max Ning, MD, PhD
Team Leader	V. Ellen Maher, MD
Date of Consultation	12/28/2011
Consultation Requestor	Nenita Crisostomo, R.N. - Regulatory Health Project Manager, Division of Reproductive and Urologic Products, Ph: 301-796-0875
Date Consult Completed	01/30/2012
Date of Addendum	03/09/2012

This addendum was generated to address an additional concern about the potential risk of increased neoplasms in the 50 mg mirabegron arm.

After evaluating relevant information in the original consult and the label of tolterodine, the control product used in the Study 178-CL-049, the consultants agreed to add the following to the previous responses:

While a signal was not evident in the mirabegron 50 mg cohort, given the study size, the consultants cannot rule out an increased risk for the development and or detection of neoplasm.

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/s/

YANGMIN NING

03/09/2012

VIRGINIA E MAHER

03/09/2012

Memorandum of Consultation

Division of Oncology Products 1 (DOP 1) Office of Hematology and Oncology Products (OHOP)

NDA #	202611
Request	Adverse event reports of a variety of solid tumors
Product	Mirabegron, 25 mg and 50 mg extended release tablets
NDA Sponsor	Astellas Pharma Global Development, Inc.
Primary Reviewer	Y Max Ning, MD, PhD
Team Leader	V. Ellen Maher, MD
Date of Consultation	12/28/2011
Consultation Requestor	Nenita Crisostomo, R.N. - Regulatory Health Project Manager, Division of Reproductive and Urologic Products, Ph: 301-796-0875
Date Consult Completed	01/30/2012

Consultation Request and Specific Questions

The original Request for Consultation from the Division of Reproductive and Urologic Products has the following background information and questions:

"NDA 202611, mirabegron, is a new marketing application indicated for overactive bladder. Mirabegron is a new molecular entity, first in its class (beta-3 adrenoceptor agonist) with a PDUFA Goal date of June 29, 2012. The submission is fully electronic and is located at this site:

<\\CDSESUB1\EVSPROD\NDA202611\202611.enx>

The application is scheduled for an Advisory Committee (AC) Meeting on April 5, 2012. We are respectfully requesting your Division to review the application in regard to adverse event reports of a variety of solid tumors (benign and malignant neoplasms). Most, but not all, of the AE reports of neoplasms occurred during the 1 year, active-controlled Study 049, with an apparent excess in the mirabegron 100 mg arm compared to both the mirabegron 50 mg arm and the tolterodine arm. At this time, we are planning to present the adverse event reports of neoplasms as a issue to the AC. Our main concern lies in the imbalance between groups in Study 049. We have less concern regarding neoplasms that were reported as AEs in the short-term (12-week) pivotal studies. We seek your input as we prepare for the AC meeting. We have the following specific questions:

1. *In your opinion, are the results of Study 178-CL-049 (Study 049) for the number of neoplasms accurately stated in the study report?*
2. *Do you agree with the Adjudication Committee's case-by-case analysis of neoplasms in Study 049? In your opinion, can any of the cases of neoplasms reported in Study 049 be excluded? If so, what is the reason for exclusion?*
3. *The number of neoplasms reported was greater in the mirabegron 100 mg group compared to the mirabegron 50 mg group in Study 049. Are you aware of any similar situation, in which the incidence of neoplasms was found responsive to a 2-fold increase in dose, such as is observed in Study 049? If not, in your opinion, would it be appropriate to pool the data from the mirabegron 50 mg and 100 mg groups to analyze the neoplasms reported in Study 049?*
4. *In your opinion, how should the neoplasm data from Study 049 be analyzed? In your response, please consider whether to include previous exposure to mirabegron, tolterodine, or placebo in studies that took place prior to Study 049.*
5. *Neoplasms were also reported in short-term (≤ 12 -week) studies. Most of the neoplasms in patients taking mirabegron (7/8) in short-term studies were reported in Study 047. In your opinion, should neoplasms reported in short-term studies be included in the FDA's overall analysis of neoplasms?*
6. *Are there any other analyses that you suggest be conducted, such as pharmacokinetic/pharmacodynamic (PK/PD) analyses, Kaplan-Meier analyses, or relative risk analysis?*

DOP1 Responses

Background:

Mirabegron is a beta 3-adrenoceptor agonist that represents a new molecular entity. In NDA 202611, the product is proposed for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. The recommended dosing schedule for the proposed indication of mirabegron is 50 mg administered orally once daily.

To support this NDA, the applicant submitted 5 randomized, double-blind, placebo- and/or tolterodine-controlled Phase 3 trials in the intended patient population. Tolterodine was used as an active control in some of the trials. These trials are listed in **Appendix 1**. Four of the five trials, including Studies 178-CL-046, 178-CL-047, 178-CL-048, and 178-CL-074, had a 12-week double-blind

treatment period; whereas one of the five, Study 178-CL-049, had a 12-month treatment period, designed to examine the long-term safety of mirabegron. For simplicity, all the studies discussed below are hereafter referred by the last three numbers of study identifiers.

For this consultation, the DRUP review is more concerned about the imbalance in the neoplasms detected among groups in Study 049. This study was conducted between April 25, 2008 and May 6, 2010, with a total of 2452 patients enrolled. Of them, 2444 patients were included for safety evaluation. The following table summarizes the neoplasms reported as an SAE from this study by the applicant. The detailed summary regarding the timing of diagnoses and the applicant's assessment of malignancy attribution to study agent is listed in **Appendix 2**. It is noted that approximately 80% of patients in Study 049 had been previously enrolled in Studies 046 or 047.

Number of Serious Neoplasms (Benign and Malignant) Reported in Study 049

	Tolterodine ER 4 mg (n=812)	Mirabegron 50 mg (n=812)	Mirabegron 100 mg (n=820)
Benign	2*		1
Malignant			
Breast Cancer	2		2
Endometrial Cancer	1	1	1
Urothelial Carcinoma			1
Prostate Cancer			2
Lung Cancer			2
Thyroid Tumor**			1
Pancreatic Carcinoma			1
Total # of Malignant Tumors	3	1	10
*One patient (ID 3020-0298) had a hamartochondroma in the right lung in addition to the diagnosis of breast cancer			
** Not fully determined since the cold nodules in the left lobe was not removed. Malignancy could not be ruled out in this case.			

Response to Question 1: *In your opinion, are the results of Study 178-CL-049 (Study 049) for the number of neoplasms accurately stated in the study report?*

Based on the examination of the submitted adverse event dataset and the review of the study report on neoplasms identified during the trial, the consultant found that the number of neoplasms reported as an SAE was accurately reflected in the study report.

Additional neoplasms reported as non-SAE, treatment emergent adverse event (TEAE) were found in the dataset and are listed in the following table by treatment arm. The majority of these non-SAE neoplasms were benign. The malignant neoplasms appear to be skin-associated. These additional neoplasms were included in the tabulation of TEAEs in Table 12.6.1.4 of the Applicant's study report.

	Tolterodine ER 4 mg (n=812)	Mirabegron 50 mg (n=812)	Mirabegron 100 mg (n=820)
Benign	ID: 178-CL-047-U00015976695 (pulmonary nodules*) ID: 178-CL-049-1656-0578 (fibroadenoma, intraductal papilloma) ID: 178-CL-049-2203-0642 (Uterine Fibroid)	ID: 178-CL-046-3028-1680 (tumor in the right breast (benign)) ID: 178-CL-047-U00008727873 (Wart on fourth finger) ID: 178-CL-047-U00020386712 (neuroma left foot) ID: 178-CL-047-U00021796744 (Uterine Fibroids)	ID: 178-CL-046-3132-2915 (basalioma cutis) ID: 178-CL-047-U00016048278 (Benign Breast Lump)
Malignant	ID: 178-CL-047-U00016436933** (cutaneous SQUAMOUS CELL CA)	ID: 178-CL-046-3232-1066 (Malignant nasal basalioma) ID: 178-CL-047-U00019417928(basal cell carcinoma, numerous sites) ID: 178-CL-049-1608-0503 (basal cell carcinoma)	ID: 178-CL-047-U00016427000 (basal cell carcinoma) ID: 178-CL-047-U00018387657 (basal cell-superior helix)
* Several small nodules of 1-4 mm scattered in the lungs, with one nodule disappeared and an additional one decreased in size in follow-up CT scan.			

Diagnosed of benign lung nodules clinically.

**Patient 00016436933 was an 80 year-old man who had a history of cuSCC

Response to Question 2: *Do you agree with the Adjudication Committee's case-by-case analysis of neoplasms in Study 049? In your opinion, can any of the cases of neoplasms reported in Study 049 be excluded? If so, what is the reason for exclusion?*

Yes. The submitted narratives show that all the serious neoplasms, except for Case 3016-1796 (fibroma), were supported by pathological evidence and cannot be excluded.

Response to Question 3: *The number of neoplasms reported was greater in the mirabegron 100 mg group compared to the mirabegron 50 mg group in Study 049. Are you aware of any similar situation, in which the incidence of neoplasms was found responsive to a 2-fold increase in dose, such as is observed in Study 049? If not, in your opinion, would it be appropriate to pool the data from the mirabegron 50 mg and 100 mg groups to analyze the neoplasms reported in Study 049?*

Not to the consultant's best knowledge. In addition, the consultant noted that the recommended dose for the proposed indication is 50 mg once daily. The investigational dose of mirabegron 100 mg once daily that was used in clinical trials is not recommended in the draft product label. The increased number of neoplasms in the mirabegron 100 mg group is of concern.

The consultant does not recommend pooling the data from the mirabegron 50 mg and 100 mg groups in Study 049 to compare with the control arm for the following reasons:

- A) The detected neoplasms were heterogeneous in tissue of origin.**
- B) Appendix 2 shows that 5 of the 11 neoplasm SAEs in the mirabegron 100 mg group were diagnosed within 12 weeks of study treatment and that 2 of the 11 diagnosed between Months 3-6 of treatment initiation.**

The remaining 4 cases, including the above case of fibroma, were found between months 6-12 of the trial. This is comparable to the time course of the 3 neoplasms found in the tolterone control arm.

- C) The consultant did not find a remarkable imbalance in the incidence of malignancies among the four 12-week Phase 3 trials of the product. However in the 1-year study, 5 of the 11 cases occurred within the first 12 weeks as stated above.**

Response to Question 4: In your opinion, how should the neoplasm data from Study 049 be analyzed? In your response, please consider whether to include previous exposure to mirabegron, tolterodine, or placebo in studies that took place prior to Study 049.

Please see Response to Question 3.

The significance of previous exposure to mirabegron, tolterodine, or placebo is difficult to estimate. There is no apparent relationship between prior exposure and neoplasm detection in Study 049, as suggested in Appendix 2, Table 24, below.

Response to Question 5: Neoplasms were also reported in short-term (≤ 12 -week) studies. Most of the neoplasms in patients taking mirabegron (7/8) in short-term studies were reported in Study 047. In your opinion, should neoplasms reported in short-term studies be included in the FDA's overall analysis of neoplasms?

Given that there were four randomized, 12-week Phase 3 trials of mirabegron 50 mg in comparison with placebo and/or tolterodine, you may conduct a pooled analysis of neoplasms across the four trials to evaluate whether treatment with mirabegron 50 mg for 12 weeks was associated with an increased diagnosis of neoplasms.

The consultant noted that Study 047 had 442 patients treated with mirabegron 50 mg once daily, representing approximately 25% of the total patients (1754) who received 50 mg mirabegron once daily in the four randomized, short-term trials.

Response to Question 6: Are there any other analyses that you suggest be conducted, such as pharmacokinetic/pharmacodynamic (PK/PD) analyses, Kaplan-Meier analyses, or relative risk analysis?

No additional recommendations with regard to the reported imbalance in neoplasms in Study 049. You may want to discuss the need for further studies at your upcoming Advisory Committee meeting.

Please also see Response to Question 3 above.

Appendix 1: Key Studies in Support of the NDA 202611 for Mirabegron

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
<i>Reports of Efficacy and Safety Studies continued</i>								
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
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

Appendix 2: (Adopted from Pages 120-121 of Study Report for Study 178-CL-049)

Table 24 Serious Treatment-emergent Adverse Events of Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) (SOC)

Patient No. Age/Race/Sex	MedDRA (v9.1) Preferred Term (Reported Term)	Onset/ Stop Day (Last Dose Day)	Severity/ Outcome	Relationship to Study Drug	Treatment in Previous Study (046/047/ Naive)
Mirabegron 50 mg					
2179-6744 54/White/Female	Endometrial cancer stage I (endometrial grade 1 cancer)	315/350 (364)	Mild/ Recovered	Not Related	placebo (047)
Mirabegron 100 mg					
1597-7875 61/White/Female	Breast cancer (left breast cancer)	86/ ongoing (294)	Moderate/ Recovering	Not Related	mirabegron 100 mg (047)
1651-8100 70/White/Male†	Prostate cancer (prostate cancer)	54/ ongoing (58)	Severe/ Not Recovered	Not Related	mirabegron 50 mg (047)
2262-0172 52/White/Female†	Endometrial cancer (endometrioid cancer)	139/216 (166)	Mild/ Recovered	Not Related	naive
3016-1796 48/White/Female	Fibroma (hypopharynx fibroma)	329/332 (364)	Moderate/ Recovered	Not Related	tolterodine SR 4 mg (046)
3016-1952 61/White/Female†	Lung neoplasm malignant (lung ca)	126/ ongoing (175)	Severe/ Not Recovered	Not Related	mirabegron 50 mg (046)
3022-0128 69/White/Male†	Prostate cancer (prostate carcinoma)	49/85 (82)	Severe/ Recovered	Not Related	naive
3025-2505 64/White/Male†	Pancreatic carcinoma (carcinoma of head of the pancreas)	323/376 (323)	Severe/ Unknown	Not Related	tolterodine SR 4 mg (046)
3032-2166 69/White/Male	Thyroid neoplasm (recurrent tumor with cold nodule)	263/269 (364)	Moderate/ Recovered	Not Related	mirabegron 100 mg (046)
3034-2276 71/White/Female	Breast cancer (Carcinoma of mamma right)	92 E/ (362)	Moderate/ Not Recovered	Not Related	placebo (046)
3062-2853 58/White/Male†	Transitional cell carcinoma (urothelial carcinoma)	309/ ongoing (308)	Severe/ Not Recovered	Not Related	placebo (046)
3235-2623 74/White/Female†	Lung neoplasm malignant (pulmonary cancer)	53/ ongoing (55)	Severe/ Not Recovered	Not Related	placebo (046)
Tolterodine ER 4 mg					
3013-0077 51/White/Female	Breast cancer (mamma carcinoma right side)	203/ ongoing (370)	Moderate/ Unknown	Not Related	naive
3020-0298 60/White/Female	Benign lung neoplasm (hamartochon-droma right lung)	300/353 (364)	Moderate/ Recovered	Not Related	naive
	Breast cancer (mamma carcinoma right)	293/ ongoing (364)	Moderate/ Not Recovered	Not Related	
3068-3245 40/White/Female	Uterine leiomyoma (uterus polomyomia)	85/149 (363)	Moderate/ Recovered	Not Related	tolterodine SR 4 mg (046)
3235-1509 64/White/Female†	Endometrial cancer (endometrial cancer)	296/ ongoing (317)	Severe/ Not Recovered	Not Related	tolterodine SR 4 mg (046)

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/s/

YANGMIN NING

01/31/2012

VIRGINIA E MAHER

02/01/2012

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	202611
Brand Name	Mirabegron
Generic Name	YM178
Sponsor	Astellas Pharma Global Development, Inc.
Indication	Overactive bladder
Dosage Form	Tablet
Drug Class	Selective human Beta 3-adrenoreceptor (AR) agonist
Therapeutic Dosing Regimen	50 mg q.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not observed in clinical studies
Submission Number and Date	SDN 001, 16 Sep 2011
Review Division	DRUP / HFD 580

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of mirabegron was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

In this randomized, blinded, four-treatment-arm parallel-crossover study, 352 healthy subjects received either mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, mirabegron 200 mg and placebo, or a single oral dose of moxifloxacin 400 mg and placebo. The overall summary of findings is presented in Table 1.

Table 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)

Treatment	Time (hour)	$\Delta\Delta Q_{TcI}$ (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.

50 mg is the proposed therapeutic dose. 25 mg is the proposed dose for patients with severe renal impairment or moderate hepatic impairment. The supratherapeutic doses of 100 mg and 200 mg produced C_{max} that is 2.9-fold and 8.4-fold, and AUC that is 2.6-fold and 6.5-fold, respectively, those with 50 mg. The exposures achieved with 200-mg dose are adequate to cover any of the known high clinical exposure scenarios. Significant and positive exposure-response relationship was observed for mirabegron. However, there is no substantial QTc prolongation expected with the exposures observed with therapeutic dose of 50 mg. Females had 40 to 50% higher exposures compared to males that may explain the larger effect of mirabegron on QTc for females. There was no effect of gender on the concentration-QT slope.

Mirabegron increased heart rate on ECG 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. These HR effect occur between 5 and 6 hours post-dose which is consistent with the T_{max} of mirabegron.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

1. Was Study 178-CL-077 performed according to your previous recommendations?

QT-IRT Response: No, they did not follow our recommendations. We recommended a 3-way crossover study using i.v. infusion with two Williams Squares instead of the parallel-crossover study design using oral tablets. However, their study design is acceptable.

2. Does the methodology used in Study 178-CL-077 adequately correct for increases in pulse rate?

QT-IRT Response: The range of baseline RR in this study is acceptable.

3. Do you agree that the Sponsor's assessment of results from Study 178-CL-037 and from Study 178-CL-077?

QT-IRT Response: For our response for Study 178-CL-037, please refer to the Appendix of our previous protocol review for IND 69416, dated 3 March 2010. We agree with the sponsor's assessment of the results from Study 178-CL-077.

4. Do you agree that the results from the TQT studies support the safety of mirabegron at doses of 25 mg and 50 mg once daily with respect to mirabegron's effect on the QT interval?

QT-IRT Response: Yes.

5. Do you have any other recommendations regarding mirabegron and the QT interval?

QT-IRT Response: No.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

The sponsor proposed following language in the package insert:

(b) (4)



2.2 QT-IRT RECOMMENDED LABEL

QT-IRT believes that a warning and precaution section is not needed. The team recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

12.2 PHARMACODYNAMICS

Cardiac Electrophysiology

The effect of multiple doses of mirabegron 50 mg, 100 mg and 200 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-treatment-arm parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. Dose and exposure related prolongation in QT interval was observed with mirabegron. However, no substantial QT prolongation is expected with clinically relevant exposures. The dose of 200 mg once daily mirabegron is adequate to represent the high exposure clinical scenario.

In this thorough QT study, mirabegron increased heart rate on ECG 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.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Mirabegron, a newly identified experimental drug, is a selective agonist for the human Beta 3-AR. The Beta 3-AR belongs to the three described Beta-adrenergic receptors.

3.2 MARKET APPROVAL STATUS

Mirabegron is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.6.2

“Two studies for the effects of mirabegron (0.03, 0.3, 3, and 30 mcmmol/L) on hERG current were performed. Both studies [Studies 178-PT-002 and 178-PT-015] used HEK293 cells expressing hERG channels. Mirabegron did not inhibit hERG current at up to 30 mcmmol/L in and inhibited hERG current by 14.7% at 30 mcmmol/L. These similar results indicate that mirabegron has no significant effect on the hERG channels up to 30 mcmmol/L.

“Effects of the human plasma metabolites M5, M11, M12, M14, and M16 (0.3, 3, and 30 mcmmol/L) of mirabegron on hERG current were investigated in HEK293 cells expressing hERG channels. M5 and M16 inhibited hERG current, with IC₅₀ values of 21 and 31 mcmmol/L, respectively. M14 at a concentration of 30 mcmmol/L inhibited hERG current by 17.3%. M11 and M12 did not inhibit hERG current at concentrations up to 30 mcmmol/L.

“Effects of mirabegron (0.3, 3, and 30 mcmmol/L) on resting membrane potential, action potential amplitude, maximum rate of rise of action potential, and action potential duration (APD₃₀, APD₅₀, and APD₉₀) were investigated in isolated guinea pig papillary muscle. Mirabegron did not affect action potential in isolated guinea pig papillary muscle at concentrations up to 30 mcmmol/L.

“Effects of the 5 most abundant human plasma metabolites M5, M11, M12, M14, and M16 (0.3, 3, and 30 mcmmol/L) of mirabegron on resting membrane potential, action potential amplitude, maximum rate of rise of action potential, and action potential duration (APD₃₀ and APD₉₀) were investigated in isolated guinea pig papillary muscle. M5 (3 mcmmol/L) prolonged APD₃₀ by 6.1% and shortened APD₃₀₋₉₀ by 7.9%, while concentrations of 30 mcmmol/L prolonged APD₃₀ by 5.6% and APD₉₀ by 4.7%. M16 prolonged APD₉₀ by 5.0% at 30 mcmmol/L. M5 and M16 did not affect other parameters. M11, M12, and M14 did not affect the action potential of isolated guinea pig papillary muscle at concentrations up to 30 mcmmol/L.

“A single dose of mirabegron at 3, 10, 30, and 100 mg/kg was administered orally to conscious cynomolgus monkeys to investigate the effect on cardiovascular and respiratory systems. Increased heart rate was observed at ≥ 10 mg/kg, while vomiting, lateral position, as well as prolongation of PR and QRS intervals were noted at the 100 mg/kg dose level. No changes in body temperature, blood pressure, blood gas, or blood electrolyte concentrations were noted.

“Effects of mirabegron and its 5 most abundant human plasma metabolites M5, M11, M12, M14, and M16 on sodium channel (hNav1.5), calcium channel (hCav1.2), and two potassium channel (hKvLQT1/hminK and hKv4.3/KChIP2.2) ion currents were investigated at 10 mcmmol/L [Study 178-PT-011]. At these high concentrations, mirabegron inhibited sodium current (I_{Na}) by 48.5% and calcium current (I_{Ca}) by 15.3%. M16 inhibited sodium and calcium currents by 10.5% and 8.8%, respectively. Neither mirabegron nor M16 affected the two potassium currents (I_{Ks} and I_{to}). M5, M11, M12, and M14 did not affect any ion current tested.

“Effects of mirabegron (3, 30, 100, and 300 ng/mL) and its human plasma metabolites M5, M11, M12, M14, and M16 (3, 10, 30, and 100 ng/mL) on the QT interval, T_{p-e}

interval (index of transmural dispersion of repolarization), and subendocardial action potential duration (APD90) on transmural ECG and arrhythmogenesis were investigated in arterially perfused canine ventricular wedge preparation. Based on the obtained results, the risk of torsade de pointes (TdP) was calculated as the TdP score.

“Mirabegron shortened QT interval and APD90 slightly at 0.76 mcmol/L (300 ng/mL), while it did not affect Tp-e interval or TdP score at any concentration, nor did it show an arrhythmogenic effect.

“M5 shortened QT interval, Tp-e interval, and APD90 slightly at 0.30 mcmol/L (100 ng/mL), while it did not affect TdP score, nor did it show an arrhythmogenic effect. M11, M12, M14, and M16 did not affect arterially perfused canine ventricular wedge preparation at up to 100 ng/mL.

“In conscious cynomolgus monkeys given a single oral dose of mirabegron (3, 10, 30, 60, and 100 mg/kg), mirabegron did not affect mean blood pressure, heart rate, or electrocardiography at doses up to 10 mg/kg. Increased heart rate was observed at doses ≥ 30 mg/kg, and prolonged QRS interval and vomiting (2 of 3 animals) at doses of 100 mg/kg.

“In conscious dogs given a single oral dose of mirabegron (0.01, 0.03, 0.3, 3, and 10 mg/kg), mirabegron did not affect respiratory rate, systolic pressure, diastolic pressure, mean blood pressure, heart rate, or ECG at the dose of 0.01 mg/kg. Increased heart rate and shortened PR interval were observed at doses ≥ 0.03 mg/kg, while increased respiratory rate and decreased systolic pressure and mean blood pressure were observed at doses ≥ 0.3 mg/kg. Shortened QT interval was observed at 10 mg/kg, while QTc interval was not affected.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

“A total of 5863 patients were treated with mirabegron across all phase 2/3 studies.

“In the Global Phase 2/3 Population, the most frequently reported TEAE (by preferred term [PT]) in the total mirabegron group were nasopharyngitis (438/5863 [7.5%]), hypertension (377/5863 [6.4%]) and blood glucose increased (275/5863 [4.7%]).

“One or more drug-related TEAE was reported in 1397/5863 (23.8%) mirabegron patients. The most frequently reported drug-related TEAE (by PT) were hypertension (234/5863 [4.0%]), dry mouth (120/5863 [2.0%]) and constipation (114/5863 [1.9%]).”

Table 2: TEAE by PT (Reported by ≥ 3.0% in the Total Mirabegron Group), Global Phase 2/3 Population

MedDRA v12.1 PT†, n (%) of Patients	Total Mirabegron (n = 5863)				
	TEAE	Mild	Moderate	Severe‡	Drug-related
Overall	3473 (59.2%)	2165 (36.9%)	1053 (18.0%)	255 (4.3%)	1397 (23.8%)
Nasopharyngitis	438 (7.5%)	364 (6.2%)	64 (1.1%)	10 (0.2%)	3 (0.1%)
Hypertension	377 (6.4%)	287 (4.9%)	86 (1.5%)	4 (0.1%)	234 (4.0%)
Blood glucose increased	275 (4.7%)	271 (4.6%)	3 (0.1%)	1 (< 0.1%)	17 (0.3%)
Headache	214 (3.7%)	139 (2.4%)	62 (1.1%)	13 (0.2%)	109 (1.9%)
UTI	199 (3.4%)	133 (2.3%)	63 (1.1%)	3 (0.1%)	25 (0.4%)
GGT increased	175 (3.0%)	150 (2.6%)	22 (0.4%)	3 (0.1%)	77 (1.3%)
Urinary sediment abnormal	175 (3.0%)	175 (3.0%)	0	0	11 (0.2%)

Studies included: 178-CL-003, 178-CL-004, 178-CL-008, 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048, 178-CL-049, 178-CL-051, 178-CL-060 and 178-CL-074.

Drug relatedness was based on investigator assessment.

GGT: gamma-glutamyltransferase; PT: preferred term; TEAE: treatment-emergent adverse event(s); UTI: urinary tract infection.

† Sorting order: PT, by decreasing frequency of TEAE in total mirabegron group.

‡ Severe category includes TEAE with missing severity [Module 5.3.5.3 ISS Table 5.4.7.1; Module 5.3.5.3 ISS Appendix 6.3.5.1].

Source: Module 5.3.5.3 ISS Tables 5.3.1, 5.4.1 and 5.5.2.1

Source: eCTD 2.7.4, Table 19

Hypertension

“In the EU/NA OAB 12-week Phase 3 Population, TEAE related to hypertension were similar for the total mirabegron (230/2736 [8.4%]), placebo (117/1380 [8.5%]) and tolterodine (48/495 [9.7%]) groups. The frequency of hypertension TEAE was comparable for mirabegron doses of 50 mg (120/1375 [8.7%]) or 100 mg (58/929 [6.2%]) and was highest in mirabegron 25 mg (52/432 [12.0%]).

“In the EU/NA Long-term Controlled Population, the occurrence of hypertension TEAE was comparable between mirabegron 50 and 100 mg (89/812 [11.0%] and 83/820 [10.1%]) and tolterodine (86/812 [10.6%]).

QT Prolongation

“In the Global OAB 12-week Phase 2/3 Population, QTc prolongation-related TEAE were reported in 4/4414 (0.1%) total mirabegron patients, 2/2142 (0.1%) placebo patients and 2/958 (0.2%) tolterodine patients.

“From the torsades de pointes/QT prolongation SMQ, no proarrhythmic findings of ventricular tachycardia, ventricular fibrillation or torsades de pointes were reported in these 12-week studies. No patients discontinued study drug due to a TEAE in the torsades de pointes/QT prolongation SMQ.

“In the EU/NA Long-term Controlled Population, QTc prolongation-related TEAE were reported in 3/812 (0.4%) mirabegron 50 mg patients, 2/820 (0.2%) mirabegron 100 mg patients and 3/812 (0.4%) tolterodine patients.

“TEAE in the torsades de pointes/QT prolongation SMQ was reported as SAE for 1/812 (0.1%) patient in the mirabegron 50 mg group, (cardiac arrest, ventricular fibrillation and ventricular tachycardia; (these concurrent CV events were adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron as a nonfatal myocardial infarction); and 1/812 (0.1%) patient in the tolterodine group (cardiac arrest,

adjudicated by the Cardiovascular Adjudication Committee for Clinical Trials with Mirabegron to ventricular fibrillation).”

Cardiac Arrhythmia, Including Tachycardia and Atrial Fibrillation

“In the Global OAB 12-week Phase 2/3 Population, TEAE related to rapid pulse rate (cardiac arrhythmia, mostly tachycardia) were more frequently observed in all active treatments (2.4 to 6.6%) than placebo (1.8%). The frequency of TEAE in cardiac arrhythmia was comparable for all mirabegron doses of 100 mg or less (2.4 to 3.1%) and tolterodine (3.1%) and was highest in mirabegron 200 mg (6.6%).

“Of the 10/4414 (0.2%) patients in the total mirabegron group who experienced a TEAE of atrial fibrillation, 5/4414 (0.1%) were SAE and 3/4414 (0.1%) led to permanent discontinuation of study drug.

“The overall occurrence of tachycardia events in the EU/NA OAB 12-week Phase 3 Population, either based on TEAE or observations of pulse rate ≥ 100 bpm captured by patient diary, was 48/1380 (3.5%) placebo, 22/432 (5.1%) mirabegron 25 mg, 57/1375 (4.1%) mirabegron 50 mg, 46/929 (5.0%) mirabegron 100 mg and 16/495 (3.2%) tolterodine patients.

“In the EU/NA Long-term Controlled Population, the occurrence of TEAE in the cardiac arrhythmia SMQ was comparable between mirabegron 50 and 100 mg (3.9 and 4.1%, respectively) and was less than tolterodine (6.0%).

Deaths

“There were 11 deaths in the mirabegron program, including 2 deaths in the ongoing 178-CL-090 study (one death on blinded treatment and one death that occurred prior to randomization). Nine deaths occurred in patients participating in completed trials (5 patients treated with mirabegron, one treated with placebo and 3 treated with tolterodine).”

Reviewer’s comments: In subjects under mirabegron, there were no seizures or sudden cardiac deaths reported. There were no reports of clinically relevant ECG changes. Hypertension cases were reported in the mirabegron and tolteradine arm with similar incidence rate.

3.5 CLINICAL PHARMACOLOGY

Appendix 5.6 summarizes the key features of mirabegron’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 69416. The sponsor submitted the study report 178-CL-077 for mirabegron, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 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

4.2.2 Protocol Number

178-CL-077

4.2.3 Study Dates

31 May 2010-17 Nov 2010

4.2.4 Objectives

The primary objective of this study was to evaluate the effect of repeat oral dosing of mirabegron (50, 100, and 200 mg q.d.) on QTcI interval in healthy male and female adult volunteers.

The secondary objectives of the study were to evaluate the effect of repeat oral doses of mirabegron (50, 100 and 200 mg q.d.) on QT interval corrected for heart rate using fixed mathematical form optimized for each subject (QTcIf) and QTcF interval in healthy adult volunteers; to characterize the pharmacokinetics of mirabegron in healthy adult volunteers and to evaluate safety and tolerability of mirabegron.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blinded, positive- and negative-controlled, parallel-crossover design with two dosing occasions. Each dosing occasion was followed by an at-least 12-day washout period.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were overencapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were two treatment arms. Because this study was a combined parallel-crossover study, subjects were given either a drug dosage or the positive control in one arm and the placebo in the other arm (see Table 3).

Table 3: Sponsor's Treatment Arms

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

Source: Sponsor's study report, page 30, Table 1.

4.2.6.2 Sponsor's Justification for Doses

The dose of 50 mg of mirabegron once daily was selected based on safety/efficacy in phase 2 trials and was the dose evaluated in phase 3 trials as a potential therapeutically relevant dose in the treatment of patients with OAB. Mirabegron doses of 100 mg and 200 mg once daily were selected as suprathreshold doses. Based on studies 178-CL-037 and 178-CL-076, which included both men and women, a 2-fold dose resulted in 2.5-fold AUC relative to the proposed therapeutic dose of 50 mg, whereas a 4-fold dose rendered AUC 6.4-fold relative to the proposed therapeutic dose of 50 mg. Therefore, evaluating mirabegron doses of 50, 100 and 200 mg once daily would fully define the dose-response and concentration-response for any effect of mirabegron on QTc interval. The following factors increase exposure to mirabegron: ketoconazole, 1.8-fold; severe renal impairment, 2.2-fold; and moderate hepatic impairment, 1.65-fold.

Reviewer's Comments: The tested doses are reasonable. 50 mg is the proposed therapeutic dose. 25 mg is the proposed dose for patients with severe renal impairment or moderate hepatic impairment. The expected high clinical exposure scenarios in C_{max} and AUC respectively are: 1) a 1.4-fold and 1.8-fold with ketoconazole, 2) 1.9-fold and 2.2-fold in severe renal impairment, and 3) 2.7-fold and 1.6-fold in moderate hepatic impairment. Although the above observations were from single dose studies, it should be reasonable to extrapolate to a steady state since there was no substantial change in $T_{1/2}$ in those scenarios. The suprathreshold doses of 100 mg and 200 mg produced 2.9-fold and 8.4-fold C_{max} and 2.6-fold and 6.5-fold AUC, respectively compared to those with 50 mg, which are adequate to cover any of the known high clinical exposure scenarios.

4.2.6.3 Instructions with Regard to Meals

Volunteers were admitted to the study center on day -4 and confined until the mid-day of day 11. Volunteers 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.

Reviewer's Comments: Administration under fasted conditions is acceptable. Co-administration of a 50-mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively.

4.2.6.4 ECG and PK Assessments

Continuous ECGs for evaluation of cardiac interval data were collected using a 12-lead (Mason-Likar electrode configuration) continuous ECG recorder storing the signals on a digital flashcard. All volunteers were connected to the continuous ECG recorder on days -3, -1, 1, 3, 10 and 11 of each treatment. In treatment periods 1 and 2 on days -3 and -1, for each treatment group, the following ECG variables in replicates of up to 5 were extracted at -0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 h postdose relative to dosing on Days 1-10 and at -0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 24 and 25 h post-dose on day 10 (24 and 25 h post-dose on day 10 correspond to 0 and 1 h, respectively, on day 11).

Blood samples were collected at the following time points: pre-dose on day 1 and day 9, and at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 14 h post-dose on day 10 and on day 11 (24 h post-dose on day 10).

Reviewer's Comment: The schedules of ECGs and blood sampling are acceptable. After oral administration of mirabegron in healthy volunteers, peak plasma concentrations (C_{max}) reached between 3 and 4 h. The ECG/PK sampling schedule is adequate to cover the steady state PK profile of mirabegron and assess drug-induced changes in the QT interval up to 25 h.

4.2.6.5 Baseline

The sponsor used a time-matched baseline.

4.2.7 ECG Collection

Continuous ECGs for evaluation of cardiac interval data were collected using a 12-lead (Mason-Likar electrode configuration) continuous ECG recorder storing the signals on a digital flashcard. All the recorders used to obtain the continuous ECGs of the study were of the same model by the same manufacturer (SEER MC version 2.0 recorders GE Healthcare, Milwaukee, WI).

The ECG monitoring devices store the captured ECG signal on flash cards with a sampling frequency of 250 Hz.

Before finalizing the QT interval data, ECG measurements were reviewed by a single senior cardiologist with the possibility of correcting the previously made measurements.

The ECG laboratory ensured that all ECGs from the same subject were always measured by the same pair of observers and by the same senior cardiologist.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 352 volunteers were randomized and received at least one dose of study drug. Of these volunteers, 33 were prematurely discontinued due to one of the following reasons: withdrawal of consent (3.1% [11/352]), protocol violations (2.3% [8/352]) or due to an AE (2.0% [7/352]) or other (1.1% [4/352]).

The mean age of volunteers in this study was 32.6 years for volunteers in the total mirabegron treatment group and 33.0 years for volunteers in the moxifloxacin treatment group with a range of 18 to 55 years across all treatment groups.

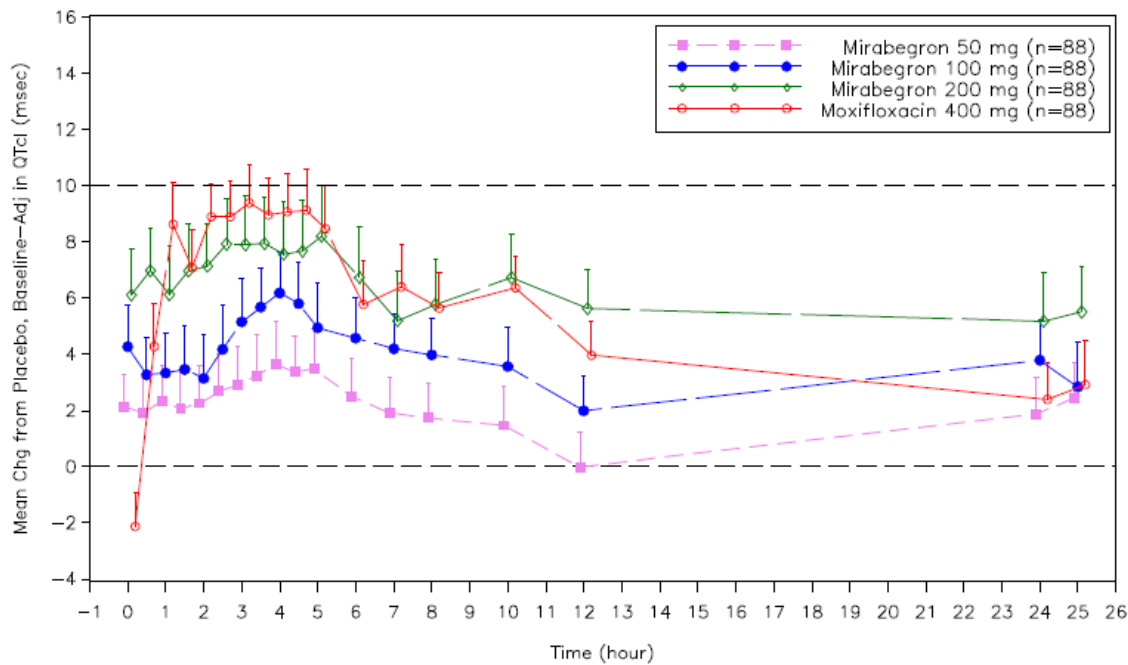
As per the design of the study, the ratio of males and females per treatment group were equal. The mean BMI for volunteers was about 25 kg/m² across all treatment groups.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the change from the baseline-adjusted mean difference between mirabegron and placebo in QTcI. The sponsor used a constrained longitudinal model. The sponsor's results are shown in Figure 1. The sponsor found that the 50 mg and 100 mg dosages of mirabegron did not result in elongated QT intervals, while the 200 mg dosage did result in elongated QT intervals only in the female subjects. While we did not separate results by gender in our independent analysis, our overall analysis agrees with the sponsor's results (see section 5.3).

Figure 1: Sponsor's Mean $\Delta\Delta$ QTcI for Mirabegron



Source: Sponsor's study report, Figure 12.5.6.2

4.2.8.2.2 Assay Sensitivity

The sponsor's results on assay sensitivity are shown in Figure 1. At least one of the lower bounds on the 90% confidence intervals is above 5 ms. Our independent analysis agrees with the sponsor's conclusions (see section 5.3).

4.2.8.3 Safety Analysis

The majority of TEAE were mild in severity. Two volunteers had a severe TEAE. Volunteer No. 2274-7163 (a 22-year-old Black or African American woman) in the mirabegron 50-mg group had a severe toothache during placebo treatment. Volunteer No. 2274-7355 (a 51-year-old American Indian or Alaska Native woman) in the mirabegron 200 mg group had severe sciatica during treatment with mirabegron 200 mg resulting in discontinuation of study drug. The TEAE was considered not related to study drug.

There was only one SAE (PT: thyroid neoplasm) reported by a female volunteer (Volunteer No. 2274-7362) in the mirabegron 100-mg group.

The most common drug-related TEAE was headache. A higher occurrence of headaches was observed in the mirabegron 200-mg (22/86 [25.6%]) group compared with the other treatment groups (placebo: 39/339 [11.5%]; mirabegron 50 mg: 11/84 [13.1%]; mirabegron 100 mg: 13/83 [15.7%] and moxifloxacin: 11/85 [12.9%]).

A higher occurrence of palpitations was observed in the mirabegron 200-mg group compared to other treatment groups (17.4 % in the 200-mg-dose group versus 6% in the 100-mg-dose group and 1.5% in the 50-mg-dose group).

The frequency of TEAE of palpitation was higher in female volunteers (placebo: 3/168 [1.8%]; mirabegron 50 mg: 5/41 [12.2%], mirabegron 100 mg: 3/42 [7.1%]; mirabegron 200 mg: 12/43 [27.9%]; moxifloxacin: 2/42 [4.8%]) compared to male volunteers (placebo: 2/171 [1.2%]; mirabegron 50 mg: 0; mirabegron 100 mg: 2/41 [4.9%]; mirabegron 200 mg: 3/43 [7.0%]; moxifloxacin: 1/43 [2.3%]).

In the mirabegron groups, 3 volunteers reported TEAE of palpitations and tachycardia that resulted in permanent discontinuation of study drug (2 in the 100-mg-dose group and 1 in the 200-mg-dose group).

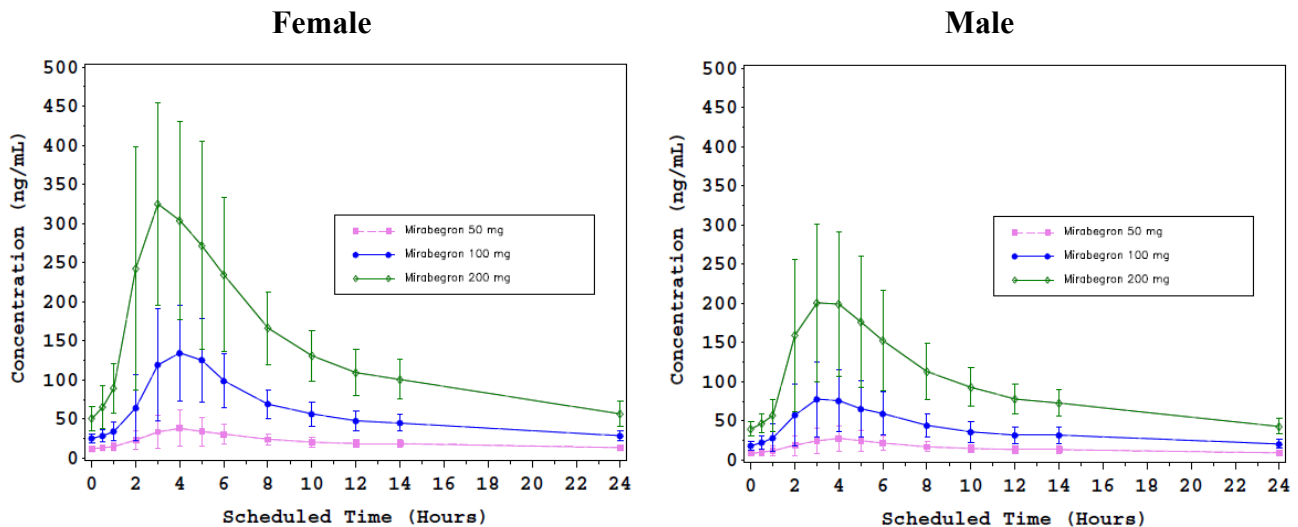
Two events of syncope were reported: one event occurred in a volunteer randomized to the mirabegron 100-mg group and the other event occurred in a volunteer randomized to the placebo group. By reviewing narratives the event was not related to study medication (i.e., the mirabegron case occurred 13 days after dosing with 100 mg mirabegron ended).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean concentration-time profiles of mirabegron by gender at different dose levels are shown in Figure 2. Mean PK parameters are shown in Table 4.

Figure 2: Mean (+/-SD) Concentration-Time Profiles of Mirabegron on Day 10, by Sex



(Source: Sponsor's Study Report, Figure 2 on Page 73)

Table 4: Summary of Plasma Pharmacokinetic Parameters of Mirabegron on Day 10, by Gender

Parameter	Mirabegron 50 mg (n = 84)		Mirabegron 100 mg (n = 82)		Mirabegron 200 mg (n = 83)	
	Female	Male	Female	Male	Female	Male
n	41	43	41	41	40	43
AUC_{tau} (ng·h/mL)						
Mean	503.4	361.0	1386.9	916.6	3273.7	2237.0
(SD)	(138.42)	(126.80)	(342.53)	(296.69)	(836.52)	(586.90)
Min-Max	264.7-927.2	45.8-646.8	724.7-2012.8	292.3-1558.7	1696.8-5445.0	1434.5-3740.1
C_{max} (ng/mL)						
Mean	47.90	36.29	171.68	105.62	409.21	266.51
(SD)	(25.601)	(17.919)	(53.927)	(46.266)	(139.373)	(94.420)
Min-Max	15.03-132.28	3.90-86.03	81.31-270.46	19.69-235.37	153.36-705.74	101.89-527.24
t_{max} (h)						
Mean	3.84	3.69	3.97	3.28	3.45	3.49
(SD)	(1.327)	(1.058)	(1.129)	(1.198)	(1.011)	(1.125)
Min-Max	1.17-8.30	2.17-6.17	2.17-6.20	1.17-6.18	2.13-6.20	2.17-6.17
C₂₄ (ng/mL)						
Mean	13.69	9.41	28.73	20.73	56.72	43.04
(SD)	(3.075)	(3.077)	(6.373)	(5.752)	(16.426)	(10.178)
Min-Max	7.57-19.94	1.25-15.43	17.22-42.63	5.61-33.18	37.46-118.04	24.42-64.47

(Source: Sponsor's Clinical Study Report, Table 11 on Page 76)

Reviewer's Comments: The sampling schedule appears adequate to characterize the steady state PK profile of mirabegron.

4.2.8.4.2 Exposure-Response Analysis

The relationship between mirabegron exposure and the changes in mean difference in baseline-adjusted QTcI from placebo ($\Delta\Delta\text{QTcI}$) was explored within each sex group through a linear mixed effects model. In female and male volunteers, the slope of the $\Delta\Delta\text{QTcI}$ versus mirabegron concentration was positive and significant, suggesting that an increase in mirabegron concentration produced an increase in $\Delta\Delta\text{QTcI}$ (Table 5). The results were similar in the overall population (both female and male volunteers).

Table 5: Relationship Between Mirabegron Plasma Concentrations and $\Delta\Delta\text{QTcI}$, by Gender

Analyte	Parameter Estimate (msec) (P-value)		Predicted Mean ddQTc (90% CI) [†]		
	Intercept	Slope	Mirabegron 50 mg	Mirabegron 100 mg	Mirabegron 200 mg
Female					
YM178	4.48 (<0.001)	0.0112 (0.0047)	4.97 (3.90, 6.03)	6.31 (5.09, 7.53)	8.81 (6.52, 11.10)
Male					
YM178	2.40 (<0.001)	0.0220 (<0.001)	3.10 (2.22, 3.97)	4.49 (3.51, 5.46)	7.91 (5.98, 9.83)

(Source: Sponsor's Clinical Study Report, Table 17 on Page 89)

Reviewer's Comments: The reviewer performed independent analysis (See section 5.3). Consistent with the sponsor's results, the slope of the concentration-response relationship is positive and significant. The mean 90% $\Delta\Delta QTcI$ upper bound exceeded 10 ms only for 200-mg-dose level in females which is consistent with the E14 analysis. However, it is important to note that the exposures achieved with this dose are several fold what is expected with the proposed therapeutic dose of 50 mg.

5 REVIEWERS' ASSESSMENT

5.1 REMARKS ON FDA ANALYSIS

Because the study design was unusual for a TQT study, our analysis has several different details compared to most FDA TQT analyses. The study was a combined crossover-parallel study, resulting in four treatment groups and four corresponding placebo groups. We checked that the placebo groups were similar in the baseline and change from baseline QTc variables before proceeding with our analysis.

Rather than perform one large analysis, we analyzed each treatment arm as a separate crossover study. This approach was appropriate because of the similarities of the placebo groups. The analysis included separate results by gender if there was a clear difference in the effect of mirabegron on the length of QT intervals between male and female subjects (see section 5.3.1.2).

5.2 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used a mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 6, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

Table 6: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	P-value
Mirabegron 50 mg	-0.0107	0.0021	0
Mirabegron 100 mg	-0.0110	-0.0006	0
Mirabegron 200 mg	-0.0048	0.0021	0
Moxifloxacin 400 mg	-0.0150	-0.0042	0

We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it also appears that QTcI is

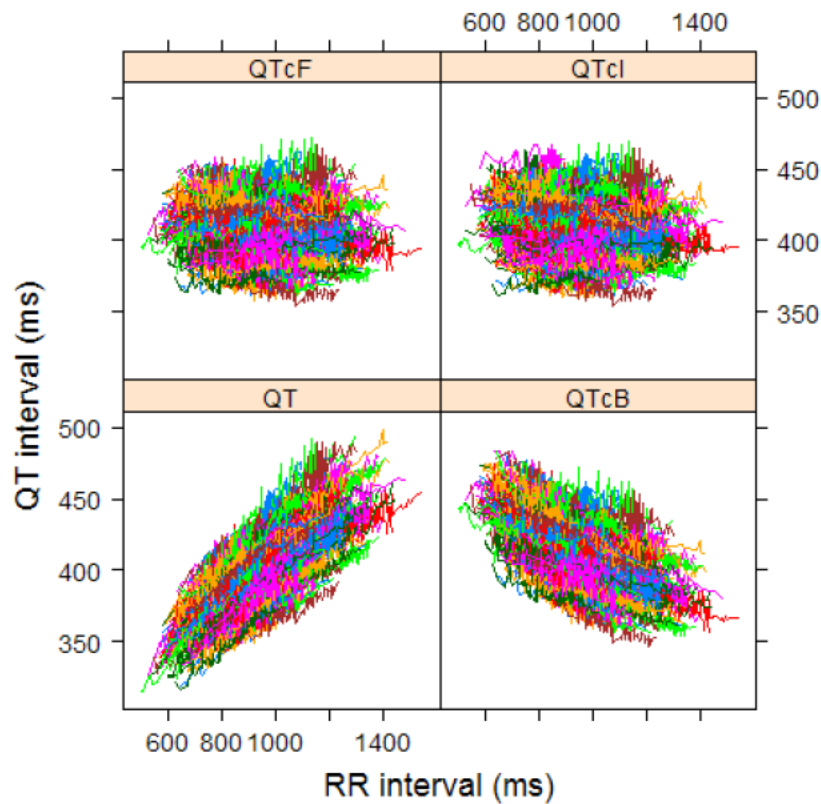
the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
Mirabegron 50 mg	84	0.0006	84	0.0003
Mirabegron 100 mg	84	0.0007	84	0.0003
Mirabegron 200 mg	87	0.0006	87	0.0004
Moxifloxacin 400 mg	86	0.0007	86	0.0004

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.3 STATISTICAL ASSESSMENTS

5.3.1 QTc Analysis

5.3.1.1 The Primary Analysis for Mirabegron

The statistical reviewer used a mixed model to analyze the ΔQTcI effect. The model includes treatment, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 8, Table 9, and Table 10.

Table 8: Analysis Results of ΔQTcI and $\Delta\Delta\text{QTcI}$ for Treatment Group A: Mirabegron 50 mg x 10 days

Time	ΔQTcI : Mirabegron 50 mg			ΔQTcI : Placebo			$\Delta\Delta\text{QTcI}$			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	84	1.0	0.6	87	-1.2	0.6	84	2.1	0.7	(0.9, 3.3)
1	84	2.2	0.7	87	-0.2	0.6	84	2.5	0.7	(1.3, 3.7)
1.5	84	2.8	0.7	87	0.6	0.7	84	2.2	0.8	(0.9, 3.5)
2	84	3.0	0.7	87	0.6	0.7	84	2.4	0.8	(1.1, 3.6)
2.5	84	2.1	0.7	87	-0.8	0.7	84	2.9	0.8	(1.6, 4.1)
3	84	1.6	0.6	87	-1.6	0.6	84	3.1	0.8	(1.8, 4.4)
3.5	84	1.9	0.7	87	-1.4	0.6	84	3.3	0.8	(2.0, 4.7)
4	84	2.0	0.7	87	-1.7	0.7	84	3.7	0.8	(2.3, 5.1)
4.5	84	2.3	0.6	87	-1.2	0.6	84	3.5	0.7	(2.2, 4.7)
5	84	2.4	0.6	87	-1.2	0.6	84	3.6	0.8	(2.3, 5.0)
6	84	2.5	0.6	87	-0.1	0.6	84	2.6	0.8	(1.4, 3.9)
7	83	1.3	0.6	86	-0.9	0.6	83	2.2	0.8	(1.0, 3.5)
8	84	1.9	0.6	86	0.0	0.6	84	1.9	0.7	(0.7, 3.1)
10	84	3.4	0.7	87	1.7	0.7	84	1.7	0.8	(0.3, 3.0)
12	83	1.7	0.6	86	1.6	0.6	83	0.1	0.7	(-1.0, 1.3)
24	84	0.8	0.6	87	-1.3	0.6	84	2.1	0.8	(0.8, 3.4)
25	84	2.0	0.6	87	-0.7	0.6	84	2.7	0.7	(1.4, 3.9)

**Table 9: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group B:
Mirabegron 100 mg x 10 days**

	Δ QTcI: Mirabegron 100 mg			Δ QTcI: Placebo			$\Delta\Delta$ QTcI			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	82	2.1	0.7	84	-1.0	0.7	82	3.1	0.8	(1.8, 4.4)
1	82	3.6	0.8	84	0.5	0.7	82	3.2	0.8	(1.8, 4.6)
1.5	82	3.9	0.8	84	0.6	0.8	82	3.3	0.9	(1.7, 4.8)
2	82	4.2	0.7	84	1.1	0.7	82	3.0	0.9	(1.4, 4.6)
2.5	82	3.3	0.7	84	-0.8	0.7	82	4.1	0.9	(2.5, 5.6)
3	82	3.6	0.7	84	-1.4	0.7	82	5.1	0.9	(3.5, 6.6)
3.5	82	3.9	0.7	84	-1.7	0.7	82	5.7	0.8	(4.3, 7.0)
4	82	4.7	0.8	84	-1.4	0.8	82	6.1	0.9	(4.7, 7.6)
4.5	82	4.0	0.7	84	-1.7	0.7	82	5.7	0.9	(4.2, 7.1)
5	82	3.9	0.7	84	-1.0	0.7	82	4.9	0.9	(3.3, 6.4)
6	81	4.8	0.7	84	0.2	0.7	81	4.6	0.9	(3.2, 6.0)
7	81	3.8	0.6	84	-0.4	0.6	81	4.2	0.8	(2.9, 5.5)
8	82	3.6	0.6	84	-0.3	0.6	82	3.9	0.8	(2.6, 5.3)
10	82	5.2	0.7	84	1.8	0.7	82	3.4	0.8	(2.1, 4.8)
12	82	2.8	0.6	84	0.8	0.6	82	2.0	0.7	(0.7, 3.2)
24	82	2.1	0.7	84	-1.5	0.7	82	3.6	0.9	(2.2, 5.1)
25	82	2.6	0.8	84	0.0	0.8	82	2.6	0.9	(1.0, 4.1)

**Table 10: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group C:
Mirabegron 200 mg x 10 days**

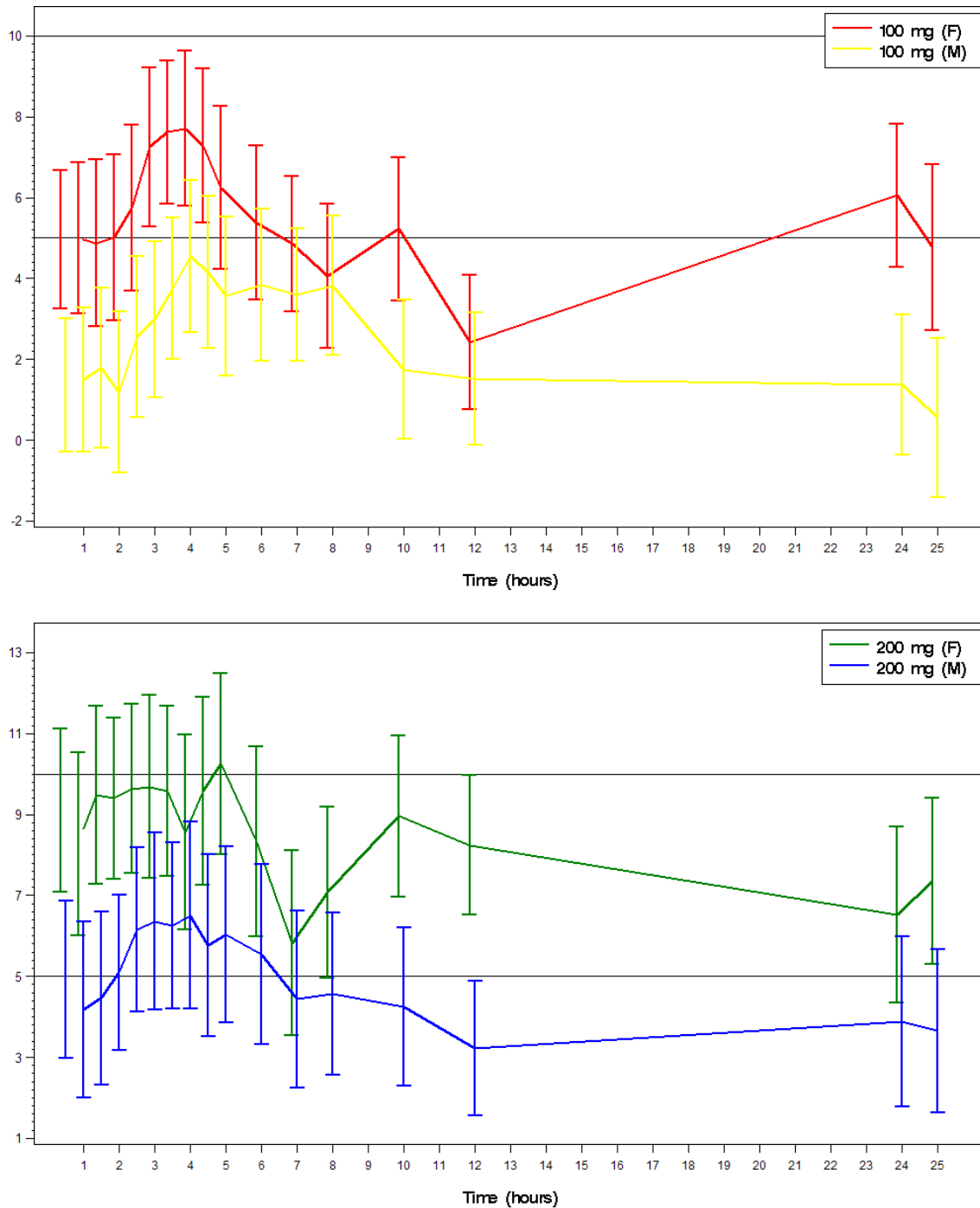
	Δ QTcI: Mirabegron 200 mg			Δ QTcI: Placebo			$\Delta\Delta$ QTcI			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	80	6.3	0.8	82	-0.6	0.8	80	6.9	0.9	(5.4, 8.4)
1	80	6.9	0.9	82	0.8	0.9	80	6.1	1.0	(4.4, 7.8)
1.5	80	8.3	0.9	82	1.4	0.9	80	6.9	1.0	(5.2, 8.5)
2	80	8.3	0.8	82	1.2	0.8	80	7.2	0.9	(5.7, 8.6)
2.5	81	7.4	0.8	82	-0.4	0.8	81	7.8	0.9	(6.3, 9.4)
3	80	6.9	0.8	82	-1.0	0.8	80	8.0	1.0	(6.3, 9.7)
3.5	81	7.1	0.8	82	-0.8	0.8	81	7.9	1.0	(6.3, 9.4)
4	80	7.0	0.8	82	-0.5	0.8	80	7.5	1.1	(5.7, 9.3)
4.5	80	6.9	0.8	82	-0.7	0.8	80	7.6	1.1	(5.8, 9.4)
5	79	6.7	0.8	82	-1.4	0.8	79	8.1	1.0	(6.3, 9.8)
6	77	7.3	0.8	81	0.5	0.8	77	6.8	1.1	(5.1, 8.6)
7	79	6.3	0.8	82	1.2	0.8	79	5.1	1.0	(3.4, 6.8)
8	80	7.1	0.7	82	1.3	0.7	80	5.7	1.0	(4.2, 7.3)
10	81	8.5	0.8	82	1.9	0.8	81	6.6	0.9	(5.0, 8.1)
12	81	7.2	0.7	82	1.6	0.7	81	5.6	0.8	(4.3, 7.0)
24	82	3.9	0.8	82	-1.2	0.8	82	5.2	1.0	(3.5, 6.8)
25	82	5.4	0.8	82	-0.0	0.8	82	5.5	0.9	(3.9, 7.0)

The largest upper bounds of the 2-sided 90% CI for the mean difference between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo were 5.1 ms, 7.6 ms, and 9.8 ms, respectively.

5.3.1.2 Gender Analysis for Mirabegron

As the sponsor noted, mirabegron appears to have a stronger affect on QT interval length in the female subjects. We repeated our analysis with the subjects split by gender. At the 50 mg dosage, the upper bound of the one-sided 95% CI is below 10 ms for both male and female subjects. Although this is true for the 100-mg dosage as well, the largest upper bound for female subjects is quite close to 10 ms (9.5 ms at hour 4). At the 200-mg dosage, the upper CI bounds for female subjects is larger than 10 ms at 11 time points. The largest upper bound is 12.9 ms at hour 5. See Figure 4.

Figure 4: Mean and 90% CI $\Delta\Delta QTcI$ Timecourse by Gender



Reviewer's comment: The $\Delta\Delta QT$ difference for the 200-mg dosage can be explained by the higher exposure for female subjects. See section 5.4 for details.

5.3.1.3 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 11. The largest unadjusted 90% lower

confidence interval is 8.1 ms. When considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.6 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 11: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin

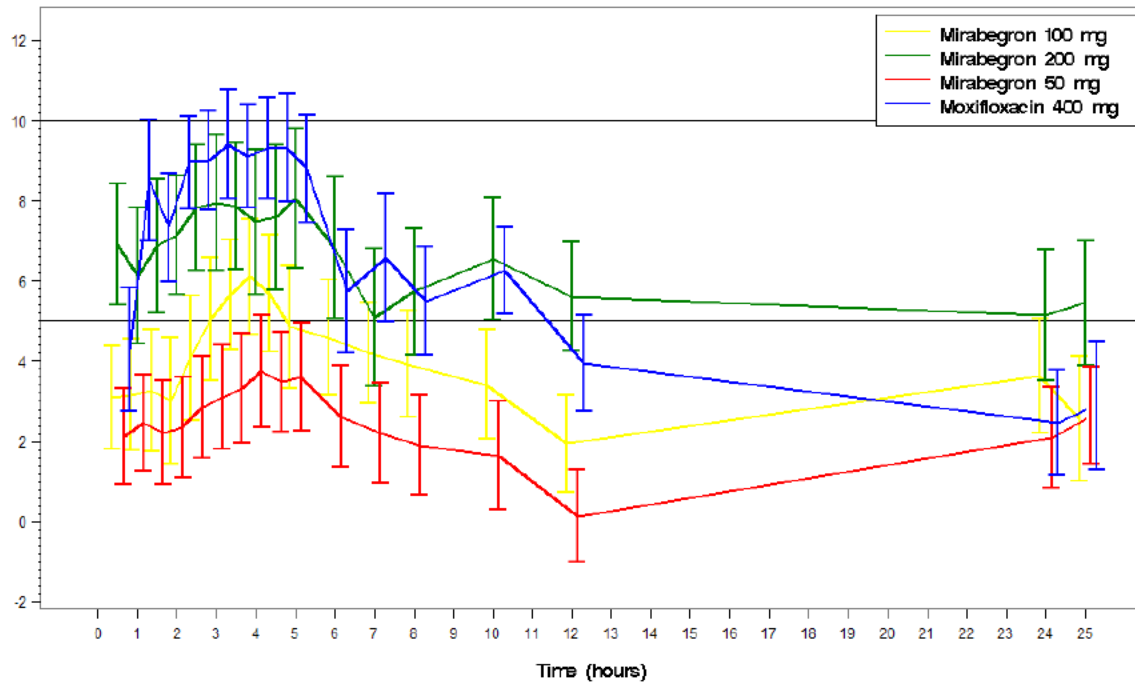
	Δ QTcI: Moxifloxacin			Δ QTcI: Placebo			$\Delta\Delta$ QTcI				
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	Unadjusted 90% CI	Adjusted* 90% CI
0.5	84	4.3	0.8	83	0.0	0.8	83	4.3	0.9	(2.8, 5.8)	(2.2, 6.4)
1	84	9.2	0.8	83	0.7	0.8	83	8.5	0.9	(7.0, 10.0)	(6.4, 10.6)
1.5	84	8.7	0.8	83	1.4	0.8	83	7.3	0.8	(6.0, 8.7)	(5.5, 9.2)
2	84	9.8	0.8	83	0.9	0.8	83	9.0	0.7	(7.8, 10.1)	(7.4, 10.6)
2.5	84	8.8	0.8	83	-0.2	0.8	83	9.0	0.7	(7.8, 10.2)	(7.3, 10.7)
3	84	9.0	0.8	83	-0.4	0.8	83	9.4	0.8	(8.1, 10.8)	(7.6, 11.3)
3.5	84	8.7	0.7	83	-0.4	0.8	83	9.1	0.8	(7.8, 10.4)	(7.4, 10.9)
4	84	8.4	0.8	83	-0.9	0.8	83	9.3	0.8	(8.1, 10.6)	(7.6, 11.0)
4.5	84	8.9	0.8	83	-0.4	0.8	83	9.3	0.8	(8.0, 10.7)	(7.5, 11.2)
5	83	8.3	0.8	83	-0.5	0.8	83	8.8	0.8	(7.5, 10.1)	(7.0, 10.6)
6	81	6.0	0.8	81	0.3	0.8	81	5.8	0.9	(4.2, 7.3)	(3.6, 7.9)
7	82	7.0	0.8	82	0.4	0.8	82	6.6	1.0	(5.0, 8.2)	(4.4, 8.8)
8	81	6.7	0.7	82	1.2	0.7	81	5.5	0.8	(4.1, 6.9)	(3.6, 7.4)
10	83	8.6	0.7	83	2.3	0.7	83	6.3	0.7	(5.2, 7.3)	(4.8, 7.7)
12	82	5.0	0.6	83	1.1	0.6	82	3.9	0.7	(2.7, 5.2)	(2.3, 5.6)
24	83	2.1	0.8	83	-0.4	0.8	83	2.5	0.8	(1.2, 3.8)	(0.7, 4.3)
25	83	3.4	0.8	83	0.5	0.8	83	2.9	1.0	(1.3, 4.5)	(0.7, 5.1)

* Bonferroni correction was applied for multiple endpoint adjustment for 4 time points.

5.3.1.4 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcI for different treatment groups.

Figure 5: Mean and 90% CI $\Delta\Delta$ QTcI Timecourse



All CIs are unadjusted, including moxifloxacin.

5.3.1.5 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms, including all placebo groups.

Table 12: Categorical Analysis for QTcI

	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms	Value > 480 ms
Treatment Group				
Mirabegron 50 mg	84	82 (97.6%)	2 (2.4%)	0 (0.0%)
Mirabegron 100 mg	82	81 (98.8%)	1 (1.2%)	0 (0.0%)
Mirabegron 200 mg	82	77 (93.9%)	5 (6.1%)	0 (0.0%)
Moxifloxacin 400 mg	84	79 (94.0%)	5 (6.0%)	0 (0.0%)

Table 13 lists the categorical analysis results for Δ QTcI. No subject's change from baseline was above 60 ms, including all placebo groups.

Table 13: Categorical Analysis of $\Delta QTCI$

	Total N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms	Value > 60 ms
Treatment Group				
Mirabegron 50 mg	83	83 (100%)	0 (0.0%)	0 (0.0%)
Mirabegron 100 mg	81	81 (100%)	0 (0.0%)	0 (0.0%)
Mirabegron 200 mg	82	80 (97.6%)	2 (2.4%)	0 (0.0%)
Moxifloxacin 400 mg	83	82 (98.8%)	1 (1.2%)	0 (0.0%)

5.3.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 14, Table 15, and Table 16. The largest upper limits of 90% CI for the HR mean differences between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo are 8.1, 12.9, and 18.7 bpm, respectively. The results for female subjects only are presented in Table 17, Table 18, and Table 19.

Table 14: Analysis Results of ΔHR and $\Delta\Delta HR$ for Treatment Group A: Mirabegron 50 mg x 10 days

Time (hr)	ΔHR : Mirabegron 50 mg			ΔHR : Placebo			$\Delta\Delta HR$			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	84	4.5	0.5	87	0.6	0.5	84	3.8	0.7	(2.6, 5.0)
1	84	4.3	0.5	87	0.0	0.5	84	4.3	0.7	(3.2, 5.5)
1.5	84	5.3	0.6	87	0.5	0.6	84	4.7	0.8	(3.4, 6.1)
2	84	5.0	0.6	87	0.5	0.5	84	4.6	0.8	(3.3, 5.9)
2.5	84	5.2	0.5	87	0.0	0.5	84	5.1	0.7	(4.0, 6.3)
3	84	5.7	0.5	87	-0.1	0.5	84	5.8	0.7	(4.5, 7.0)
3.5	84	5.4	0.5	87	0.1	0.5	84	5.3	0.7	(4.1, 6.5)
4	84	6.0	0.6	87	-0.5	0.6	84	6.4	0.8	(5.1, 7.8)
4.5	84	6.6	0.5	87	-0.1	0.5	84	6.7	0.8	(5.4, 7.9)
5	84	6.1	0.6	87	-0.7	0.6	84	6.7	0.9	(5.3, 8.1)
6	84	6.6	0.7	87	0.8	0.7	84	5.8	0.9	(4.2, 7.4)
7	83	5.9	0.7	87	0.5	0.6	83	5.5	0.9	(3.9, 7.0)
8	84	6.0	0.8	87	1.0	0.7	84	5.0	1.0	(3.3, 6.8)
10	84	5.7	0.7	87	0.5	0.7	84	5.2	1.0	(3.6, 6.8)
12	83	6.0	0.7	87	1.2	0.7	83	4.8	0.9	(3.3, 6.4)
24	84	6.2	0.6	87	2.4	0.5	84	3.9	0.8	(2.6, 5.2)
25	84	7.2	0.6	87	3.4	0.6	84	3.7	0.8	(2.4, 5.1)

**Table 15: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group B: Mirabegron
100 mg x 10 days**

	Δ HR: Mirabegron 100 mg			Δ HR: Placebo			$\Delta\Delta$ HR			
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	82	7.1	0.6	84	-0.2	0.6	82	7.3	0.8	(5.9, 8.6)
1	82	7.2	0.6	84	0.0	0.6	82	7.2	0.9	(5.7, 8.7)
1.5	82	8.0	0.6	84	-0.1	0.6	82	8.1	0.9	(6.6, 9.6)
2	82	8.3	0.6	84	0.1	0.6	82	8.2	0.8	(6.9, 9.5)
2.5	82	8.1	0.6	84	0.1	0.6	82	8.0	0.9	(6.6, 9.4)
3	82	8.6	0.6	84	0.1	0.6	82	8.5	0.8	(7.1, 9.8)
3.5	82	9.5	0.6	84	0.1	0.6	82	9.5	0.9	(8.0, 10.9)
4	82	10.6	0.6	84	-0.4	0.6	82	11.0	0.9	(9.6, 12.5)
4.5	82	10.6	0.6	84	-0.0	0.6	82	10.6	0.9	(9.1, 12.1)
5	82	10.4	0.7	84	-0.6	0.7	82	11.0	1.0	(9.4, 12.6)
6	82	11.9	0.8	84	1.0	0.8	82	11.0	1.1	(9.1, 12.9)
7	81	10.5	0.8	84	0.4	0.8	81	10.2	1.1	(8.3, 12.0)
8	82	11.0	0.8	84	-0.1	0.8	82	11.1	1.1	(9.2, 12.9)
10	82	9.3	0.7	84	0.2	0.7	82	9.2	1.0	(7.4, 10.9)
12	82	8.4	0.7	84	0.8	0.7	82	7.5	1.0	(5.9, 9.1)
24	82	9.3	0.6	84	1.8	0.6	82	7.5	0.9	(6.1, 9.0)
25	82	10.2	0.6	84	2.8	0.6	82	7.5	0.9	(6.1, 8.9)

Table 16: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group C: Mirabegron 200 mg x 10 days

	Δ HR: Mirabegron 200 mg			Δ HR: Placebo			$\Delta\Delta$ HR			
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	81	11.1	0.6	83	-0.2	0.6	81	11.4	0.8	(10.0, 12.8)
1	81	10.9	0.7	83	-0.3	0.7	81	11.2	1.0	(9.6, 12.7)
1.5	81	12.0	0.7	83	-0.5	0.7	81	12.5	0.9	(10.9, 14.0)
2	81	13.3	0.7	83	0.1	0.7	81	13.2	0.9	(11.6, 14.7)
2.5	82	14.0	0.7	83	-0.1	0.7	82	14.0	1.0	(12.4, 15.7)
3	81	15.0	0.8	83	0.2	0.8	81	14.8	1.1	(13.1, 16.6)
3.5	82	15.7	0.7	83	-0.3	0.7	82	16.0	1.1	(14.3, 17.7)
4	81	16.1	0.8	83	0.0	0.8	81	16.1	1.2	(14.2, 18.0)
4.5	81	16.5	0.7	83	0.1	0.7	81	16.4	1.0	(14.8, 18.1)
5	80	16.2	0.7	83	-0.8	0.7	80	17.0	1.0	(15.3, 18.7)
6	80	16.5	0.8	82	0.6	0.8	80	15.9	1.1	(14.1, 17.8)
7	81	16.0	0.8	83	0.9	0.8	81	15.1	1.2	(13.2, 17.0)
8	82	16.6	0.8	83	1.1	0.8	82	15.5	1.1	(13.7, 17.3)
10	82	14.3	0.7	83	0.1	0.7	82	14.2	1.0	(12.6, 15.9)
12	82	14.0	0.7	83	0.6	0.7	82	13.4	1.0	(11.8, 15.1)
24	83	12.8	0.6	83	1.6	0.6	83	11.2	0.8	(9.9, 12.5)
25	83	13.4	0.6	83	2.8	0.6	83	10.6	0.9	(9.1, 12.0)

Table 17: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group A: Mirabegron 50 mg x 10 days (Female Subjects Only)

	Δ HR: Mirabegron 50 mg			Δ HR: Placebo			$\Delta\Delta$ HR			
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	41	5.0	0.8	44	-0.2	0.7	41	5.2	1.1	(3.4, 6.9)
1	41	4.8	0.8	44	-0.5	0.7	41	5.3	1.1	(3.5, 7.1)
1.5	41	6.4	0.9	44	0.1	0.9	41	6.3	1.3	(4.1, 8.5)
2	41	5.4	0.9	44	-0.1	0.9	41	5.5	1.2	(3.5, 7.6)
2.5	41	5.8	0.8	44	0.1	0.7	41	5.7	1.1	(3.9, 7.5)
3	41	7.3	0.8	44	0.1	0.8	41	7.2	1.1	(5.3, 9.0)
3.5	41	6.9	0.8	44	-0.1	0.8	41	7.0	1.1	(5.2, 8.8)
4	41	7.2	0.9	44	-0.8	0.9	41	8.0	1.3	(5.9, 10.2)
4.5	41	8.0	0.9	44	-0.3	0.8	41	8.3	1.2	(6.3, 10.3)
5	41	7.6	1.0	44	-0.8	1.0	41	8.3	1.4	(6.0, 10.7)
6	41	7.7	1.1	44	-0.3	1.1	41	8.0	1.5	(5.5, 10.6)
7	41	6.9	1.0	44	-0.8	0.9	41	7.6	1.3	(5.4, 9.9)
8	41	7.0	1.2	44	0.4	1.2	41	6.6	1.7	(3.8, 9.4)
10	41	7.3	1.1	44	0.5	1.0	41	6.7	1.5	(4.2, 9.2)
12	40	7.2	1.0	44	0.8	1.0	40	6.4	1.4	(4.0, 8.7)
24	41	7.2	0.8	44	1.9	0.7	41	5.3	1.1	(3.6, 7.1)
25	41	8.4	0.8	44	2.4	0.8	41	5.9	1.2	(4.0, 7.9)

Table 18: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group B: Mirabegron 100 mg x 10 days (Female Subjects Only)

	Δ HR: Mirabegron 100 mg			Δ HR: Placebo			$\Delta\Delta$ HR			
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	41	7.1	0.9	41	-0.9	0.9	41	8.0	1.3	(5.9, 10.1)
1	41	7.7	1.0	41	-0.3	1.0	41	8.0	1.4	(5.7, 10.3)
1.5	41	9.4	0.9	41	-0.6	0.9	41	9.9	1.3	(7.8, 12.1)
2	41	9.5	0.8	41	-0.4	0.8	41	9.9	1.1	(8.0, 11.7)
2.5	41	9.4	0.9	41	-0.2	0.9	41	9.6	1.3	(7.4, 11.8)
3	41	10.2	0.8	41	-0.8	0.8	41	11.0	1.2	(9.0, 13.0)
3.5	41	10.7	1.0	41	-0.5	0.9	41	11.2	1.3	(9.0, 13.5)
4	41	12.4	0.9	41	-1.6	0.9	41	14.0	1.3	(11.8, 16.1)
4.5	41	12.3	1.0	41	-0.6	1.0	41	12.8	1.4	(10.5, 15.2)
5	41	12.3	1.0	41	-1.3	1.0	41	13.6	1.5	(11.2, 16.0)
6	41	13.2	1.3	41	0.3	1.3	41	12.8	1.8	(9.8, 15.8)
7	40	11.8	1.3	41	0.5	1.2	40	11.3	1.8	(8.4, 14.3)
8	41	11.7	1.2	41	-0.6	1.2	41	12.2	1.7	(9.4, 15.1)
10	41	11.8	1.1	41	0.6	1.1	41	11.2	1.6	(8.6, 13.8)
12	41	10.2	0.9	41	1.4	0.9	41	8.8	1.2	(6.8, 10.8)
24	41	10.0	0.9	41	0.8	0.9	41	9.2	1.2	(7.2, 11.3)
25	41	11.3	0.9	41	2.5	0.9	41	8.8	1.3	(6.6, 11.0)

Table 19: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group C: Mirabegron 200 mg x 10 days (Female Subjects Only)

	Δ HR: Mirabegron 200 mg			Δ HR: Placebo			$\Delta\Delta$ HR			
Time (hr)	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	38	12.3	0.9	42	-0.6	0.8	38	12.9	1.2	(10.9, 14.9)
1	38	12.3	0.9	42	-0.2	0.9	38	12.5	1.3	(10.4, 14.6)
1.5	38	15.1	0.9	42	-0.7	0.9	38	15.8	1.3	(13.6, 18.0)
2	38	16.5	1.0	42	0.2	0.9	38	16.3	1.3	(14.1, 18.5)
2.5	39	18.0	1.0	42	0.2	1.0	39	17.8	1.4	(15.5, 20.1)
3	38	18.6	1.1	42	0.5	1.1	38	18.1	1.5	(15.5, 20.6)
3.5	39	19.4	1.0	42	-0.4	1.0	39	19.7	1.4	(17.4, 22.1)
4	38	19.4	1.3	42	0.2	1.2	38	19.2	1.8	(16.3, 22.2)
4.5	38	20.1	1.0	42	0.5	1.0	38	19.6	1.4	(17.3, 21.9)
5	38	18.9	1.0	42	-1.1	1.0	38	20.0	1.4	(17.6, 22.3)
6	38	18.5	1.1	41	-0.1	1.0	38	18.6	1.5	(16.1, 21.1)
7	39	17.4	1.1	42	0.2	1.0	39	17.2	1.5	(14.7, 19.7)
8	39	18.3	1.0	42	0.6	1.0	39	17.8	1.4	(15.4, 20.1)
10	39	17.0	0.9	42	-0.4	0.9	39	17.3	1.3	(15.2, 19.5)
12	39	16.7	0.9	42	0.6	0.9	39	16.1	1.3	(13.9, 18.3)
24	40	14.0	0.9	42	1.0	0.9	40	13.0	1.2	(10.9, 15.1)
25	40	15.0	0.9	42	2.4	0.9	40	12.7	1.3	(10.5, 14.9)

5.3.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 20, Table 21, and Table 22. The largest upper limits of 90% CI for the PR mean differences between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo are 0.7 ms, 1.3 ms, and 5.6 ms, respectively.

The outlier analysis results for PR are presented in Table 23.

**Table 20: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group A: Mirabegron
50 mg X 10 days**

	Δ PR: Mirabegron 50 mg			Δ PR: Placebo			$\Delta\Delta$ PR			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	84	0.4	0.8	87	3.3	0.8	84	-2.9	1.1	(-4.7, -1.1)
1	84	-0.1	0.7	87	2.0	0.7	84	-2.0	1.0	(-3.7, -0.4)
1.5	84	-0.4	0.7	87	2.2	0.7	84	-2.6	1.0	(-4.3, -1.0)
2	84	0.0	0.8	87	2.3	0.8	84	-2.2	1.1	(-4.0, -0.4)
2.5	84	0.3	0.8	87	2.9	0.8	84	-2.6	1.1	(-4.5, -0.8)
3	84	0.6	0.8	87	2.6	0.8	84	-2.0	1.1	(-3.9, -0.2)
3.5	84	-0.2	0.7	87	2.6	0.7	84	-2.7	1.0	(-4.4, -1.1)
4	84	-1.1	0.8	87	3.4	0.8	84	-4.5	1.1	(-6.3, -2.7)
4.5	84	-1.7	0.9	87	2.6	0.9	84	-4.4	1.2	(-6.4, -2.4)
5	84	-1.4	0.8	87	2.3	0.8	84	-3.7	1.2	(-5.6, -1.7)
6	84	-1.6	0.8	87	2.6	0.8	84	-4.2	1.2	(-6.1, -2.3)
7	83	0.4	0.9	87	3.1	0.9	83	-2.8	1.3	(-4.8, -0.7)
8	84	1.1	0.9	87	2.6	0.9	84	-1.5	1.3	(-3.7, 0.7)
10	84	0.3	1.0	87	3.4	0.9	84	-3.1	1.4	(-5.3, -0.8)
12	83	-0.6	0.8	86	2.1	0.8	83	-2.7	1.1	(-4.6, -0.9)
24	84	-0.2	0.9	87	1.8	0.9	84	-2.1	1.3	(-4.2, 0.1)
25	84	-0.6	0.9	87	1.0	0.9	84	-1.6	1.2	(-3.6, 0.4)

**Table 21: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group B: Mirabegron
100 mg X 10 days**

	Δ PR: Mirabegron 100 mg			Δ PR: Placebo			$\Delta\Delta$ PR			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	82	0.3	0.9	84	3.7	0.9	82	-3.4	1.3	(-5.4, -1.3)
1	82	0.2	0.9	84	2.5	0.8	82	-2.3	1.2	(-4.3, -0.3)
1.5	82	-0.1	0.8	84	3.1	0.8	82	-3.2	1.2	(-5.1, -1.3)
2	82	-0.5	0.9	84	2.8	0.9	82	-3.3	1.2	(-5.3, -1.3)
2.5	82	-1.3	0.8	84	2.5	0.8	82	-3.7	1.1	(-5.6, -1.8)
3	82	-0.8	0.8	84	2.8	0.8	82	-3.6	1.1	(-5.4, -1.8)
3.5	82	-0.6	0.8	84	2.5	0.8	82	-3.1	1.2	(-5.1, -1.2)
4	82	-1.4	0.8	84	3.3	0.7	82	-4.7	1.1	(-6.5, -2.9)
4.5	82	-0.7	0.8	84	2.2	0.8	82	-2.9	1.1	(-4.7, -1.0)
5	82	-1.1	0.9	84	2.4	0.8	82	-3.5	1.2	(-5.5, -1.5)
6	82	-2.5	0.8	84	1.5	0.8	82	-4.0	1.1	(-5.9, -2.2)
7	81	-0.1	0.8	84	1.6	0.8	81	-1.7	1.1	(-3.5, 0.1)
8	82	-0.6	0.8	84	1.1	0.8	82	-1.7	1.1	(-3.5, 0.1)
10	82	-0.5	0.7	84	0.4	0.7	82	-1.0	1.0	(-2.6, 0.7)
12	82	0.2	0.7	84	0.5	0.7	82	-0.3	1.0	(-1.9, 1.3)
24	82	-0.9	0.7	84	2.1	0.7	82	-2.9	1.0	(-4.5, -1.4)
25	82	-1.2	0.8	84	1.3	0.8	82	-2.5	1.1	(-4.4, -0.7)

Table 22: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group C: Mirabegron 200 mg X 10 days

Time	Δ PR: Mirabegron 100 mg			Δ PR: Placebo			$\Delta\Delta$ PR			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	81	0.2	0.8	83	3.3	0.8	81	-3.0	1.1	(-4.9, -1.2)
1	81	-0.3	0.8	83	2.9	0.8	81	-3.2	1.1	(-5.0, -1.4)
1.5	81	0.5	0.8	83	2.3	0.8	81	-1.8	1.1	(-3.7, 0.0)
2	81	0.3	0.8	83	2.0	0.8	81	-1.8	1.2	(-3.7, 0.2)
2.5	82	3.1	0.9	83	1.4	0.9	82	1.7	1.3	(-0.4, 3.8)
3	81	4.4	1.1	83	1.9	1.0	81	2.5	1.5	(0.0, 5.0)
3.5	82	5.7	1.0	83	2.6	1.0	82	3.1	1.4	(0.7, 5.4)
4	81	5.5	1.0	83	2.2	1.0	81	3.3	1.4	(1.0, 5.6)
4.5	81	4.2	1.0	83	2.2	1.0	81	2.0	1.4	(-0.2, 4.3)
5	80	4.4	1.0	83	1.9	0.9	80	2.5	1.3	(0.3, 4.7)
6	79	2.9	0.9	82	1.5	0.9	79	1.5	1.3	(-0.7, 3.6)
7	80	4.4	0.8	83	1.7	0.8	80	2.6	1.2	(0.7, 4.6)
8	81	3.7	0.8	83	2.6	0.8	81	1.1	1.2	(-0.8, 3.0)
10	82	1.9	0.8	83	1.7	0.8	82	0.2	1.1	(-1.6, 2.0)
12	82	1.6	0.8	83	1.7	0.8	82	-0.1	1.2	(-2.0, 1.9)
24	83	-0.0	0.8	83	2.4	0.8	83	-2.4	1.1	(-4.2, -0.6)
25	83	-1.0	0.9	83	2.4	0.9	83	-3.4	1.2	(-5.4, -1.4)

Table 23: Categorical Analysis for PR

	N	PR < 200 ms	PR $\geq$ 200 ms
Treatment Group			
Mirabegron 50 mg	84	79 (94.0%)	5 (6.0%)
Placebo (50 mg)	87	79 (90.8%)	8 (9.2%)
Mirabegron 100 mg	82	77 (93.9%)	5 (6.1%)
Placebo (100 mg)	84	78 (92.9%)	6 (7.1%)
Mirabegron 200 mg	83	71 (85.5%)	12 (14.5%)
Placebo (200 mg)	83	72 (86.7%)	11 (13.3%)

5.3.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 24, Table 25, and Table 26. The largest upper limits of 90% CI for the QRS mean differences between mirabegron 50 mg and placebo, mirabegron 100 mg and placebo, and mirabegron 200 mg and placebo are 0.9 ms, 2.1 ms, and 4.7 ms, respectively.

The outlier analysis results for QRS are presented in Table 27.

Table 24: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group A: Mirabegron 50 mg X 10 days

	Δ QRS: Mirabegron 50 mg			Δ QRS: Placebo			$\Delta\Delta$ QRS			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	84	1.1	0.1	87	0.8	0.1	84	0.4	0.1	(0.1, 0.6)
1	84	1.0	0.1	87	0.7	0.1	84	0.3	0.1	(0.1, 0.6)
1.5	84	1.0	0.1	87	0.7	0.1	84	0.3	0.2	(0.1, 0.6)
2	84	1.1	0.1	87	0.6	0.1	84	0.5	0.1	(0.3, 0.7)
2.5	84	1.0	0.1	87	0.7	0.1	84	0.3	0.2	(0.0, 0.5)
3	84	1.1	0.1	87	0.6	0.1	84	0.4	0.1	(0.2, 0.7)
3.5	84	1.1	0.1	87	0.8	0.1	84	0.3	0.1	(0.1, 0.6)
4	84	1.2	0.1	87	0.6	0.1	84	0.6	0.2	(0.3, 0.9)
4.5	84	1.4	0.1	87	0.7	0.1	84	0.6	0.2	(0.3, 0.9)
5	84	1.4	0.2	87	0.8	0.1	84	0.6	0.2	(0.3, 0.9)
6	84	1.4	0.2	87	0.9	0.2	84	0.5	0.2	(0.1, 0.8)
7	83	1.2	0.2	87	0.7	0.2	83	0.5	0.2	(0.2, 0.8)
8	84	1.2	0.1	87	0.8	0.1	84	0.4	0.2	(0.1, 0.7)
10	84	1.1	0.1	87	0.7	0.1	84	0.4	0.2	(0.1, 0.7)
12	83	1.1	0.1	87	0.7	0.1	83	0.4	0.2	(0.1, 0.6)
24	84	1.1	0.1	87	0.7	0.1	84	0.4	0.1	(0.2, 0.6)
25	84	1.0	0.1	87	0.5	0.1	84	0.5	0.1	(0.2, 0.7)

**Table 25: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group B:
Mirabegron 100 mg X 10 days**

	Δ QRS: Mirabegron 100 mg			Δ QRS: Placebo			$\Delta\Delta$ QRS			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	82	1.2	0.1	84	0.4	0.1	82	0.8	0.2	(0.5, 1.0)
1	82	1.3	0.1	84	0.5	0.1	82	0.8	0.2	(0.4, 1.1)
1.5	82	1.2	0.1	84	0.4	0.1	82	0.8	0.2	(0.5, 1.1)
2	82	1.5	0.1	84	0.4	0.1	82	1.1	0.2	(0.8, 1.4)
2.5	82	1.5	0.1	84	0.3	0.1	82	1.1	0.2	(0.8, 1.5)
3	82	1.7	0.2	84	0.4	0.2	82	1.3	0.2	(0.9, 1.6)
3.5	82	2.0	0.2	84	0.4	0.2	82	1.6	0.2	(1.2, 1.9)
4	82	2.1	0.2	84	0.5	0.2	82	1.7	0.3	(1.2, 2.1)
4.5	82	2.1	0.2	84	0.4	0.2	82	1.6	0.2	(1.3, 2.0)
5	82	2.1	0.2	84	0.5	0.2	82	1.6	0.2	(1.2, 2.0)
6	82	2.2	0.2	84	0.5	0.2	82	1.6	0.3	(1.1, 2.1)
7	81	1.7	0.2	84	0.5	0.2	81	1.2	0.3	(0.8, 1.7)
8	82	1.4	0.2	84	0.5	0.2	82	0.9	0.2	(0.6, 1.2)
10	82	1.4	0.1	84	0.4	0.1	82	1.0	0.2	(0.7, 1.3)
12	82	1.0	0.1	84	0.5	0.1	82	0.5	0.2	(0.2, 0.8)
24	82	1.3	0.1	84	0.4	0.1	82	1.0	0.2	(0.7, 1.2)
25	82	1.2	0.1	84	0.5	0.1	82	0.8	0.2	(0.5, 1.0)

**Table 26: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group C:
Mirabegron 200 mg X 10 days**

	Δ QRS: Mirabegron 200 mg			Δ QRS: Placebo			$\Delta\Delta$ QRS			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	81	2.2	0.2	83	0.6	0.2		1.5	0.2	(1.2, 1.9)
1	81	2.3	0.2	83	0.7	0.2		1.6	0.2	(1.3, 1.9)
1.5	81	2.3	0.2	83	0.7	0.2		1.6	0.2	(1.3, 2.0)
2	81	2.9	0.2	83	0.5	0.2		2.3	0.3	(1.9, 2.8)
2.5	82	3.7	0.2	83	0.5	0.2		3.2	0.3	(2.7, 3.7)
3	81	4.4	0.3	83	0.3	0.3		4.1	0.4	(3.5, 4.7)
3.5	82	4.7	0.3	83	0.5	0.3		4.1	0.3	(3.6, 4.7)
4	81	4.5	0.2	83	0.5	0.2		4.1	0.3	(3.5, 4.6)
4.5	81	4.6	0.2	83	0.4	0.2		4.2	0.3	(3.6, 4.7)
5	80	4.3	0.2	83	0.6	0.2		3.8	0.3	(3.3, 4.3)
6	80	4.5	0.2	82	0.7	0.2		3.9	0.3	(3.3, 4.4)
7	81	3.9	0.2	83	0.5	0.2		3.4	0.3	(2.9, 3.9)
8	82	3.4	0.2	83	0.5	0.2		2.8	0.3	(2.4, 3.3)
10	82	2.7	0.2	83	0.5	0.2		2.2	0.2	(1.8, 2.6)
12	82	2.8	0.2	83	0.5	0.2		2.3	0.2	(1.9, 2.6)
24	83	2.1	0.2	83	0.6	0.2		1.5	0.2	(1.2, 1.9)
25	83	2.1	0.2	83	0.5	0.2		1.5	0.2	(1.2, 1.8)

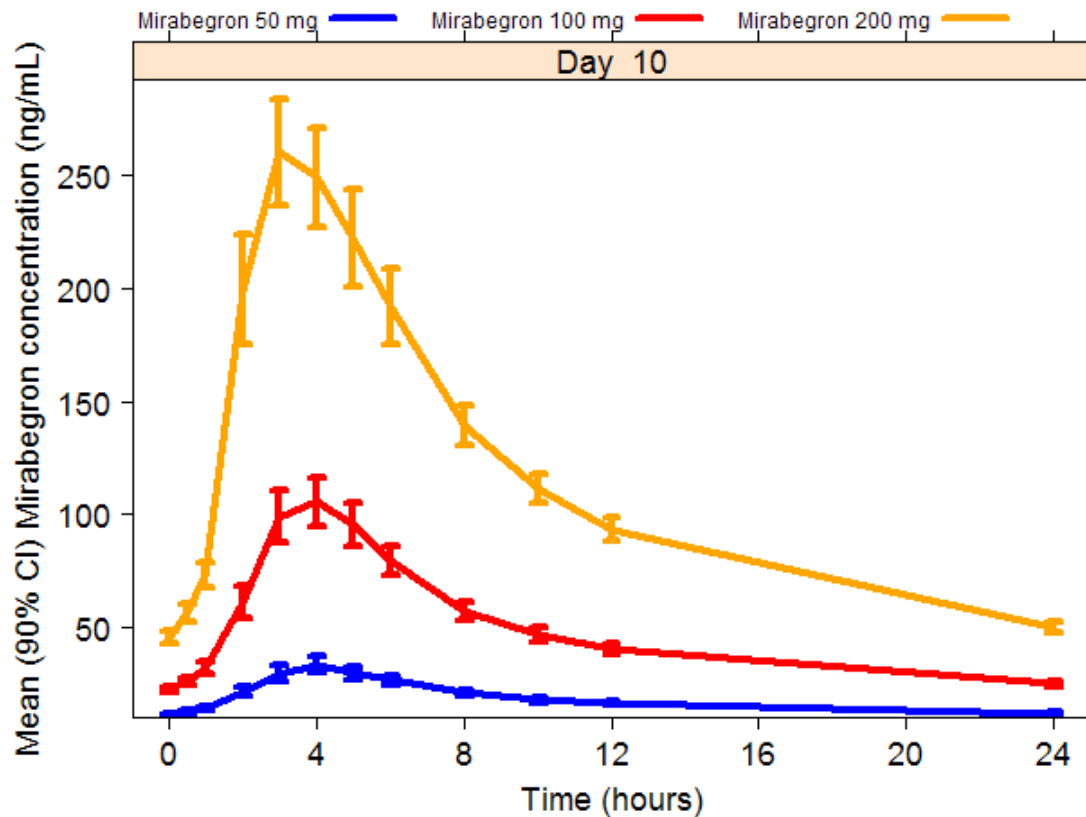
Table 27: Categorical Analysis for QRS

	N	QRS < 110 ms	QRS $\geq$ 110 ms
Treatment Group			
Mirabegron 50 mg	84	80 (95.2%)	4 (4.8%)
Placebo (50 mg)	87	86 (98.9%)	1 (1.1%)
Mirabegron 100 mg	82	80 (97.6%)	2 (2.4%)
Placebo (100 mg)	84	84 (100%)	0 (0.0%)
Mirabegron 200 mg	83	76 (91.6%)	7 (8.4%)
Placebo (200 mg)	83	83 (100%)	0 (0.0%)

5.4 CLINICAL PHARMACOLOGY ASSESSMENTS

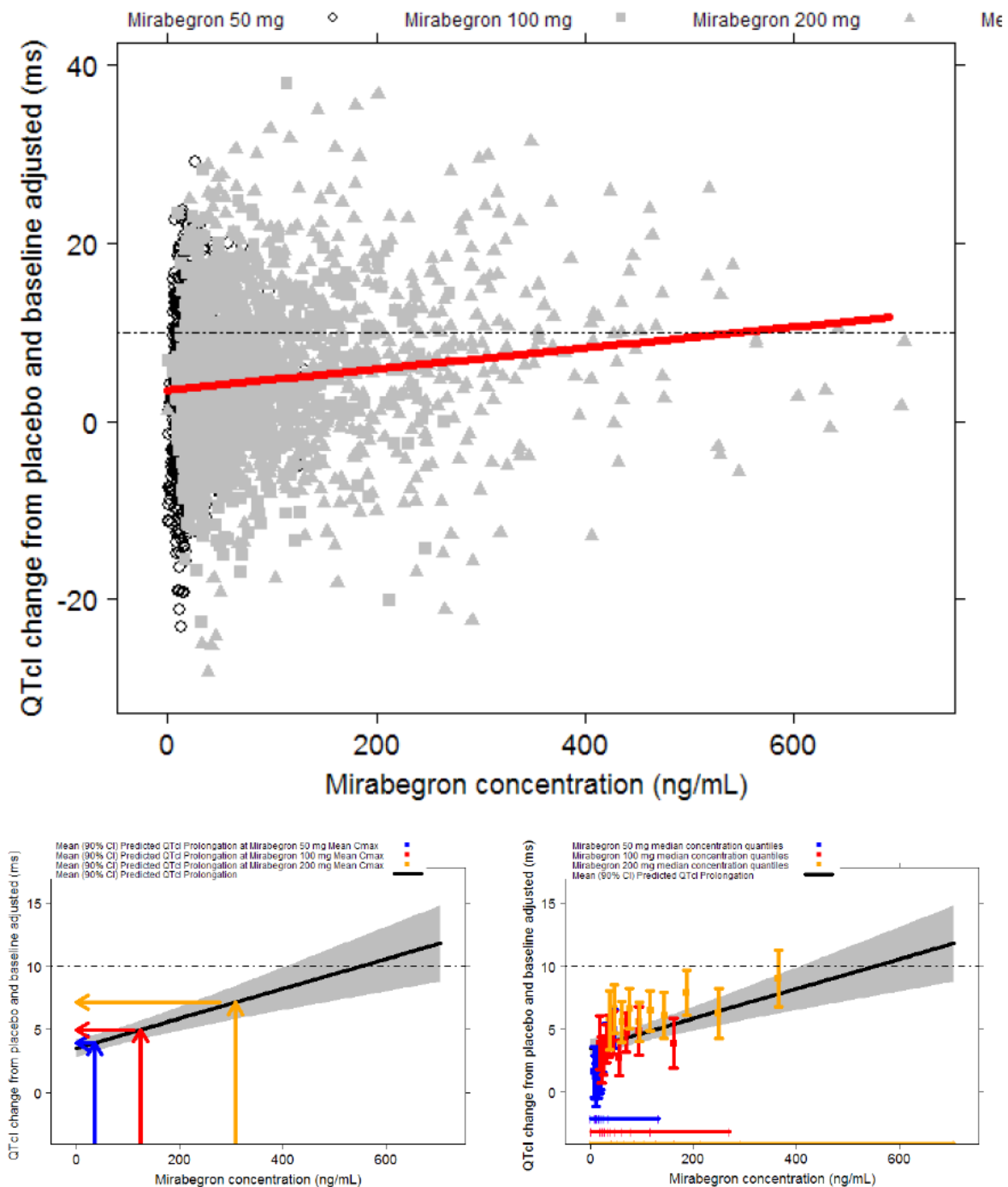
The mean drug concentration-time profile is illustrated in Figure 6.

Figure 6: Mean Mirabegron Concentration-Time Profiles For 50-mg (blue line), 100-mg (red line) and 200-mg Dose (orange line)



The relationship between $\Delta\Delta QTcI$ and mirabegron concentrations is visualized in Figure 7 with a positive and significant exposure-response relationship. The simple linear model allowed random effects on both intercept and slope for mirabegron concentration. The estimated intercept and slope were 3.5 ms (p-value <0.0001) and 0.012 ms per ng/mL (p-value <0.0001), respectively. However, there is no substantial QTc prolongation in the exposure range at the therapeutic dose of 50 mg. We also explored the gender effect on the concentration QT relationship by including gender as a covariate in the above linear mixed effect model. No significant effect of gender was observed on the concentration-QTc slope.

Figure 7: $\Delta\Delta\text{QTcI}$ vs. Mirabegron Concentration (top), Predicted $\Delta\Delta\text{QTcI}$ at C_{max} by Dose (bottom left), and $\Delta\Delta\text{QTcI}$ vs. Mirabegron Concentration Quantile Plot by Dose (bottom right)



5.5 CLINICAL ASSESSMENTS

5.5.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

The frequency of TEAE of palpitation was higher in female volunteers (see 4.2.8.3 for additional information). In the mirabegron groups, three volunteers reported TEAE of palpitations and tachycardia that resulted in permanent discontinuation of study drug (2 in the 100-mg-dose group and 1 in the 200-mg-dose group).

One event of syncope was reported in a volunteer randomized to the mirabegron 100-mg group. By reviewing the narrative the event was related to study medication (i.e., the mirabegron case occurred 13 days after dosing with 100 mg mirabegron ended).

5.5.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 92.5% of the ECGs were annotated in the primary lead II, with less than 0.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.5.3 PR and QRS Interval

Three subjects in the 50-mg-dose group, two in the 100-mg-dose group and twelve subjects in the 200-mg-dose group had a post baseline PR > 200 ms; in all cases the PR increase over baseline was <15%.

Four subjects had a post-baseline QRS >110 ms (50 mg dose) no post-baseline QRS duration was > 120 ms.

APPENDIX

5.6 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	<Include maximum proposed clinical dosing regimen.> The recommended dose of mirabegron is 50 mg orally once daily with or without food. The recommended dose is 25 mg orally once daily with or without food in the following populations: - severe renal impairment (creatinine clearance [CL_{cr}] 15 to 29 mL/min or estimated glomerular filtration rate [$eGFR$] 15 to 29 mL/min/1.73 m²) - moderate hepatic impairment (Child-Pugh Class B)					
Maximum Tolerated Dose	<Include if studied or NOAEL dose> Mirabegron has been dosed as immediate release (IR) formulation up to a maximum tolerated dose (MTD) of 340 mg [Study 178-CL-001]. The maximum tolerated dose for the oral controlled absorption system (OCAS) formulation was not determined. Mirabegron OCAS has been administered to healthy volunteers at single doses up to 400 mg [Study 178-CL-034] and multiple doses up to 300 mg once daily [Study 178-CL-031].					
Principal Adverse Events	<Include most common adverse events; dose limiting adverse events> At the MTD for the IR formulation (340 mg single dose), the most common treatment emergent adverse events were postural dizziness (5 of 6 volunteers) and headache (2 of 6 volunteers) [Study 178-CL-001]. At the maximum single dose tested for the OCAS formulation (400 mg), adverse events reported included palpitations (1 of 6 volunteers) and increased pulse rate exceeding 100 bpm (3 of 6 volunteers) [Study 178-CL-034]. At the maximum multiple OCAS dose tested (300 mg once daily for 10 days), the most frequently reported treatment related adverse events were dizziness (9 of 12 volunteers), headache (7 of 12 volunteers) and palpitations (6 of 12 volunteers) [Study 178-CL-031].					
Maximum Dose Tested	Single Dose	<Specify dose> 340 mg IR under fasted conditions in healthy male volunteers [Study 178-CL-001] 400 mg OCAS under fasted conditions in healthy male volunteers [Study 178-CL-034]				
	Multiple Dose	<Specify dosing interval and duration> 240 mg qd IR in healthy male volunteers. Single dose followed by 7 days of once daily dosing [Study 178-CL-002] 150 mg bid IR for 4 weeks in patients with overactive bladder (OAB) [Study 178-CL-008] 300 mg qd OCAS in healthy young (18-55 years) and 200 mg qd OCAS in elderly (65-80 years) volunteers. Single dose followed by 10 days of once daily dosing [Study 178-CL-031] 200 mg qd OCAS for 12 weeks in patients with OAB [Study 178-CL-044] 100 mg qd OCAS for 52 weeks in patients with OAB [Study 178-CL-049]				
Exposures Achieved At Maximum Tested Dose	Single Dose	<Mean (%CV) C_{max} and AUC>				
		Statistic	Mirabegron IR 340 mg [n=6] (Study 178-CL-001)		Mirabegron OCAS 400 mg [n=6] (Study 178-CL-034)	
			AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)
		Mean	4076	635	4140	720
		SD	951	181	736	264
		CV (%)	23	29	18	37

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Exposures Achieved At Maximum Tested Dose (continued)	Multiple Dose	<Mean (%CV) C _{max} and AUC>				
		▪ Exposure at 240 mg IR under fasted conditions after 7 days of once daily dosing [Study 178-CL-002]:				
		Statistic	AUC _{tau} (ng·h/mL) [n=5]		C _{max} (ng/mL) [n=5]	
		Mean	4960		755	
		SD	1060		125	
		CV (%)	21		17	
		▪ Exposure at 300 mg (young) or 200 mg (elderly) mirabegron OCAS under fasted conditions after 10 days of once daily dosing [Study 178-CL-031]:				
		AUC _{tau} (ng·h/mL)	300 mg qd Young Females [n=6]	300 mg qd Young Males [n=6]	200 mg qd Elderly Females [n=6]	200 mg qd Elderly Males [n=6]
		Mean	3890	2470	2110	1460
		SD	861	689	802	613
		CV (%)	22	28	38	42
		C _{max} (ng/mL)	300 mg qd Young Females [n=6]	300 mg qd Young Males [n=6]	200 mg qd Elderly Females [n=6]	200 mg qd Elderly Males [n=6]
		Mean	530	381	290	205
		SD	183	161	127	134
		CV (%)	34	42	44	65
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Exposures Achieved At Maximum Tested Dose (continued)	Multiple Dose	• Exposure at 200 mg mirabegron OCAS under fasted conditions after 10 days of once daily dosing [Study 178-CL-077]:						
		Compound	Statistic	AUC _{0-∞} (ng·h/mL)		C _{max} (ng/mL)		
200 mg qd Females [n=40]	200 mg qd Males [n=43]			200 mg qd Females [n=40]	200 mg qd Males [n=43]			
		Mirabegron	Mean	3270	2240	409	267	
			SD	837	587	139	94.4	
			CV (%)	26	26	34	35	
		M5	Mean	618	512	36.0	28.8	
			SD	262	238	17.9	13.3	
			CV (%)	42	47	50	46	
		M11	Mean	1270	767	141	79.7	
			SD	421	282	52.5	36.0	
			CV (%)	33	37	37	45	
		M12	Mean	912	663	107	72.5	
			SD	474	360	62.9	40.9	
			CV (%)	52	54	59	56	
		M13	Mean	131	84.2	22.8	13.0	
			SD	72.8	45.9	14.7	7.63	
			CV (%)	55	55	65	59	
		M14	Mean	400	319	32.9	25.2	
			SD	150	125	11.8	10.4	
			CV (%)	38	39	36	41	
		M15	Mean	358	205	48.0	27.1	
			SD	146	78.0	19.7	12.8	
			CV (%)	41	38	41	47	
		M16	Mean	367	266	23.9	16.1	
			SD	164	96.5	16.5	5.87	
			CV (%)	45	36	69	37	
		Note: M8 was demonstrated to be the least abundant of all circulating metabolites in Study 178-CL-072 and was not determined in Study 178-CL-077.						
		• Exposure at 200 mg mirabegron OCAS once daily with food in patients with OAB [178-PK-015]: mean (%CV) = 1760 (42) ng·h/mL [n=155]						
Range of Linear PK	<Specify dosing regimen>							
	No deviations from dose proportionality in mirabegron PK parameters were observed after single-dose intravenous administration of mirabegron over a 7.5 to 50 mg dose range [Studies 178-CL-033, 178-CL-076].							
	After oral administration, a greater than dose-proportional increase in mirabegron C _{max} and AUC was observed, due to an increase in absolute bioavailability with increasing dose [Studies 178-CL-033, 178-CL-076]. In an overall population of healthy males and females, a 2-fold increase in dose increased mirabegron C _{max} and AUC by approximately 2.9- and 2.6-fold, respectively, within a single-dose range of 25 mg to 100 mg [Study 178-CL-076] and multiple-dose range of 50 mg to 200 mg [Study 178-CL-077]. Similar fold increases were obtained for males and females separately. Mirabegron metabolites also demonstrated a more than dose-proportional increase in C _{max} and AUC _{0-∞} after multiple mirabegron doses (25 to 200 mg qd), similar to the parent compound [Studies 178-CL-072, 178-CL-077].							
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Accumulation at Steady State	<Mean (%CV); specify dosing regimen>							
	The accumulation ratio (R_{acc} ; assessed as $AUC_{0-24h, day 14} / AUC_{0-24h, day 1}$) after once daily dosing for 10 days (day 5-14) ranged from 2.02 to 2.17 and was independent of dose (50 mg to 300 mg) [Study 178-CL-031]. No differences were observed between males and females and between young and elderly volunteers.							
	R_{acc}	50 mg qd Young [n=12]	100 mg qd Young [n=12]	200 mg qd Young [n=12]	300 mg qd Young [n=12]	50 mg qd Elderly [n=12]	200 mg qd Elderly [n=12]	
	Mean	2.15	2.02	2.06	2.07	2.07	2.17	
	SD	1.24	0.80	0.75	0.51	0.68	0.62	
	CV (%)	58	40	36	25	33	29	
Metabolites	<Include listing of all metabolites and activity>							
	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. All metabolites were adequately formed in animal species used in nonclinical toxicity studies. M11 and M12 were considered to be major metabolites according to the ICH M3 (R2) guidance; both are glucuronides representing 16% and 11%, respectively, of total exposure in plasma [Studies 178-CL-072, 178-CL-077].							
	None of the metabolites observed in human plasma are pharmacologically active. Agonist activities of the above metabolites on beta 3-adrenoceptors (ARs) were less than 1/400-fold that of mirabegron and those on other beta ARs were negligible. In addition, no other relevant affinities at biological targets were observed. Therefore, unchanged mirabegron is proposed to be the drug moiety mainly responsible for the pharmacological effects of the drug.							
Absorption	Absolute/ Relative Bioavailability	<Mean (%CV)>						
		The absolute bioavailability increased with dose following single doses of mirabegron OCAS under fasted conditions [Study 178-CL-076]						
		F (%)	25 mg		50 mg		100 mg	
			Females [n=12]	Males [n=17]	Females [n=12]	Males [n=14]	Females [n=10]	Males [n=17]
		Mean	35.0	24.6	36.6	34.4	53.0	40.3
		SD	5.61	10.4	13.9	6.15	13.3	6.84
		CV (%)	16	42	38	18	25	17
	t_{max}	<Median (range) for parent and metabolites>						
	Mean mirabegron t_{max} was reached between 3 and 4.3 hours after administration of mirabegron OCAS under fasted conditions. There was no difference in t_{max} between males and females or between single and multiple doses. No dose-relationship was observed. The time course of the metabolite plasma concentration profiles was generally delayed by about 0.5 to 1.5 hours compared with the parent profile, with mean t_{max} values ranging between 3.6 and 6.3 hours.							

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Absorption (continued)	t_{max}	• Data following mirabegron OCAS 50 to 200 mg under fasted conditions after 10 days of once daily dosing [Study 178-CL-077]:					
		Compound	t_{max} (h)	50 mg qd [n=84] †	100 mg qd [n=82] †	200 mg qd [n=83] †	
		Mirabegron	Median	4.11	3.20	3.17	
			Range	1.17-8.30	1.17-6.20	2.13-6.20	
		M5	Median	6.17	5.70	6.17	
			Range	3.17-12.2	3.15-10.2	2.17-10.2	
		M11	Median	5.20	5.17	4.17	
			Range	2.17-10.2	2.17-8.20	3.17-8.20	
		M12	Median	5.17	5.17	4.20	
			Range	2.17-8.20	2.17-10.2	3.05-10.2	
		M13	Median	4.20	4.17	3.20	
			Range	2.17-8.20	1.17-6.20	2.17-6.17	
		M14	Median	5.17	5.17	5.17	
			Range	2.17-10.2	2.22-8.18	3.17-10.2	
		M15	Median	4.20	4.18	4.17	
			Range	2.17-6.23	1.17-6.25	2.17-8.17	
		M16	Median	6.17	6.17	6.17	
			Range	2.17-12.2	2.17-10.2	2.17-14.0	
† Number of subjects may vary for some metabolites. Note: M8 was demonstrated to be the least abundant of all circulating metabolites in Study 178-CL-072 and was not determined in Study 178-CL-077. Median (range) for M8 t_{max} was 5.00 (3.0-8.0) [n=48] at mirabegron 100 mg qd in Study 178-CL-072.							
Distribution	V_z	Mean (%CV)					
		Mirabegron is extensively distributed. The volume of distribution at steady state (V_z) is approximately 1670 L.					
		V_z (L)	Study 178-CL-033		Study 178-CL-076		
			15 mg iv [n=4]	50 mg iv [n=6]	7.5 mg iv [n=29]	15 mg iv [n=30]	30 mg iv [n=30]
		Mean	1610	1470	1760	1640	1660
		SD	427	406	510	344	441
		CV (%)	27	28	29	21	27
		% bound	Mean (%CV)				
	In healthy volunteers, mirabegron was moderately bound (approximately 71%) to human plasma proteins, including albumin and alpha-1 acid glycoprotein. ^{14}C -mirabegron binding to human plasma proteins was non-saturable over a concentration range of 200 to 5000 ng/mL in vitro.						
	Fraction unbound		Study 178-CL-038		Study 178-CL-039		
			100 mg [n=8]		100 mg [n=8]	100 mg [n=8]	
	Mean		0.32		0.27	0.30	
SD	0.07		0.04	0.03			
CV (%)	21		15	9.4			
Continued on next page							

Elimination	Route	<Primary route; percent dose eliminated> Following a single oral solution dose of 160 mg ¹⁴ C-mirabegron, an average of 34% and 55% of radioactivity was recovered in the feces and urine, respectively. In feces, the radioactivity was present almost entirely as the unchanged form. Of the radioactivity recovered in urine, 45% was excreted as unchanged mirabegron, indicating that mirabegron metabolites are predominantly eliminated in urine. No excretion of radioactivity was shown in expired air. Renal clearance is approximately 13 L/h, which corresponds to nearly 25% of CL. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged mirabegron was dose-dependent and ranged from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg OCAS. <Other routes> Not applicable.					
	t _{1/2}	Mean (%CV) for parent The terminal t _{1/2} of mirabegron is approximately 50 hours. The t _{1/2} was similar after single and multiple dosing and independent of dose, route of administration (iv vs. oral) and formulation (IR vs OCAS). The effective half-life is estimated to be about 19 hours (based on population PK analysis).					
	t _{1/2} (h)	Single OCAS Dose (Study 178-CL-076)			Multiple OCAS Dose (Study 178-CL-072)		
		25 mg [n=29]	50 mg [n=26]	100 mg [n=27]	25 mg qd [n=47]	50 mg qd [n=46]	100 mg qd [n=48]
	Mean	42.9	41.0	37.7	63.9	60.5	57.5
	SD	16.3	9.39	7.32	12.1	12.7	8.18
	CV (%)	38	23	20	19	21	14

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Elimination (continued)	t _{1/2}	<Mean (%CV) for metabolites>					
		Plasma concentration–time profiles of the metabolites were truncated at various time points when the metabolite concentrations fell below the assay lower limit of quantification, resulting in t _{1/2} estimates that were shorter than the parent t _{1/2} .					
		Metabolite	t _{1/2} (h)	Multiple Dose (Study 178-CL-072)			
				25 mg qd [n=42]†	50 mg qd [n=46]†	100 mg qd [n=48]†	
		M5	Mean	37.1	36.5	40.6	
			SD	14.2	10.9	11.1	
			CV (%)	38	30	27	
		M8	Mean	-	-	10.8	
			SD	-	-	7.59	
			CV (%)	-	-	71	
		M11	Mean	27.6	40.5	52.1	
			SD	15.9	20.3	17.1	
			CV (%)	58	50	33	
		M12	Mean	20.9	30.9	44.6	
			SD	12.8	11.8	16.7	
			CV (%)	61	38	37	
		M13	Mean	3.22	5.86	11.9	
			SD	1.27	5.29	7.18	
			CV (%)	40	90	61	
		M14	Mean	6.36	16.3	30.6	
			SD	3.74	11.7	13.1	
			CV (%)	59	72	43	
		M15	Mean	7.99	13.8	20.5	
			SD	9.08	8.72	8.77	
			CV (%)	114	63	43	
		M16	Mean	32.1	40.5	47.0	
			SD	19.3	13.9	11.7	
			CV (%)	60	34	25	
		- Not reported. † Number of subjects with t _{1/2} estimates may vary for some metabolites.					
	CL	<Mean (%CV)>					
		Mirabegron CL from plasma was approximately 57 L/hr following single intravenous doses of 7.5 to 50 mg [Studies 178-CL-033, 178-CL-076].					
		CL (L/h)	Study 178-CL-033		Study 178-CL-076		
			15 mg iv [n=4]	50 mg iv [n=6]	7.5 mg iv [n=29]	15 mg iv [n=30]	30 mg iv [n=30]
		Mean	67.6	60.8	58.2	54.3	55.1
		SD	16.1	9.2	11.2	10.8	9.79
		CV (%)	24	15	19	20	18

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Intrinsic Factors	Age	<Specify mean changes in C _{max} and AUC> There were no statistically significant differences in mirabegron C _{max} and AUC _{0-∞} between older healthy volunteers (aged 55 years and above) and younger healthy volunteers (18-45 years) following once daily doses of 25 to 100 mg mirabegron OCAS [Study 178-CL-072; see table below]. Similar results were obtained for the elderly subpopulation aged 65 years and above. In a population PK analysis of phase 2 and 3 data, the typical AUC _{0-∞} was predicted to be 11% higher in a subject aged 90 years compared to the average OAB subject aged 60 years.				
		Parameter	Older (≥ 55 yrs) versus Young		Elderly (≥ 65 yrs) versus Young	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
		AUC _{0-∞}	0.98	0.93, 1.04	1.07	1.01, 1.13
		C _{max}	0.91	0.82, 1.01	0.92	0.82, 1.03
		LS: least squares				
	Sex	<Specify mean changes in C _{max} and AUC> Mirabegron C _{max} and AUC were approximately 40% to 50% higher, respectively, in females compared with males following single and once daily doses of 25 to 100 mg mirabegron OCAS [Studies 178-CL-076, 178-CL-072 (see table below), 178-CL-077]. The higher exposure in female volunteers than male volunteers was partly due to a lower mean body weight in females and partly due to higher bioavailability in females [Study 178-CL-076].				
		Parameter	Study 178-CL-072			
			Females versus Males		Females versus Males; body weight-corrected	
			LS Mean Ratio	90% CI	LS Mean Ratio	90% CI
	AUC _{0-∞}	1.38	1.31, 1.45	1.18	1.12, 1.25	
	C _{max}	1.44	1.30, 1.59	1.23	1.11, 1.36	
	LS: least squares.					
Race	<Specify mean changes in C _{max} and AUC> There were no apparent differences in PK parameters among healthy volunteers of White, Black, Asian or other racial origin [Study 178-CL-077 (see table below); pooled phase 1 analysis]. In addition, race was not found to influence any of the PK parameters in a population PK analysis of phase 2 and 3 data. Plasma exposure in Japanese healthy volunteers was higher than in Western volunteers, which was largely related to differences in body weight.					
	Dose	Parameter	Study 178-CL-077			
			White	Black	Asian	Other
	50 mg qd	n	33	44	4	3
		AUC _{0-∞} (ng·h/mL)	435 (35)	431 (37)	455 (14)	345 (21)
		C _{max} (ng/mL)	41.6 (58)	41.4 (54)	53.0 (44)	39.5 (30)
	100 mg qd	n	39	39	3	1
		AUC _{0-∞} (ng·h/mL)	1160 (37)	1150 (33)	1170 (37)	1100 (-)
		C _{max} (ng/mL)	145 (45)	131 (42)	157 (45)	154 (-)
	200 mg qd	n	41	36	2	4
		AUC _{0-∞} (ng·h/mL)	2640 (33)	2720 (30)	4210 (42)	3140 (21)
		C _{max} (ng/mL)	318 (46)	339 (38)	539 (27)	381 (14)
	Values are mean (CV%). (-) : not evaluable					

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Intrinsic Factors (continued)	Hepatic & Renal Impairment	<Specify mean changes in C_{max} and AUC>		
		Following single dose administration of 100 mg mirabegron in volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m ² as estimated by the Modification of Diet in Renal Disease [MDRD] equation), mean mirabegron C_{max} and AUC _{inf} were increased by 6% and 31% relative to volunteers with normal renal function [Study 178-CL-038]. In volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m ²), C_{max} and AUC were increased by 23% and 66%, respectively. In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m ²), mean C_{max} and AUC _{inf} values were 92% and 118% higher. Mirabegron has not been studied in patients with End Stage Renal Disease (CL _{cr} <15 mL/min or eGFR < 15 mL/min/1.73 m ² or patients requiring hemodialysis).		
		Following single dose administration of 100 mg mirabegron in volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC _{inf} were increased by 9% and 19% relative to volunteers with normal hepatic function [Study 178-CL-039]. In volunteers with moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC _{inf} values were 175% and 65% higher. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).		
		Renal or Hepatic Function Group	Parameter	n
			Ratio (%) Impaired/Healthy Volunteers	90% CI (%)
		Mild renal impairment	AUC _{inf}	8
			C_{max}	8
		Moderate renal impairment	AUC _{inf}	8
			C_{max}	8
		Severe renal impairment	AUC _{inf}	8
			C_{max}	8
		Mild hepatic impairment	AUC _{inf}	8
			C_{max}	8
		Moderate hepatic impairment	AUC _{inf}	8
			C_{max}	8
	CYP2D6 Polymorphism	<Specify mean changes in C_{max} and AUC>		
		Following a single 160 mg dose of mirabegron IR, mean mirabegron C_{max} and AUC _{inf} were 14% and 19% higher, respectively, in CYP2D6 poor metabolizers (PMs) compared to extensive metabolizers (EMs) [Study 178-CL-005]. Following multiple 50 mg and 100 mg doses of mirabegron OCAS, mean AUC ₀₋₂₄ was 8% and 12% higher, respectively, in CYP2D6 PMs compared to EMs, and mean C_{max} values were similar between the two phenotypes [Study 178-CL-077]. In a pooled analysis across Phase 1 studies, there was considerable overlap in exposure between the different predicted phenotypes and volunteers who were poor metabolizers of CYP2D6 demonstrated AUC values in the range of those observed in extensive metabolizers.		
		Dose	Parameter	CYP2D6 EM
		160 mg IR	n	8
			AUC _{inf} (ng·h/mL)	1250 (12)
			C_{max} (ng/mL)	230 (23)
		50 mg qd	n	56
			AUC ₀₋₂₄ (ng·h/mL)	438 (38)
			C_{max} (ng/mL)	43.0 (61)
		100 mg qd	n	43
			AUC ₀₋₂₄ (ng·h/mL)	1170 (32)
			C_{max} (ng/mL)	141 (42)
		Values are mean (CV%)		

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Extrinsic Factors	Effect of Other Drugs on Mirabegron	<Include listing of studied DDI studies with mean changes in C _{max} and AUC>				
		The largest changes in mirabegron plasma exposure were observed during co-administration with potent modulators of cytochrome 450 (CYP) 3A and P-gp. The potent CYP3A and P-gp inhibitor ketoconazole (400 mg qd) caused a 45% increase in C_{max} and an 81% increase in AUC_{inf} of mirabegron (100 mg sd) [Study 178-CL-036]. Co-administration of rifampin (600 mg qd), a potent CYP3A and P-gp inducer, resulted in a 35% decrease in C_{max} and a 44% decrease in AUC_{inf} of mirabegron (100 mg sd) [Study 178-CL-070]. These results indicate that mirabegron is not a sensitive substrate for CYP3A4 in vivo. No dose adjustment is needed for mirabegron when co-administered with ketoconazole, rifampin or other modulators of CYP3A or P-gp. CYP2D6 PMs (used as a surrogate for CYP2D6 inhibition) exhibited only slightly higher mirabegron plasma exposure compared with EMs [Study 178-CL-005; pooled analysis]. Based on these results, an interaction of mirabegron with an inhibitor of CYP2D6 is not expected and therefore, the effect of a potent CYP2D6 inhibitor on mirabegron PK was not studied. No dose adjustment is needed for mirabegron when coadministered with inhibitors of CYP2D6. Mirabegron PK was not affected to a clinically significant extent by metformin, solifenacin or tamsulosin [Studies 178-CL-006, 178-CL-069, 178-CL-080]. In addition, there was no clinically relevant cardiovascular pharmacodynamic (PD) interaction between tamsulosin and mirabegron [178-CL-080]. As a result, no dose adjustment for mirabegron is necessary when combined with these drugs.				
		Effect of Coadministered 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)
Continued on next page						

Extrinsic Factors (continued)	Food Effects	<Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)>			
		Mirabegron OCAS tablets exhibited a decrease in plasma exposure with food that was dependent on meal composition (greater decrease with low-fat than high-fat meal). There were no apparent differences in the magnitude of the food effect between a 50 and 100 mg dose, between Western and Japanese healthy volunteers or between males and females. In the phase 3 studies, mirabegron was administered with or without food and demonstrated both safety and efficacy.			
	Study	Dose (mg)	Meal type/Fasted	Ratio of C _{max} (%) (90% CI)	Ratio of AUC _{inf} (%) (90% CI)
	178-CL-041 (US)	50	With high-fat meal	54.8 (43.7, 68.7)	83.2 (74.2, 93.4)
		50	With low-fat meal	25.0 (19.9, 31.3)	48.7 (43.3, 54.7)
		100	With high-fat meal	61.3 (47.8, 78.7)	82.4 (72.6, 93.5)
		100	With low-fat meal	36.3 (28.2, 46.8)	53.2 (46.8, 60.5)
	178-CL-078 (Japan)	50	With high-fat meal	47.4 (36.6, 61.5)	71.2 (63.4, 80.0)
		50	With low-fat (normal) meal	34.2 (26.3, 44.3)	49.4 (44.0, 55.5)
		100	With high-fat meal	51.4 (41.4, 63.9)	72.8 (65.9, 80.5)
		100	With low-fat (normal) meal	35.7 (28.8, 44.4)	50.7 (45.9, 56.0)
Expected High Clinical Exposure Scenario	<Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.>				
	The following factors were found to increase mirabegron plasma exposure in dedicated Phase 1 studies:				
	- co-administration with ketoconazole, a strong CYP3A/P-gp inhibitor: 1.45-fold in mirabegron C_{max} and 1.81-fold in AUC_{inf} - severe renal impairment: 1.92-fold in mirabegron C_{max} and 2.18-fold in AUC_{inf} - moderate hepatic impairment: 2.75-fold in mirabegron C_{max} and 1.65-fold in AUC_{inf}				
	At a supratherapeutic dose of mirabegron 200 mg, a QTc prolongation, according to ICH E14 criteria, was observed in female but not male volunteers [Study 178-CL-077]. At the 200 mg dose, mean C _{max} and AUC ₀₋₂₄ were approximately 8.4- and 6.5- fold higher, respectively, relative to the proposed therapeutic dose of 50 mg. In the event of drug-drug interaction between mirabegron and strong inhibitors of CYP3A/P-gp, mirabegron exposure at 50 mg will not reach exposures at which QTc interval prolongation was demonstrated. Likewise, in patients with severe renal or moderate hepatic impairment, for whom a dose of 25 mg is recommended, mirabegron levels will not reach the level of QTc interval prolongation.				
	In addition, the population pharmacokinetic analysis of phase 2/3 data found several covariates that affect exposure, including dose, weight, age, renal function, sex and co-administration of proton pump inhibitors. The typical OAB patient is female, weight of 70 kg, 60 years of age, has a renal function (CL _{cr}) of 92 mL/min and is not taking proton pump inhibitors. For the typical patient receiving a 50 mg dose of mirabegron, the AUC ₀₋₂₄ is predicted to be 218 ng·h/mL. An atypical patient (female, 80 years of age, weight of 50 kg, CL _{cr} of 30 mL/min, taking proton pump inhibitors) receiving a 50 mg dose would be predicted to have an AUC ₀₋₂₄ of 406 ng·h/mL, i.e. within 2-fold of the exposure for the typical OAB patient. Therefore, exposure from the supratherapeutic dose of 200 mg in the TQT study 178-CL-077 is sufficient to cover the predicted high clinical exposure scenario in an atypical patient who is female, 80 years of age, weight of 50 kg, CL _{cr} of 30 mL/min, taking proton pump inhibitors, receiving a 50 mg dose.				

Extrinsic Factors (continued)	Effect of Mirabegron on Other Drugs	◁Include listing of studied DDI studies with mean changes in C _{max} and AUC▷				
		Multiple qd dosing of 160 mg mirabegron IR resulted in a 90% increase in C _{max} and a 229% increase in AUC _{inf} of a single 100 mg dose of the CYP2D6 substrate metoprolol [Study 178-CL-005]. Multiple qd dosing of 100 mg mirabegron resulted in a 79% increase in C _{max} and a 241% increase in AUC _{inf} of a single 50 mg dose of the CYP2D6 substrate desipramine [Study 178-CL-058]. At 15 days after the last mirabegron dose no relevant effect on the PK of desipramine was measured.				
		Mirabegron (100 mg qd) did not affect the pharmacokinetics of ethinyl estradiol and levonorgestrel (both CYP3A4 substrates; combined oral contraceptive) or solifenacin (a CYP3A4 substrate) to a clinically significant extent [Study 178-CL-068, Study 178-CL-069]. Mirabegron (100 mg qd) increased plasma exposure of the CYP2D6 and CYP3A4 substrate tamsulosin (0.4 mg sd) by approximately 60% [Study 178-CL-080]. Cardiovascular PD results do not suggest a clinically relevant PD interaction between tamsulosin and mirabegron.				
		No effects of mirabegron on the pharmacokinetics of R-warfarin or S-warfarin (probe substrate for CYP2C9) or on prothrombin time were observed when mirabegron (100 mg qd) was co-administered with warfarin (25 mg sd) [Study 178-CL-040]. Plasma exposure of metformin (500 mg bid) was not changed to a clinically relevant extent by mirabegron co-administration (160 mg IR qd).				
		With multiple dosing of 100 mg mirabegron qd, the C _{max} of the probe P-gp substrate digoxin (0.25 mg sd) increased 29%, while AUC _{inf} increased 27% [Study 178-CL-059].				
		Effect of Mirabegron on the PK of Coadministered Drugs				
		Coadministered drug and dose	n	Mirabegron dose	Ratio (%) with/without Mirabegron (90% CI)	
					C _{max}	AUC
		CYP2D6 Substrates				
		Metoprolol 100 mg sd	12	160 mg IR qd	190 (154, 233)	329 (270, 400)
		Desipramine 50 mg sd	28	100 mg qd	179 (169, 190)	341 (307, 380)
		CYP3A4 Substrates				
		Solifenacin 10 mg sd	20	100 mg qd	123 (115, 131)	126 (117, 135)
		COC (EE 30 mcg + LNG 150 mcg)	23	100 mg qd	EE: 96 (87, 105) LNG: 94 (86, 102)	EE: 96 (89, 104) LNG: 96 (88, 103)
		P-gp Substrates				
Digoxin 0.250 mg sd	23	100 mg qd	129 (117, 142)	127 (114, 142)		
Other						
Metformin 500 mg bid	32	160 mg IR qd	90 (79, 101)	97 (87, 108)		
Warfarin 25 mg sd	24	100 mg qd	S-warfarin: 104 (98, 110) R-warfarin: 105 (99, 110)	S-warfarin: 110 (106, 115) R-warfarin: 110 (104, 116)		
Tamsulosin 0.4 mg sd	24	100 mg qd	159 (143, 177)	161 (149, 173)		
COC; combined oral contraceptives; EE: ethinyl estradiol; LNG: levonorgestrel						
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/s/

JOANNE ZHANG
01/23/2012

JANICE B BRODSKY
01/23/2012

JIANG LIU
01/24/2012

NITIN MEHROTRA
01/24/2012

MONICA L FISZMAN
01/24/2012

NORMAN L STOCKBRIDGE
01/24/2012



Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

Consultation for NDA 202611

DATE: Consult requested: 29 August 2011
Date of reassignment: 10 November 2011
Desired Completion date: 20 January 2012
Date of review: 2 January 2011
PDUFA Goal Date: 29 June, 2011

FROM: Preston M. 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)

SPONSOR: Astellas
Drug Class: Beta-3 adrenergic receptor (AR) agonist
NAME OF DRUG: 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)

APPLICATION No: NDA 202611
RELATED APP No: IND 69416

DEVELOPMENT INDICATION: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

CONSULT QUESTIONS: With respect to the sponsor's interpretations of the vital signs data from phase III studies in their Cardiovascular Research Report (NDA-CTD module 5.3.5.3),

1. Does the DCRP consultant agree with sponsor's assessment of the effect of mirabegron on blood pressure?
2. Does the DCRP consultant agree with sponsor's assertion that small incremental increases in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been found to be associated with an increased cardiovascular risk?

3. Are there any differences in mirabegron's effects on blood pressure in the pre-hypertensive, hypertensive 1, 2 or 3 groups?
4. Please refer to Table 22 page 70 and Figure 15 page 93 of report. Please provide your assessment of the sponsor's categorical analysis based upon proportions of blood pressure outliers?

DOCUMENTS AVAILABLE FOR REVIEW:

NDA 202611 submissions, with particular attention to CTD Module 5.3.5.3, entitled Cardiovascular Research Report (CRR), the Integrated Summary of Safety (ISS), Individual Phase III FSRs, and analysis datasets.

Summary Assessment and Recommendation

DCRP agrees with the sponsor's assessment of the effect of mirabegron on blood pressure. There is no evidence that pre-existing hypertension (Hypertension Status 1 definition) increases the risk of medically important elevations in SBP or DBP in patients treated with mirabegron relative to the normotensive population.

Categorical changes from baseline displayed in Table 22 show numerically higher percentages of patients at the final visit SBP and DBP elevations on 50mg mirabegron than for tolterodine, a commonly used anticholinergic used to treat overactive bladder (OAB), but the same is true for placebo. This may be an artifact of the program design, in that all of the phase III tolterodine data in this table is generated from European trial 046, while the placebo and mirabegron data columns are an integration of data from trials 046 and 047, the latter of which includes data from the US. Thus, comparing 50mg mirabegron only to placebo, the differences in final visit categorical SBP/DBP elevation rates are less $\leq 2\%$. Consecutive visit category elevations demonstrate that the numerical differences in rates between placebo and mirabegron are mostly driven by lower degrees of SBP/DBP elevations, and that some of the PM tolterodine elevation rates are higher than for 50mg mirabegron.

We do not agree with the sponsor's assertion that small incremental increases in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been found to be associated with an increased cardiovascular risk. Increasing risks for cardiovascular events with increasing levels of blood pressure are a continuum (i.e., these risk curves do not demonstrate risk thresholds as a function blood pressure, but increase continuously), and the increase in relative risk per mmHg of BP increase is the same regardless of baseline BP. Consequently, the absolute risk of increasing SBP from 169 to 170 is much worse than increasing SBP from 119 to 120. Superimposed on this phenomenon are the effects of other risk modifiers such as smoking status and diabetes.

We recommend 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 CV event rates for the observed blood pressure effects. This can be done using the actual data for each subject's true blood pressure shifts (as opposed to assuming that all patients

experienced the mean change in BP seen for the overall/integrated clinical trial data). If the target population's baseline Framingham risk for CV events is low, then the effect of small BP elevations will be small, but non-zero. For the patients who are at substantially higher Framingham risk (i.e. the high-BMI, diabetic, hypertensive smokers over the age of 70), the effect of these same small BP increments may be more impressive, and a benefit/risk determination different for a higher baseline risk subgroup. This analysis should be performed both for mirabegron and for the tolterodine positive control that was incorporated into the phase III program.

Introduction

Overactive Bladder (OAB)

OAB is a syndrome that includes urgency as an essential symptom, associated with increased urinary frequency and urge urinary incontinence. Its etiology is not completely understood, but overactivity of the detrusor muscle, an indicator of increased bladder sensitivity to contraction-mediating neurotransmitters and mediators originating from the urothelium have been observed. Detrusor overactivation involves afferent signaling and conveys a bladder sensation of urgency in OAB patients. Currently, antimuscarinic agents are used as a standard therapy for overactive bladder; however, their mechanism of action can be associated with inhibition of bladder contractile force during urination which can lead to impaired voiding function. Antimuscarinics have also been associated with adverse events such as dry mouth, constipation, and blurred vision.

During filling, the human urinary bladder is under control of the sympathetic nerve system and the release of noradrenalin leads to activation of both alpha 1 and beta-ARs in the bladder. During filling, the relaxation-mediating beta-ARs functionally dominate the contraction-mediating alpha 1-ARs in the bladder leading to detrusor muscle relaxation. Functional pharmacology studies as well as mRNA expression data have shown that the beta 3-AR is the dominant beta-AR involved in relaxation of the human urinary bladder.

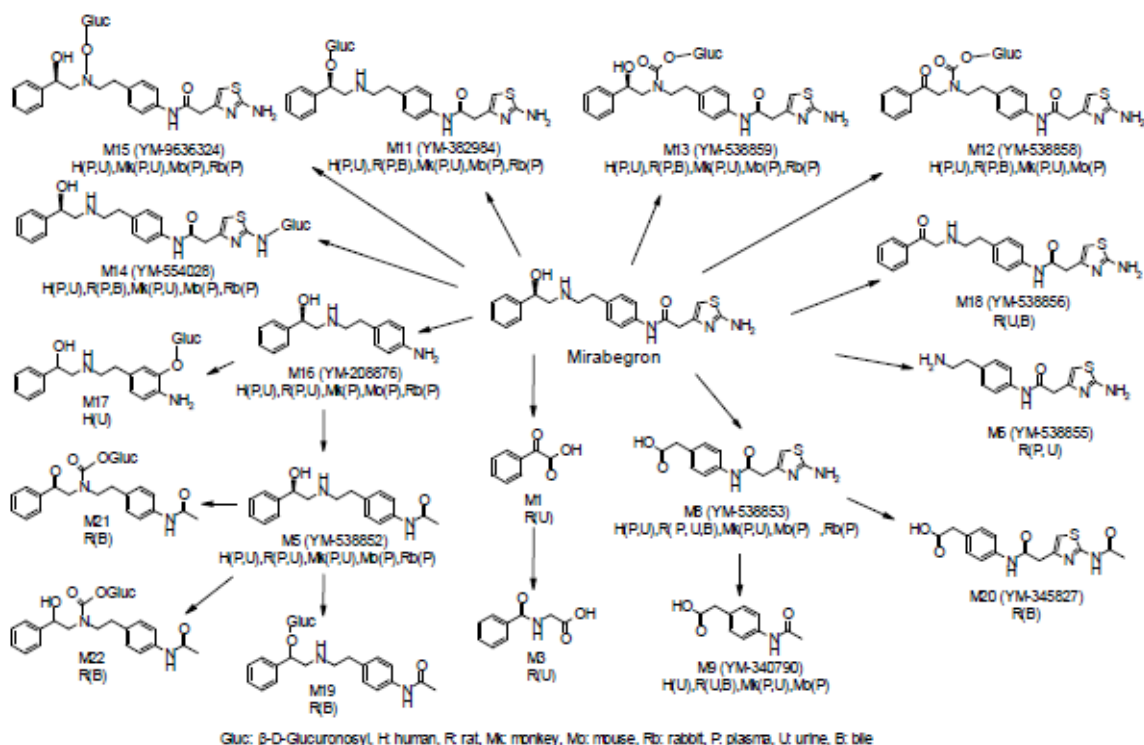
The beta-AR family consists of beta 1, beta 2 and beta 3-ARs. The distribution and function of the various beta-AR subtypes differ in the detrusor muscles from different species. The beta 3-AR is the functionally dominant beta-AR for bladder relaxation in man, cynomolgus monkey, dog and rat, whereas, in cats and guinea pigs, beta 1-ARs are functionally dominant in the bladder. On the other hand in rabbit bladder, beta 2- subtype is dominant [Nergardh et al, 1977; Yamazaki et al, 1998; Takeda, Yamazaki, Akahane et al, 2002].

Mirabegron

Mirabegron is a relatively selective small molecule agonist of the beta 3-AR with a fairly complex in vivo metabolism as shown in

Figure 1 below (from figure 1 of the sponsor's nonclinical overview):

Figure 1. Postulated Metabolic Pathways of Mirabegron



According to the sponsor, the two major metabolites, M11 and M12, are devoid of relevant pharmacological activity.

In humans, the elimination pathway of radioactivity was higher through urinary than for fecal excretion, with the urinary excretion comprising 55.0% and fecal excretion 34.2% of the total radioactivity administered after oral administration of a single 160 mg dose of ¹⁴C mirabegron. In vitro studies and chemical structures of the metabolites suggest that butyrylcholinesterase, uridine diphospho-glucuronosyltransferase (UGT), cytochrome P450 (CYP) 3A4 and 2D6 enzymes, and possibly alcohol dehydrogenase are involved in the metabolism of mirabegron.

Oral controlled absorption system (OCAS) mirabegron reaches C_{max} between 3.0 and 4.3 hours after both single and multiple dosing. Bioavailability increases with dose due to saturation of efflux transporters in the intestine. Steady state concentrations are achieved within 7 days of once daily dosing. Steady state concentrations after once daily administration are approximately double that of single dose administration. Mirabegron is extensively distributed. The effective half-life is approximately 19 hours and the terminal elimination half-life is approximately 50 hours.

In the receptor binding study using membrane fractions from Chinese hamster ovary (CHO) cells expressing human beta-AR subtypes, mirabegron showed high affinity for the human beta 3-AR (105-fold higher affinity for beta 3-AR versus beta 1-AR and 33-

fold higher affinity for beta 3-AR vs beta 2-AR), as seen in [Table 1](#) below (from sponsor's non-clinical overview):

Table 1. Affinity of Mirabegron for Human Beta-AR Subtypes

Test article	K _i (nmol/L)		
	Beta 1	Beta 2	Beta 3
Mirabegron	4,200 ± 900	1,300 ± 300	40 ± 20.2

K_i values are expressed as the mean ± SE of 3 runs.

Agonistic activity of mirabegron to beta-AR subtypes (beta 1-, 2-, and 3-AR) from human was examined with CHO cells expressing each of these beta AR subtypes. Intracellular cyclic adenosine monophosphate (cAMP) concentrations were used as an indicator of beta-AR agonistic activity. Mirabegron showed an agonistic activity to the human beta 3-AR with a 50% effective concentration (EC₅₀) value of 1.5 nmol/L [Module 2.6.2, Section 2.1.2.1, Study 178-PH-044]. The intrinsic activity at the human beta 3-AR, defined as the cAMP concentration relative to the maximum response induced by isoproterenol, for mirabegron was 0.8, indicating that mirabegron is a full agonist at this receptor subtype. On the other hand, mirabegron showed intrinsic activities for human beta 1- and beta 2-AR of 0.1, and 0.2, respectively, and the potency was low as compared to that at the human beta 3-AR [Module 2.6.2, Section 2.1.2.1, Study 178-PH-044].

Regulatory and Clinical Development Background

Mirabegron, a beta-3 AR, is a first in mechanistic class, new molecular entity (NME) being submitted under NDA 202611 for the treatment of overactive bladder. Mirabegron was approved in 2011 in Japan for the treatment of OAB, and the Japanese label was submitted as part of NDA 202611.

In Phase 1 studies of mirabegron, several patients reported mild increases in blood pressure. Therefore, the review division voiced a concern about increases in heart rate possibly coupled with increases in blood pressure. The sponsor agreed to conduct intensive assessment of vital signs in phase 2 and phase 3 studies. The mirabegron NDA application is being submitted simultaneously with the MAA application to the European Medicines Agency for the Centralized Procedure. The US and EU applications share a common efficacy and safety data package.

The sponsor notes that evidence for the efficacy of mirabegron in the treatment of patients with symptoms of OAB comes from 3 randomized, placebo-controlled studies (046, 047, and 074) conducted in North America and Europe. The protocols for primary phase 3 studies 046 and 047 were submitted for SPA review in December 2007.

As part of phase 3 evaluation, patients measured their own home blood pressures. Blood pressure and pulse rate were measured at Visit 1 (screening) by the investigator, using the device that the patient was going to use for self-measurement thereafter. The investigator

measured the circumference of the upper arm to give the patient the right cuff type. The blood pressure measurement was performed in the sitting position at both arms. The arm with the highest blood pressure was taken for the following blood pressure measurements, which were to be done by the patient during the 5 diary days preceding Visits 2, 3, 4, 5 and 6 (baseline, and Weeks 1, 4, 8 and 12) after waking up in the morning and between 2 and 4 p.m. At Visit 1, the investigator instructed the patient on how to perform and document in the diary the self-measurement of the blood pressure and pulse rate according to the “Guidelines for measuring blood pressure at home” (Current Medical Research and Opinion 2002, 18(4): 177-184, CHMP Guidelines, CPMP/EWP/238/95 Rev.2 Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension, European Medicines Agency, London, 23 June 2004). Three readings were taken, each about 2 minutes apart. The patient kept records of the readings (date, time, pulse rate, systolic and diastolic pressure were documented). The sponsor makes the following summary statements/conclusions from their analyses of these data:

- The adjusted mean differences vs placebo for change from baseline in systolic blood pressure (SBP) in the EU/NA OAB 12-week Phase 3 study population for mirabegron 25, 50 and 100 mg and tolterodine were -0.5, 0.6, 0.4 and -0.1 mm Hg for AM measurements and -1.0, 0.5, 0.9 and -0.0 mm Hg for PM measurements, respectively. The adjusted mean differences vs placebo for change from baseline diastolic BP (DBP) in the EU/NA OAB 12-week Phase 3 study population for mirabegron 25, 50 and 100 mg and tolterodine were -0.1, 0.4, 0.2 and 0.7 mm Hg for AM measurements and -0.3, 0.4, 0.5 and 1.0 mm Hg for PM measurements, respectively.
- In the EU/NA Long-term Controlled Study 178-CL-049, the adjusted mean changes from baseline SBP/DBP following mirabegron 50 mg, mirabegron 100 mg and tolterodine were generally similar. The adjusted mean change from baseline for SBP in mirabegron 50 and 100 mg and tolterodine was 0.2, 0.4 and -0.5 mm Hg for AM measurements and -0.3, 0.1 and -0.0 mm Hg for PM measurements. The adjusted mean change from baseline for DBP in mirabegron 50 and 100 mg and tolterodine was -0.3, 0.4 and 0.1 mm Hg for AM measurements and -0.0, 0.1 and 0.6 mm Hg for PM measurements.
- Categorical increases from baseline in SBP and DBP for the EU/NA OAB 12-week Phase 3 and the EU/NA Long-term Controlled Study 178-CL-049 populations were generally similar across all treatment groups.
- The observed increases in SBP/DBP appeared to be reversible upon discontinuation of treatment.
- In both the EU/NA OAB 12-week Phase 3 and EU/NA Long-term Controlled Study populations, the proportions of patients meeting categorical criteria for decreases in SBP and DBP (e.g. ≥ 15 and ≥ 20 mmHg) were low and similar across the mirabegron, placebo and tolterodine treatment groups.

- The Sponsor states that small incremental increases in vital signs such as 1 mm Hg elevation in blood pressure have not been found to be associated with an increased cardiovascular risk.

With respect to the consult questions, the review division calls DCRP's attention to CTD Module 5.3.5.3, entitled Cardiovascular Research Report (CRR), noting that that ambulatory BP monitoring (ABPM) was not performed during the mirabegron drug development program, nor was it requested by the review division.

In the sponsor's CRR, evaluations for cardiovascular safety parameters were focused on the following 3 populations:

- **Global OAB 12-week Phase 2/3:** This population consists of pooled data from 6 placebo-controlled double-blind 12-week phase 2/3 studies conducted globally in Europe, North America, Japan and Australia in 7514 patients with OAB (Studies 178-CL-044, 178-CL-045, 178-CL-046, 178-CL-047, 178-CL-048 and 178-CL-074). Three of the 6 studies also included tolterodine extended release (ER) 4 mg as an active comparator group.
- **EU/NA OAB 12-week Phase 3:** This population is a subset of the Global OAB 12-week Phase 2/3 Population and includes pooled data from 3 placebo-controlled, double-blind, 12-week phase 3 studies conducted in Europe, North America and Australia/New Zealand (henceforth described as Europe and North America) in 4611 patients with OAB (Studies 178-CL-046, 178-CL-047 and 178-CL-074). One of the 3 studies also included tolterodine ER 4 mg as an active comparator group.
- **EU/NA Long-term Controlled:** This population consists of Study 178-CL-049, a 12-month, double-blind phase 3 study with an active-controlled tolterodine ER 4 mg comparator arm conducted in Europe, North America, Australia/New Zealand and South Africa (henceforth described as Europe and North America) in 2444 patients with OAB. Patients who had previously participated in studies 046 and 047 could enroll in this study if they met the inclusion/exclusion criteria.

In the 12 week studies, changes from baseline of cuff blood pressure measurements (triplicate measures for 5 days preceding clinic visit) were analyzed with descriptive statistics, average change from baseline using an ANCOVA model with treatment group, geographical region, and sex as fixed factors and baseline value as a covariate, and repeated measure methodology (the model for which contains terms for treatment group, baseline measurement, time (each relevant visit), time by treatment group, gender, gender by time, and geographical region). In the Long-term Controlled study, changes from baseline of cuff blood pressure measurements were also analyzed using both ANCOVA and repeated measures models. In a small ABPM sub-study within study 049, mean SBP/DBP values were calculated for each patient based on the non-missing measurements taken every 15 minutes over 24 hours prior to baseline, at month 6, and at

month 12, and these data analyzed with a repeated measures model (ANCOVA analysis was not performed for the ABPM parameters). Except for the ABPM analyses, missing data was handled using LOCF methodology.

Assessments and Answers to Questions

1. Do you agree with sponsor's assessment of the effect of mirabegron on blood pressure? Specifically, is the Sponsor's summary of the results of blood pressure monitoring (summary statements in bullet points above) accurate?

Assuming that no data integrity issues were found during the primary medical review, and that the data integration was done correctly, the sponsor's summary from the CRR describes accurately the overall central tendency and categorical data results obtained for the integrated EU/NA OAB 12 week studies, as well as the EU/NA long-term study (see tables 10, 11, 18, 19, 22, and 23 of the CRR). For convenience of review, the CRR is linked to this document in DARRTS, and is embedded here for ease of reference to these tables:



Interestingly, for the BP data, it appears that patients that were not on beta blockers had smaller changes than those on beta blockers, though the changes in both groups were small.

Additional evidence for the minimal overall effects of mirabegron on SBP, DBP, and Pulse based on the phase III clinical trial data is demonstrated by the sponsor in study ISN 178-PK-016, titled, "Modeling to explore the relationship between mirabegron exposure and selected cardiovascular safety parameters (i.e. pulse rate, diastolic and systolic blood pressures) in overactive bladder patients." In this study, the hemodynamic effects of mirabegron were assessed from an integrated dataset including one phase II study that tested the 50 mg dose (study 044), and the two pivotal phase III trials that were given SPA approval by the review division (studies 046 and 047). Study 074, a third phase III trial that tested a lower range of doses, but included the 50 mg dose, was used for external validation of the generated models for predicting HR and BP responses to various exposures of mirabegron. The integrated results for dose-specific and exposure-specific effects of mirabegron on individual changes from baseline for Pulse, DBP, and SBP, are shown below in Figures 5, 14, and 23 as excerpted from the study ISN 178-PK-016 FSR:

Figure 5: Individual morning and afternoon pulse rate change from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047] (top graphs) and corresponding cumulative number of observations as a function of mirabegron exposure per dose (bottom graph). The dashed black lines are smoothes through the data. The plain black zero lines indicate no change from baseline.

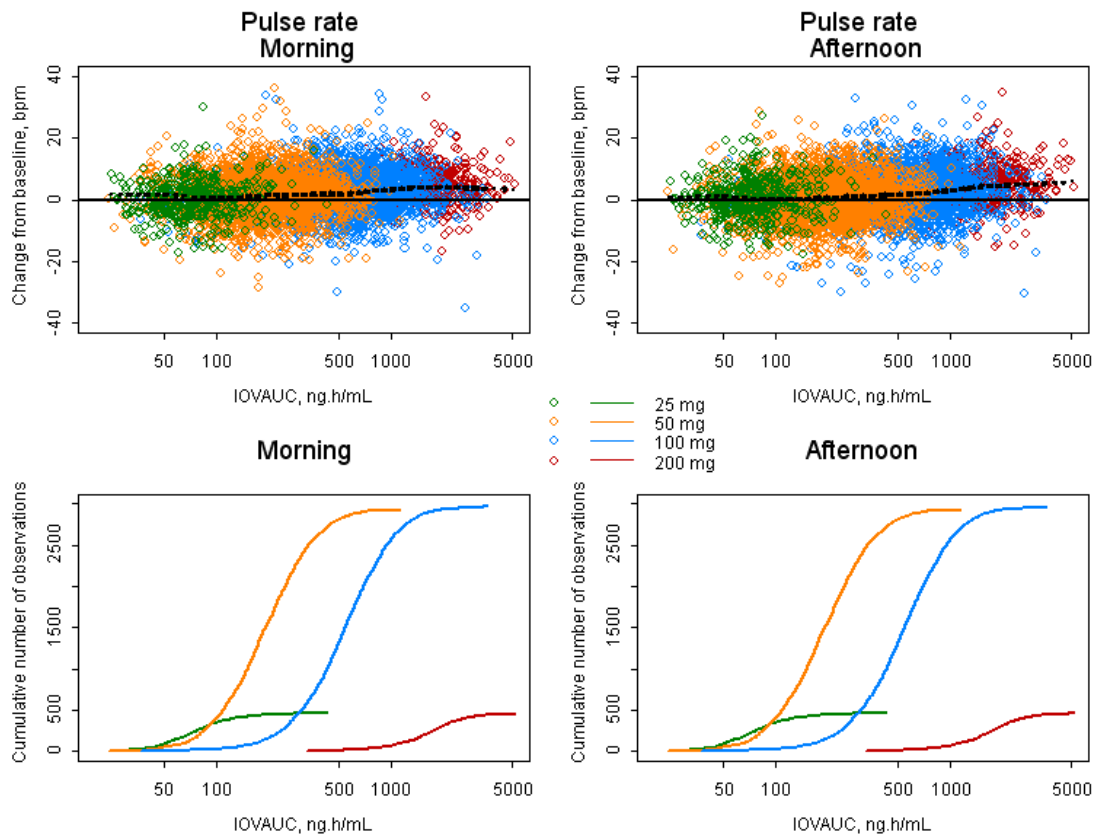


Figure 14: Individual morning and afternoon diastolic blood pressure (DBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047] (top graphs) and corresponding cumulative number of observations as a function of mirabegron exposure per dose (bottom graphs). The dashed black lines are smoothes through the data. The solid black lines indicate no change from baseline.

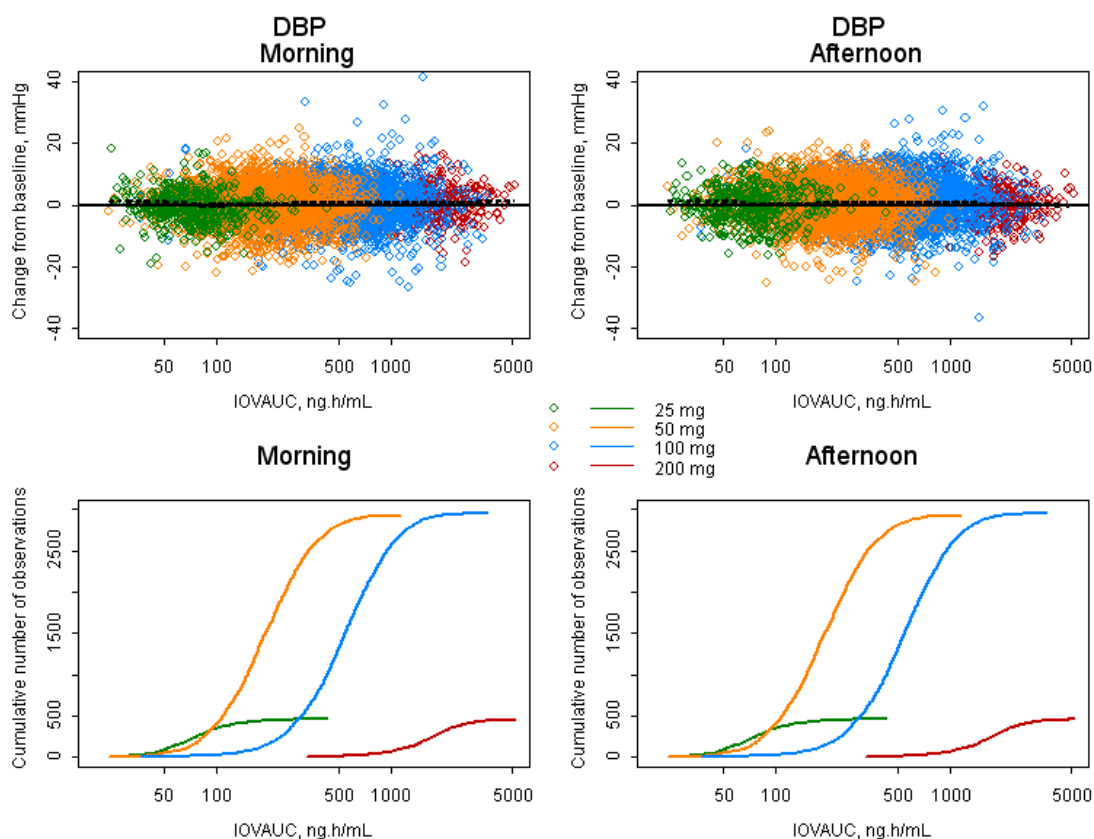
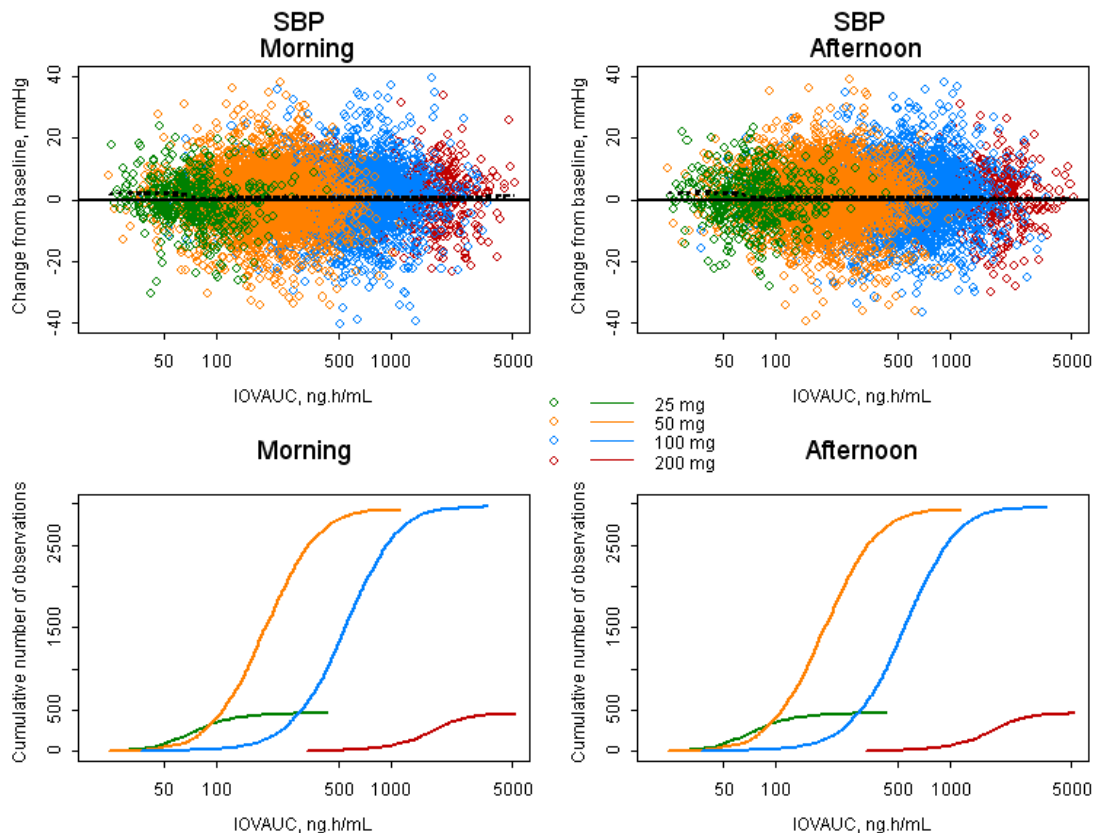


Figure 23. Individual morning and afternoon systolic blood pressure (SBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047] (top graphs) and corresponding cumulative number of observations as a function of mirabegron exposure per dose level (bottom graph). The dashed black lines are smoothes through the data. The solid black zero lines indicate no change from baseline.



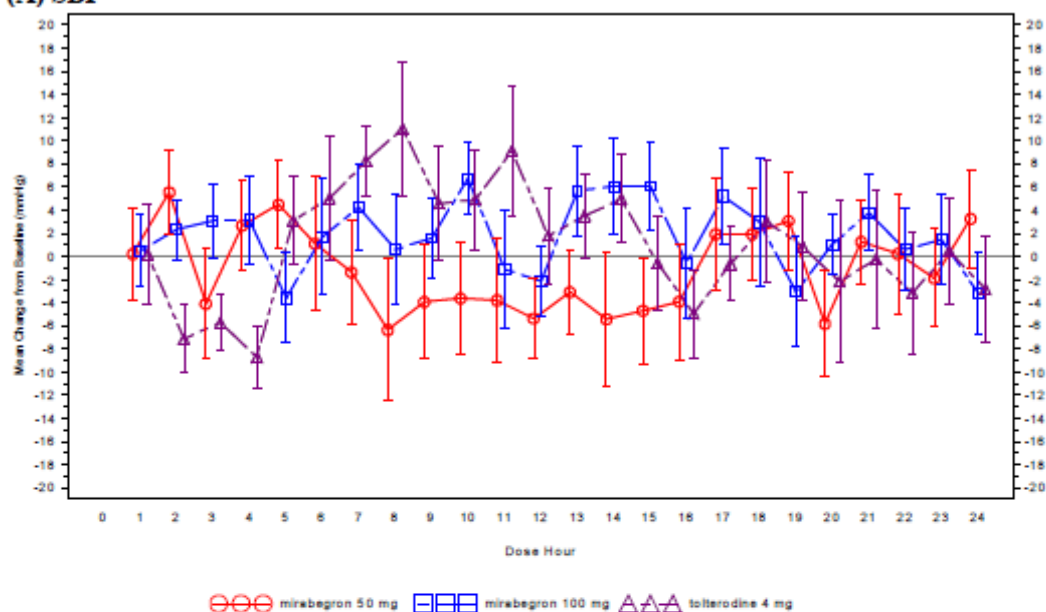
Finally, data supporting the limited impact of 50mg mirabegron on SBP and DBP comes from the small ABPM sub-study in the EU/NA Long-term Controlled Population that was performed in a subset of patients at selected investigational sites in the US (n = 21 for mirabegron 50 mg; n = 28 for mirabegron 100 mg; and n = 24 for tolterodine); pulse rate and blood pressure assessments were collected for a 24-hour period prior to visits at baseline, month 6 and month 12. The ABPM data for SBP and DBP is excerpted below for each post-baseline visit in Table 43 and for month 12 in Figure 29 from the sponsor's CRR. Overall, mirabegron demonstrated SBP/DBP effects similar to those of tolterodine, and a dose response in SBP/DBP effects between 50 mg and 100 mg mirabegron was demonstrated.

Table 43 Summary of Mean Change from Baseline to Month 6, Month 12 and Final Visit in ABPM Mean 24-hour SBP and DBP Measurements, EU/NA Long-term Controlled Population

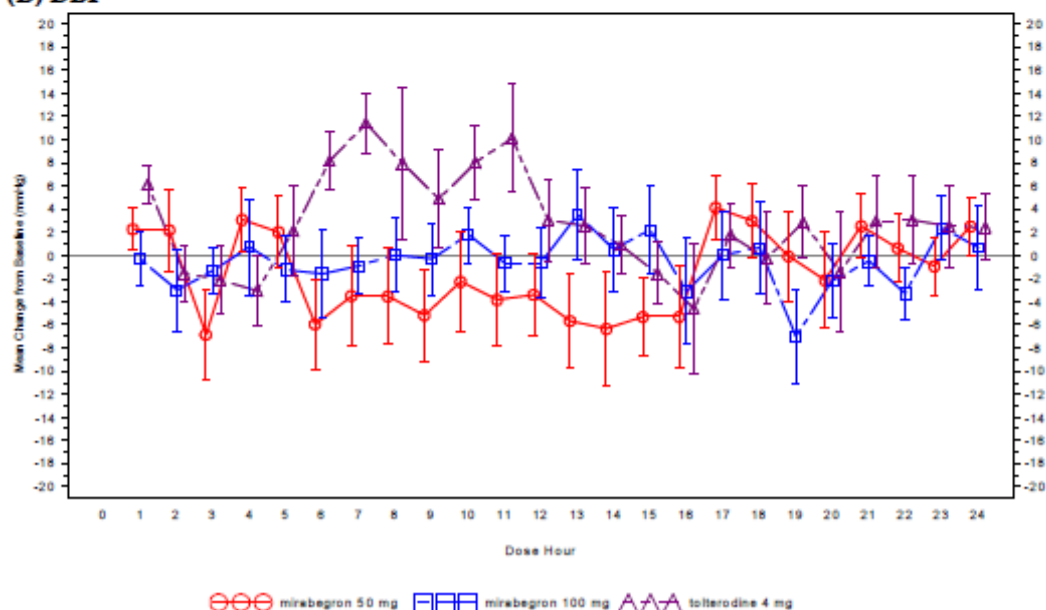
Parameter (mm Hg)	Mirabegron				Tolterodine ER 4 mg	
	50 mg		100 mg		SBP	DBP
	SBP	DBP	SBP	DBP		
	(n = 21)		(n = 28)		(n = 24)	
Baseline						
Mean (SD)	124.0 (15.30)	72.9 (6.07)	122.7 (12.30)	72.6 (7.27)	125.9 (13.25)	71.8 (8.25)
Median	119.2	73.9	120.4	71.2	127.0	69.6
Range	105 to 171	62 to 87	106 to 155	59 to 87	97 to 149	59 to 91
Month 6						
n	15	15	16	16	13	13
Mean (SD)	119.4 (13.43)	70.5 (4.79)	120.5 (12.40)	72.4 (10.26)	122.6 (8.00)	71.7 (7.58)
Median	118.2	69.0	119.8	70.2	119.0	73.7
Range	100 to 157	65 to 82	101 to 152	60 to 96	112 to 134	54 to 82
Change from baseline to month 6						
Mean (SD)	-3.2 (7.51)	-2.6 (5.20)	1.9 (7.05)	-0.1 (4.13)	-0.5 (7.62)	0.9 (6.24)
Median	-4.5	-4.4	2.4	0.1	-3.9	0.3
Range	-13 to 10	-11 to 5	-13 to 15	-8 to 9	-11 to 15	-10 to 14
Month 12						
n	10	10	12	12	9	9
Mean (SD)	120.6 (13.71)	70.4 (5.52)	120.8 (11.44)	72.7 (8.85)	121.8 (11.70)	71.6 (6.59)
Median	118.4	70.2	117.0	71.3	122.4	71.8
Range	104 to 155	65 to 82	107 to 146	60 to 89	102 to 142	63 to 83
Change from baseline to month 12						
Mean (SD)	-1.3 (8.76)	-1.7 (5.24)	1.5 (7.24)	-0.7 (5.25)	1.1 (5.78)	2.7 (4.06)
Median	2.0	-0.9	-1.0	-1.3	0.3	2.8
Range	-16 to 10	-11 to 5	-7 to 20	-6 to 14	-10 to 11	-3 to 8
Final visit						
n	15	15	16	16	13	13
Mean (SD)	119.5 (11.84)	70.0 (4.76)	119.5 (10.39)	71.3 (8.37)	122.4 (10.38)	72.2 (7.40)
Median	117.1	69.9	117.0	69.7	122.4	72.7
Range	104 to 155	65 to 82	107 to 146	60 to 89	102 to 142	59 to 83
Change from baseline to final visit						
Mean (SD)	-3.0 (7.71)	-3.0 (4.85)	0.9 (7.16)	-1.3 (4.75)	-0.7 (5.83)	1.4 (5.22)
Median	-3.4	-4.5	-1.0	-2.2	-0.6	2.5
Range	-16 to 10	-11 to 5	-9 to 20	-6 to 14	-10 to 11	-10 to 8

Figure 28 Mean Change from Time-matched Baseline in Blood Pressure at Month 12 Measured by ABPM, EU/NA Long-term Controlled Population

(A) SBP



(B) DBP



Note that the global OAB population was not assessed for vital sign changes, according to the sponsor, due to lack of concordance of data structures (i.e., vital signs not systematically recorded in a way that could be integrated from the other studies). I would prefer that they submit some sort of summary analysis of this data, rough though it undoubtedly is, just to see what's in it.

2. Do you agree with sponsor's assertion that small incremental increases in vital signs (such as 1 mm Hg elevation in systolic or diastolic blood pressure) have not been found to be associated with an increased cardiovascular risk?

No, we do not agree. Increasing risks for cardiovascular events with increasing levels of blood pressure are a continuum (i.e., these risk curves do not demonstrate risk thresholds as a function blood pressure, but increase continuously), and the increase in relative risk per mmHg of BP increase is the same regardless of baseline BP. Therefore, the absolute risk of increasing SBP from 169 to 170 is much worse than increasing SBP from 119 to 120. Superimposed on this phenomenon are the effects of other risk modifiers such as smoking status and diabetes.

We recommend 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 CV event rates for the observed blood pressure effects. This can be done using the actual data for each subject's true blood pressure shifts (as opposed to assuming that all patients experienced the mean change in BP seen for the overall/integrated clinical trial). If the target population's baseline Framingham risk for CV events is low, then the effect of small BP elevations will be small, but non-zero. For the patients who are at substantially higher Framingham risk (i.e. the high-BMI, diabetic, hypertensive smokers over the age of 70), the effect of these same small BP increments may be more impressive, and a benefit/risk determination different for a higher baseline risk subgroup.

This analysis should be performed both for mirabegron and for the tolterodine positive control that was incorporated into the phase III program.

3. Are there any differences in mirabegron's effects on blood pressure in the pre-hypertensive, hypertensive 1, 2 or 3 groups?

There were two definitions of hypertension that were assessed in the sponsor's CRR as follows:

- Hypertension Status 1 (clinical history)
 - Hypertensive – any patient with a medical history of hypertension and receiving concurrent antihypertensive treatment at the time of the screening visit
 - Past History of Hypertension: any patient with a medical history of hypertension and no concurrent antihypertensive treatment at the time of the screening visit. Patients included in the past history of hypertension were also included in the normotensive population.
 - Normotensive: any patient who did not meet the definition of hypertensive
- Hypertension Status 2 (JNC-7 definitions)
 - Normal: SBP < 120 mm Hg AND DBP < 80 mm Hg

- o Prehypertension: SBP 120 to 139 mm Hg OR DBP 80 to 89 mm Hg
- o Stage 1 Hypertension: SBP 140 to 159 mm Hg OR DBP 90 to 99 mm Hg
- o Stage 2 Hypertension: SBP $\geq$ 160 mm Hg OR DBP $\geq$ 100 mm Hg

Hypertension Status 1 definitions were primarily utilized in the clinical development program, so all of the in-text displays of the CRR are based on these criteria. Accordingly, all of the following data displays in this section are based on the Hypertension Status 1 definitions. Hypertension Status 2 definitions were utilized only to generate a series of tables in the CRR that included descriptive statistics for SBP, DBP, and change in these parameters at protocol-specified follow-up intervals. Manual review of this sequence of Hypertension Status 2 descriptive statistics in the CRR reveals no medically important differences in the change from baseline SBP/DBP parameters between the 50mg mirabegron and tolterodine groups. Further analysis based on Hypertension Status 2 nomenclature would be of limited utility, since the categorical analyses already performed by the sponsor are defined by absolute shifts in SBP/DBP. It is possible (and in fact not surprising) that the JNC7 stage 2 patients may be the ones that are demonstrating the more prominent BP shifts in the categorical analysis tables, but this would undoubtedly be the case across all treatment groups.

From CRR Appendix 4 (Comprehensive Summary of Blood Pressure), Tables 3, 4, 5, 6, 10, and 11 corroborate the mirabegron's minimal and comparator-similar impact on change from baseline of SBP and DBP in the short-term and long-term phase III studies:

Table 3 Change from Baseline to Final Visit in SBP Measured by Patient Diary, ANCOVA Model, EU/NA OAB 12-week Phase 3 Population, Hypertension status 1

Population Parameter (mm Hg)	Placebo	Mirabegron			Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	
AM					
Normotensive†	(n = 857)	(n = 250)	(n = 873)	(n = 555)	(n = 300)
n	825	239	845	532	289
Baseline mean (SE)	121.4 (0.55)	123.8 (0.97)	121.9 (0.55)	120.2 (0.63)	123.8 (0.85)
Adjusted mean change from baseline (SE)	0.6 (0.29)	0.2 (0.62)	1.4 (0.28)	1.2 (0.37)	-0.0 (0.52)
Mean difference vs placebo (SE)		-0.4 (0.67)	0.7 (0.40)	0.6 (0.48)	-0.7 (0.61)
95% 2-sided CI		-1.7, 0.9	-0.1, 1.5	-0.3, 1.5	-1.9, 0.5
Past history of hypertension†	(n = 58)	(n = 22)	(n = 67)	(n = 35)	(n = 15)
n	54	20	65	33	15
Baseline mean (SE)	136.9 (1.97)	134.7 (3.64)	137.7 (2.19)	131.8 (3.07)	132.5 (2.66)
Adjusted mean change from baseline (SE)	-0.3 (1.36)	-0.1 (2.56)	-2.0 (1.27)	-3.9 (1.88)	-1.7 (2.85)
Mean difference vs placebo (SE)		0.3 (2.86)	-1.6 (1.85)	-3.5 (2.36)	-1.3 (3.20)
95% 2-sided CI		-5.4, 5.9	-5.3, 2.0	-8.2, 1.1	-7.7, 5.0
Hypertensive†	(n = 523)	(n = 182)	(n = 502)	(n = 374)	(n = 195)
n	504	171	482	359	187
Baseline mean (SE)	133.4 (0.74)	136.8 (1.16)	134.2 (0.76)	132.3 (0.87)	134.8 (1.22)
Adjusted mean change from baseline (SE)	-0.5 (0.45)	-1.2 (0.92)	0.1 (0.46)	-0.5 (0.57)	0.2 (0.81)
Mean difference vs placebo (SE)		-0.7 (1.01)	0.6 (0.65)	0.0 (0.73)	0.7 (0.94)
95% 2-sided CI		-2.7, 1.3	-0.7, 1.9	-1.4, 1.4	-1.1, 2.6
PM					
Normotensive†	(n = 857)	(n = 250)	(n = 873)	(n = 555)	(n = 300)
n	824	239	845	532	289
Baseline mean (SE)	122.1 (0.50)	125.5 (0.89)	122.9 (0.51)	120.8 (0.59)	125.4 (0.78)
Adjusted mean change from baseline (SE)	0.9 (0.29)	0.0 (0.63)	1.4 (0.29)	2.2 (0.38)	0.5 (0.54)
Mean difference vs placebo (SE)		-0.8 (0.69)	0.5 (0.41)	1.3 (0.49)	-0.4 (0.62)
95% 2-sided CI		-2.2, 0.5	-0.3, 1.3	0.3, 2.2	-1.6, 0.8
Past history of hypertension†	(n = 58)	(n = 22)	(n = 67)	(n = 35)	(n = 15)
n	54	20	65	33	15
Baseline mean (SE)	133.3 (1.59)	131.2 (3.02)	136.9 (1.94)	130.6 (2.34)	134.3 (2.83)
Adjusted mean change from baseline (SE)	-0.5 (1.41)	-0.3 (2.65)	-2.2 (1.32)	-1.6 (1.94)	3.6 (2.94)
Mean difference vs placebo (SE)		0.1 (2.95)	-1.7 (1.93)	-1.1 (2.43)	4.1 (3.30)
95% 2-sided CI		-5.7, 6.0	-5.5, 2.1	-5.9, 3.7	-2.4, 10.6

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Hypertensive†	(n = 523)	(n = 182)	(n = 502)	(n = 374)	(n = 195)
n	502	171	482	358	187
Baseline mean (SE)	129.9 (0.65)	133.9 (1.08)	130.3 (0.70)	127.9 (0.78)	130.5 (1.08)
Adjusted mean change from baseline (SE)	0.1 (0.46)	-1.2 (0.92)	0.6 (0.47)	0.2 (0.58)	0.4 (0.82)
Mean difference vs placebo (SE)		-1.3 (1.02)	0.5 (0.65)	0.1 (0.74)	0.3 (0.95)
95% 2-sided CI		-3.3, 0.7	-0.8, 1.8	-1.3, 1.6	-1.6, 2.2

Table 4 Change from Baseline to Final Visit in SBP Measured by Patient Diary, ANCOVA Model, EU/NA Long-term Controlled Population, Hypertension status 1

Population Parameter (mm Hg)	Mirabegron		Tolterodine ER 4 mg (n = 812)
	50 mg (n = 812)	100 mg (n = 820)	
AM			
Normotensive†	(n = 488)	(n = 509)	(n = 478)
n	474	498	469
Baseline mean (SE)	122.3 (0.70)	121.9 (0.67)	122.1 (0.67)
Adjusted mean change from baseline (SE)	0.3 (0.38)	1.0 (0.37)	-0.3 (0.38)
95% 2-sided CI	-0.4, 1.1	0.3, 1.7	-1.1, 0.4
Past history of hypertension†	(n = 33)	(n = 52)	(n = 43)
n	31	51	43
Baseline mean (SE)	133.1 (2.88)	134.5 (2.34)	129.9 (2.49)
Adjusted mean change from baseline (SE)	-2.8 (1.67)	-0.5 (1.31)	-2.9 (1.41)
95% 2-sided CI	(-6.1, 0.5)	(-3.1, 2.1)	(-5.7, -0.1)
Hypertensive†	(n = 324)	(n = 311)	(n = 334)
n	317	304	324
Baseline mean (SE)	133.4 (0.87)	132.6 (0.88)	133.7 (0.80)
Adjusted mean change from baseline (SE)	0.0 (0.59)	-0.4 (0.60)	-0.7 (0.58)
95% 2-sided CI	-1.1, 1.2	-1.6, 0.7	-1.9, 0.4
PM			
Normotensive†	(n = 488)	(n = 509)	(n = 478)
n	474	498	469
Baseline mean (SE)	123.5 (0.62)	123.3 (0.61)	123.4 (0.62)
Adjusted mean change from baseline (SE)	-0.4 (0.39)	0.9 (0.38)	-0.0 (0.39)
95% 2-sided CI	-1.1, 0.4	0.2, 1.6	-0.8, 0.7
Past history of hypertension†	(n = 33)	(n = 52)	(n = 43)
n	31	51	43
Baseline mean (SE)	131.6 (2.58)	133.6 (1.95)	130.9 (2.06)
Adjusted mean change from baseline (SE)	-1.8 (1.78)	1.1 (1.40)	-4.4 (1.49)
95% 2-sided CI	(-5.4, 1.7)	(-1.6, 3.9)	(-7.3, -1.4)
Hypertensive†	(n = 324)	(n = 311)	(n = 334)
n	315	304	324
Baseline mean (SE)	130.8 (0.79)	129.6 (0.80)	130.6 (0.75)
Adjusted mean change from baseline (SE)	-0.2 (0.58)	-1.0 (0.59)	-0.1 (0.57)
95% 2-sided CI	-1.4, 0.9	-2.2, 0.1	-1.2, 1.1

Table 5 Change from Baseline to Final Visit in DBP Measured by Patient Diary, ANCOVA Model, EU/NA OAB 12-week Phase 3 Population, Hypertension status 1

Population Parameter (mm Hg)	Placebo	Mirabegron			Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	
AM					
Normotensive†	(n = 857)	(n = 250)	(n = 873)	(n = 555)	(n = 300)
n	825	239	845	532	289
Baseline mean (SE)	76.1 (0.31)	76.4 (0.58)	76.2 (0.30)	76.1 (0.38)	75.4 (0.48)
Adjusted mean change from baseline (SE)	0.4 (0.20)	0.2 (0.42)	0.7 (0.19)	0.7 (0.26)	1.0 (0.36)
Mean difference vs placebo (SE)		-0.2 (0.46)	0.3 (0.28)	0.4 (0.33)	0.6 (0.42)
95% 2-sided CI		-1.1, 0.7	-0.2, 0.9	-0.3, 1.0	-0.2, 1.4
Past history of hypertension†	(n = 58)	(n = 22)	(n = 67)	(n = 35)	(n = 15)
n	54	20	65	33	15
Baseline mean (SE)	82.7 (1.33)	76.9 (2.43)	84.5 (1.07)	81.0 (2.03)	81.6 (2.14)
Adjusted mean change from baseline (SE)	0.0 (0.89)	-0.8 (1.68)	-1.0 (0.82)	1.6 (1.22)	-0.4 (1.85)
Mean difference vs placebo (SE)		-0.8 (1.87)	-1.0 (1.21)	1.6 (1.53)	-0.4 (2.08)
95% 2-sided CI		-4.5, 2.9	-3.4, 1.4	-1.4, 4.6	-4.5, 3.7
Hypertensive†	(n = 523)	(n = 182)	(n = 502)	(n = 374)	(n = 195)
n	504	171	482	358	187
Baseline mean (SE)	78.9 (0.43)	80.8 (0.76)	78.8 (0.41)	79.4 (0.45)	79.0 (0.65)
Adjusted mean change from baseline (SE)	-0.5 (0.27)	-0.6 (0.54)	-0.1 (0.27)	-0.6 (0.34)	0.4 (0.48)
Mean difference vs placebo (SE)		-0.0 (0.60)	0.4 (0.38)	-0.1 (0.43)	1.0 (0.55)
95% 2-sided CI		-1.2, 1.1	-0.3, 1.2	-1.0, 0.7	-0.1, 2.0
PM					
Normotensive†	(n = 857)	(n = 250)	(n = 873)	(n = 555)	(n = 300)
n	824	239	845	532	289
Baseline mean (SE)	75.2 (0.29)	75.5 (0.57)	75.4 (0.31)	75.1 (0.36)	75.2 (0.46)
Adjusted mean change from baseline (SE)	0.6 (0.20)	0.2 (0.43)	0.9 (0.20)	1.4 (0.26)	1.7 (0.36)
Mean difference vs placebo (SE)		-0.4 (0.46)	0.3 (0.28)	0.8 (0.33)	1.1 (0.42)
95% 2-sided CI		-1.3, 0.5	-0.2, 0.9	0.2, 1.5	0.3, 2.0
Past history of hypertension†	(n = 58)	(n = 22)	(n = 67)	(n = 35)	(n = 15)
n	54	20	65	33	15
Baseline mean (SE)	79.6 (1.21)	74.8 (2.71)	83.0 (1.29)	80.2 (1.87)	80.9 (2.48)
Adjusted mean change from baseline (SE)	-0.7 (0.95)	-3.2 (1.79)	-0.8 (0.88)	1.3 (1.30)	3.0 (1.98)
Mean difference vs placebo (SE)		-2.5 (1.98)	-0.1 (1.29)	1.9 (1.63)	3.7 (2.22)
95% 2-sided CI		-6.5, 1.4	-2.7, 2.4	-1.3, 5.1	-0.7, 8.1
Hypertensive†	(n = 523)	(n = 182)	(n = 502)	(n = 374)	(n = 195)
n	502	171	482	358	187
Baseline mean (SE)	75.5 (0.40)	76.8 (0.75)	75.5 (0.40)	75.6 (0.44)	75.6 (0.66)
Adjusted mean change from baseline (SE)	0.0 (0.28)	-0.2 (0.57)	0.5 (0.29)	0.1 (0.36)	1.0 (0.50)
Mean difference vs placebo (SE)		-0.2 (0.63)	0.4 (0.40)	0.1 (0.45)	1.0 (0.58)
95% 2-sided CI		-1.4, 1.1	-0.3, 1.2	-0.8, 0.9	-0.2, 2.1

Table 6 Change from Baseline to Final Visit in DBP Measured by Patient Diary, ANCOVA Model, EU/NA Long-term Controlled Population, Hypertension status 1

Population Parameter (mm Hg)	Mirabegron		Tolterodine
	50 mg (n = 812)	100 mg (n = 820)	ER 4 mg (n = 812)
AM			
Normotensive†	(n = 488)	(n = 509)	(n = 478)
n	474	498	469
Baseline mean (SE)	76.4 (0.38)	76.1 (0.36)	76.5 (0.39)
Adjusted mean change from baseline (SE)	-0.2 (0.25)	0.8 (0.25)	0.2 (0.26)
95% 2-sided CI	-0.7, 0.3	0.3, 1.3	-0.3, 0.7
Past history of hypertension†	(n = 33)	(n = 52)	(n = 43)
n	31	51	43
Baseline mean (SE)	84.5 (1.56)	78.6 (1.21)	80.4 (1.67)
Adjusted mean change from baseline (SE)	-1.3 (1.14)	-0.7 (0.88)	-0.2 (0.94)
95% 2-sided CI	-3.6, 1.0	-2.5, 1.0	-2.1, 1.6
Hypertensive†	(n = 324)	(n = 311)	(n = 334)
n	317	304	324
Baseline mean (SE)	79.4 (0.52)	79.0 (0.49)	79.0 (0.47)
Adjusted mean change from baseline (SE)	-0.4 (0.35)	-0.3 (0.35)	-0.0 (0.34)
95% 2-sided CI	-1.1, 0.2	-1.0, 0.4	-0.7, 0.6
PM			
Normotensive†	(n = 488)	(n = 509)	(n = 478)
n	474	498	469
Baseline mean (SE)	76.1 (0.36)	75.9 (0.36)	76.1 (0.38)
Adjusted mean change from baseline (SE)	0.1 (0.26)	0.4 (0.26)	0.4 (0.27)
95% 2-sided CI	-0.4, 0.6	-0.1, 0.9	-0.1, 1.0
Past history of hypertension†	(n = 33)	(n = 52)	(n = 43)
n	31	51	43
Baseline mean (SE)	82.0 (1.22)	77.1 (1.14)	80.3 (1.36)
Adjusted mean change from baseline (SE)	-0.6 (1.14)	-0.4 (0.89)	-1.7 (0.95)
95% 2-sided CI	-2.9, 1.7	-2.1, 1.4	-3.6, 0.2
Hypertensive†	(n = 324)	(n = 311)	(n = 334)
n	315	304	324
Baseline mean (SE)	76.4 (0.53)	76.0 (0.50)	76.1 (0.46)
Adjusted mean change from baseline (SE)	-0.2 (0.36)	-0.3 (0.37)	0.9 (0.36)
95% 2-sided CI	-0.9, 0.5	-1.0, 0.4	0.2, 1.6

Table 10 Adjusted Mean Difference vs Placebo for Change (SE) from Baseline to Each Visit in SBP, by Hypertension Status 1, EU/NA OAB 12-week Phase 2/3 Population

Parameter (mm Hg)	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Normotensive										
Baseline	825	824	239	239	845	845	532	532	289	289
n	121.4	122.1	123.8	125.5	121.9	122.9	120.2	120.8	123.8	125.4
Mean (SE)	(0.55)	(0.50)	(0.97)	(0.89)	(0.55)	(0.51)	(0.63)	(0.59)	(0.85)	(0.78)
Week 4										
n	825	824	239	239	841	841	531	531	288	288
Adjusted mean change from baseline (SE)	0.0 (0.26)	0.4 (0.27)	-0.4 (0.55)	-0.4 (0.56)	0.7 (0.26)	0.8 (0.27)	1.0 (0.34)	1.4 (0.35)	-0.7 (0.47)	-0.0 (0.48)
Mean difference vs placebo (SE)			-0.4 (0.60)	-0.8 (0.62)	0.7 (0.37)	0.4 (0.38)	1.0 (0.43)	1.0 (0.44)	-0.8 (0.55)	-0.4 (0.56)
95% 2-sided CI			(-1.6, 0.8)	(-2.0, 0.4)	(-0.0, 1.4)	(-0.3, 1.2)	(0.2, 1.9)	(0.1, 1.8)	(-1.8, 0.3)	(-1.5, 0.7)
Week 8										
n	767	767	231	231	795	795	500	500	280	280
Adjusted mean change from baseline (SE)	0.3 (0.28)	0.5 (0.29)	-0.0 (0.57)	0.1 (0.59)	1.3 (0.28)	1.3 (0.29)	1.5 (0.36)	1.9 (0.37)	-1.1 (0.50)	-0.1 (0.51)
Mean difference vs placebo (SE)			-0.3 (0.63)	-0.4 (0.65)	1.0 (0.39)	0.8 (0.41)	1.2 (0.46)	1.5 (0.47)	-1.4 (0.58)	-0.6 (0.59)
95% 2-sided CI			(-1.5, 0.9)	(-1.7, 0.9)	(0.2, 1.8)	(0.0, 1.6)	(0.3, 2.1)	(0.5, 2.4)	(-2.5, -0.3)	(-1.8, 0.6)
Week 12										
n	749	749	224	224	769	769	489	489	267	267
Adjusted mean change from baseline (SE)	0.7 (0.30)	1.0 (0.30)	0.3 (0.60)	-0.1 (0.61)	1.5 (0.29)	1.5 (0.30)	1.2 (0.38)	2.3 (0.39)	-0.1 (0.52)	0.5 (0.53)
Mean difference vs placebo (SE)			-0.5 (0.66)	-1.1 (0.68)	0.8 (0.42)	0.5 (0.43)	0.5 (0.48)	1.2 (0.49)	-0.9 (0.61)	-0.5 (0.62)
95% 2-sided CI			(-1.8, 0.8)	(-2.4, 0.3)	(-0.1, 1.6)	(-0.3, 1.3)	(-0.4, 1.5)	(0.3, 2.2)	(-2.1, 0.3)	(-1.7, 0.7)
Past history of hypertension										
Baseline	54	54	20	20	65	65	33	33	15	15
n	136.9	133.3	134.7	131.2	137.7	136.9	131.8	130.6	132.5	134.3
Mean (SE)	(1.97)	(1.59)	(3.64)	(3.02)	(2.19)	(1.94)	(3.07)	(2.34)	(2.66)	(2.83)
Week 4										
n	54	54	20	20	64	64	33	33	15	15
Adjusted mean change from baseline (SE)	-0.6 (1.34)	-1.7 (1.28)	-0.8 (2.42)	-0.4 (2.33)	-1.6 (1.25)	-0.5 (1.20)	-0.6 (1.80)	1.7 (1.73)	-3.7 (2.71)	1.9 (2.60)
Mean difference vs placebo (SE)			-0.2 (2.73)	1.3 (2.62)	-1.1 (1.82)	1.2 (1.75)	-0.0 (2.27)	3.4 (2.18)	-3.1 (3.06)	3.6 (2.93)
95% 2-sided CI			(-5.6, 5.2)	(-3.8, 6.5)	(-4.7, 2.5)	(-2.2, 4.7)	(-4.5, 4.5)	(-0.9, 7.7)	(-9.2, 2.9)	(-2.2, 9.4)
Week 8										
n	51	51	19	19	64	64	30	30	15	15
Adjusted mean change from baseline (SE)	-0.3 (1.29)	-1.5 (1.33)	3.1 (2.34)	-1.2 (2.41)	-2.0 (1.18)	-0.7 (1.23)	-1.2 (1.77)	1.6 (1.82)	-3.2 (2.58)	0.8 (2.66)
Mean difference vs placebo (SE)			3.4 (2.63)	0.3 (2.72)	-1.7 (1.74)	0.8 (1.81)	-0.9 (2.21)	3.2 (2.27)	-2.9 (2.91)	2.3 (2.99)
95% 2-sided CI			(-1.8, 8.6)	(-5.0, 5.7)	(-5.2, 1.7)	(-2.8, 4.4)	(-5.3, 3.5)	(-1.3, 7.6)	(-8.6, 2.8)	(-3.6, 8.2)
Week 12										
n	52	52	19	19	61	60	31	31	13	13
Adjusted mean change from baseline (SE)	-0.6 (1.39)	-0.6 (1.42)	0.4 (2.51)	0.3 (2.55)	-1.9 (1.30)	-2.1 (1.34)	-4.0 (1.90)	-1.8 (1.93)	-2.2 (2.89)	2.2 (2.93)
Mean difference vs placebo (SE)			1.0 (2.84)	1.0 (2.89)	-1.4 (1.90)	-1.5 (1.95)	-3.5 (2.37)	-1.2 (2.41)	-1.6 (3.23)	2.9 (3.28)
95% 2-sided CI			(-4.6, 6.6)	(-4.7, 6.7)	(-5.1, 2.4)	(-5.3, 2.4)	(-8.2, 1.2)	(-6.0, 3.5)	(-8.0, 4.8)	(-3.6, 9.3)
<i>Table continued on next page</i>										

	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
Hypertensive										
Baseline	504	502	171	171	482	482	359	358	187	187
n	133.4	129.9	136.8	133.9	134.2	130.3	132.3	127.9	134.8	130.5
Mean (SE)	(0.74)	(0.65)	(1.16)	(1.08)	(0.76)	(0.70)	(0.87)	(0.78)	(1.22)	(1.08)
Week 4										
n	503	501	171	171	480	480	357	356	187	187
Adjusted mean change from baseline (SE)	-0.4 (0.42)	-0.5 (0.44)	-0.3 (0.82)	-0.7 (0.86)	0.1 (0.43)	0.4 (0.45)	0.1 (0.53)	1.1 (0.55)	-1.3 (0.74)	-1.1 (0.77)
Mean difference vs placebo (SE)			0.2 (0.92)	-0.3 (0.96)	0.5 (0.60)	0.8 (0.63)	0.5 (0.68)	1.5 (0.71)	-0.9 (0.86)	-0.6 (0.90)
95% 2-sided CI			(-1.6, 2.0)	(-2.2, 1.6)	(-0.6, 1.7)	(-0.4, 2.1)	(-0.8, 1.9)	(0.1, 2.9)	(-2.6, 0.8)	(-2.4, 1.2)
Week 8										
n	471	468	165	165	453	453	347	346	182	182
Adjusted mean change from baseline (SE)	-0.3 (0.46)	0.1 (0.46)	-1.0 (0.87)	-1.6 (0.87)	-0.5 (0.47)	-0.3 (0.47)	-0.5 (0.56)	0.4 (0.56)	-1.4 (0.78)	0.0 (0.79)
Mean difference vs placebo (SE)			-0.7 (0.97)	-1.7 (0.98)	-0.3 (0.65)	-0.3 (0.65)	-0.2 (0.72)	0.3 (0.73)	-1.1 (0.91)	-0.1 (0.92)
95% 2-sided CI			(-2.6, 1.2)	(-3.6, 0.2)	(-1.6, 1.0)	(-1.6, 0.9)	(-1.6, 1.2)	(-1.1, 1.8)	(-2.9, 0.7)	(-1.8, 1.7)
Week 12										
n	451	449	163	163	435	435	337	336	171	171
Adjusted mean change from baseline (SE)	-0.4 (0.47)	0.2 (0.48)	-1.1 (0.88)	-1.3 (0.89)	0.2 (0.48)	0.7 (0.49)	-0.7 (0.57)	0.2 (0.58)	-0.2 (0.81)	0.2 (0.82)
Mean difference vs placebo (SE)			-0.8 (0.99)	-1.6 (1.01)	0.6 (0.67)	0.5 (0.68)	-0.4 (0.74)	-0.1 (0.75)	0.1 (0.94)	-0.0 (0.95)
95% 2-sided CI			(-2.7, 1.2)	(-3.5, 0.4)	(-0.7, 1.9)	(-0.9, 1.8)	(-1.8, 1.1)	(-1.5, 1.4)	(-1.7, 2.0)	(-1.9, 1.9)

Table 11 Adjusted Mean Difference vs Placebo for Change (SE) from Baseline to Each Visit in DBP, by Hypertension Status 1, EU/NA OAB 12-week Phase 2/3 Population

Parameter (mm Hg)	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Normotensive										
Baseline										
n	825	824	239	239	845	845	532	532	289	289
Mean (SE)	76.1 (0.31)	75.2 (0.29)	76.4 (0.58)	75.5 (0.57)	76.2 (0.30)	75.4 (0.31)	76.1 (0.38)	75.1 (0.36)	75.4 (0.48)	75.2 (0.46)
Week 4										
n	825	824	239	239	841	841	531	531	288	288
Adjusted mean change from baseline (SE)	-0.1 (0.18)	0.2 (0.19)	0.1 (0.38)	0.1 (0.39)	0.5 (0.18)	0.6 (0.19)	0.8 (0.24)	1.1 (0.24)	0.5 (0.33)	1.3 (0.34)
Mean difference vs placebo (SE)			0.2 (0.42)	-0.0 (0.43)	0.6 (0.26)	0.4 (0.27)	0.9 (0.30)	1.0 (0.31)	0.6 (0.38)	1.1 (0.39)
95% 2-sided CI			(-0.6, 1.0)	(-0.9, 0.8)	(0.1, 1.1)	(-0.1, 0.9)	(0.3, 1.5)	(0.3, 1.6)	(-0.2, 1.3)	(0.4, 1.9)
Week 8										
n	767	767	231	231	795	795	500	500	280	280
Adjusted mean change from baseline (SE)	0.1 (0.20)	0.4 (0.20)	-0.3 (0.40)	0.1 (0.41)	0.7 (0.20)	0.8 (0.20)	1.2 (0.25)	1.6 (0.26)	0.6 (0.35)	1.3 (0.35)
Mean difference vs placebo (SE)			-0.5 (0.45)	-0.3 (0.45)	0.6 (0.28)	0.5 (0.28)	1.1 (0.33)	1.2 (0.33)	0.4 (0.41)	0.9 (0.41)
95% 2-sided CI			(-1.3, 0.4)	(-1.1, 0.6)	(0.1, 1.1)	(-0.1, 1.0)	(0.5, 1.8)	(0.6, 1.8)	(-0.4, 1.2)	(0.1, 1.7)
Week 12										
n	749	749	224	224	770	769	489	489	267	267
Adjusted mean change from baseline (SE)	0.4 (0.21)	0.6 (0.21)	0.1 (0.41)	0.1 (0.42)	0.7 (0.20)	0.9 (0.20)	0.8 (0.26)	1.5 (0.26)	0.9 (0.36)	1.7 (0.36)
Mean difference vs placebo (SE)			-0.4 (0.46)	-0.6 (0.46)	0.3 (0.29)	0.3 (0.29)	0.3 (0.33)	0.9 (0.34)	0.5 (0.42)	1.0 (0.42)
95% 2-sided CI			(-1.3, 0.5)	(-1.5, 0.3)	(-0.3, 0.9)	(-0.3, 0.8)	(-0.3, 1.0)	(0.2, 1.5)	(-0.4, 1.3)	(0.2, 1.8)
Past history of hypertension										
Baseline										
n	54	54	20	20	65	65	33	33	15	15
Mean (SE)	82.7 (1.33)	79.6 (1.21)	76.9 (2.43)	74.8 (2.71)	84.5 (1.07)	83.0 (1.29)	81.0 (2.03)	80.2 (1.87)	81.6 (2.14)	80.9 (2.48)
Week 4										
n	54	54	20	20	64	64	33	33	15	15
Adjusted mean change from baseline (SE)	-0.3 (0.89)	-0.4 (0.86)	-1.6 (1.62)	-2.9 (1.58)	-1.6 (0.83)	-1.2 (0.81)	2.2 (1.20)	1.7 (1.17)	-2.6 (1.80)	1.0 (1.76)
Mean difference vs placebo (SE)			-1.3 (1.83)	-2.5 (1.78)	-1.3 (1.21)	-0.8 (1.18)	2.5 (1.51)	2.1 (1.47)	-2.4 (2.03)	1.4 (1.98)
95% 2-sided CI			(-4.9, 2.3)	(-6.0, 1.1)	(-3.7, 1.1)	(-3.1, 1.6)	(-0.5, 5.5)	(-0.8, 5.0)	(-6.4, 1.6)	(-2.5, 5.3)
Week 8										
n	51	51	19	19	64	64	30	30	15	15
Adjusted mean change from baseline (SE)	0.7 (0.88)	0.2 (0.89)	-1.1 (1.60)	-3.8 (1.63)	-0.5 (0.80)	0.3 (0.82)	1.6 (1.20)	2.2 (1.22)	-0.6 (1.75)	1.4 (1.78)
Mean difference vs placebo (SE)			-1.8 (1.81)	-4.0 (1.83)	-1.2 (1.19)	0.2 (1.21)	1.0 (1.50)	2.0 (1.52)	-1.3 (1.97)	1.2 (2.00)
95% 2-sided CI			(-5.3, 1.8)	(-7.6, -0.4)	(-3.5, 1.2)	(-2.2, 2.5)	(-2.0, 3.9)	(-1.0, 5.0)	(-5.1, 2.6)	(-2.8, 5.2)
Week 12										
n	52	52	19	19	61	60	31	31	13	13
Adjusted mean change from baseline (SE)	-0.1 (0.91)	-0.7 (0.96)	-1.4 (1.67)	-3.4 (1.74)	-0.9 (0.85)	-0.7 (0.90)	1.8 (1.24)	1.3 (1.30)	-0.3 (1.88)	2.4 (1.98)
Mean difference vs placebo (SE)			-1.3 (1.88)	-2.7 (1.97)	-0.9 (1.24)	-0.1 (1.32)	1.9 (1.55)	2.0 (1.63)	-0.2 (2.11)	3.0 (2.22)
95% 2-sided CI			(-5.1, 2.4)	(-6.6, 1.2)	(-3.3, 1.6)	(-2.7, 2.5)	(-1.2, 4.9)	(-1.2, 5.2)	(-4.3, 4.0)	(-1.4, 7.4)
<i>Table continued on next page</i>										

	Placebo		Mirabegron 25 mg		Mirabegron 50 mg		Mirabegron 100 mg		Tolterodine ER 4 mg	
Hypertensive										
Baseline										
n	504	502	171	171	482	482	358	358	187	187
Mean (SE)	78.9 (0.43)	75.5 (0.40)	80.8 (0.76)	76.8 (0.75)	78.8 (0.41)	75.5 (0.40)	79.4 (0.45)	75.6 (0.44)	79.0 (0.65)	75.6 (0.66)
Week 4										
n	503	501	171	171	480	480	356	356	187	187
Adjusted mean change from baseline (SE)	-0.7 (0.25)	-0.4 (0.27)	-0.8 (0.49)	-0.3 (0.52)	-0.1 (0.25)	0.2 (0.27)	0.0 (0.31)	0.3 (0.33)	0.1 (0.44)	0.4 (0.47)
Mean difference vs placebo (SE)			-0.1 (0.54)	0.0 (0.58)	0.5 (0.35)	0.6 (0.38)	0.7 (0.40)	0.7 (0.43)	0.8 (0.51)	0.8 (0.54)
95% 2-sided CI			(-1.2, 0.9)	(-1.1, 1.2)	(-0.2, 1.2)	(-0.2, 1.3)	(-0.1, 1.5)	(-0.1, 1.5)	(-0.2, 1.8)	(-0.3, 1.8)
Week 8										
n	471	468	165	165	453	453	346	346	182	182
Adjusted mean change from baseline (SE)	-0.4 (0.27)	-0.3 (0.28)	-1.4 (0.52)	-0.7 (0.54)	-0.6 (0.28)	-0.2 (0.29)	-0.5 (0.33)	0.4 (0.34)	-0.6 (0.47)	0.8 (0.48)
Mean difference vs placebo (SE)			-1.0 (0.58)	-0.5 (0.60)	-0.1 (0.39)	0.1 (0.40)	-0.1 (0.43)	0.7 (0.45)	-0.2 (0.54)	1.1 (0.56)
95% 2-sided CI			(-2.1, 0.2)	(-1.6, 0.7)	(-0.9, 0.6)	(-0.7, 0.9)	(-0.9, 0.8)	(-0.2, 1.6)	(-1.2, 0.9)	(0.0, 2.2)
Week 12										
n	451	449	163	163	435	435	336	336	171	171
Adjusted mean change from baseline (SE)	-0.5 (0.28)	-0.1 (0.29)	-0.6 (0.52)	-0.2 (0.55)	-0.1 (0.28)	0.5 (0.30)	-0.7 (0.34)	0.1 (0.35)	0.2 (0.48)	0.7 (0.50)
Mean difference vs placebo (SE)			-0.1 (0.59)	-0.2 (0.62)	0.5 (0.40)	0.5 (0.41)	-0.1 (0.44)	0.2 (0.46)	0.7 (0.56)	0.8 (0.58)
95% 2-sided CI			(-1.3, 1.1)	(-1.4, 1.0)	(-0.3, 1.3)	(-0.3, 1.4)	(-1.0, 0.7)	(-0.7, 1.1)	(-0.4, 1.8)	(-0.4, 1.9)

Finally, figures F-7, F-8 and F-9 below from study ISN 178-PK-016 show that there are virtually no differences in the increase of pulse rate, DBP, or SBP as a function of mirabegron exposure between normotensive patients and hypertensive patients or patients with past history of hypertension

For a discussion of differential categorical SBP/DBP event rates based on hypertensive status, as well as an analysis of potentially clinically significant (PCS) blood pressure changes, see question 4.

Figure F- 7 Individual morning and afternoon pulse rate changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (linear scale: left graphs, log scale: right graphs) in patients with OAB: normotensive patients (NO HTA) and hypertensive patients or patients with past history of hypertension (HTA) from studies [178-CL-044], [178-CL-046] and [178-CL-047]. The orange and blue solid lines are Loess fits using the S-PLUS GAM function. The red zero lines indicate no change from baseline. The green dots are placebo data. Y axes are truncated.

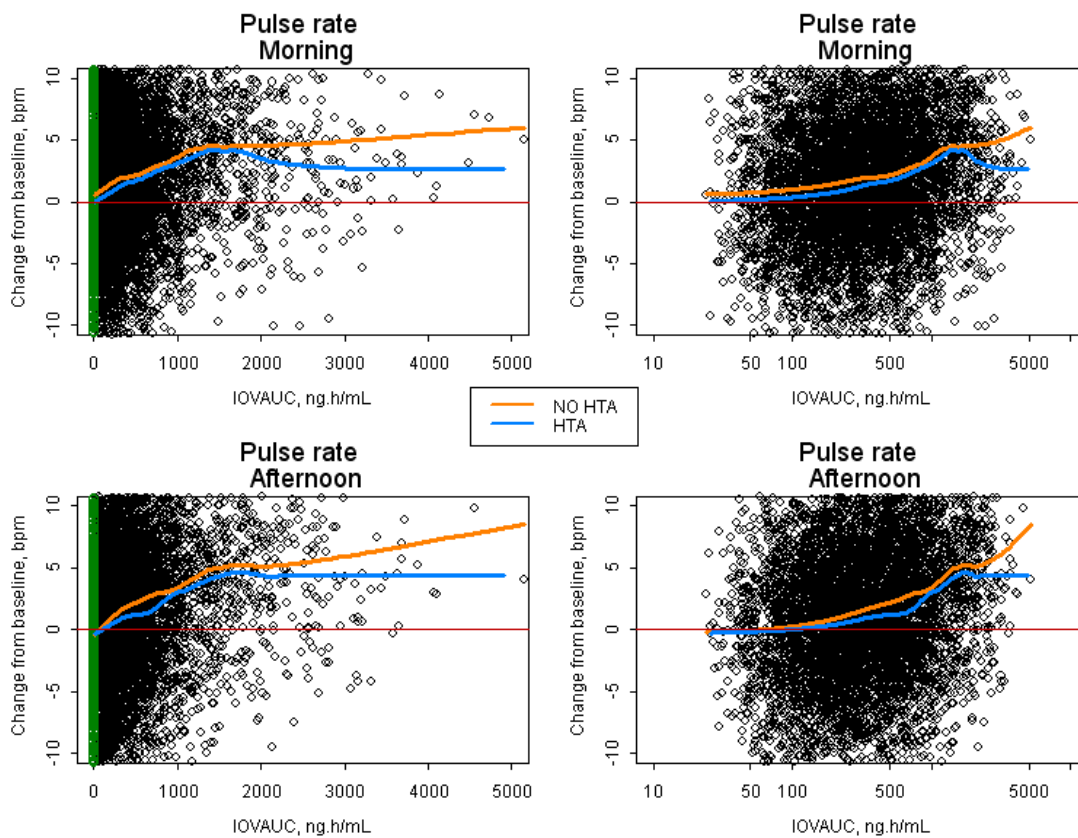


Figure F- 8 Individual morning and afternoon diastolic blood pressure (DBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (linear scale: left graphs, log scale: right graphs) in patients with OAB: normotensive patients (NO HTA) and hypertensive patients or patients with past history of hypertension (HTA) from studies [178-CL-044], [178-CL-046] and [178-CL-047]. The solid orange and blue lines are Loess fits using the S-PLUS GAM function. The red zero lines indicate no change from baseline. The green dots are placebo data. Y axes are truncated.

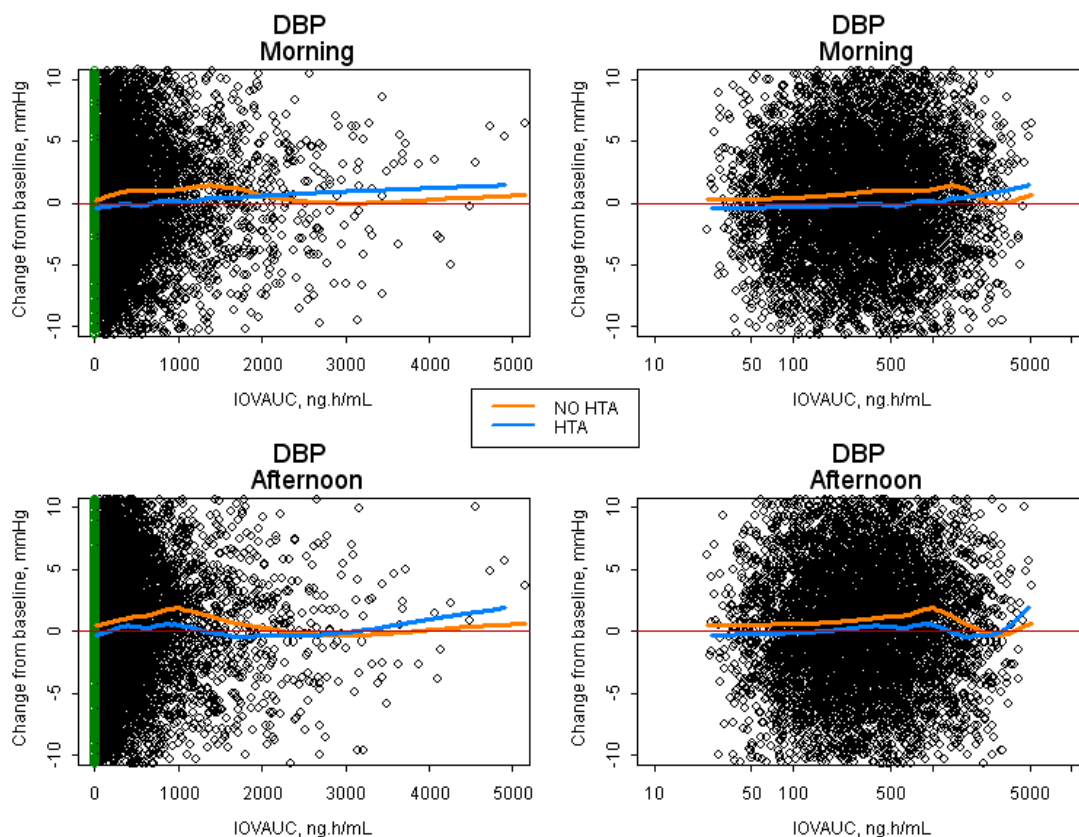
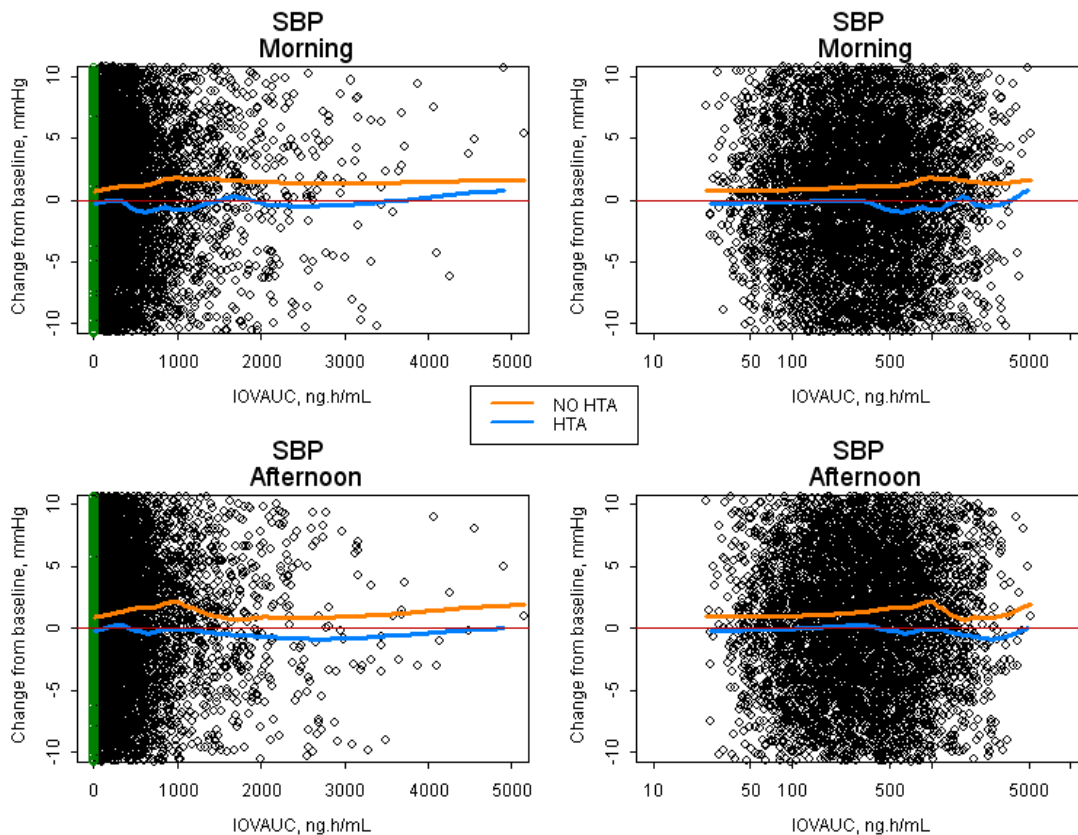


Figure F- 9 Individual morning and afternoon systolic blood pressure (SBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (linear scale: left graphs, log scale: right graphs) in patients with OAB: normotensive patients (NO HTA) and hypertensive patients or patients with past history of hypertension (HTA) from studies [178-CL-044], [178-CL-046] and [178-CL-047]. The solid orange and blue lines are Loess fits using the S-PLUS GAM function. The red zero lines indicate no change from baseline. The green dots are placebo data. Y axes are truncated.



4. Please refer to Table 22 page 70 and Figure 15 page 93 of report. Please provide your assessment of the sponsor's categorical analysis based upon proportions of blood pressure outliers?

For convenience of reference, Table 22 from the sponsor's CRR is reproduced below:

Table 22. Patients Whose AM or PM SBP or DBP Measurements from the Patient Diary Met Selected Criteria, EU/NA OAB 12-week Phase 3 Population

Parameter, n/n (%) of Patients	Placebo	Mirabegron			Tolterodine ER 4 mg
		25 mg	50 mg	100 mg	
SBP					
AM	(n = 1380)	(n = 432)	(n = 1375)	(n = 929)	(n = 495)
Final visit					
Change from baseline $\leq$ 15 mm Hg	70/1329 (5.3%)	21/410 (5.1%)	89/1327 (6.7%)	53/891 (5.9%)	17/476 (3.6%)
2 consecutive postbaseline visits					
Change from baseline $\geq$ 2 mm Hg	438/1242	128/396 (32.3%)	483/1247 (38.7%)	315/852 (37.0%)	142/463 (30.7%)
Change from baseline $\geq$ 5 mm Hg	(35.3%)	78/396 (19.7%)	303/1247 (24.3%)	204/852 (23.9%)	83/463 (17.9%)
Change from baseline $\leq$ 10 mm Hg	263/1242	34/396 (8.6%)	100/1247 (8.0%)	63/852 (7.4%)	26/463 (5.6%)
Change from baseline $\leq$ 15 mm Hg	(21.2%)	6/396 (1.5%)	28/1247 (2.2%)	20/852 (2.3%)	7/463 (1.5%)
Change from baseline $\leq$ 20 mm Hg	94/1242 (7.6%)	2/396 (0.5%)	15/1247 (1.2%)	10/852 (1.2%)	3/463 (0.6%)
PM	(n = 1380)	(n = 432)	(n = 1375)	(n = 929)	(n = 495)
Final visit					
Change from baseline $\leq$ 15 mm Hg	86/1326 (6.5%)	23/410 (5.6%)	94/1327 (7.1%)	69/890 (7.8%)	35/476 (7.4%)
2 consecutive postbaseline visits					
Change from baseline $\geq$ 2 mm Hg	444/1239	118/396 (29.8%)	448/1247 (35.9%)	362/851 (42.5%)	167/463 (36.1%)
Change from baseline $\geq$ 5 mm Hg	(35.8%)	74/396 (18.7%)	307/1247 (24.6%)	240/851 (28.2%)	105/463 (22.7%)
Change from baseline $\leq$ 10 mm Hg	285/1239	26/396 (6.6%)	109/1247 (8.7%)	85/851 (10.0%)	41/463 (8.9%)
Change from baseline $\leq$ 15 mm Hg	(23.0%)	8/396 (2.0%)	31/1247 (2.5%)	25/851 (2.9%)	11/463 (2.4%)
Change from baseline $\leq$ 20 mm Hg	101/1239 (8.2%)	4/396 (1.0%)	11/1247 (0.9%)	9/851 (1.1%)	4/463 (0.9%)
DBP					
AM	(n = 1380)	(n = 432)	(n = 1375)	(n = 929)	(n = 495)
Final visit					
Change from baseline $\leq$ 10 mm Hg	61/1329 (4.6%)	17/410 (4.1%)	88/1327 (6.6%)	53/890 (6.0%)	25/476 (5.3%)
2 consecutive postbaseline visits					
Change from baseline $\leq$ 2 mm Hg	329/1242 (26.5%)	99/396 (25.0%)	410/1247 (32.9%)	292/851 (34.3%)	151/463 (32.6%)
Change from baseline $\leq$ 5 mm Hg	150/1242 (12.1%)	47/396 (11.9%)	180/1247 (14.4%)	122/851 (14.3%)	61/463 (13.2%)
Change from baseline $\leq$ 10 mm Hg	29/1242 (2.3%)	5/396 (1.3%)	31/1247 (2.5%)	25/851 (2.9%)	8/463 (1.7%)
Change from baseline $\leq$ 15 mm Hg	3/1242 (0.2%)	1/396 (0.3%)	2/1247 (0.2%)	5/851 (0.6%)	2/463 (0.4%)
PM	(n = 1380)	(n = 432)	(n = 1375)	(n = 929)	(n = 495)
Final visit					
Change from baseline $\leq$ 10 mm Hg	71/1326 (5.4%)	18/410 (4.4%)	91/1327 (6.9%)	78/890 (8.8%)	38/476 (8.0%)
2 consecutive postbaseline visits					
Change from baseline $\leq$ 2 mm Hg	374/1239 (30.2%)	99/396 (25.0%)	393/1247 (31.5%)	319/851 (37.5%)	186/463 (40.2%)
Change from baseline $\leq$ 5 mm Hg	166/1239 (13.4%)	43/396 (10.9%)	193/1247 (15.5%)	173/851 (20.3%)	86/463 (18.6%)
Change from baseline $\leq$ 10 mm Hg	26/1239 (2.1%)	9/396 (2.3%)	31/1247 (2.5%)	38/851 (4.5%)	12/463 (2.6%)
Change from baseline $\leq$ 15 mm Hg	0/1239	1/396 (0.3%)	5/1247 (0.4%)	5/851 (0.6%)	1/463 (0.2%)

Categorical changes from baseline displayed in Table 22 above show numerically higher percentages of patients at the final visit with SBP and DBP elevations on 50mg mirabegron than for patients on tolterodine, but the same is true for placebo. This may be an artifact of the program design, in that all of the phase III tolterodine data in this table is generated from European study 046, while the placebo and mirabegron data columns are an integration of data from 046 and 047, the latter of which includes

data from the US. Thus, comparing 50mg mirabegron only to placebo, the differences in final visit SBP/DBP elevation rates are less $\leq 2\%$. Consecutive visit category elevations demonstrate that the numerical differences in rates between placebo and mirabegron are mostly driven by lower degrees of SBP/DPB elevations, and the some of the tolterodine PM elevation rates are higher than for 50mg mirabegron.

To dissect this data more thoroughly, we went back to the 046 dataset to look at within-study differences of these categorical SBP/DBP elevation rates between placebo, mirabegron, and tolterodine, for the overall patient population, normotensives, and hypertensives (Hypertensive Status 1 definitions), split by AM and PM, data which is shown below in tables 69 – 72 from the 046 FSR:

Table 69 Incidence of Patients Whose AM Systolic Blood Pressure Value Measured by Patient’s Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	(n=494)	(n=493)	(n=496)	(n=495)
Final Visit				
Change from baseline ≥ 15 mm Hg	26/481 (5.4%)	28/474 (5.9%)	27/479 (5.6%)	17/476 (3.6%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	14/449 (3.1%)	10/437 (2.3%)	13/443 (2.9%)	8/436 (1.8%)
Change from baseline ≥ 15 mm Hg	5/449 (1.1%)	3/437 (0.7%)	5/443 (1.1%)	2/436 (0.5%)
Change from baseline ≥ 20 mm Hg	4/449 (0.9%)	2/437 (0.5%)	3/443 (0.7%)	2/436 (0.5%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	40/464 (8.6%)	27/450 (6.0%)	35/456 (7.7%)	26/461 (5.6%)
Change from baseline ≥ 15 mm Hg	16/464 (3.4%)	10/450 (2.2%)	14/456 (3.1%)	7/461 (1.5%)
Change from baseline ≥ 20 mm Hg	8/464 (1.7%)	6/450 (1.3%)	7/456 (1.5%)	3/461 (0.7%)
Normotensive	(n=298)	(n=321)	(n=313)	(n=300)
Final Visit				
Change from baseline ≥ 15 mm Hg	12/288 (4.2%)	15/312 (4.8%)	19/302 (6.3%)	7/289 (2.4%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	5/270 (1.9%)	7/288 (2.4%)	9/276 (3.3%)	2/265 (0.8%)
Change from baseline ≥ 15 mm Hg	1/270 (0.4%)	1/288 (0.3%)	5/276 (1.8%)	1/265 (0.4%)
Change from baseline ≥ 20 mm Hg	1/270 (0.4%)	1/288 (0.3%)	3/276 (1.1%)	1/265 (0.4%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	21/276 (7.6%)	16/296 (5.4%)	22/285 (7.7%)	10/279 (3.6%)
Change from baseline ≥ 15 mm Hg	6/276 (2.2%)	6/296 (2.0%)	8/285 (2.8%)	2/279 (0.7%)
Change from baseline ≥ 20 mm Hg	2/276 (0.7%)	3/296 (1.0%)	4/285 (1.4%)	1/279 (0.4%)
Hypertensive Population	(n=196)	(n=172)	(n=183)	(n=195)
Final Visit				
Change from baseline ≥ 15 mm Hg	14/193 (7.3%)	13/162 (8.0%)	8/177 (4.5%)	10/187 (5.3%)
3 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	9/179 (5.0%)	3/149 (2.0%)	4/167 (2.4%)	6/171 (3.5%)
Change from baseline ≥ 15 mm Hg	4/179 (2.2%)	2/149 (1.3%)	0	1/171 (0.6%)
Change from baseline ≥ 20 mm Hg	3/179 (1.7%)	1/149 (0.7%)	0	1/171 (0.6%)
2 Consecutive Postbaseline Visits				
Change from baseline ≥ 10 mm Hg	19/188 (10.1%)	11/154 (7.1%)	13/171 (7.6%)	16/182 (8.8%)
Change from baseline ≥ 15 mm Hg	10/188 (5.3%)	4/154 (2.6%)	6/171 (3.5%)	5/182 (2.7%)
Change from baseline ≥ 20 mm Hg	6/188 (3.2%)	3/154 (1.9%)	3/171 (1.8%)	2/182 (1.1%)

Table 70 Incidence of Patients Whose PM Systolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	(n=494)	(n=493)	(n=496)	(n=495)
Final Visit				
Change from baseline $\geq$ 15 mm Hg	34/479 (7.1%)	24/474 (5.1%)	37/478 (7.7%)	33/476 (6.9%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 10 mm Hg	11/447 (2.5%)	18/437 (4.1%)	21/442 (4.8%)	16/436 (3.7%)
Change from baseline $\geq$ 15 mm Hg	2/447 (0.4%)	5/437 (1.1%)	7/442 (1.6%)	4/436 (0.9%)
Change from baseline $\geq$ 20 mm Hg	1/447 (0.2%)	1/437 (0.2%)	3/442 (0.7%)	2/436 (0.5%)
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 10 mm Hg	36/462 (7.8%)	38/450 (8.4%)	46/455 (10.1%)	41/461 (8.9%)
Change from baseline $\geq$ 15 mm Hg	8/462 (1.7%)	9/450 (2.0%)	16/455 (3.5%)	11/461 (2.4%)
Change from baseline $\geq$ 20 mm Hg	2/462 (0.4%)	5/450 (1.1%)	8/455 (1.8%)	4/461 (0.9%)
Normotensive	(n=298)	(n=321)	(n=313)	(n=300)
Final Visit				
Change from baseline $\geq$ 15 mm Hg	16/288 (5.6%)	15/312 (4.8%)	21/302 (7.0%)	12/289 (4.2%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 10 mm Hg	2/270 (0.7%)	11/288 (3.8%)	13/276 (4.7%)	7/265 (2.6%)
Change from baseline $\geq$ 15 mm Hg	0	4/288 (1.4%)	3/276 (1.1%)	1/265 (0.4%)
Change from baseline $\geq$ 20 mm Hg	0	1/288 (0.3%)	2/276 (0.7%)	0
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 10 mm Hg	15/276 (5.4%)	26/296 (8.8%)	32/285 (11.2%)	18/279 (6.5%)
Change from baseline $\geq$ 15 mm Hg	1/276 (0.4%)	7/296 (2.4%)	9/285 (3.2%)	6/279 (2.2%)
Change from baseline $\geq$ 20 mm Hg	0	4/296 (1.4%)	5/285 (1.8%)	1/279 (0.4%)
Hypertensive Population	(n=196)	(n=172)	(n=183)	(n=195)
Final Visit				
Change from baseline $\geq$ 15 mm Hg	18/191 (9.4%)	9/162 (5.6%)	16/176 (9.1%)	21/187 (11.2%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 10 mm Hg	9/177 (5.1%)	7/149 (4.7%)	8/166 (4.8%)	9/171 (5.3%)
Change from baseline $\geq$ 15 mm Hg	2/177 (1.1%)	1/149 (0.7%)	4/166 (2.4%)	3/171 (1.8%)
Change from baseline $\geq$ 20 mm Hg	1/177 (0.6%)	0	1/166 (0.6%)	2/171 (1.2%)
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 10 mm Hg	21/186 (11.3%)	12/154 (7.8%)	14/170 (8.2%)	23/182 (12.6%)
Change from baseline $\geq$ 15 mm Hg	7/186 (3.8%)	2/154 (1.3%)	7/170 (4.1%)	5/182 (2.7%)
Change from baseline $\geq$ 20 mm Hg	2/186 (1.1%)	1/154 (0.6%)	3/170 (1.8%)	3/182 (1.6%)

Table 71 Incidence of Patients Whose AM Diastolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	(n=494)	(n=493)	(n=496)	(n=495)
Final Visit				
Change from baseline $\geq$ 10 mm Hg	21/481 (4.4%)	26/474 (5.5%)	23/478 (4.8%)	25/476 (5.3%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	29/449 (6.5%)	27/437 (6.2%)	34/442 (7.7%)	28/436 (6.4%)
Change from baseline $\geq$ 10 mm Hg	5/449 (1.1%)	4/437 (0.9%)	7/442 (1.6%)	2/436 (0.5%)
Change from baseline $\geq$ 15 mm Hg	0	0	2/442 (0.5%)	1/436 (0.2%)
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	65/464 (14.0%)	65/450 (14.4%)	70/455 (15.4%)	60/461 (13.0%)
Change from baseline $\geq$ 10 mm Hg	14/464 (3.0%)	6/450 (1.3%)	12/455 (2.6%)	7/461 (1.5%)
Change from baseline $\geq$ 15 mm Hg	2/464 (0.4%)	0	3/455 (0.7%)	2/461 (0.4%)
Normotensive Population	(n=298)	(n=321)	(n=313)	(n=300)
Final Visit				
Change from baseline $\geq$ 10 mm Hg	13/288 (4.5%)	19/312 (6.1%)	19/302 (6.3%)	16/289 (5.5%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	17/270 (6.3%)	19/288 (6.6%)	24/276 (8.7%)	17/265 (6.4%)
Change from baseline $\geq$ 10 mm Hg	3/270 (1.1%)	2/288 (0.7%)	6/276 (2.2%)	1/265 (0.4%)
Change from baseline $\geq$ 15 mm Hg	0	0	2/276 (0.7%)	1/265 (0.4%)
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	37/276 (13.4%)	50/296 (16.9%)	45/285 (15.8%)	36/279 (12.9%)
Change from baseline $\geq$ 10 mm Hg	8/276 (2.9%)	4/296 (1.4%)	9/285 (3.2%)	5/279 (1.8%)
Change from baseline $\geq$ 15 mm Hg	1/276 (0.4%)	0	3/285 (1.1%)	2/279 (0.7%)
Hypertensive Population	(n=196)	(n=172)	(n=183)	(n=195)
Final Visit				
Change from baseline $\geq$ 10 mm Hg	8/193 (4.1%)	7/162 (4.3%)	4/176 (2.3%)	9/187 (4.8%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	12/179 (6.7%)	8/149 (5.4%)	10/166 (6.0%)	11/171 (6.4%)
Change from baseline $\geq$ 10 mm Hg	2/179 (1.1%)	2/149 (1.3%)	1/166 (0.6%)	1/171 (0.6%)
Change from baseline $\geq$ 15 mm Hg	0	0	0	0
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	28/188 (14.9%)	15/154 (9.7%)	25/170 (14.7%)	24/182 (13.2%)
Change from baseline $\geq$ 10 mm Hg	6/188 (3.2%)	2/154 (1.3%)	3/170 (1.8%)	2/182 (1.1%)
Change from baseline $\geq$ 15 mm Hg	1/188 (0.5%)	0	0	0

Table 72 Incidence of Patients Whose PM Diastolic Blood Pressure Value Measured by Patient's Diary Met Selected Criteria, by Subpopulation

Parameter, n/n (%)	Placebo	Mirabegron		Tolterodine SR 4 mg
		50 mg	100 mg	
Overall	(n=494)	(n=493)	(n=496)	(n=495)
Final Visit				
Change from baseline $\geq$ 10 mm Hg	23/479 (4.8%)	29/474 (6.1%)	40/478 (8.4%)	37/476 (7.8%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	20/447 (4.5%)	21/437 (4.8%)	41/442 (9.3%)	43/436 (9.9%)
Change from baseline $\geq$ 10 mm Hg	3/447 (0.7%)	0	6/442 (1.4%)	7/436 (1.6%)
Change from baseline $\geq$ 15 mm Hg	0	0	3/442 (0.7%)	1/436 (0.2%)
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	51/462 (11.0%)	68/450 (15.1%)	94/455 (20.7%)	85/461 (18.4%)
Change from baseline $\geq$ 10 mm Hg	8/462 (1.7%)	9/450 (2.0%)	18/455 (4.0%)	12/461 (2.6%)
Change from baseline $\geq$ 15 mm Hg	0	0	4/455 (0.9%)	1/461 (0.2%)
Normotensive Population	(n=298)	(n=321)	(n=313)	(n=300)
Final Visit				
Change from baseline $\geq$ 10 mm Hg	14/288 (4.9%)	21/312 (6.7%)	28/302 (9.3%)	21/289 (7.3%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	11/270 (4.1%)	15/288 (5.2%)	29/276 (10.5%)	27/265 (10.2%)
Change from baseline $\geq$ 10 mm Hg	0	0	5/276 (1.8%)	2/265 (0.8%)
Change from baseline $\geq$ 15 mm Hg	0	0	3/276 (1.1%)	1/265 (0.4%)
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	30/276 (10.9%)	54/296 (18.2%)	61/285 (21.4%)	51/279 (18.3%)
Change from baseline $\geq$ 10 mm Hg	3/276 (1.1%)	6/296 (2.0%)	12/285 (4.2%)	5/279 (1.8%)
Change from baseline $\geq$ 15 mm Hg	0	0	3/285 (1.1%)	1/279 (0.4%)
Hypertensive Population	(n=196)	(n=172)	(n=183)	(n=195)
Final Visit				
Change from baseline $\geq$ 10 mm Hg	9/191 (4.7%)	8/162 (4.9%)	12/176 (6.8%)	16/187 (8.6%)
3 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	9/177 (5.1%)	6/149 (4.0%)	12/166 (7.2%)	16/171 (9.4%)
Change from baseline $\geq$ 10 mm Hg	3/177 (1.7%)	0	1/166 (0.6%)	5/171 (2.9%)
Change from baseline $\geq$ 15 mm Hg	0	0	0	0
2 Consecutive Postbaseline Visits				
Change from baseline $\geq$ 5 mm Hg	21/186 (11.3%)	14/154 (9.1%)	33/170 (19.4%)	34/182 (18.7%)
Change from baseline $\geq$ 10 mm Hg	5/186 (2.7%)	3/154 (1.9%)	6/170 (3.5%)	7/182 (3.8%)
Change from baseline $\geq$ 15 mm Hg	0	0	1/170 (0.6%)	0

So within trial 046, from which all of the comparative phase III tolterodine data is generated, the following observations are made:

- AM SBP
 - Rates of final visit categorical elevations for mirabegron are numerically higher than for tolterodine in normotensives and hypertensives, but the differential rates are small. The same is true for placebo.
 - Notably, hypertensive patients on placebo demonstrate higher “consecutive” categorical event rates compared to their 50 mg mirabegron-treated counterparts

- PM SBP
 - There are numerically higher final visit event rates for mirabegron vs tolterodine in normotensives, but numerically higher final visit event rates for tolterodine in hypertensives, but the differential rates are small.
 - Again, hypertensives on placebo demonstrate higher “consecutive” categorical event rates compared to their 50 mg mirabegron-treated counterparts
- AM DBP
 - Similar final visit event rates between placebo, mirabegron, and tolterodine in normotensives
 - Numerically lower categorical event rates in hypertensives on mirabegron as compared to placebo
- PM DBP
 - Lower final visit event rates for 50 mg mirabegron in normotensives and hypertensives as compared to tolterodine, with generally lower categorical events for mirabegron in both subsets
 - Both mirabegron and tolterodine with numerically higher categorical event rates compared to placebo, but the differences are small.

Given the small differences in the categorical event rates above, which may not be true differences, the graphical displays of individual changes from baseline as a function of exposure for the integrated phase III safety population is instructive. Note that Figure 15 of the sponsor’s CRR that is specifically pointed out in the consult request is identical to Figure 23 of the study ISN 178-PK-016 FSR, which is shown above under question 1, and it displays individual morning and afternoon systolic blood pressure (SBP) changes from baseline (weeks 4, 8 and 12 combined) as a function of mirabegron AUC (log scale) in patients with OAB from studies [178-CL-044], [178-CL-046] and [178-CL-047]. Note that this same type of graphical display is included in question 1 above for the DBP changes from baseline as well. As discussed in question 1, there are no trends for change from baseline in DBP or SBP with increasing exposure to mirabegron (see question 1, figure 14 and figure 23, respectively).

Finally, potentially clinically significant blood pressure findings were assessed for both the 12-week phase III and the long-term controlled EU/NA populations, as shown in Tables 28 and 29 below (from CRR Appendix 4). The occurrence of these events was comparable between all of the treatment groups.

Table 28 Patients Meeting PCS Criteria for AM or PM SBP and DBP Measured by Patient's Diary, EU/NA OAB 12-week Phase 3 Population, Hypertension status 1

Parameter	Time Point	Placebo (n = 1380)	Mirabegron			Tolterodine ER 4 mg (n = 495)
			25 mg (n = 432)	50 mg (n = 1375)	100 mg (n = 929)	
Normotensive†		(n = 857)	(n = 250)	(n = 873)	(n = 555)	(n = 300)
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)						
Final visit	AM	1/825 (0.1%)	0/239	1/845 (0.1%)	1/532 (0.2%)	0/289
	PM	0/824	0/239	1/845 (0.1%)	0/532	0/289
Any visit	AM	1/825 (0.1%)	0/239	2/845 (0.2%)	1/532 (0.2%)	0/289
	PM	0/824	0/239	1/845 (0.1%)	0/532	0/289
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)						
Final visit	AM	1/825 (0.1%)	0/239	1/845 (0.1%)	1/532 (0.2%)	0/289
	PM	1/824 (0.1%)	0/239	0/845	1/532 (0.2%)	0/289
Any visit	AM	1/825 (0.1%)	0/239	2/845 (0.2%)	1/532 (0.2%)	0/289
	PM	1/824 (0.1%)	0/239	1/845 (0.1%)	1/532 (0.2%)	0/289
Past history of hypertension†		(n = 58)	(n = 22)	(n = 67)	(n = 35)	(n = 15)
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)						
Final visit	AM	0/54	0/20	0/65	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
Any visit	AM	0/54	0/20	1/65 (1.5%)	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)						
Final visit	AM	1/54 (1.9%)	0/20	0/65	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
Any visit	AM	1/54 (1.9%)	0/20	1/65 (1.5%)	0/33	0/15
	PM	0/54	0/20	0/65	0/33	0/15
Hypertensive†		(n = 523)	(n = 182)	(n = 502)	(n = 374)	(n = 195)
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)						
Final visit	AM	1/504 (0.2%)	1/171 (0.6%)	1/482 (0.2%)	0/359	1/187 (0.5%)
	PM	0/502	0/171	0/482	0/358	0/187
Any visit	AM	3/504 (0.6%)	1/171 (0.6%)	3/482 (0.6%)	1/359 (0.3%)	1/187 (0.5%)
	PM	0/502	1/171 (0.6%)	1/482 (0.2%)	0/358	0/187
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)						
Final visit	AM	1/504 (0.2%)	0/171	1/482 (0.2%)	0/358	0/187
	PM	0/502	0/171	0/482	1/358 (0.3%)	0/187
Any visit	AM	1/504 (0.2%)	0/171	1/482 (0.2%)	1/358 (0.3%)	0/187
	PM	0/502	0/171	1/482 (0.2%)	1/358 (0.3%)	0/187

Table 29 Patients Meeting PCS Criteria for AM or PM SBP or DBP Measured by Patient Diary, EU/NA Long-term Controlled Population, Hypertension status 1

Visit	Time Point	Mirabegron		Tolterodine ER 4 mg (n = 812)
		50 mg (n = 812)	100 mg (n = 820)	
Normotensive†		(n = 488)	(n = 509)	(n = 478)
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	0	0	0
	PM	0	0	0
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	1/474 (0.2%)	0	0
Any visit	AM	0	0	1/469 (0.2%)
	PM	1/474 (0.2%)	0	1/469 (0.2%)
Past history of hypertension†		(n = 33)	(n = 52)	(n = 43)
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	0	0	0
	PM	0	0	0
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	0	0	0
	PM	0	0	0
Hypertensive†		(n = 324)	(n = 311)	(n = 334)
SBP (≥ 180 mm Hg and ≥ 20 mm Hg change from baseline)				
Final visit	AM	0	0	0
	PM	0	0	0
Any visit	AM	1/317 (0.3%)	1/304 (0.3%)	3/324 (0.9%)
	PM	0	0	0
DBP (≥ 105 mm Hg and ≥ 15 mm Hg change from baseline)				
Final visit	AM	0	1/304 (0.3%)	1/324 (0.3%)
	PM	0	0	2/324 (0.6%)
Any visit	AM	0	1/304 (0.3%)	5/324 (1.5%)
	PM	1/315 (0.3%)	0	3/324 (0.9%)

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/s/

PRESTON M DUNNMON
01/20/2012

THOMAS A MARCINIAK
01/20/2012

NORMAN L STOCKBRIDGE
01/20/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202611

Name of Drug: mirabegron, 25mg and 50 mg extended release tablets

Applicant: Astellas Pharma Global Development, Inc.

Labeling Reviewed

Submission Date: August 26, 2011

Receipt Date: August 29, 2011

Background and Summary Description

Mirabegron is a human beta 3 adrenoceptor agonist indicated for the treatment of overactive bladder, with symptoms of urge urinary incontinence, urgency, and urinary frequency. It is a new molecular entity, and thus far, there are no drugs in its class that has been approved. This NDA is planned for discussion at an Advisory Committee Meeting on April 5, 2012, with special attention to cardiac safety. The related IND is 069416. The clinical development program consists of 41 studies comprising of 10,552 subjects.

An NDA application for mirabegron is simultaneously submitted to the European Medicines Agency for the Centralised Procedure, sharing common safety and efficacy data package as with US FDA, per Sponsor.

Proprietary name is planned for submission to DMEPA in October 2011.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- ☒ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

PM Comment: The top margin is less than ½ inch.

- ☒ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

PM Comment: The highlight section is greater than ½ page.

- ☒ There is no redundancy of information.

PM Comment: Redundancy of information for renal impairment and hepatic impairment under DOSAGE AND ADMINISTRATION and USE IN SPECIFIC INFORMATION.

- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

- ☐ A horizontal line must separate the HL and Table of Contents (TOC).

- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

- ☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

PM Comment: Under DOSAGE FORMS AND STRENGTHS, the summarized statements do not reference the section or subsection of the Full Prescribing Information. References are also missing for the last statement under DOSAGE AND ADMINISTRATION and for

the first statement under ADVERSE REACTIONS.

☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- ☒ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

PM Comment: When proprietary name is deemed acceptable, replace the [Product Name] that is now being used as a placeholder.

- **Logos**

- ☒ Do not include logos in Highlights or in the SPL file. However, in WORD labeling documents, a small company logo can appear at the end of the labeling with the manufacturer information.

PM Comment: Under DOSAGE FORMS AND STRENGTHS, only include the dosage form and the strength and not all identifying characteristics of the dosage form. This information should appear under DOSAGE FORMS AND STRENGTHS section in the Full Prescribing Information, not in Highlights. It should read as follows:

- **Extended-Release Tablets: 25 mg, 50 mg (3)**

- **Product Title**

- ☒ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

PM Comment: Product title should read: “*extended-release tablets, for oral use*”

- **Initial U.S. Approval**

- ☒ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

PM Comment: Format for initial US Approval is a 4-digit-year, not Month Year.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “*See full prescribing information for complete boxed warning.*”

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- ☐ Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ removal 2/2010.”

- **Indications and Usage**

- ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☒ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

PM Comment: Provide a brief description of the contraindicated situation and any demographic or identifiable predisposing characteristics. Also provide a description of anticipated consequences of the contraindicated use. Refer to more detailed information about the contraindication, i.e., Adverse Reactions section.

- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☒ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other

terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

PM Comment: Criteria used to determine adverse reaction inclusion (e.g., >X%) is missing. There should be a white space before the headings for INDICATIONS AND USAGE, DOSAGE FORMS AND STRENGTHS, and ADVERSE REACTIONS.

- ☒ For drug products other than vaccines, the verbatim **bolded** statement, “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch” must be present. Only include toll-free numbers.

PM Comment: This statement should be a separate paragraph from the statement of adverse reactions.

- Patient Counseling Information Statement

- ☒ Must include the verbatim statement: “See 17 for Patient Counseling Information” or if the product has FDA-approved patient labeling: “See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).

PM Comment: Must read: “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling, **not** “See 17 for PATIENT COUNSELING INFORMATION”

- Revision Date

- ☒ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

PM Comment: Revision date is month/year that the application is approved.

Contents: Table of Contents (TOC)

PM Comment: Delete subsection heading 17.2 FDA Approved Patient Labeling from Table of Contents. SPL Release 4 validation does not permit including FDA-Approved Patient labeling as a subsection heading under the Patient Counseling Information section.

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC

must match the headings and subheadings in the FPI.

- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling.

Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- ☒ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

PM Comment: This statement should be under the Clinical Trials Experience subsection, not immediately after the ADVERSE REACTIONS section. The Clinical Trials Data Source subsection is not recognized as a subsection in the FPI. Clarify if information is most fitted under CLINICAL STUDIES section.

- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

- ☒ Do not include 17.2 FDA Approved Patient Labeling as a subsection under the Patient Counseling Information section.

PM Comment: See PM Comment under Table of Contents.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and are identified in details above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies within three weeks from the date of this letter. The resubmitted labeling will be used for further labeling discussions.

Nenita Crisostomo, R.N.

September 23, 2011

Regulatory Project Manager

Date

Jennifer Mercier

September 30, 2011

Chief, Project Management Staff

Date

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NENITA I CRISOSTOMO
11/09/2011

JENNIFER L MERCIER
11/10/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: November 8, 2011

Reviewer(s): Teresa McMillan, PharmD, Safety Evaluator
Division of Medication Error, Prevention, and Analysis

Team Leader Zachary Oleszczuk, PharmD, Team Leader
Division of Medication Error, Prevention, and Analysis

Division Director Carol Holquist, RPh, Division Director
Division of Medication Error, Prevention, and Analysis

Drug Name(s): Mirabetan (Mirabegron) Extended Release Tablets
& Strength 25 mg & 50 mg

Application Type/Number: NDA 202611

Applicant/sponsor: Astellas Pharma Global Development, Inc.

OSE RCM #: 2011-3355

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed carton labeling, container labels, and prescribing information that was submitted by Astellas Pharma Global Development on October 20, 2011 for (b) (4) (Mirabegron) extended release tablets, NDA 202611, for areas of vulnerability that can lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

In OSE Review # 2010-436, August 10, 2010, DMEPA found the proprietary name (b) (4) for Mirabegron tablets unacceptable due to vulnerability to name confusion with (b) (4). Astellas Pharma Global Development submitted a request to the Agency to reconsider the proposed proprietary name, (b) (4) on January 19, 2011. In OSE Review #2011-238, July 15, 2011, DMEPA reconsidered the proprietary name, (b) (4) and maintained our original finding that the name is unacceptable.

On October 13, 2011, Astellas Pharma Global Development submitted an amendment to the 505(b)1 New Drug Application for Mirabegron requesting a proprietary name review for (b) (4).

On October 20, 2011, Astellas Pharma Global Development submitted another amendment to the 505(b)1 New Drug Application for Mirabegron which included the draft Prescribing Information, carton labeling and container labels containing the proposed proprietary name (b) (4).

1.2 PRODUCT INFORMATION

Mirabegron is a beta-3 receptor agonist indicated for overactive bladder. The recommended dose is 50 mg or 100 mg by mouth once daily with or without food. The recommended dose for severe renal impairment (CrCl 15 to 29 ml/min) or moderate hepatic impairment (Child-Pugh Class B) is 25 mg orally once daily with or without food. Mirabegron should be taken with liquid and swallowed whole. It should not be chewed, divided, or crushed.

Mirabegron is supplied in bottles of 30 and 90 tablets and 10 day blister packages, as well as a 7 count blister sample package. Mirabegron is to be stored at room temperature.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principals of Human Factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels and Carton Labeling submitted on October 20, 2011 (See Appendices A-C for images submitted on October 20, 2011)
- Insert Labeling submitted on October 20, 2011 (No image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 RESULTS AND DISCUSSION

The following describes the findings of our analysis.

3.1 CONTAINER LABELS AND CARTON LABELING

The proposed container labels and carton labeling for Mirabegron 25 mg and 50 mg are not well differentiated from each other due to a similar layout and overlapping colors which can cause selection errors. Although the applicant provided some differentiation by providing different colored bars for the 25 mg (b) (4) and 50 mg (b) (4) strengths on the container label and carton labeling for Mirabegron, the labels and labeling for both products still appear similar. Providing more color differentiation can help mitigate confusion resulting in wrong strength selection errors. In addition, the strength, graphics, and Rx only statements on the principal display panel of the container labels and carton labeling are more prominent than the proprietary and established names due to the use of a larger font. The company logo and name also appear more prominent on the principal display panel of the container labels and on the side panel of the carton labeling. This distracts from product and patient information.

Additionally, this product is available as an extended release tablet. It should be swallowed whole with liquid and should not be chewed, divided, or crushed. However, this information is not presented on the container labels or the carton labeling. This information should be displayed on the principal display panels of the container labels and carton labeling to help minimize administration errors.

3.2 INSERT LABELING

Section 17, Patient Counseling Information, under the “How should I take Mirabegron?” section states “Do not crush or chew tablet”. However, Section 2, Dosage and Administration, in the Prescribing Information states that the tablets should not be chewed, divided, or crushed. It is important to be consistent with the wording of warning statements throughout the Prescribing Information. This helps alleviate confusion which could potentially result in administration errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed label and labeling for Mirabegron 25 mg and 50 mg introduce vulnerability that can lead to medication errors. We recommend the following revisions:

4.1 COMMENTS TO THE DIVISION

A. Prescribing Information

1. Remove all instances of the proprietary name (b) (4) throughout the labeling since this name was found unacceptable.

In the currently proposed Prescribing Information, the proposed proprietary name does not appear throughout the Prescribing Information. Once a proprietary name has been approved, insert the approved proprietary name in all the appropriate places.

2. Section 17, Patient Counseling Information, under the “How should I take Mirabegron?” section does not state that the tablet should not be divided. However, Section 2, Dosage and Administration section in the Prescribing Information states that the tablet should not be chewed, divided, or crushed. All warning statements should be consistent throughout the Prescribing Information. We recommend the statement, “Swallow tablets whole. Do not cut, crush, or chew tablet.
3. The Dosage Forms and Strengths Section in the Highlights and Full Prescribing Information presents Mirabegron as (b) (4) extended release tablets. However all other sections state Mirabegron extended release tablets. The product name should be presented consistently throughout the Prescribing Information. The modifier (b) (4) and the statement (b) (4) should be removed from the Dosage Forms and Strengths Section in the Highlights and Full Prescribing Information.

4.2 COMMENTS TO THE APPLICANT

A. General Comments for the Container Label, Blister Label, and Carton Labeling

1. Provide more color differentiation on the container labels and carton labeling to help mitigate confusion that may result in wrong strength selection errors due to the similar appearance of these labels and labeling. Although the proposed labels and labeling for the 25 mg strength are accented with a (b) (4) heavy colored bar on the bottom of the principal display panel and the 50 mg strength has a (b) (4) heavy colored bar, all other graphics and the overall layout of each label and labeling are identical. Therefore, the (b) (4) bars do not adequately differentiate these products.
2. Delete or decrease the size and prominence of all (b) (4) graphics that appear superimposed on the principal display panel on the container labels and carton labeling and the yellow signs that appear next to the proprietary name on the carton labeling, container labels, and blister labels. As currently presented, these graphics detract from the proprietary name, established name, and strength.
3. Delete or decrease the size and prominence of all instances of the company name and logo that appear on the side panel of the carton labeling and blister labels and on the principal display panel of the container labels, as well as the heavy colored bar on the bottom of the principal display panel on the carton labeling and under the “once daily” statement on the container and blister labels. As currently presented, the company name and logo and graphics detract from the proprietary name.
4. Decrease the size and prominence of all “Rx only” statements on the principal display panel of the container and blister labels and on all panels of the carton labeling, as well as the strengths (i.e. 25 mg or 50 mg) that appear in the colored bar at the bottom of all panels on the carton labeling, and above the “once daily” statement on the container labels. As currently presented, these statements detract from the proprietary name and other important information such as strength.

5. Add the statement “Swallow tablet whole. Do not cut, crush, or chew tablet.” to the principal display panel of the container and blister labels, and carton labeling. This can be accomplished by removing the company name and logo on the container label and the company name from the blister label.
6. Increase the size of the statement “extended release tablets” to be the same size as the established name.

B. Container Label

1. Add the statement “Keep this and all drugs out of reach of children” to one of the side panels.
2. Delete the 25 mg and 50 mg strengths that appear above the ‘Once-daily’ phrase and increase the size of the 25 mg and 50 mg strengths that appear next to the ‘extended release tablets’ phrase.
3. Decrease the prominence of the (b) (4) heavy colored bars that appear beneath the ‘Once-daily’ phrase.

C. Carton Labeling

1. Add the statement “Keep this and all drugs out of reach of children” to one of the side panels.
2. Replace XXX-XXX-XXX with actual numbers on the back and side panels of the container labeling.
3. Decrease the size and prominence of the statement “100 tablets- Single Unit Package (10 per blister)” as it competes for prominence with the proprietary and established names and relocate this statement above the colored bar at the bottom of the principal display panel.
4. Delete the statement “100 tablets” that appears above the colored bar at the bottom of the principal display panel.
5. Delete the 25 mg and 50 mg strengths that appear above the ‘Once-daily’ phrase and increase the size of the 25 mg and 50 mg strengths that appear next to the ‘extended release tablets’ phrase.

D. Blister Label

1. Provide more differentiation between the 25 mg and 50 mg strengths to help mitigate confusion that may result in wrong strength selection errors due to the similar appearance of these labels.
2. Decrease the size and prominence of the company name. As currently presented, the company name detracts from the proprietary and established name as well as the strength.
3. Relocate the lot number, expiration date, and bar code to appear vertically to allow more space on the label.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TERESA S MCMILLAN
11/08/2011

ZACHARY A OLESZCZUK
11/10/2011

CAROL A HOLQUIST
11/10/2011