

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202611Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Crisostomo, Nenita

From: Greeley, George
Sent: Wednesday, June 13, 2012 4:35 PM
Crisostomo, Nenita
Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Beitz, Julie G
Subject: NDA 202-611 Mirabegron
Importance: High
Attachments: 1_Pediatric_Record.pdf

Hi Nita,

The email serves as confirmation of the review for the Mirabegron (YM178) product conducted by the PeRC PREA Subcommittee on May 30, 2012.

The Division presented a partial waiver in patients birth through 4 years because studies are impossible or highly impracticable because overactive bladder is not a condition in infants or young children and a deferral in patients 5-17 years until additional safety or efficacy data have been collected. Mirabegron is being studied for the treatment of overactive bladder.

The waiver is being requested because overactive bladder is not a condition in infants or young children 0 to 4 years and 11 months who are not yet bladder trained. While the Sponsor's proposed pediatric plan appears reasonable, we advise that human studies among subjects 5 to 17 years and 11 months should be deferred. There are nonclinical and clinical reasons for deferring studies in pediatric patients older than 5 years. First, appropriate animal studies have not yet been performed. An area of nonclinical concern is a potential effect on maturation. Second, the main clinical areas of concern are the effect of mirabegron on increasing blood pressure and a potential effect on new malignant events in adult. Both these clinical concerns will be addressed in required postmarketing adult studies to inform future pediatric studies.

(b) (4)

The PeRC agreed with the Division to grant a partial waiver in patients birth through 4 years and to the deferral in patients 5 through 17 years of age.

The pediatric record is attached for Mirabegron.



1_Pediatric_Record
.pdf (61 KB)...

Thanks,

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
V/CDER/OND
1903 New Hampshire Avenue

Bldg. 22, Room 6467
Silver Spring, MD 20993-0002

Phone: 301.796.4025

Email: george.greeley@fda.hhs.gov

Please consider the environment before printing this e-mail.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 202611 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: Division of PDUFA Goal Date: June 29, Stamp Date: 8/29/2012
Reproductive and Urologic 2012
Products

Proprietary Name: (to be determined)
Established/Generic Name: mirabegron
Dosage Form: 25mg extended release tablets
Applicant/Sponsor: Astellas Pharma Global Development, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of overactive bladder

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	4 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver **(check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): Overactive bladder is not a condition in infants or young children 0 to 4 yrs and 11 months who are not yet bladder trained

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	5 yr. __ mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason:

The review Division wishes to defer clinical studies in pediatric subpopulation ages 5 years to 17 years 11 months of age for the following reasons:

1. Completion and interpretation of the results of juvenile preclinical studies has not occurred.
2. Sponsor has agreed to perform 2 postmarketing epidemiology studies, as follows:
 - To evaluate cardiovascular outcomes in adults related to a modest increase in blood pressure due to mirabegron.
 - To evaluate the potential association of mirabegron with neoplasia as a result of an increase in new malignant events observed in the mirabegron 100 mg group compared to the mirabegron 50 mg and tolterodine groups in a 1-year safety study.

The information derived from these postmarketing studies is needed to better inform a decision to go forward with pediatric development.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is

complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications.

Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

Nenita Crisostomo, R.N.

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

EXCLUSIVITY SUMMARY

NDA # 202611

SUPPL #

HFD # 580

Trade Name Myrbetriq

Generic Name mirabegron extended release tablets, 25 mg and 50 mg

Applicant Name Astellas Phama Global Development, Inc.

Approval Date, If Known June 28, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====
Name of person completing form: Nenita Crisostomo, R.N.
Title: Regulatory Health Project Manger
Date: June 7, 2012

Name of Office/Division Director signing form: Victoria Kusiak, M.D.
Title: Deputy Director, Office of Drug Evaluation III

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

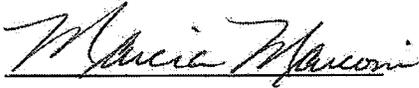
/s/

NENITA I CRISOSTOMO
06/28/2012

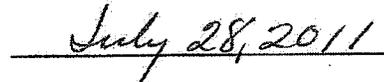
VICTORIA KUSIAK
06/28/2012

1.3.3 Debarment Certification

Astellas Pharma US, Inc. 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.



Marcia Marconi
Vice President
Regulatory Affairs and Quality Assurance
Astellas Pharma Global Development, Inc.



Date

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Category: NDA Review: Status Meeting, FDA-requested
Meeting Date and Time: June 21, 2012, at 12:15 P.M. – 12:45 P.M.
Application Number: NDA 202611
Product Name: Myrbetriq (mirabegron), 25 mg and 50 mg extended release tablets
Indication: Treatment of overactive bladder
Applicant Name: Astellas Pharma Global Development, Inc.
Meeting Chair: Mark S. Hirsch, M.D.
Meeting Recorder: Nenita Crisostomo, R.N.

FDA ATTENDEES

Victoria Kusiak, M.D. - Deputy Director, Office of Drug Evaluation III
Audrey Gassman, M.D. - Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark S. Hirsch, M.D. - Medical Team Leader, DRUP
Roger Wiederhorn, M.D. - Medical Officer, DRUP
Judy A. Staffa, Ph.D., R.Ph. - Director, Division of Epidemiology II (DEPI II), Office of Surveillance and Epidemiology (OSE)
Rita Ouellet-Hellstrom, Ph.D., M.P.H. - Associate Director for Epidemiology, DEPI II, OSE
David Moeny, R.Ph., M.P.H., U.S.P.H.S., - Epidemiology Team Leader-, DEPI II, OSE
Shawnetta Jackson, Public Health Analyst, Project Management Staff, OSE
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP

ASTELLAS PHARMA GLOBAL DEVELOPMENT, INC. ATTENDEES

Steven Ryder, M.D., F.A.C.P. - President, Astellas Pharma Global Development, Inc.
William Fitzsimmons, Pharm.D., M.S. - Executive Vice President, Regulatory Affairs, Drug Safety and Pharmacovigilance
Neha Sheth, Pharm.D. - Executive Director, Product Safety and Pharmacovigilance
Judy Kannenberg, M.B.A. - Director, Regulatory Affairs

(b) (4)

BACKGROUND

This new drug application was submitted by Astellas Pharma Global Development, Inc. on August 26, 2012, seeking authorization to market mirabegron, 25 mg and 50 mg extended release tablets for the treatment of overactive bladder (OAB). On May 3, 2012, a teleconference was held between the Division and Astellas to discuss remaining NDA review issues to date, including increases in blood pressure and neoplasms. As recommended by DRUP, the Applicant submitted synopses of two protocols for required postmarketing studies. These were consulted to the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE),

who conducted a review of the protocol synopses. General FDA comments and recommendations for the protocols were conveyed to the Applicant via eMAIL on June 15, 2012.

The purpose of this teleconference is to allow for discussion and clarification inquiries from the Sponsor regarding these recommendations.

DISCUSSION

The Division began the discussion by stating that the purpose of this teleconference is to discuss the recommendations emailed to the Applicant on June 15, 2012, as attached, concerning a post marketing study to evaluate cardiovascular events and a post marketing study to evaluate new malignant events. The Division stated that the goal of the discussion was to address high level issues only; specific details regarding the protocols will be discussed in the post-authorization period.

During the teleconference, the Applicant and their expert external consultants acknowledged Items 1 through 5 of Section **I** of the June 15, 2012 communication, entitled “**Recommendations and comments regarding your proposed protocol synopses**”. The Applicant further stated, that in writing the protocols, they will coordinate with both EMA and FDA. There was no additional discussion of any specific item.

The Applicant next acknowledged Section **II** of the June 15, 2012 communication, entitled “**Additional recommendations regarding determination that the studies are inadequate to assess their proposed outcomes**”. The Applicant understood that the utility of post-marketing epidemiologic safety studies using electronic healthcare data may not be successful to address the signals of concern; and if the studies proposed in the electronic healthcare data are not successful, an interview (or survey)-based, prospective cohort study would follow. The Applicant clearly stated that they understood that this additional study may be necessary and that this study could be a large effort.

The Applicant and their external expert consultants were given opportunity for clarification of the Division’s recommended considerations for developing a prospective survey based cohort study. No additional clarification was requested.

With these acknowledgements by Applicant, the Division stated their intent to convey a document to Applicant containing the post-marketing requirement (PMR) goals and milestones. The Applicant was advised that their agreement to these PMRs must be submitted officially in writing. These submissions should be submitted formally and via eMAIL for immediate review by the Division.

Lastly, the Division reminded the Applicant that because review time is necessary to agree to a final protocol, their proposed protocols should be submitted as promptly as possible.

ATTACHMENTS

“Postmarketing Requirement Recommendations”, dated June 15, 2012, *Food and Drug Administration, Division of Reproductive and Urologic Products*

**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.

The da

▪

•

▪

▪

(b) (4)

2. Regarding outcomes and validation

▪

(b) (4)

1

(b) (4)

(b) (4)

3. Regarding exposure

-
-
-

(b) (4)

4. Regarding covariate selection

(b) (4)

2

(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 develo

-
-
-
-
-
-
-
-
-
-

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.

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

/s/

NENITA I CRISOSTOMO
06/28/2012

MARK S HIRSCH
07/03/2012

MEMORANDUM

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

DATE: June 28, 2012

TO:

THROUGH:

FROM: Nenita Crisostomo, R.N. – Regulatory Health Project Manager

SUBJECT: Final Agreed-upon labeling

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

Background: On June 27, 2012, The Division emailed an edited version of the labeling to Astellas Pharma Global Development, Inc. who in turn responded with the attached version. The Division had no further changes. This version will be submitted officially by the Sponsor as the final agreed-upon labeling and is attached to the Approval letter. The purpose of this Memo is to document the email communication to Astellas Pharma Global Development that led to this final labeling version.

From: Crisostomo, Nenita
Sent: Thursday, June 28, 2012 11:04 AM
To: 'Kannenberg, Judy'
Subject: RE: NDA 202611 Myrbetriq package insert text FDA version 6/27/2012

Great! We will use today's date for the label submission.
--nita

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Thursday, June 28, 2012 11:04 AM
To: Crisostomo, Nenita
Subject: RE: NDA 202611 Myrbetriq package insert text FDA version 6/27/2012

That is great news! Thank you. We will work on the final label submission now. I will send a copy via email later today.

Judy

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Thursday, June 28, 2012 10:02 AM

To: Kannenberg, Judy
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: RE: NDA 202611 Myrbetriq package insert text FDA version 6/27/2012

Hi Judy,

We accept all your changes. Please submit a clean version to the electronic document room today.

Thank you so much,
nita

From: Kannenberg, Judy [<mailto:Judy.Kannenberg@us.astellas.com>]
Sent: Wednesday, June 27, 2012 7:13 PM
To: Crisostomo, Nenita
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: RE: NDA 202611 Myrbetriq package insert text FDA version 6/27/2012
Importance: High

Nita,

Please find attached updated labeling text based on the comments received this afternoon, June 27th. Astellas has accepted the FDA changes and incorporated revised figures 1 and 2 with the new footnote. We have also added text to the suggested footnote to provide clarity to the prescriber and to make it consistent with section 5.2. Please review and let me know if the FDA team is in agreement with the attached suggestions.

Thank you,
Judy

From: Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]
Sent: Wednesday, June 27, 2012 3:42 PM
To: Kannenberg, Judy
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: RE: NDA 202611 Myrbetriq package insert text FDA version 6/25/2012

Hi Judy,

With our minor edits, attached is our marked version of the labeling. Please email your response back to me as soon as possible, or before 10:00 A.M. tomorrow on June 28, 2012. If you have any questions, please feel free to contact me.

Thanks,
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*

From: Kannenberg, Judy [<mailto:Judy.Kannenberg@us.astellas.com>]
Sent: Wednesday, June 27, 2012 12:23 PM
To: Crisostomo, Nenita
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: RE: NDA 202611 Myrbetriq package insert text FDA version 6/25/2012
Importance: High

Dear Nita,

Please find attached updated labeling text based on the comments received from the Agency yesterday, June 26th. Astellas has accepted the FDA changes and has made only a few, minor corrections in the attached text. A redline version and a clean copy have been provided to assist with the action letter process.

Please let me know if you are in agreement with the proposed minor corrections. Also, please advise whether an official NDA submission through the electronic gateway is required at this time for the final label text.

Thank you,
Judy

From: Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]
Sent: Tuesday, June 26, 2012 11:31 AM
To: Kannenberg, Judy
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: NDA 202611 Myrbetriq package insert text FDA version 6/25/2012

Hi Judy,

In response to your June 22, 2012, version, attached is our version of the labeling, marked with few of our edits. Please accept all of our changes and mark your changes on a clean copy and email your marked labeling to me within 24 hours for our immediate review.

However, if you have no other changes, then please inform that to me in the email as well, so that we can begin to use this version for the Action processes, while enroute for official submission to the Document Room.

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

Thanks,
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*

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

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

/s/

NENITA I CRISOSTOMO
06/28/2012

MEMORANDUM

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

DATE: June 27, 2012

TO:

THROUGH:

FROM: Nenita Crisostomo, R.N. – Regulatory Health Project Manager

SUBJECT: Milestone Recommendations to the CV and Neoplasms PMR Protocols

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

Background: On June 25, 2012, Astellas Pharma Global Development, Inc. submitted their alternative milestone dates in response to the Division's June 21, 2012, recommended milestone dates. The Division, in turn, provided the recommendations below which were conveyed to Astellas on June 27, 2012 via email. The purpose of this Memo is to document the email communication to Astellas Pharma Global Development.

From: Crisostomo, Nenita
Sent: Wednesday, June 27, 2012 10:40 AM
To: 'Kannenberg, Judy'; Simon-Wilson, Melinee; Essig, Eva
Subject: RE: NDA 202611 - PMR proposals

<< File: NDA202611PMRtemplates draft062612.doc >>
[Hi Judy,](#)

[Attached are our recommendations in response to your milestone proposals yesterday, June 26, 2012. We look forward to speaking with you and your Team at 11:30 am, Eastern time.](#)

[I will be at my desk until 11:00 AM, Eastern, should you have any questions.](#)

[Thank you,](#)
[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 27, 2012

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

Reference is made to our teleconference June 21, 2012 and June 26, 2012, to discuss our recommendations regarding the two postmarketing requirements and our request for your acknowledgement of the two study descriptions and agreement to the proposed milestone outlined below.

We received your proposed milestones and have the following counterproposal:

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
Assessment and Summary Report Submission:	March 2015
Interim Study Completion: (US study completed)	June 2017
Interim Analysis Report: (US report completed)	June 2018
Final Study Completion: (EU and US completed):	July 2018
Final Report Submission:	June 2019
(EU and US report completed)	

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
Assessment and Summary Report Submission:	March 2015
Interim Study Completion: (US study completed)	June 2017
Interim Analysis Report: (US report completed)	June 2018
Final Study Completion (EU and US completed):	July 2018
Final Report Submission:	June 2019

(EU and US report completed)

- The details for each interim report are outlined below:
 - Assessment and Summary Report Submission: – Report detailing progress on the US and EU portions of the study (including market uptake, coding used, linkages planned and feasibility/pilot assessments)
 - Interim Study Completion – US portion of the study completed, including validation
 - Interim Analysis Report – US portion of study submitted
 - Final Study Completion – EU portion of the study completed, including validation
 - Final Report Submission – include US and EU data with total planned sample size

Please contact Nita Crisostomo at 301-796-0875 with any outstanding questions.

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

/s/

NENITA I CRISOSTOMO
06/27/2012



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Category: FDA-requested Status Meeting

Meeting Date and Time: May 3, 2012, at 1:00 P.M. – 2:00 P.M., Teleconference

Application Number: NDA 202611
Product Name: mirabegron, 25 mg extended release tablets
Indication: Treatment of overactive bladder
Applicant Name: Astellas Pharma Global Development, Inc.

Meeting Chair: Mark S. Hirsch, M.D.
Meeting Recorder: Nenita Crisostomo, R.N.

FDA ATTENDEES

Audrey Gassman, M.D. - Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark S. Hirsch, M.D. - Medical Team Leader, DRUP
Roger Wiederhorn, M.D. - Medical Officer, DRUP
Myong-Jin Kim, Pharm.D. - Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP3), Office of Clinical Pharmacology (OCP)
Sayed Al-Habet, Ph.D. - Clinical Pharmacology Reviewer, DCP3
Mahboob Sobhan, Ph.D. - Biostatistics Team Leader, Division of Biostatistics III (DBIII)
Jia Guo, Ph.D. - Biostatistics Reviewer, DBIII
Rajinikanth Madabushi, M.D. - Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 1 (DCP1), OCP
Nenita Crisostomo, R.N. - Regulatory Health Project Manager, DRUP

ASTELLAS PHARMA GLOBAL DEVELOPMENT, INC.

Steven Ryder MD, FACP, President, Astellas Pharma Global Development
Leticia Delgado-Herrera RPh, MS, Executive Director, Global Development Project Leader
William Fitzsimmons, PharmD, MS, Executive Vice President, Regulatory Affairs, Drug Safety and Pharmacovigilance
Salim Mujais, MD, Executive Medical Director, Global Medical Sciences
Marlowe Schneidkraut, PhD, DABT, Senior Director, Toxicology
Judy Kannenberg, MBA, Director, Regulatory Affairs

1.0 BACKGROUND

The new drug application for mirabegron was received on August 29, 2011. Mirabegron, a beta-3 adrenergic receptor agonist, is a new molecular and first in its class. An Advisory Committee (AC) meeting was held on April 5, 2012 to discuss the efficacy and safety of mirabegron for the treatment of overactive bladder (OAB). This teleconference was requested by the Division to discuss remaining review issues for this application.

2. DISCUSSION

The Division began the discussion by informing the Sponsor that the review is ongoing. The purpose of this meeting is to share with the Sponsor the remaining review issues identified at the Division's post-AC debriefing meeting and NDA wrap-up meeting. The Division listed the issues and proposed avenues for resolving those issues:

- 1) *Increases in Blood Pressure*: The Division agreed with the Sponsor's proposal to conduct a postmarketing cardiovascular outcomes observational cohort study to assess the clinical significance of the observed increases in blood pressure. The Division requested that a protocol synopsis be submitted promptly for FDA review, and the Sponsor agreed. The Division informed the Sponsor that the protocol synopsis would be consulted to the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE), and the Sponsor should expect comments and recommendations from DEPI.
- 2) *Neoplasms/New Malignant Events*: The clinical significance of this finding in the mirabegron 100 mg dose group in study 178-CL-049 is not known. To further investigate this issue, the Division recommended that Sponsor continue assessment in the postmarketing period. The Division proposed that a postmarketing observational cohort study be conducted for neoplastic events, and the Sponsor agreed. The Sponsor will submit a protocol synopsis for FDA review and it will be consulted to DEPI. The Sponsor should expect comments and recommendations from DEPI.
- 3) *Hepatotoxicity*: The Division recommended that hepatic adverse events be monitored in the postmarketing period using an enhanced pharmacovigilance strategy, and the Sponsor agreed. The Sponsor will submit a plan for FDA review.
- 4) *Dose Selection*: The Division briefly discussed the efficacy and safety results for mirabegron doses of 25 mg and 50 mg. In order to maximize the benefit/risk profile for mirabegron, the Division recommended a starting dose of 25 mg in all patients. Subsequently, the dose may be increased to 50 mg based upon individual efficacy and tolerability. The Sponsor agreed and will submit revised labeling with this new dosing strategy.

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

/s/

NENITA I CRISOSTOMO
06/25/2012

MARK S HIRSCH
06/25/2012

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.

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

/s/

NENITA I CRISOSTOMO
06/21/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Date: Wednesday, June 20, 2012 2:12 PM
Subject: 'Kannenberg, Judy'
NDA 202611 mirabegron: FDA edits. PI.PPI.draft.6.20.12doc
Attachments: PI.PPI.draft.doc



PI.PPI.draft.doc (1
MB)

Hi Judy,

Attached is version of the labeling in response to your June 13, 2012, emailed version. Please accept all of our changes and respond to the comments accordingly and make your edits visible by marking them on a clean copy.

Please email to me your version as quickly as possible or at the latest, close of business on Friday, June 22, 2012. 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
Phone: 301-796-0875
Fax: 301-796-9897



NDA 202611

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Astellas Pharma Global Development, Inc.
1 Astellas Way
Northbrook, IL 60062

ATTENTION: Judy Kannenberg
Director, Regulatory Affairs

Dear Ms. Kannenberg:

Please refer to your New Drug Application (NDA) dated August 26, 2011, received August 29, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Mirabegron Extended-release Tablets, 25 mg and 50 mg.

We also refer to your April 16, 2012, correspondence, received April 17, 2012, requesting review of your proposed proprietary name, Myrbetriq. We have completed our review of the proposed proprietary name, Myrbetriq and have concluded that it is acceptable.

The proposed proprietary name, Myrbetriq, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 16, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Nenita Crisostomo, Regulatory Project Manager in the Division of Reproductive and Urologic Products (DRUP), at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
06/18/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, June 14, 2012 10:10 AM
To: 'Kannenberg, Judy'
Subject: RE: Myrbetriq

Hi Judy,

Per DMEPA, it should not be much of a problem. She just needs to make an addendum to her review and obtain a supervisory sign-off. I provided her your email below per her request as documentation of your request.

Thanks,
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*

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Wednesday, June 13, 2012 1:39 PM
To: Crisostomo, Nenita
Subject: RE: Myrbetriq

Nita,

Yes, we would like to consider changing Meer-beh-trick to Meer-beh-treek. Only the last syllable would change. However, if this is an issue for DMEPA, or changes their review or decision in any way, we would of course leave the pronunciation as is.

I will send you the updated label with Myrbetriq not in caps momentarily.

Thank you for your help,
Judy

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, June 13, 2012 12:26 PM
To: Kannenberg, Judy
Subject: Myrbetriq

Hi Judy,

Would this be close to the pronunciation that you described?

Mēr-bētrīk`

I was not able to reach DMEPA by phone, but I just thought I'd give them an email heads up before I call them back again.

Thanks,
nita

6/20/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Friday, June 08, 2012 1:53 PM
Subject: 'Kannenberg, Judy'
NDA 202611 mirabegron: PPI
Attachments: PPI.FDA edits.6.8.12.sent to sp.doc



PPI.FDA
Edits.6.8.12.sent to s.

Hi Judy,

Attached is our edited version of the Patient labeling. Please accept all of our changes and respond to the comments accordingly and make your edits visible by marking them on a clean copy. Please email to me your version as quickly as possible or at the latest, close of business on Tuesday, June 12, 2012. If you have any problems with the timeline, please let me know, and likewise, 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
301-796-9897

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

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, May 29, 2012 3:23 PM
'Kannenberg, Judy'
Simon-Wilson, Melinee
Subject: RE: NDA 202611 mirabegron: Enhanced Pharmacovigilance - Clinical Recommendations

Hi Judy,

Please refer to your submission dated May 11, 2012, containing your proposal for enhanced pharmacovigilance for hepatotoxicity events in the post-marketing setting. We are currently reviewing your submission and we recommend the following:

We agree to your proposal of submitting all cases that have an ALT greater than three times the upper limit of normal levels (3XULN) and Bilirubin greater than two times the upper limit of normal values (2XULN) for adjudication by an external expert, followed by further evaluation of suspect drug-induced liver injury (DILI) cases which include the provision of targeted data collection forms from reporters.

In addition to cases that have an ALT>3XULN and Bilirubin>2XULN, we ask that you include cases that have an ALT elevation of ten times and/or greater than the upper limit of normal values ($\geq 10XULN$).

Please submit your response with a revised hepatotoxicity pharmacovigilance plan marked with your edits on or before June 1, 2012. If you have any questions, please feel free to contact me.

Best Regards,

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

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, May 15, 2012 4:41 PM
'Kannenberg, Judy'
Simon-Wilson, Melinee; Shiley, Kimberly; Lucarelli, Pamela K
Subject: NDA 202611 mirabegron: DMEPA's comments re May 11 container labeling

Hi Judy,

Please refer to your submission dated May 11, 2012, containing revisions to your proposed carton and container labeling. Listed below are comments from the Division of Medication Error Prevention And Analysis (DMEPA)

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)

- 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).
- 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.
- 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)

- See comment B1 above.
- 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.

Please submit your response as soon as possible, or on/before **Friday, May 18, 2012**, keeping in mind that this pending NDA 202611 is nearing its Action Date. If you have any problems with this timeline, please let Kimberly Shiley or Pamela Lucarelli know, who are cc'd here, during my absence from May 16 to May 25, 2012.

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
Phone: 301-796-0875
Fax: 301-796-9897

Tracking:

Recipient

'Kannenberg, Judy'
Simon-Wilson, Melinee
Shiley, Kimberly
Lucarelli, Pamela K

Read

Read: 5/15/2012 4:50 PM
Read: 5/21/2012 7:07 AM

MEMORANDUM OF MEETING MINUTES

Division of Reproductive and Urologic Products

Meeting Category: NDA Review: Status Meeting, FDA-requested
Meeting Date and Time: February 9, 2012
Application Number: NDA 202611
Product Name: mirabegron, 25 mg and 50 mg extended release tablets
Indication: Treatment of overactive bladder
Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.
Meeting Chair: Mark S. Hirsch, M.D.
Meeting Recorder: Nenita Crisostomo, R.N.

FDA ATTENDEES

Audrey Gassman, M.D. – Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark S. Hirsch, M.D. – Medical Team Leader, DRUP
Roger Wiederhorn, M.D. – Medical Officer, DRUP
Preston Dunnmon, M.D. – Medical Officer, Division of Cardiovascular and Renal Products (DCRP)
Rajnikanth Madabushi, Ph.D. – Team Leader, Division of Clinical Pharmacology I (DCPI)
Tzu-Yun McDowell, Ph.D. – Clinical Pharmacology Reviewer (CV risk modeling), DCPI
Sayed (Sam) Al Habet, R.Ph., Ph.D. – Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III (DCPIII)
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP
Charlene Williamson – Regulatory Health Project Manager, DRUP
Meredith Alpert, M.S. – Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Steven Ryder MD, FACP - President, Astellas Pharma Global Development
Leticia Delgado-Herrera RPh, MS, Executive Director, Global Development Project Leader
William Fitzsimmons, PharmD, MS, Sr Vice President, Astellas Pharma Global Development
Salim Mujais, MD, Executive Medical Director, Global Medical Sciences
Judy Kannenberg, MBA, Director, Regulatory Affairs

1.0 BACKGROUND

This new drug application (NDA) was received on August 29, 2011, with an action date of June 29, 2012. The related IND is 69416. The Filing letter (74 day letter), containing a list of Clinical review issues, was sent to the Sponsor on November 9, 2011. Many, but not all, of the review issues noted upon filing have been resolved.

This teleconference was requested to convey to the Sponsor the remaining Clinical review issues to date, and to discuss in greater depth the continued analysis of the effect of mirabegron on blood pressure.

The attached document was sent to the Sponsor via email on February 8, 2012, and it contains items for discussion during the teleconference.

2. DISCUSSION

The teleconference began with an introductory statement by the Division leading to the items for discussion.

2.1. Continuing Review of the Effect of Mirabegron on Blood Pressure

The Division informed the Sponsor that the clinical impact of the mirabegron-related increase in blood pressure was being analyzed using a cardiovascular risk analysis model. The Division sought the Sponsor's help with mirabegron's specific data entry into the model. The Division began the discussion with alternatives (e.g., including diastolic blood pressure in a categorical analysis versus a more contemporary approach using systolic blood pressure [SBP] only in a Cox proportional hazards regression model). The Division requested that the Sponsor use the latter approach and the Sponsor agreed. The Division noted this was a change from the request outlined in the pre-meeting communication, as attached.

The Sponsor confirmed that because BP was not ascertained by the same method or on the same schedule in the global non-"pivotal" trials as it was in the "pivotal", Phase 3 trials done in North America and Europe (NA/EU), the global BP/Pulse data was not integrated or displayed in the summary of safety. The Division requested that the Sponsor collate the hemodynamics data from these global trials and display this on a table so that the global data can be assessed with respect to consistency of the central tendency and spread of the change from baseline of the various HR and BP parameters against the EU/NA data that we are using in the model.

Finally, the Division agreed with the Sponsor that analysis of the integrated 12 week and 12 month EU/NA data would not be helpful because a large percentage of patients in the long-term study rolled over from the short-term studies.

2.2. Remaining Clinical Issues Currently Under Review

In reference to the remaining review items listed on the attached document, the Division clarified that there are no information requests pertaining to these issues. These items are being conveyed as an update to let the Sponsor know that these are several remaining Clinical issues while the NDA review is ongoing. However, the Sponsor may choose to respond to these items as deemed appropriate in their view.

2.3. Advisory Committee Meeting

The Division informed the Sponsor that the Advisory Committee Meeting Agenda is currently being drafted. Timeframe for presentations is still under consideration. The Sponsor stated that 60 minutes would be adequate for their presentation.

3.0 ACTION ITEMS

The Sponsor will submit within a week their cardiovascular risk analysis based on the Phase 3 blood pressure data, using the Cox proportional hazards regression model, 2008 version.

4.0 ATTACHMENT

List of Discussion Points – *“Requests for Information and Comments in Advance of the February 9, 2012, Teleconference Between the Division of Reproductive and Urologic Products and Astellas Regarding NDA 202611 (Mirabegron)”*

**Requests for Information and Comments in Advance of the February 9, 2012,
Teleconference Between the Division of Reproductive and Urologic Products and
Astellas Regarding NDA 202611 (Mirabegron)**

1. In collaboration with the Division of Cardiovascular and Renal Products (DCRP), we request the following additional information to complete our review of mirabegron's effect on blood pressure:

In order to define the clinical significance of the systolic and diastolic blood pressure increases observed in the mirabegron development program, we request that you model the actual change in patients' Framingham risk scores on active therapy, and then display those changes as a function of their baseline Framingham risk. These analyses should be performed by-dose for mirabegron, as well as for the tolterodine active control, for the following populations:

- a. EU/NA OAB 12-week Phase 3
- b. EU/NA Long-term Controlled
- c. All exposed (i.e., the first two groups above integrated).

Please calculate the change in the Framingham risk scores utilizing a model that incorporates both systolic and diastolic blood pressure changes, and use actual patient blood pressure changes (as opposed to assuming that each patient experiences the mean BP change for the entire study population). We acknowledge that ambulatory blood pressure data is not available for the majority of the clinical trial patients. Therefore, it is acceptable to model the Framingham risk score shifts either by incorporating AM and PM blood pressure data into an aggregated dataset to represent the entire 24 hour period, or alternatively, defaulting to the time period data for which the largest blood pressure shifts are seen. All patients with a post-baseline (on-therapy) blood pressure measurement should be included, using the last reliable BP data when the patient was known to be taking study drug.

2. Subsequent to our mid-cycle meeting, we are sharing with you the following Clinical issues which remain under review:
 - a. A number of pregnancies and spontaneous abortions, as well as a congenital abnormality were reported in patients taking mirabegron.
 - b. We currently find that there is a small effect of mirabegron on blood pressure. There have also been reports of exacerbated hypertension in patients with pre-existing hypertension.
 - c. We currently find that tachycardia and palpitations are mirabegron-related AEs. We also find a modest increase in pulse rate secondary to mirabegron.

- d. Syncope was highest in incidence in the mirabegron 25 mg group.
- e. There was an increased incidence of serious adverse events (SAEs) in patients taking alpha blockers.
- f. We find a possible effect of mirabegron on renal colic.
- g. We find that UTI is a mirabegron-related AE.
- h. The incidence of neoplasms in patients taking mirabegron 100 mg versus placebo in the long-term study remains of some concern.
- i. We find that mirabegron may induce hepatotoxicity, although not frequently.
- j. We find that mirabegron has the potential to cause non-serious and serious cutaneous adverse reactions. A case of hemolytic anemia/thrombocytopenia remains under review.

We remind you that all review disciplines are continuing their reviews, and additional issues may arise from these ongoing reviews.

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

/s/

NENITA I CRISOSTOMO
06/14/2012

MARK S HIRSCH
06/14/2012



NDA 202611

LABELING PMR/PMC DISCUSSION COMMENTS

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your New Drug Application (NDA) dated August 26, 2011, received August 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mirabegron, 25 mg tablets.

We also refer to our November 9, 2011, letter in which we notified you of our target date of May 11, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

We further refer to the May 3, 2012, teleconference with your firm and the Division of Reproductive and Urologic Products to discuss the starting dose and post-marketing activities for continued monitoring of hepatotoxicity, cardiovascular and new malignant events. We plan to have further discussions with you regarding these post-marketing activities as we continue our review of your application.

We are providing in the attached labeling Pharmacology/Toxicology and Chemistry, Manufacturing and Controls (CMC) revisions and comments. Please note that significant labeling revisions are forthcoming as we complete our reviews.

If you have any questions, please call me, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Package Insert

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

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

/s/

NENITA I CRISOSTOMO
05/10/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, May 08, 2012 12:10 PM
To: 'Kannenberg, Judy'
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: RE: Mirabegron NDA 202611 Pediatric Administrative Information Amendment

Hi Judy,

We have received your juvenile Pediatric Tox Study plan. Thank you!

Could you also submit the protocol to the IND and make reference of it in the NDA?

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*

6/8/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, April 17, 2012 1:29 PM
To: 'Kannenberg, Judy'
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: RE: Mirabegron NDA 202611 Pediatric Administrative Information Amendment

Hi Judy,

Basically, the Pediatric Plan, which generally should be submitted with the original NDA, usually accompanies a request for Deferral of Pediatric Studies. This plan generally contains a brief description of the study (ies) in addition to:

- Protocol submission dates
- Study Completion dates
- Final Study Report Submission dates

Unless you have specific revisions to your Waiver and Deferral requests from the original submission, you do not have to resubmit them.

PeRC Meeting has been rescheduled to May 30, 2012.

Thanks,
 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*

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Monday, April 16, 2012 4:45 PM
To: Crisostomo, Nenita
Cc: Simon-Wilson, Melinee; Essig, Eva
Subject: Mirabegron NDA 202611 Pediatric Administrative Information Amendment

Nita,

In follow-up to your discussion with Eva Essig last week regarding mirabegron pediatric studies, Astellas plans to submit a Pediatric Administrative Information Amendment to the mirabegron NDA 202611 tomorrow April 17, which will include the following:

- Updated Request for Waiver of Pediatric studies (1.9.1)
- Updated Request for Deferral of Pediatric Studies (1.9.2)
- (b) (4)
- Protocol submission dates
- Study Completion dates
- Final Study Report Submission dates

6/7/2012

Eva indicated that a Pediatric Review Committee meeting has been scheduled for April 25, but may be delayed. Can you confirm whether the meeting has been delayed and if there is a new date scheduled?

Thank you, please let me know if you have questions on this proposed Amendment.

Kind regards,
Judy

*Judy Kannenberg, MBA, RAC
Director, Regulatory Affairs
Astellas Pharma Global Development, Inc.
847-317-1277
224-515-6027 (mobile)
847-317-7286 (FAX)
judy.kannenberg@us.astellas.com*

6/7/2012



NDA 202611

INFORMATION REQUEST

Astellas Pharma US, Inc.
Attention: Judy Kannenberg, Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mirabegron tablets.

We also refer to your submission dated January 13, 2012.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by April 6, 2012 in order to continue our evaluation of your application. Please send your response via email to rebecca.mcknight@fda.hhs.gov as well as sending an amendment to your application.

- In the drug product container/closure section your application lists three options for (b) (4)

[Redacted]

The information included in DMF (b) (4), referenced for the detailed description of the container/closure, is not sufficient to establish proper functionality of the (b) (4) and the (b) (4). Please update the drug product container/closure section so it lists only (b) (4), and commit to using only closures with (b) (4) made of this material.

If you have questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE
03/26/2012
Chief, Branch IV

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, March 20, 2012 6:40 PM
To: 'Kannenberg, Judy'
CC: Simon-Wilson, Melinee
Subject: NDA 202611 mirabegron: Recommendations for carton/container labeling

Hi Judy,

Please refer to your submission dated February 9, 2012, containing your response to the comments and recommendations from DMEPA. We also refer to our email communications with you on February 22, 2012, conveying to you the CMC recommendations regarding the placement of the name of the manufacturer, packer, or distributor on the blister.

CMC:

- **After further review of your February 9, 2012, submission, it appears that the blister strip is perforated. If each blister can be removed from the strip, then the manufacturer's name must appear on every blister well section and not on one section of the whole strip. Please clarify.**

DMEPA:

A. General Comments (All container labels and carton labeling)

- **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.**
- **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.**

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

- **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.**
- **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 any questions, please feel free to contact me. Have a great evening.

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*

Tracking:

Recipient

'Kannenberg, Judy'
Simon-Wilson, Melinee
Hirsch, Mark S

Read



NDA 202611

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, M.B.A., R.A.C.
Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mirabegron, 25 mg and 50 mg extended release tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 1, 2012. The purpose of the meeting was to provide clarifications to our comments listed in the regulatory letter dated February 28, 2012, specifically, Comments #3 and #7e.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nenita Crisostomo, R.N., at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Roger Wiederhorn, M.D.
Medical Officer
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance, FDA-requested
Meeting Date and Time: March 1, 2012
Application Number: NDA 202611
Product Name: mirabegron, 25 mg and 50 mg extended release tablets
Indication: Treatment of overactive bladder
Applicant Name: Astellas Pharma Global Development, Inc.
Meeting Chair: Roger Wiederhorn, M.D.
Meeting Recorder: Nenita Crisostomo, R.N.

FDA ATTENDEES

Roger Wiederhorn, M.D. – Medical Officer, Division of Reproductive and Urologic Products (DRUP)
Preston Dunnmon, M.D. – Medical Officer, Division of Cardiovascular and Renal Products (DCRP)
Rajnikanth Madabushi, Ph.D. – Team Leader, Division of Clinical Pharmacology I (DCPI)
Nenita Crisostomo, R.N. – Regulatory Health Project Manager, DRUP

APPLICANT ATTENDEES

William Fitzsimmons, Pharm.D., M.S. – Senior Vice President, Astellas Pharma Global Development
Leticia Delgado-Herrera, R.Ph., M.S. – Executive Director, Global Development Project Leader
Salim Mujais, M.D. – Executive Medical Director, Global Medical Sciences
Mary Beth Blauwet, Dr.P.H. – Associate Director, Biostatistics
Judy Kannenberg, M.B.A. – Director, Regulatory Affairs

1.0 BACKGROUND

This new drug application (NDA) for mirabegron was received on August 29, 2011, from Astellas Pharma Global Development, Inc. The related IND is 69,416. DRUP requested a consultation from the Division of Cardiovascular and Renal Products (DCRP), and the DCRP analysis of blood pressure is ongoing. A teleconference was held with the Applicant on February 9, 2012, to request information regarding cardiovascular risk analysis. In response to this request, the Applicant submitted an analysis plan on February 17, 2012. Following the review of this submission, an FDA regulatory letter containing our comments and recommendations were sent to the Applicant on February 28, 2012.

This teleconference was requested by the Division to provide further clarifications to the requested items in the letter, specifically Items #3 and #7e.

2. DISCUSSION

The teleconference began with an introductory statement by the Division leading to the items for discussion:

2.1. Item #3: In addition to your proposal, we recommend that you conduct independent analyses of incremental cardiovascular risk using the mean AM SBP as well as mean PM SBP separately. Both your proposed analysis and our requested analysis of AM SBP and PM SBP should be conducted using maximal observed SBPs, as opposed to mean SBPs.

The Division explained that both the sponsor's proposed analysis and the FDA requested analysis (using the mean AM SBP as well as mean PM SBP separately instead of combined) should also be conducted using maximal observed SBPs.

Accordingly, the second sentence in item three is restated as follows:

*Both your proposed analysis and our requested analysis of AM SBP and PM SBP should **then** be conducted using maximal observed SBPs, as opposed to mean SBPs.*

The applicant expressed their understanding to this clarification.

2.2. Item #7e: Perform a sensitivity analysis for all of the above excluding the Open label Study 178-CL-049.

The Division explained the requests for a combined analysis by the specific dose and study for Studies 178-CL-046, 178-CL-047, and 178-CL-074, and Study 178-CL-049 separately. For further clarification of the request, the above statement may be revised as follows:

Perform all analyses noted above for Studies 178-CL-046, 178-CL-047, and 178-CL-074 combined, and then for active-controlled Study 178-CL-049 separately, because patients from Studies 178-CL-046 and 178-CL-047 were rolled over into Study 178-CL-049.

The Applicant expressed their understanding to the request.

2.3. Regarding the hemodynamics data as requested during the February 29, 2012, teleconference.

The Division reiterated the importance of submitting the requested data in a tabular format and inquired on the submission timeline of this request. The Applicant concurred that the data will be tabulated and plans to submit along with the responses to the February 28, 2012, requests following the above-mentioned clarifications.

Post meeting note: If the tables are available, we recommend that the Applicant submit them at the earliest timepoint possible.

2.4. Differences of blood pressure (BP) readings between Phase 1 and Phase 3

The Division asked for the Applicant's opinion regarding the differences observed in the mean systolic BP (SBP) data from Phase 1, such as in the Thorough QT (TQT) Study, and the Phase 3 studies. The Applicant stated that in the TQT study, the subjects were normal, healthy, and young volunteers in a more calm setting (a Phase 1 clinical research site setting) unlike the Phase 3 studies. The Applicant stated that the study conditions may be responsible for the elevations in blood pressure readings noted in the study. The Applicant confirmed that the moxifloxacin group was included in the study analysis. The Division inquired as to whether the moxifloxacin control group demonstrated the same degree of SBP elevations as did the mirabegron-treated patients. The Applicant stated that the data was not immediately available. This information will be reviewed by FDA.

2.5. Submission Timeline

Because of the preparations necessary to complete the background information for the Advisory Committee (AC) Meeting, the Division requested that the information be submitted within the next few days. The Applicant stated that they are not able to commit to submitting all the requested analyses in this time frame, but will submit at least the analysis using SBP means, and potentially the separate AM and PM analyses using SBP means. The requested analyses using maximal observed blood pressures will be submitted shortly thereafter. The Agency agreed to Applicant's proposal of using data from Carroll, et al for imputing the total cholesterol and the HDL for the Framingham simulations. It was also agreed that the Applicant will use the smoking status for the year 2010 from the NHIS for the purpose of simulations.

2.6. Advisory Committee Meeting

Because Astellas is required to submit their AC Backgrounder to the AC Staff on March 5, 2012, and they have not included the items on blood pressure differences between Phase 1 and Phase 3, they asked if the backgrounder can be revised once it is submitted. They were advised to inquire with the AC Staff directly regarding this matter.

3.0 ACTION ITEMS

The Applicant will submit the mean data analyses by March 7, 2012.

4.0 ATTACHMENT

None.

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

/s/

A R WIEDERHORN
03/13/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, February 29, 2012 4:43 PM
Subject: 'Kannenberg, Judy'
NDA 202611 mirabegron: Microbiology Information Request

Hi Judy,

Below is a comment and request from the Microbiology reviewer as consulted by the ONDQA:

The proposal to perform [REDACTED] ^{(b)(4)} for Microbial Limits is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). As an alternative to [REDACTED] ^{(b)(4)}, you may propose to omit finished product microbial limits testing for batch release. In addition, microbial limits testing should be performed at the initial time point (at a minimum) on stability samples.

Please submit your response on or before close of business on Tuesday, March 6, 2012. If you have any questions, please feel free to contact me.

Thank you,
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

Linking:	Recipient	Read
	'Kannenberg, Judy'	
	Hirsch, Mark S	
	Kurtyka, Bogdan	Read: 3/1/2012 8:08 AM
	Christner, Donna	Read: 2/29/2012 4:45 PM
	Wiederhorn, Roger	Read: 2/29/2012 5:30 PM
	McKnight, Rebecca	Read: 3/1/2012 7:21 AM

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, February 28, 2012 11:34 AM
To: 'Kannenberg, Judy'
Cc: 'Wilson, Melinee'
Subject: RE: NDA 202611 Status of CV analysis plan review

Hi Judy,

Thanks for the reminder over the phone earlier, that Study 049 is active-controlled, and not an open-label study.

We requested you to conduct sensitivity analysis excluding Study 178-CL-049 as we do not have a placebo control. This analysis is in addition to the analysis of the pooled data (178-CL-046, 178-CL-047, 178-CL-074 and 178-CL-049).

Hope this provides clarification.

Thanks so much,
nita

From: Crisostomo, Nenita
Sent: Tuesday, February 28, 2012 10:46 AM
To: 'Kannenberg, Judy'
Cc: 'Wilson, Melinee'
Subject: RE: NDA 202611 Status of CV analysis plan review

Hi Judy,

Also coming to you in the postal mail, attached is an Advice letter following our review of your 2/17/12 CV risk analysis plan. Have a great day!

Regards,
--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*

From: Crisostomo, Nenita
Sent: Monday, February 27, 2012 11:03 AM
To: 'Kannenberg, Judy'
Cc: Wilson, Melinee
Subject: FW: NDA 202611 Status of CV analysis plan review

6/8/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, February 28, 2012 11:14 AM
To: 'Kannenberg, Judy'; 'Wilson, Melinee'
Subject: RE: NDA 202-611 mirabegron - CMC Request: revision to Blister Label

Tracking:

Recipient	Read
'Kannenberg, Judy'	
'Wilson, Melinee'	
Christner, Donna	Read: 2/28/2012 11:23 AM
Kurtyka, Bogdan	Read: 2/28/2012 11:16 AM

Hi Judy,

As I informed you over the phone this morning, we have the following revised comment after further discussions of your inquiry:

After further review of your 09-Feb-2012 submission, it appears that the blister strip is perforated. If each blister can be removed from the strip, then the manufacturer's name must appear on every blister well section and not on one section of the whole strip. Please clarify.

If you have any questions, please contact me anytime.

Thank you,
 nita

From: Crisostomo, Nenita
Sent: Monday, February 27, 2012 3:16 PM
To: 'Kannenberg, Judy'; Wilson, Melinee
Subject: FW: NDA 202-611 mirabegron - CMC Request: revision to Blister Label

Hi Judy,

Unfortunately the regs are quite specific that the manufacturer's name has to be there.

However, this information (manufacturer's name) does not have to be repeated 10 times at each tablet location. It is sufficient if it shows in one location on the whole blister.

Hope this helps. Please let me know if further clarification is needed.

Thanks so much,
 nita

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Monday, February 27, 2012 12:40 PM
To: Crisostomo, Nenita
Cc: Simon-Wilson, Melinee
Subject: RE: NDA 202-611 mirabegron - CMC Request: revision to Blister Label

6/7/2012

Nita,

In response to the request from the CMC reviewer regarding the blister change, Astellas is proposing to add the company logo to the blister, as space is very limited. Can you confirm whether this would be an acceptable approach for the reviewer?

Thank you,
Judy

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, February 22, 2012 5:17 PM
To: Kannenberg, Judy
Subject: NDA 202-611 mirabegron - CMC Request: revision to Blister Label

Hi Judy,

Please refer to your recent submission of the carton/container labels dated February 8, 2012, in response to the comments and recommendations from DMEPA. Below is a request from the CMC reviewer to revise the Blister label:

"According to 21 CFR 201.10(h)(2)(i)(1)(iv), place on the blister, the name of the manufacturer, packer, or distributor".

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

Thank you and have a great evening,
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*

6/7/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, February 22, 2012 6:17 PM
Subject: 'Kannenberg, Judy'
NDA 202-611 mirabegron - CMC Request: revision to Blister Label

Hi Judy,

Please refer to your recent submission of the carton/container labels dated February 8, 2012, in response to the comments and recommendations from DMEPA. Below is a request from the CMC reviewer to revise the Blister label:

"According to 21 CFR 201.10(h)(2)(i)(1)(iv), place on the blister, the name of the manufacturer, packer, or distributor".

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

Thank you and have a great evening,
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*

Tracking:	Recipient	Read
	'Kannenberg, Judy'	
	Kurtyka, Bogdan	Read: 2/23/2012 7:25 AM
	Christner, Donna	
	Mcmillan, Teresa	Read: 2/27/2012 9:20 AM
	Townsend, Karen	Read: 2/23/2012 1:58 PM
	Wiederhorn, Roger	



NDA 202611

**METHODS VALIDATION
MATERIALS RECEIVED**

Astellas Pharma Global Development
Attention: Judy Kannenberg
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Ms. Judy Kannenberg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [REDACTED]^{(b) (4)} (mirabegron) Extended Release Tablets, 25 mg and 50 mg and to our 11/29/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 1/25/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JAMES F ALLGIRE
01/26/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Friday, January 06, 2012 5:37 PM
To: 'Kannenberg, Judy'
Subject: NDA 202611 mirabegron: Clinical Information Request

Hi Judy,

Please provide the serious adverse event (SAE) narratives for Patient 3027-2518 for Study 178-CL-049. There seems to be no link for it and we could not find it in the narratives appendix.

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*



NDA 202611

INFORMATION REQUEST

Astellas Pharma US, Inc.
Attention: Judy Kannenberg, Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Ms. Kannenberg:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirabegron, 25 mg and 50 mg Extended Release Tablets.

We also refer to your submission dated August 26, 2011.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your new drug application. Please also submit a copy of your response via email to rebecca.mcknight@fda.hhs.gov.

Regarding drug substance specification:

1. Add limit for (b) (4) to the specification. Justify the proposed limit. Submit validated analytical procedure for content of (b) (4).
2. Provide data to support no testing for (b) (4) in starting material (b) (4) or in drug substance or implement control of (b) (4).
3. Discontinuation of testing for genotoxic impurities (b) (4) after 10 first commercial batches is not acceptable. Modify the specification appropriately.

Regarding composition of drug product:

4. (b) (4), describe how it is taken into account during manufacturing.

Regarding stability of drug product:

5. Your proposed expiration dating period for drug product stored in HDPE bottles is not supported by stability data, in particular BHT level results. Since the BHT level during storage decreases significantly, drug product quality is not assured past 24 months. Based on the provided data an expiration dating period of [REDACTED] (b) (4) can be granted at the proposed storage conditions. Note that this comment does not apply to drug product packed in aluminum blisters.
6. Test for BHT content should be added to the post-approval stability commitment protocols.

Regarding Comparability Protocol:

7. The reporting category you propose in the Comparability Protocol is not correct. “Guidance for Industry - Changes to an Approved NDA or ANDA” specifically states that any fundamental change in the manufacturing process or technology, such as [REDACTED] (b) (4) or vice versa, constitutes a major change and requires a Prior Approval Supplement.
8. Your Comparability Protocol does not mention source of starting materials. At the pre-NDA meeting you were informed that after the NDA is approved, any change in the manufacturing process for the starting materials or a new manufacturer requires notification via a supplement.
9. The proposed Comparability Protocol includes drug substance specification which is not adequate; see comments regarding drug substance specification.

If you have questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE
01/05/2012
Chief, Branch IV



NDA 202611

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Astellas Pharma US, Inc.
Three Parkway North
Deerfield, IL 60015-2548

ATTENTION: Judy Kannenberg
Associate Director, Regulatory Affairs

Dear Ms. Kannenberg:

Please refer to your New Drug Application (NDA) dated August 26, 2011, received August 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirabegron Extended Release Tablets, 25 mg and 50 mg.

We also refer to your October 13, 2011, correspondence, received October 13, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reason:



We note that you have proposed an alternate proprietary name in your submission dated October 13, 2011. In order to initiate the review of the alternate proprietary name, ^{(b) (4)} submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Nenita Crisostomo at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
12/23/2011

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, December 15, 2011 5:08 PM
To: 'Kannenberg, Judy'
Cc: 'Wilson, Melinee'
Subject: RE: NDA 202611 Carton/container label recommendations
Attachments: IR.carton.container label.doc

Hi Judy,

Attached are the comments and recommendations from the Division of Medication Error Prevention Analysis regarding the carton/container labels for NDA 202611. Timeline for submission of your response to these requests will be discussed at a later date in light of the proposed trade name. Please call me at your earliest convenience.

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*

6/8/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Saturday, December 03, 2011 1:09 PM
'Kannenberg, Judy'
Essig, Eva; Wilson, Melinee
Subject: NDA NDA 202611: mirabegron - Clinical Information Request re: Pts w/ low platelets

Hi Judy,

Below is a Clinical Information Request.

From Study 178-CL-047, Table 49, please provide patient identification and platelet values for the seven patients listed as having low platelets.

For our immediate review, while enroute for official submission in the Electronic Document Room, please email your response to me on or before close of business on December 7, 2011. If you have any questions, please feel free to contact me. Have a great weekend!

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*

Tracking:	Recipient	Read
	'Kannenberg, Judy'	
	Essig, Eva	
	Wilson, Melinee	
	Wiederhorn, Roger	Read: 12/5/2011 9:41 AM
	Hirsch, Mark S	Read: 12/5/2011 8:40 AM

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Friday, December 02, 2011 10:51 AM
Subject: 'Kannenberg, Judy'; Essig, Eva; Wilson, Melinee
RE: NDA 202611 Submission of resized datasets

Hi Judy,

In consultation with the FDA OIT, here are our recommendations:

Please follow these instructions for submitting on external hard drive as media type:

1. prepare an eCTD submission for filing based on current FDA and ICH specifications
2. copy the four digit submission folder (i.e. 0001) to the external hard drive
3. include a coverletter.pdf in this submission, which should include loading instructions, submission size, number of folders and files
4. call eSUB (301-796-7591) and provide password and/or encryption code for the submission
5. email cover letter with loading instructions to eSUB@fda.hhs.gov
6. send the external hard drive to the FDA Central Document Room [5901-B Ammendale Rd, Beltsville, MD 20705], and include a pre-paid postage envelope for return of the USB drive

Hope this helps. Have a great day!

Thanks,
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
: 301-796-9897

-----Original Message-----

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Wednesday, November 30, 2011 12:32 PM
To: Crisostomo, Nenita; Essig, Eva; Wilson, Melinee
Subject: RE: NDA 202611 Update

Nita,

In regards to using a hard drive, we were concerned about the time required to send via the gateway. It is estimated to take 12 - 24 hours through the gateway, and an interruption may be possible during that time. Please confirm with Informatics if this is a correct assumption for a submission of this size.

Thank you,
Judy

-----Original Message-----

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, November 30, 2011 11:26 AM
To: Kannenberg, Judy; Essig, Eva; Wilson, Melinee
Subject: RE: NDA 202611 Update

Hi Judy/Eva,

May I know why you would rather submit an external drive rather than through the gateway, especially now that the submission is so much smaller?

Thanks,
nita

-----Original Message-----

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Wednesday, November 30, 2011 5:27 AM
To: Crisostomo, Nenita; Essig, Eva; Wilson, Melinee
Subject: NDA 202611 Update

...ca,
I will be traveling this week, if you need to reach Astellas please contact Eva Essig while I am out.

I would like to provide a brief status update regarding ongoing requests for information, per the filing letter we submitted updated labeling on Monday Nov 28. In addition we will be submitting the clinical pharmacology response and the statistical programs by the end of this week. The resized datasets will take a bit longer as some datasets now require splitting to be under 1GB. Submission of the resized and split datasets will exceed 50 GB, therefore Astellas is proposing to submit them on an external hard drive. Please confirm that this approach is acceptable. We plan to submit the datasets by Dec 15th.

Thank you
Judy

Tracking:	Recipient	Read
	'Kannenberg, Judy'	
	Essig, Eva	
	Wilson, Melinee	
	Chhatre, Dhananjay	Read: 12/2/2011 10:57 AM
	Warfield, Douglas	Read: 12/2/2011 11:20 AM
	Wiederhorn, Roger	
	Guo, Jia	Read: 12/2/2011 10:52 AM
	Sobhan, Mahboob	Read: 12/2/2011 2:14 PM



NDA 202611

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Astellas Pharma Global Development
Attention: Judy Kannenberg
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Ms. Judy Kannenberg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (mirabegron) Extended Release Tablets, 25 mg and 50 mg.

We will be performing methods validation studies on (b) (4) (mirabegron) Extended Release Tablets, 25 mg, as described in NDA 202611

In order to perform the necessary testing, we request the following sample materials and equipments:

CURRENT METHODS

- Control of Drug Substance
 - Related Substances
 - Impurities (b) (4)
 - Impurities (b) (4)
 - (b) (4)
 - Assay
- Control of Drug Product
 - Related Substances
 - Uniformity of Dosage Units
 - Dissolution
 - Assay (b) (4)

SAMPLES

- (b) (4)
- (b) (4) Mirabegron Drug Substance (b) (4) (mirabegron) Extended Release Tablets, 25 mg

REFERENCE MATERIAL

- (b) (4)
- (b) (4) Mirabegron (b) (4)



(b) (4)

COLUMNS



(b) (4)

Send the MSDSs and certificates of analysis for the samples and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

JAMES F ALLGIRE
11/29/2011

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Friday, November 18, 2011 2:45 PM
To: 'Kannenberg, Judy'
Cc: Wilson, Melinee; Essig, Eva
Subject: NDA 202611 mirabegron: eData question regarding resizing of datasets
Attachments: runresiz.sas; resiz.sas; NDA202611 - eData Guidance and responses to Sponsor questions 11172011.doc

Tracking:

Recipient	Read
'Kannenberg, Judy'	
Wilson, Melinee	
Essig, Eva	
Sobhan, Mahboob	Read: 11/18/2011 3:11 PM
Wiederhorn, Roger	
Hirsch, Mark S	Deleted: 11/18/2011 3:18 PM
Guo, Jia	
Warfield, Douglas	
Chhatre, Dhananjay	

Hi Judy & Eva,

Attached are our responses to your clarification questions, general guidance for dataset sizes in a submission, and sample SAS code provided to sponsors. The naming of the resized data will be up to you. According to the IT folks, the resized data will automatically update the previously submitted files once you submit the newly resized data. You can keep this in mind in the process.

Please note, the SAS software samples for resizing are only samples and the Agency does not make any representation as the software's use or performance. Please let me know if you have problems opening the documents.

Thanks and have a great weekend!

--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*

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Thursday, November 17, 2011 9:54 AM
To: CDER edata
Cc: Cleve, Scott; Blauwet, Mary Beth; Crisostomo, Nenita; Wilson, Melinee

6/8/2012

Subject: eData question regarding resizing of datasets

Dear eData group,

Astellas has received correspondence from the Division of Reproductive and Urologic Products indicating the need to resize large data files. Astellas would like to request the FDA's SAS program for resizing.

In addition, we have the following questions regarding the resizing:

- 1) Should the key fields STUDYID, USUBJID, and SUBJID remain the original lengths of 20, 40, 20, so that merging by these key fields in SAS will not result in a warning due to different lengths?
- 2) Should the resized length be the maximum length in the data, or is there a preference for lengths in multiples of 5? In the 'SDTM Column Resizing: Background and Industry Testing Results', many of the resized lengths are in multiples of 5.

Thank you for your assistance,
Judy

Judy Kannenberg, MBA, RAC
Associate Director, Regulatory Affairs
Astellas Pharma Global Development, Inc.
847-317-1277
224-515-6027 (mobile)
847-317-7286 (FAX)
judy.kannenberg@us.astellas.com

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

NDA 202611 mirabegron

Response to Sponsor's Clarification emails

In response to your email dated November 3, 2011:

ASTELLAS QUESTION: *Can you provide clarification regarding the extremely large datasets that require resizing at this time? Can we apply this to datasets that exceed 2GB or another specific criterion? Many of the phase 1 datasets are small and should allow easy reviewer access as originally provided in the NDA. It is our assumption that this request does not include the PK/PD modeling datasets, please confirm.*

In regards to the naming conventions, please note that none of the datasets included in the NDA have been split, therefore the numbering does indicate separate analyses as provided in the associated define files. With this clarification, is it still requisite that Astellas rename the datasets that contain a number in the name, please confirm.

Once we have clarification on the items above, Astellas can then provide an indication of the timing required for this request.

FDA RESPONSE: The Agency prefers the sponsor keep all standardized datasets under one gigabyte. The CDER Common Data Standards Issues Document guidance referring to 400 MB, "Individual file size up to 400 megabytes is usually fine; however, it is recommended to confirm this with the review division" (pg. 7), underscores the preference for smaller standardized datasets. Performing review activities where the submitted standardized dataset(s) exceeds one gigabyte can be problematic for some review processes and tools. As such, the Agency prefers the sponsors limit all standardized datasets to less than one gigabyte. The techniques for providing the standardized data to meet this preference includes resizing the transport file(s) (.xpt) (see attachments for SAS sample code) and/or splitting of datasets, as defined in the Study Data Specifications, the CDISC/SDTM Implementation Guide and the CDER Common Data Standards Issues Document.

We will leave the renaming of the resized files to your preferred method.

If you have any further questions, please feel free to send an email to edata@fda.hhs.gov.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)

In response to your email dated November 17, 2011 to eData:

ASTELLAS QUESTION: *Astellas has received correspondence from the Division of Reproductive and Urologic Products indicating the need to resize large data files. Astellas would like to request the FDA's SAS program for resizing.*

In addition, we have the following questions regarding the resizing:

- 1) Should the key fields STUDYID, USUBJID, and SUBJID remain the original lengths of 20, 40, 20, so that merging by these key fields in SAS will not result in a warning due to different lengths?*
- 2) Should the resized length be the maximum length in the data, or is there a preference for lengths in multiples of 5? In the 'SDTM Column Resizing: Background and Industry Testing Results', many of the resized lengths are in multiples of 5.*

FDA RESPONSE:

- a. Please see the sample SAS code attached for resizing.
- b. Regarding resizing:
 - 1) Should the key fields STUDYID, USUBJID, and SUBJID remain the original lengths of 20, 40, 20, so that merging by these key fields in SAS will not result in a warning due to different lengths?*

The Agency prefers the sponsor resize all variables based on the maximum length used in the column.

- 2) Should the resized length be the maximum length in the data, or is there a preference for lengths in multiples of 5? In the 'SDTM Column Resizing: Background and Industry Testing Results', many of the resized lengths are in multiples of 5.*

The Agency prefers the sponsor resize all variables based on the maximum length used in the column.

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, November 17, 2011 1:22 PM
Subject: 'Kannenberg, Judy'
NDA202611 - Clinical info request

Hi Judy,

Listed below are requests from the Clinical Team:

1. For Study 178-CL-046, Subjects 3193-3404 and Subject 3072-3069, provide additional information, if available, relating to fatigue and state of attention and concentration at the time of injury.
2. For Study 178-CL-046, Subject 3140-1859, provide amylase and lipase levels.
3. For Study 178-CL-074, Subject 1645-70556, provide information on reported fatigue, and any changes in concentration and attention. Provide additional detail on the circumstances of the injury.
4. For Study 178-CL-074, Subject 2210-71167, provide information relating to reason that MIBI Persantine scan was part of routine follow-up.

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

Thanks 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

Tracking:

Recipient

'Kannenberg, Judy'

Wiederhorn, Roger

Hirsch, Mark S

Read

Read: 11/17/2011 4:07 PM

Read: 11/17/2011 2:01 PM

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, November 16, 2011 4:55 PM
To: 'Kannenberg, Judy'
Cc: Wilson, Melinee
Subject: RE: NDA 202611 mirabegron: Filing Letter

Hi Judy,

This specific comment refers only to Highlights because it cites the regulation for HL - 21 CFR 201.57(a)(11). For the Full Prescribing Information, the comment that refers to 21 CFR 201.57(c)(7) would apply. The bottom line is to only include "adverse reactions" in labeling and terms, such as treatment-emergent adverse events (TEAE), adverse events, etc., should be avoided.

Thanks,
nita

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Tuesday, November 15, 2011 5:15 PM
To: Crisostomo, Nenita
Cc: Wilson, Melinee
Subject: RE: NDA 202611 mirabegron: Filing Letter

Nita,

Per my voicemail regarding the filing letter, can you clarify the labeling comment on page 8, regarding Adverse Reactions (item 1), is this comment only related to the Highlights Section or should the comment be applied to Section 6 Adverse Reactions as well?

Thank you for your assistance,

Judy

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, November 09, 2011 3:06 PM
To: Kannenberg, Judy
Subject: NDA 202611 mirabegron: Filing Letter

Hello Judy,

Also coming to you in the mail, attached is the the Filing Communication letter. If you have any questions, please feel free to contact me.

Thanks,
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*

6/8/2012



NDA 202611

FILING COMMUNICATION

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your New Drug Application (NDA) dated August 26, 2011, received August 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for mirabegron, extended release tablets, 25 mg and 50 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 11, 2012.

During our filing review of your application, we identified the following potential review issues:

PHARMACOLOGY/TOXICOLOGY:

-  (b) (4)

CLINICAL:

Efficacy

A difference in efficacy between older (≥ 65 years) and younger (< 65 years) subjects was observed in Study 178-CL-046.

Safety

1. The role of mirabegron in the deaths of two subjects: Patient Number 1530-6120 (multi-system organ failure) and Patient Number 3034-2380 (cardiac failure) in Study 178-CL-049 is under review.
2. Regarding serious adverse events (SAEs):
 - a. In the EU/NA, 12-Week, Phase 3 Population:
 - i. A small difference was observed in incidence of atrial fibrillation SAEs between mirabegron and placebo.
 - ii. Three urolithiasis SAEs were reported in the mirabegron group versus none in placebo.
 - iii. A difference is noted between mirabegron and placebo in total number of infection SAEs when a variety of different infections, each reported by 1 subject, are added together.
 - iv. A difference is noted between mirabegron and placebo in total number of neoplasm SAEs when a variety of different tumors, each reported by 1 subject, are added together. The relationship of these events to mirabegron in short-term (12-week) studies is unclear.
 - v. There are several injury SAEs in the mirabegron group versus none with placebo. Factors that may have contributed to these injuries (e.g. fatigue) will be considered during our case-by-case review.
 - b. In the EU/NA Long-term Controlled Population:
 - i. A higher incidence of atrial fibrillation SAEs was observed in the mirabegron group compared to the tolterodine group.
 - ii. A greater number of SAEs reported as “hepatic chemistry abnormalities” was observed in the mirabegron group (n=3) compared to the tolterodine group (n=1).
 - iii. A higher incidence of SAEs reported as “neoplasms” was observed in the 100 mg mirabegron group (1.3%) compared to the tolterodine group (0.5%).

iv. A higher incidence of SAES reported as Musculoskeletal and Connective Tissue Disorders was observed in the mirabegron group compared to the tolterodine group.

3. Regarding discontinuations due to adverse events:

a. In the EU/NA, 12-Week, Phase 3 Population:

i. Incidences of discontinuations due to hepatic chemistry abnormalities and “hypertension” were higher in the mirabegron group compared to the placebo group.

ii. Incidence of discontinuation due to Skin and Subcutaneous adverse events was higher in the mirabegron group compared to placebo. Although no skin-related adverse event was reported in greater than 1 subject, there were multiple, single adverse event terms (n=5) reported, possibly indicative of an allergic or hypersensitivity phenomenon.

iii. “Hypertension” leading to study discontinuation was reported in 6 mirabegron subjects versus 2 placebo subjects. There are two reports of “hypertensive crisis” leading to discontinuation.

b. In the EU/NA Long-term Controlled Population:

i. Fatigue was reported as a reason for discontinuation in 4 mirabegron subjects compared to 1 tolterodine subject.

ii. Palpitations and tachycardia were reported as reasons for discontinuation in 0.6% and 1.0 % of mirabegron subjects, respectively.

4. Regarding laboratory abnormalities:

Patient Number 2037-0516 in Study 178-CL-049 developed hemolytic anemia and thrombocytopenia as part of an apparent hypersensitivity reaction on Day 183. The role of mirabegron in this event is under review.

5. Regarding vital signs:

a. At 50 mg once daily, mirabegron appears to increase mean pulse rate by approximately 1-2 beats per minute over placebo. The increase in pulse rate secondary to mirabegron appears to be greater in women compared to men, as well as in younger compared to older subjects.

b. At 50 mg once daily, mirabegron appears to increase mean blood pressure by approximately 1 mm Hg over placebo.

6. Regarding electrocardiograms (ECGs):
 - a. An increase in mean QTc interval was observed in female subjects dosed with mirabegron 200 mg.
 - b. Higher incidence of outliers with QTcF > 450 msec was observed in subjects receiving mirabegron compared to placebo in 12-week studies.
 - c. Higher incidences of outliers with QTcF > 450 msec were observed in female subjects compared to male subjects, and in elderly (≥ 65 years) compared to non-elderly (< 65 years) subjects in 12-week studies.
7. Regarding intrinsic and extrinsic factors that may affect safety:
 - a. In the Global OAB 12-Week Population, the incidence of overall adverse events was generally higher in female subjects compared to male subjects across treatment groups.
 - b. In the EU/NA OAB 12-Week Population, the incidence of “hypertension” reported as an adverse event was higher in male subjects than in female subjects across treatment groups.
 - c. In the EU/NA OAB 12-Week population, the incidence of SAEs and discontinuations due to adverse events was generally higher in subjects who were using alpha-1 adrenergic antagonists (alpha-1 blockers) at baseline compared to those not using alpha-1 blockers at baseline.
8. Regarding specific safety issues:
 - a. Cardiovascular safety
 - i. The increases in blood pressure and pulse related to mirabegron, and the clinical significance of these increases, are under review.
 - ii. In the EU/NA 12-Week OAB Population, the incidence of adverse events of “hypertension” leading to discontinuation was higher in the mirabegron group (all doses) (0.4%), compared to placebo (0.2%) and compared to tolterodine (0.2%).
 - iii. The degree of QT prolongation associated with mirabegron is under review.
 - iv. There was a single case of cardiac arrest with ventricular tachycardia and ventricular fibrillation in a mirabegron-treated subject in Study 178-CL-049.
 - v. Mirabegron appears to be associated with an increased risk of tachycardia as compared to placebo and tolterodine. Adverse events related to rapid pulse rate (e.g., cardiac arrhythmia, sinus tachycardia) are under review.

vi. The independent role of mirabegron in atrial fibrillation is under review.

b. Urinary tract disorders

There appears to be an increased incidence of urinary tract infection (UTI) adverse events in mirabegron subjects compared to those using placebo.

c. Liver function test abnormalities

i. The mean increases from baseline in serum AST and ALT in the Global 12-Week Phase 2/3 Population are slightly greater for mirabegron compared to placebo.

ii. The following subjects had increases of liver function tests of concern:

- Patient Number 3353-1381 in Study 178-CL-049 experienced serum ALT and/or AST concentrations > 3 x upper limit of normal (ULN) and serum total bilirubin > 2 x ULN, with serum alkaline phosphatase (ALP) < 2 x ULN on the same date.
- Patient Number J5405034-P00244 in Study 178-CL-045 experienced potentially clinically significant increases from baseline in serum transaminases coupled with at least 2-fold increases in serum bilirubin.
- Two mirabegron subjects experienced greater than 10-fold increases from baseline in serum transaminases (Patient Numbers 3051-264 and U00020446398 in Study 178-CL-049).

d. Hypersensitivity reactions

i. Hypersensitivity reactions have been reported in subjects taking mirabegron. The relationship of these events to mirabegron and their severity are under review.

ii. Severe hypersensitivity reactions experienced by two subjects are under review:

- Patient Number P00244 in Study 178-CL-045, who was also taking Kufu Gold herbal medication, and;
- Patient Number U0002298121 in Study 178-CL-076, who experienced hypersensitivity, vasculitis and polyarthritis.

e. Glaucoma/Increased intraocular pressure (IOP)

All clinical adverse event reports of glaucoma and increased IOP, as well as data from the dedicated, placebo-controlled, non-inferiority intraocular pressure study are under review.

f. Neoplasms

- i. There were 12 subjects with adverse event reports in the Neoplasm category in the mirabegron groups in Study 178-CL-049 (1 in mirabegron 50 mg [1/812; 0.1%] and 11 in mirabegron 100 mg groups [11/820; 1.3%]). In comparison, there were 4 subjects with adverse event reports in the Neoplasm category among 812 subjects in the tolterodine group (4/812; 0.5%).
- ii. The analysis of incidences of Neoplasm AEs by re-categorizing subjects to mirabegron only, tolterodine only, or both mirabegron and tolterodine requires further consideration.
- iii. The analysis of Neoplasm AEs by re-categorizing the events as “new malignant events” requires further consideration.
- iv. The analysis of incidences of Neoplasm AEs by patient-years of exposure requires further consideration and is under review.
- v. The Adjudication Committee’s determinations regarding drug-relatedness for each new malignant event are under review.
- vi. The observed imbalance in new malignant events between mirabegron and placebo in the Global Phase 2/3 Population, and the effect of an imbalance of such events in short-term studies such as 178-CL-047, are under review.
- vii. Whether any of the Neoplasm AEs reflect pre-existing conditions, and whether differences between treatment groups in incidences of Neoplasm AEs remain after excluding certain cases, require further consideration.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

CLINICAL PHARMACOLOGY:

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

BIOSTATISTICS:

- Submit statistical analysis programming code of primary and key secondary efficacy endpoints for Study 178-CL-046, 047, and 074.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL)

- General comments
 1. 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. The top margin is less than ½ inch.
 2. 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. The highlight section is greater than ½ page.
 3. There is redundancy of information for renal impairment and hepatic impairment under DOSAGE AND ADMINISTRATION and USE IN SPECIFIC POPULATIONS.
 4. Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. 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.
- Highlights Limitation Statement
 1. 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).**” When the proprietary name is deemed acceptable, replace the [Product Name] that is now being used as a placeholder.
- Logos
 1. 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. 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
 1. 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. Product title should read: “*extended-release tablets, for oral use*”

- Initial U.S. Approval
 1. The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. Because this is an NME, the year must correspond to the current approval action. Format for initial US Approval is a 4-digit-year, not Month Year.
- Contraindications
 1. 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. 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.
- Adverse Reactions
 1. 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%). 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.
 2. 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. This statement should be a separate paragraph from the statement of adverse reactions.
- Patient Counseling Information Statement
 1. 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”)**”. Must read: “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling, **not** “See 17 for PATIENT COUNSELING INFORMATION”.
- Revision Date
 1. 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. Revision date is month/year that the application is approved.

Contents: Table of Contents (TOC)

- 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.
- Adverse Reactions
 1. 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.” 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.
- Patient Counseling Information
 1. Do not include 17.2 FDA Approved Patient Labeling as a subsection under the Patient Counseling Information section. See comment under Table of Contents.

We request that you resubmit labeling that addresses these issues by November 28, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies in patients less than five years of age for this application.

We also acknowledge receipt of your request for a deferral of pediatric studies with overactive bladder, five to less than 18 years of age, (b) (4)

Once we have reviewed your requests, we will notify you if your requests are denied and a pediatric drug development plan is required.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
11/09/2011

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, November 09, 2011 4:14 PM
To: 'Kannenberg, Judy'
Cc: Wilson, Melinee
Subject: RE: NDA 202611 mirabegron: Information Request- Stats

Hi Judy,

Your plan is acceptable.

Thanks so much,
nita

From: Kannenberg, Judy [mailto:Judy.Kannenberg@us.astellas.com]
Sent: Tuesday, November 08, 2011 5:24 PM
To: Crisostomo, Nenita
Cc: Wilson, Melinee
Subject: RE: NDA 202611 mirabegron: Information Request- Stats

Dear Nita,

In regards to the Biostatistician request for programming code, Astellas proposes for the 3 primary studies (178-CL-046, 178-CL-047, and 178-CL-074) to submit efficacy programs based on the primary analysis method (ANCOVA or stratified rank ANCOVA) performed on the primary efficacy dataset (FAS or FAS-I) for the coprimary and key secondary endpoints. In addition, Astellas proposes to submit the efficacy programs for the repeated measures analysis on the coprimary endpoints and the key secondary endpoint of mean volume voided per micturition. Does this proposal meet the intent of the request? Please let me know if you are in agreement with this approach.

Thank you,
Judy

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Thursday, November 03, 2011 5:03 PM
To: Kannenberg, Judy
Cc: Wilson, Melinee
Subject: NDA 202611 mirabegron: Information Request- Stats

Hi Judy,

Here is an Information Request from the Biostatistician:

Submit statistical analysis programming code of primary and key secondary efficacy endpoints for study 178-cl-046, 047, and 074.

Thank you so much,

6/8/2012

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*

6/8/2012

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, November 03, 2011 3:13 PM
To: 'Kannenberg, Judy'
Subject: NDA 202611 mirabegron: Information Request- Datasets

Hi Judy,

As we discussed in our earlier phone conversation, below is our request for resizing the datasets:

Regarding the extremely large datasets in your submission, we request that you resubmit all datasets, ensuring that for all datasets in your submission, you are only using the required columns length needed. Do not pad the lengths by a set limit, or arbitrarily set column lengths to a pre-defined limit (i.e. 200). Doing so will reduce your average dataset size by ~70%, on average. This reduction in submission sizes allows for faster submission through the gateway (for future submissions), and quicker access to the submission and data by the review team, allowing for timely reviews of your submission.

Also, please clarify the naming convention of your analysis datasets, as well as what is contained in the contents of each analysis datasets. Your naming convention used is not preferred. Numbering the datasets (e.g. ADAE1, ADAE2, etc.) implies that you have split the ADAE dataset and the numbering indicates the order for the different analysis datasets to be concatenated together. It appears from your define.xml file that the different numbered analysis datasets (i.e. ADAE1 and ADAE2) contain different analyses. Please re-name your analysis datasets to clearly reflect that dataset's description.

For technical information, please refer to the CDER Data Standards Common Issues Document (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Elect>) and the Study Data Specifications (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Elect>)

If you would like to see sample SAS code which re-sizes .xpt datasets to the actual length used, or if you have any other questions about re-sizing data files, please contact the CDER Electronic Data Team at: eData@fda.hhs.gov.

Please respond as soon as possible, and provide a timeline on how soon this process can be completed. Please feel free to contact me anytime.

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*

6/8/2012



NDA 202611

NDA ACKNOWLEDGMENT

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, M.B.A., R.A.C.
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

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

Date of Application: August 26, 2011

Date of Receipt: August 29, 2011

Our Reference Number: NDA 202611

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 28, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202611** submitted on August 26, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please call me at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

NENITA I CRISOSTOMO
09/06/2011



IND 069416

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg, MBA, RAC
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM178 (mirabegron).

We also refer to the June 15, 2011, face-to-face meeting between representatives from your firm and the FDA to orient the reviewers to the electronic submission of your NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Eufrecina DeGuia, Senior Regulatory Health Project Manager at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: June 15, 2011 @ 10:30AM – 12PM
Meeting Location: CDER WO Building 51, Room 1417

Application Number: IND 069416
Product Name: YM178 (mirabegron)
Indication: treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency

Sponsor/Applicant Name: Astellas Pharma

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Eufrecina DeGuia

FDA ATTENDEES

George Benson, M.D. – Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D. – Medical Team Leader, DRUP
Roger Wiederhorn, M.D. – Medical Officer, DRUP
Eric Andreasen, Ph.D. – Pharmacology and Toxicology Reviewer, DRUP
Eufrecina DeGuia – Senior Regulatory Health Project Manager, DRUP
Jia Guo, Ph.D. – Statistical Reviewer, Division of Biometrics II, Office of Biometrics
Roy Blay, Ph.D. – Associate Director, Division of Good Clinical Practices, Division of Scientific Investigations (DSI), Office of Compliance
Jeffry Florian, Ph.D. - Reviewer, Division of Pharmacometrics, Office of Clinical Pharmacology
Connie Robinson, RAC, PMP – Regulatory Information Specialist, Office of Business Informatics (OBI), Division of Regulatory Review Support (DRRS)
Dhananjay Chhatre - Operations Research Analyst, OBI, DRRS
Nita Crisostomo, RN - Senior Regulatory Health Project Manager, DRUP

Astellas Pharma Attendees

Karen Reeves, M.D. – Vice President, Global Medical Services
Nancy Martin, M.D., Pharm.D., FCP – Medical Director, Medical Services
Mary Beth Blauwet, DrPH - Associate Director, Biostatistics
Judy Kannenberg – Associate Director, Regulatory Affairs
Cathy Bezek – Clinical Programming Manager
Scott Cleve – Director, Regulatory Affairs
Melinee Wilson – Associate Director, Regulatory Affairs

1.0 BACKGROUND

YM178 (mirabegron), a selective human beta 3-adrenoreceptor (AR) agonist, is being developed for the treatment of patients with overactive bladder (OAB). Sponsor will seek approval of 50 mg dose once daily with the option for 25 mg daily for use in specific populations.

2. DISCUSSION

Preliminary draft responses were provided to the sponsor on June 10, 2011, in response to questions posed in the May 17, 2011, Briefing Package. The sponsor's questions from the meeting package are presented below (bolded text), followed by the Agency's responses presented in normal text. Additional discussion and comments made at the meeting are presented below in *italics*.

Question 1: Astellas intends to provide a review guide with the NDA to orient the reviewer to the electronic submission. The review guide will be included as a separate leaf document in Section 1.2 (Cover Letter).

Does the Agency concur with the use of a review guide and the proposed location of the guide?

Division Response: Yes.

There was no further discussion at the meeting.

Question 2: SDTM datasets which are greater than 4 GB in size will be split by parameter into multiple datasets for submission to allow WebSDM to run. SDTM datasets less than 4 GB in size will not be split for the NDA submission.

Does the Agency agree with this approach for SDTM datasets?

Division Response: Yes.

There was no further discussion at the meeting.

Question 3: At the Pre-NDA meeting, agreement was reached that ADaM datasets up to 12 GB could be submitted without splitting the datasets. The NDA submission will contain at least one ADaM dataset greater than 12 GB, estimated to be 20 GB. Astellas proposes to not split ADaM datasets which are greater than 12 GB.

Does the Agency agree with this approach for ADaM datasets?

Division Response: Yes.

There was no further discussion at the meeting.

Question 4: Astellas anticipates the mirabegron NDA submission will exceed 130 GB in size. It is estimated that the NDA content will be approximately 20 GB and the clinical datasets will be approximately 110 GB in total (SDTM datasets will be approximately 30 GB and the ADaM datasets will be approximately 80 GB).

Does the Agency recommend sending the submission to the Division via the Electronic Submissions Gateway? If it is recommended that Astellas provide the submission on a different (electronic) medium, what media are acceptable?

Division Response: No. We do not recommend that you send the submission via the gateway due to the size of the submission. Instead, you should send the submission on media and comply with Transmission Specifications. Due to the size of the submission, we recommend that it be submitted using DLT or LTO (35/70 or 40/80 DLT tapes using Windows 2000/2003 native backup or LTO 1, 2, 3, or 4 tapes using Windows 2000/2003 native backup). If the submission is submitted on multiple tapes, please provide loading instructions.

There was no further discussion at the meeting. Please refer to the Post-Meeting Addendum.

Question 5: Astellas intends to provide ECGs for the QT studies (Studies 178-CL-037 and 178-CL-077) which will be stored at the (b) (4). Which members of the FDA review team will need access to the (b) (4) to conduct the review?

Division Response: The DRUP Clinical reviewers (Drs. Wiederhorn and Hirsch) will need access to the (b) (4). We remind you that the Interdisciplinary Review Team for QT Studies (IRT-QT) will be formally consulted to assess the QT studies.

There was no further discussion at the meeting.

Question 6: Studies which include data to support nonclinical Absorption, Distribution, Metabolism and Excretion are typically written as one study report. Data from these study reports are included in the respective written summaries and tabulations in Module 2.6.4 and 2.6.5. Astellas proposes to include these reports in one location within Module 4 (e.g. Module 4.2.2.2) with HREF links as necessary to subsequent sections within Module 4 (e.g. Module 4.2.2.3 to 4.2.2.5).

Does the Agency agree with this approach?

Division Response: Yes. If a study is used to support multiple sections, we prefer that the study resides in one section only, and that the other sections include just a single page PDF containing a reference link to the study, the title of study, the location where the study resides, and all eCTD sections that the study supports.

Additional discussion at the meeting:

The Division requested that citations of study reports in the nonclinical sections should be referenced by the Astellas study number and not by the primary author.

Question 7: As previously discussed at the pre-NDA meeting, the Division of Scientific Investigations (DSI) has requested specific data be summarized for studies 178-CL-046, 178-CL-047, and 178-CL-074 and included in the NDA submission.

Does the Agency recommend this information be included as part of the study tagging

file (STF) for each individual study or submitted in aggregate in another location? What would be the recommended location?

Division response: We recommend that this information be included as part of the part of the study tagging file (STF) for each individual study, **and also** be referenced in Module 5.3.5.4 in additional STF files created specifically for Bioresearch Monitoring (BIMO) site level data (see below). In general, each study's information should be placed under that study, referenced in the appropriate study's STF and have the appropriate file tag.

Data submitted for DSI's review belongs in Module 5 of the eCTD. For items I and II in the chart below, a Study Tagging File (STF) must be constructed for each study that data are being submitted. The STF leaf titles for this data should be named "BIMO [study title]." For item III in the table below, an STF for site-level data across studies should be created and placed in Module 5.3.5.4, Other Study reports and related information. The leaf title for the site-level dataset should be "BIMO Site-level Data."

DSI Pre-NDA Request Item	STF File Tag	Used For	Allowable File Formats
I	data-tabulation-dataset	Tabular listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Line listings, by study	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

A. In addition, the data files should be organized into folders.

Files pertaining to items I and II above should be located in the study folders with which they are associated.

B. The item III site-level dataset should be placed in the M5 folder as follows:



C. We further recommend that a Reviewer's Guide in PDF format be included in Module 1, under heading 1.2 Cover Letters. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

Post Meeting Addendum: Since there were minor changes to the BIMO submission process since the Guidance Meeting on June 15, 2011, please see the attached BIMO Submission Instructions.

In order to select sites for inspection, we would request site-level data for all of the sites involved in the pivotal Phase 3 trials.

Question 8: As described at the pre-NDA meeting, Astellas intends to provide patient narratives in the NDA. As the safety data are reviewed and additional information is collected, narratives that exist in the clinical reports may be updated, as well as new narratives may be added to the NDA. To ensure clarity in the narrative process, and to provide a roadmap for the narratives, Astellas will provide a “Narrative Repository” located in Module 5.3.5.3 which will include a table of contents by study for all narratives in the submission as well as updated and new narratives. The repository will provide appropriate hyperlinks to narratives located within the individual study reports and/or within the repository to ensure ease of use. Safety summaries which reference an individual narrative will be linked directly to the repository.

Does the Agency concur with this approach for patient narratives?

Division Response: No. While we concur with a Narrative Repository in Section 5.3.5.3, it should contain only the roadmap (tabular listing of narratives). No actual narratives should be contained within Section 5.3.5.3. All narratives including updated narratives, enhanced narratives or new narratives should be provided under the study to which they belong. The patient narratives in each study should be provided in a single pdf with a linked TOC and bookmarks, and categorized by deaths, discontinuations due to adverse events, other serious events, and notable adverse events.

In order to facilitate our review, we ask that the roadmap in the Narrative Repository be organized in 4 discrete sections:

1. All narratives by Subject ID number.
2. All narratives by study.
3. All narratives by reason for narrative (deaths, serious adverse events, discontinuations and other notable adverse events).
4. All narratives by MedDRA System Organ System (SOC).

Additional discussion at the meeting:

The Sponsor stated their proposed approach to locate new and enhanced narratives from the safety evaluations with the associated topic-based Research Reports. The Division reiterated that all new and enhanced narratives should be included with the original CSR. All information regarding patients in a single study should be within the study tagging file for that study. Because the reviewers review each study report one at a time, having a complete narrative within each study is important. These are reviewed before the ISS and ISE.

The Division also stated that enhanced narratives should be displayed first or linked from the study report. The Division recognized that some of the AEs of interest may not have been prespecified in the CSRs. The Division asked that the study report should contain the most current narratives (enhanced and original).

Astellas agreed to provide the narratives (enhanced and original) in a single pdf file with the CSR for each given study.

Question 9: Astellas is aware of requests from the Agency for file types not supported by the ICH eCTD standard (e.g., PK modeling file types such as .ssc, .prn, .txt). In previous cases when files not supported by the ICH eCTD standard were requested, Astellas provided these files on a separate CD directly to the reviewing Division (via the Project Manager). A coordinated sequence submission to the eCTD was made referencing the non-eCTD provision of the requested files. Should a request for file types not supported by ICH eCTD standard be made, is the above-referenced approach acceptable or does the Agency have another preference for how these files are to be provided to the reviewer(s)?

Division Response: Submission of file types not supported by the ICH eCTD standard is not acceptable. All information for our review must be submitted in the allowable file types as listed in the ICH and FDA eCTD specifications for archiving purposes which includes .txt and .pdf (refer to the ICH and FDA specifications for allowable file types). PK and PK/PD modeling file types not supported by ICH eCTD standards should be converted to ASCII text files with *.txt extensions, when applicable, and provided in the eCTD submission.

There was no further discussion at the meeting.

Question 10: As previously discussed at the pre-NDA meeting, Astellas intends to include modeling reports in the eCTD submission. For the majority of the population PK and population PK/PD analyses the datasets, control streams and output listings for the major model building steps will be submitted. For analyses conducted early during the development of mirabegron, 178-PK-005 and 178-PK-009, subsequent analysis (178-PK-017) has superseded these results. Therefore, Astellas proposes not to submit the datasets, control streams and output listings for 178-PK-005 and 178-PK-009 due to the exploratory nature of these analyses. Astellas proposes that for population PK analysis conducted with the initial IR formulation (which will not be marketed) the final dataset, control stream and output listing will be submitted (178-PK-003 and 178-PK-004). Attachment 5 includes a proposed list of datasets, control streams and output listings for submission of the population PK and PK/PD analyses. Does the Agency concur with the proposed approach for submitting datasets, control streams and output listings?

Division Response: Yes. We agree with the proposed approach for submitting datasets, control streams and output listings, and with the planned exclusion of datasets, control streams and output listings for Studies 178-PK-005 and 178-PK-009. In addition, we have the following requests:

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model,

and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

- Initial estimates and covariance parameterizations for analyses performed in MONOLIX should be provided in ASCII format (*.txt) in addition to Matlab format (*.mat).

There was no further discussion at the meeting.

Additional Comments:

CMC:

From the CMC standpoint, Modules 2 and 3 are adequate. For Module 1, please provide information on "Section 1.12.5: Request for waiver", if it involves a request for a biowaiver. All other CMC-related portions of Module 1 are adequate. (*Note: In an email communication from Sponsor on June 13, 2011, it was clarified that the request for waiver is not related to CMC. The waiver indicated is for submission of CRFs. The phase 3 studies were conducted using Electronic Data Capture in lieu of paper CRFs. As allowed under 21 CFR 314.50(f), Astellas plans to request a waiver of the requirement to submit paper CRFs for these studies.*)

Additional Items discussed at the meeting:

- *Both split domains and whole domains datasets should be provided in the NDA submission.*
- *Further discussion ensued regarding the structure and size of the datasets. The sponsor indicated that the default width of 200 is not used but would review the datasets to determine if the size could be reduced.*
- *The use of define.pdf vs. define.xml files was discussed. The Division indicated that hyperlinks were not needed in the define.pdf file as it is only used for printing. Astellas noted that both bookmarks and hyperlinks are provided in the define.xml file.*
- *Regarding Study Tagging Files (STF), the Division noted that if the study report body tag is used more than once, the actual study report body should come first. The study title and the STF title should match.*

Post-Meeting Addendum:

On June 30, 2011, Marina Kalinina of the Office of Business Informatics, Division of Regulatory Review Support (OBI/DRRS) held a brief teleconference with Judy Kannenberg of Astellas to discuss the large size of the planned mirabegron NDA submission. The following resulted from the discussion:

1. *FDA is making an exception due to the size of submission and will accept submission on external drive.*
2. *Astellas can send an external test drive with smaller test submission that should contain variation of file types that future submissions will contain.*
3. *Astellas can send the planned submission on an external drive if test submission had succeeded. Otherwise they should submit on LTO or DLT as previously discussed.*

For technical question, Astellas was instructed to contact esub@fda.hhs.gov to the attention of Marina Kalinina.

Instructions for sending test drive are as follows:

- 1) Send the test submission to the same postal address that is used for sending tapes.*
- 2) Clearly indicate in the Cover Letter that a test submission is being provided.*
- 3) Send an email to esub@fda.hhs.gov notifying us that the submission is in transit.*

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that were identified requiring further discussion.

4.0 ACTION ITEMS

- Astellas Pharma plans to submit their NDA in August 2011.

5.0 ATTACHMENTS AND HANDOUTS – See attached BIMO Data Submission Instructions and the Astellas Slide Presentation

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of required data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

10 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

MARK S HIRSCH
07/20/2011



IND 069416

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Astellas Pharma Global Development, Inc.
Three Parkway North
Deerfield, Illinois 60015-2548

ATTENTION: Judy Kannenberg
Associate Director, Regulatory Affairs

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND), submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Mirabegron Tablets, 25 mg and 50 mg.

We also refer to your January 19, 2011, correspondence, received January 20, 2011, requesting reconsideration of your proposed proprietary name, (b) (4) and also your January 26, 2011, correspondence, received January 26, 2011, amending the original request for proprietary name review. We have completed our re-review of the proposed proprietary name, (b) (4) and continue to conclude that this name is unacceptable for the following reasons.

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Eufrecina Deguia, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
07/19/2011



IND 069416

MEETING MINUTES

Astellas Pharma
Attention: Judy Kannenberg
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM178 (mirabegron).

We also refer to the November 2, 2010, face-to-face meeting between representatives from your firm and the FDA to 1) discuss any unresolved issues, 2) identify studies that you will be relying on to support mirabegron's effectiveness and safety, 3) acquaint the Division with the information to be submitted, 4) discuss appropriate methods for statistical analysis of data and 5) seek agreement on the overall format, structure and content of your upcoming New Drug Application (NDA) submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Eufrecina DeGuia, Senior Regulatory Health Project Manager at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 2, 2010 @ 11AM – 12:30PM
Meeting Location: CDER WO Building 51, Room 1311

Application Number: IND 069416
Product Name: YM178 (mirabegron)
Indication: treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency

Sponsor/Applicant Name: Astellas Pharma

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Eufrecina DeGuia

FDA ATTENDEES

George Benson, M.D. – Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D. – Medical Team Leader, DRUP
Roger Wiederhorn, M.D. – Medical Officer, DRUP
Lynnda Reid, Ph.D. – Pharmacology and Toxicology Supervisor, DRUP
Eric Andreasen, Ph.D. – Pharmacology and Toxicology Reviewer, DRUP
Hyunjin Kim, Pharm.D. – Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCP3)
Donna Christner, Ph.D. – CMC Lead, Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment (ONDQA)
Eufrecina DeGuia – Senior Regulatory Health Project Manager, DRUP
Mahboob Sobhan, Ph.D. – Team Leader, Division of Biometrics II, Office of Biometrics
Jia Guo, Ph.D. – Statistical Reviewer, DB II, OB
Maria Walsh – Associate Director of Regulatory Affairs, Office of Drug Evaluation III
Roy Blay, Ph.D. – Reviewer, Division of Good Clinical Practices, Division of Scientific Investigations (DSI), Office of Compliance
Elisabeth Piault-Louis, Pharm.D., MA – Endpoint Qualification Fellow, Study Endpoint and Development (SEALD), Office of New Drugs (OND)
Jun Yan, Pharm.D. – Labeling Reviewer, SEALD, OND

Astellas Pharma Attendees

Nancy Martin, M.D., Pharm.D., FCP – Medical Director, Medical Services
Neha Sheth, Pharm.D. – Senior Director, Product Safety and Pharmacovigilance

Marcel Van Gelderen, Ph.D. – Director, Clinical Pharmacology
Marlowe Schneidkraut, Ph.D., DABT – Associate Director, Toxicology
Mary Beth Blauwet, DrPH - Associate Director, Biostatistics
Kenji Yasukawa, Ph.D., - Vice President, Head Global Therapeutic Area Urology
Bill Fitzsimmons, Pharm.D., MS. – Senior VP, US Development
Paul de Konig, M.D. , Ph.D. – VP, Head Global Clinical Pharmacology and Exploratory Development
Donald Raineri, Pharm.D. – Senior Director, Regulatory Affairs
Judy Kannenberg – Associate Director, Regulatory Affairs
Ton Kos, Ph.D. – Senior Director, Global Development Project Leader
Ahsan Arozullah, M.D., MPH, Medical Director, Product Safety & Pharmacovigilance
Eisuke Nozawa – Senior Director, Regulatory Affairs (Japan)

(b) (4)

1.0 BACKGROUND

YM178 (mirabegron), a selective human beta 3-adrenoreceptor (AR) agonist, is being developed for the treatment of patients with overactive bladder (OAB). It is the first of a new class of compounds with a different mechanism of action compared to the currently approved antimuscarinic drugs for OAB.

The clinical program for mirabegron includes 41 studies; a total of 26 phase 1 studies and 12 phase 2 and 3 studies (9 in OAB patients, one in patients with lower urinary tract symptoms and bladder outlet obstruction [LUTS/BOO] and 2 in patients with Type 2 diabetes). An additional phase 1 study to evaluate cardiovascular and pharmacokinetic interaction between mirabegron and tamsulosin is ongoing.

Sponsor will seek approval of 50 mg dose once daily with the option for 25 mg daily for use in specific populations.

2. DISCUSSION

Preliminary draft responses were provided to the sponsor on October 28, 2010, in response to questions posed in the October 1, 2010, Briefing Package. The sponsor's questions from the meeting package are presented below (bolded text), followed by the Division's responses presented in normal text as provided to the sponsor on October 28, 2010. Additional discussion and comments made at the meeting are presented below in *italics*.

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

Question 1: Nonclinical Development Program

Astellas believes that the results of the nonclinical studies conducted to date with mirabegron, as outlined in the briefing document [See Section 6.1], are adequate to support the submission of an NDA for mirabegron. Does the Agency concur?

Response: Requests for additional nonclinical investigation are not anticipated at this time. The

review of the nonclinical data is, however, still ongoing. The incidence of neoplasms observed in clinical study 178-CL-049 is a concern. Pending further evaluation of the clinical and nonclinical data, additional information may be needed to address the potential for tumor promotion.

The Sponsor had no further questions. They agreed with the above response.

Question 2: Nonclinical QT Characterization

The nonclinical in vitro data showed that neither mirabegron nor the five most abundant metabolites significantly altered the IKr (hERG), IKs (hKvLQT1/mink), Ito (hKv4.3/KChip2.2), INa (hNav1.5) and ICa (hCav1.2) conductance at clinically relevant concentrations. In addition, there was no indication that mirabegron or its metabolites altered action potential duration in guinea pig papillary muscle. Data from the dog ventricular wedge study indicate that mirabegron showed mild shortening of the QT interval, mild shortening of the action potential duration, but had no effect on ventricular wall transmural current dispersion. The major metabolites of mirabegron had no effect on any of these parameters in the dog ventricular wedge model. Furthermore, neither mirabegron nor its metabolites were arrhythmogenic (no ventricular tachycardia, premature ventricular contractions, or ectopic beats) in the concentration range tested. These nonclinical data have not identified a mechanism for QT interval prolongation. As such, it is concluded that orally administered mirabegron, at the maximum human recommended dose (MHRD), poses a low risk for ventricular arrhythmias. [See Section 6.1.3] Does the Agency find the preclinical mechanistic assessment of the proarrhythmic risk of mirabegron to be sufficient for NDA submission and review?

Response: Yes, at this time additional requests for nonclinical investigation of cardiac toxicity are not anticipated.

Additional Clinical Comment:

Despite the extensive nonclinical investigations that have been conducted, QT prolongation observed in women in the mirabegron 100 mg and 200 mg dose groups in the re-analysis of study 178-CL-037 is concerning. We acknowledge that you are conducting an additional TQT study (178-CL-077) and that results from this study will be submitted with the original NDA.

The Sponsor had no further questions. They agreed with the above response.

Question 3: Nonclinical Evaluation of Pregnancy on the Pharmacokinetics

At a Type C Meeting with the Agency in December, 2009, a safety concern was raised regarding the nonclinical toxicokinetic data from the rabbit embryo-fetal development study which suggested that the mean systemic exposures to mirabegron were higher in pregnant rabbits than those seen at steady state in non-pregnant rabbits. Astellas has conducted an assessment of the effect of pregnancy on the pharmacokinetics of mirabegron by comparing the systemic exposure in pregnant and non-pregnant rats. Data from these assessments are summarized in the briefing document [See Section 6.1.4]. In addition, an assessment of the species selectivity of the finding is being conducted by comparing the pharmacokinetics of mirabegron in non-pregnant and pregnant rabbits in a repeat study.

Does the Agency find this approach acceptable to evaluate the effect of pregnancy on the metabolism of mirabegron?

Response: Yes, however a justification of the relevance of the 100 mg/kg dose group in the ongoing toxicokinetic study in pregnant and non-pregnant rabbits should be provided in the study report since this dose was acutely toxic in previous studies.

Additional discussion at the meeting:

The Sponsor clarified that the ongoing toxicokinetic study in pregnant and non-pregnant rabbits was conducted at the same doses used in the embryo/fetal developmental toxicity study in rabbits (3, 10 and 30 mg/kg). They further clarified that a 100 mg/kg group was not investigated in the ongoing toxicokinetic study.

Additional Nonclinical Comment:

To avoid confusion, the NDA package should contain a brief discussion indicating what clinical and nonclinical data are most applicable for calculating multiples of human exposure. Due to the difference in clinical exposure between subpopulations, the clinical subpopulation with the greatest exposure (i.e., fasted older females) is recommended for dose multiple comparisons.

The Sponsor had no further questions. They agreed with the above response.

Clinical Pharmacology and Pharmacokinetics

Question 4: Clinical Pharmacology

Astellas believes that the clinical pharmacology program conducted to date, as outlined in the briefing document [See Section 6.2.2], is sufficient for labeling purposes and adequate to support the submission of an NDA for mirabegron. Does the Agency concur?

Response: Overall, the clinical pharmacology studies conducted to date appear to be adequate for labeling purposes and NDA submission. In addition, please provide the following information:

- The exposure comparison of the OCAS-M formulation with QD dosing and the IR formulation with QD dosing. Some of the clinical pharmacology studies were conducted with the IR formulation, although the to-be -marketed formulation is the OCAS-M formulation. In order to draw meaningful interpretation from those clinical pharmacology studies, you need to provide the exposure comparison of two formulations.
- A table describing the doses, formulations, and release rates of the formulation used in all the clinical and clinical pharmacology studies.

The Sponsor confirmed that exposure comparisons of QD dosing with the OCAS-M formulation versus the IR formulation will be provided in the NDA.

Question 5: Effect of Food

The effect of food on the pharmacokinetics of mirabegron has been evaluated in volunteers. Studies 178-CL-041 and 178-CL-078 evaluated the effect of high and low fat breakfasts on the pharmacokinetics of single doses of mirabegron 50 and 100 mg in male and female

Western volunteers and Japanese trial volunteers, respectively. Overall, the food effect observed with mirabegron was independent of the dose tested (50 or 100 mg) and the population in which it was studied (Western versus Japanese volunteers), as similar reductions were observed for C_{max} and AUC_{inf} in the fed state compared with the fasted state. In addition, a greater reduction in C_{max} and AUC_{inf} was observed in the low fat meal condition compared with the high fat meal condition. The phase 3 studies conducted in the US and Europe did not include restrictions relative to food intake; efficacy and safety of the regimen. Therefore, Astellas is proposing that mirabegron be administered with or without food at the recommended doses. [See Section 6.2.2.5] A food effect research report will be included in the mirabegron NDA and will present a comprehensive evaluation of the findings that have been observed with the administration of mirabegron in the fasted and fed states. The research report will include summaries of effect of food on mirabegron in clinical pharmacology studies as well as an analysis of the effect of food in relationship to efficacy and safety parameters in the completed phase 3 12-week studies conducted in Europe and North America. Does the Agency have any comments on this proposal?

Response: The effect of food on mirabegron administration will be addressed during the NDA review cycle. Without reviewing data, we can not concur with your proposal for mirabegron to be administered with or without food.

The Sponsor had no further questions. They agreed with the above response.

Additional Clinical Comment:

Due to the notable effect of food on exposure, we request an analysis of safety and efficacy by fed versus fasted states in Studies 046, 047, and 074. These analyses should be included in the food effect research report as well as in the ISS/ISE.

The Sponsor confirmed that analysis of safety and efficacy by fed vs. fasted states in Studies 046, 047 and 074 is already being conducted. Food intake is recorded in the patient diary (+ or – 30 minutes within consumption).

Clinical Development

Question 6: Recommended Dosing

In the primary phase 3 studies conducted in the US and Europe, 178-CL-046, 178-CL-047, and 178-CL-074, the primary efficacy analyses showed a statistically significant reduction from baseline to final visit in mean number of incontinence episodes per 24 hour and mean number of micturitions per 24 hour in patients who received mirabegron 25 mg, 50 mg and 100 mg once daily compared with placebo. A clear incremental efficacy benefit for mirabegron 100 mg was not demonstrated compared to mirabegron 50 mg. Although the efficacy of mirabegron 25 mg was similar to that of mirabegron 50 mg for the co-primary endpoints, mirabegron 25 mg appears to be less effective than mirabegron 50 mg based on key secondary endpoints. These data suggest that mirabegron 25 mg, while efficacious, does not represent the maximally effective dose. Based upon the efficacy demonstrated in the phase 3 study and the evaluation of mirabegron exposure in the special population studies 178-CL-038 [renal impairment study, See Section 6.2.2.3.1] and 178-CL-039

[hepatic impairment study, See Section 6.2.2.3.2], mirabegron 25 mg once daily would provide benefit to patients with severe renal impairment (CLCR 15 to 29 mL/min or eGFR 15 to 29 mL/min per 1.73 m²) or moderate hepatic impairment (Child-Pugh Class B). Additionally, in supportive phase 3 study 178-CL-048 conducted in Japan, the primary efficacy analysis showed statistically significant reduction from baseline to final visit in mean number of micturitions per 24 hr in patients who received mirabegron 50 mg once daily compared with placebo. The global phase 3 studies unequivocally demonstrate the efficacy of mirabegron 50 mg once daily on the co-primary endpoint of mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. Therefore, Astellas is proposing the recommended therapeutic dose of mirabegron as 50 mg once daily, with the option for mirabegron 25 mg once daily for use in special populations as described above. Does the Agency concur that the data from the phase 3 studies identified above are sufficient to support submission and review of an NDA for mirabegron?

Response: Yes, we agree that the data from the primary phase 3 studies 178-CL-046, 178-CL-047, and 178-CL-074 are sufficient to support submission and review of an NDA for mirabegron.

The Sponsor had no further questions. They agreed with the above response.

Does the Agency concur with the rationale for the recommended therapeutic dose of 50 mg for mirabegron and the option for mirabegron 25 mg for use in special populations?

Response: Yes, overall we concur with the rationale for the recommended dose of 50 mg for mirabegron and the option for mirabegron 25 mg for use in special populations. However, we remind you that the effect of hepatic or renal impairment on the exposure to mirabegron is a review issue that will be addressed during the NDA review cycle.

The Sponsor understood and agreed with the above response. There were no further questions.

Question 7: Patient Exposure

In the mirabegron phase 2 and 3 clinical development program, approximately 5800 patients have been exposed to mirabegron treatment, including approximately 1500 patients exposed to mirabegron for 6 months and approximately 600 patients exposed for 12 months. The briefing document describes mirabegron exposure by dose [See Section 6.2.3]. These data will form the basis of the mirabegron safety assessment for the NDA. Astellas believes that the data package completed to date represents adequate exposure for the proposed NDA. Does the Agency agree?

Response: Yes, we agree that the data package completed to date represents adequate exposure for submission of the proposed NDA.

The Sponsor had no further questions.

Question 8: Integrated Summary of Efficacy

Astellas plans to integrate data across studies for the integrated summary of efficacy (ISE). The briefing document summarizes the studies to be integrated for efficacy [See Section 6.2.4.6]. A formal ISE will be provided in Module 5, Section 5.3.5.3, of the NDA. The statistical analysis plan (SAP) for the ISE and the proposed table of contents for the ISE document is provided in Attachment 5. Does the agency agree with the approach for the planned analyses for efficacy?

Response: Yes, we agree with the approach for the planned analyses for efficacy. We have two additional comments regarding the planned analyses:

1. Further discussion is needed regarding the secondary efficacy variables #6 (mean level of urgency) and #8 (mean number of urgency episodes Grade 3 or 4), which are derived from the Patient Perception of Intensity of Urgency Scale (PPIUS). In order to support claims from these two endpoints 1) the PPIUS would need to be shown to be well-defined and reliable and 2) mirabegron would need to demonstrate clinically and statistically significant results over placebo. Refer to our response to Question 13 regarding the PPIUS itself.
2. In light of the increased mirabegron exposure in females compared to males, the analyses in the ISE should include a discussion of efficacy results by gender.

Does the Agency consider these analyses to be adequate to support review of the NDA?

Response: Yes, we consider these analyses adequate to support review of the NDA.

The Sponsor had no further questions. They understood and agreed with the above response.

Question 9: Integrated Summary of Safety

A formal integrated summary of safety (ISS) will be provided in Module 5, Section 5.3.5.3., of the NDA. The SAP for the ISS and associated Research Reports and the proposed table of contents for the ISS document is provided in Attachment 6. As described in Section 6.2.5.3.1, the overall safety evaluation will be based on the following six safety populations:

- **Global Phase 2 and 3:** This population will combine data from all patients who received at least 1 dose of mirabegron in any of the 12 phase 2 and 3 studies conducted globally in Europe, Australia/New Zealand, South Africa, North America, and Japan. This population includes patients who have received IR or OCAS formulations of mirabegron and patients with OAB, LUTS/BOO, or type 2 diabetes mellitus.
- **Global OAB 12-week Phase 2 and 3:** This population will combine data from 6 12-week, double-blind, placebo-controlled, phase 2 and 3 studies conducted globally in Europe, Australia, North America, and Japan in patients with OAB. Three of the 6 studies also include an active comparator group (tolterodine ER 4 mg).
- **EU/NA OAB 12-week Phase 3:** This population is a subset of the Global OAB 12-week Phase 2 and 3 population and will pool data from 3 12-week, double-blind, placebo-controlled, phase 3 studies conducted in Europe, Australia and North America in patients with OAB. One of the 3 studies also includes an active comparator group (tolterodine ER

4 mg). This subset will be assessed where data for a particular event of interest was collected more rigorously than in the entire set of 12 week OAB studies including ECG analyses, vital sign analyses and analysis of TEAEs which were specifically defined per protocol, such as hypertension.

- **EU/NA Long-term Controlled:** This population consists only 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, Australia/New Zealand, South Africa, Canada and the United States.
- **Japan Long-term Uncontrolled:** This population consists only of Study 178-CL-051, a 12 month open-label phase 3 dose escalation study with a starting dose of 50 mg mirabegron and potential increase to mirabegron 100 mg conducted in Japan.
- **Global Phase 1:** This population includes data pooled from 26 phase 1 studies conducted globally in Europe, US and Japan. Studies 178-CL-080, 178-CL-077 and 178-CL-081 will not be pooled with these phase 1 studies but will be discussed as individual studies.

Does the Agency agree with the approach and populations for the planned analyses for safety?

Response: Yes, we agree with the approach and populations for the planned analyses for safety. Please refer to our response to Question 10 for additional comments regarding the planned analyses for safety.

Does the Agency consider these analyses to be adequate to support review of the NDA?

Response: Yes, we consider these analyses to be adequate to support review of the NDA.

The Sponsor had no further questions. They accepted the above responses.

Question 10: Adverse Events of Interest

Described within the ISS SAP are several adverse events of interest which will be systematically reviewed [See Attachment 6]. The AEs of interest categories for the program wide evaluation were generated based on the following criteria 1) potential or theoretical risk based on the pharmacology of the drug 2) observed finding in the preclinical or clinical data to date or 3) feedback from health authorities recommending surveillance for specific events. The adverse events of interest for mirabegron are as follows:

- **Cardiovascular events including hypertension, QT prolongation or its sequelae, cardiac arrhythmias, and cardiac failure;**
- **Urinary tract events, including urinary retention/acute urinary retention, urinary tract infection, and urolithiasis;**
- **Hypersensitivity reactions;**
- **Syncope, postural hypotension and falls;**
- **Seizures;**
- **Hepatotoxicity;**
- **Endocrine/metabolic events;**
- **Glaucoma; and**

- **Neoplasms**

Does the Agency agree with the approach to identify and characterize the adverse events of interest?

Response: Yes, we agree with the approach to identify and characterize the adverse events of interest. We have the following additional comments regarding the adverse events of interest:

1. Each of the identified adverse events of interest will be treated as a clinical review issue.
2. We note an approximate mean increase in systolic BP of 0.5-2 mmHg in mirabegron-treated patients compared to placebo, and an increased incidence of hypertension reported as an adverse event. The Hypertension section of Appendix 8 in the ISS should contain information regarding the clinical relevance of these findings.

The Sponsor stated that the mean increase in blood pressure for mirabegron is up to 1.5 mmHg in placebo-controlled studies. The Division asked the Sponsor to address the clinical relevance of this increase in terms of major adverse cardiac events (e.g., stroke, MI).

3. We acknowledge that a vision study (178-CL-081) is being conducted to assess the potential for mirabegron to raise intraocular pressure, and that the results of this study will be submitted in the original NDA.

Dr. Chambers stated that the protocol seems acceptable. There are some issues regarding analysis that need to be addressed. Comments regarding the protocol will be conveyed in a formal regulatory letter.

4. The Neoplasm section of Appendix 8 in the ISS should contain justification that the observed difference between treatment groups in rates of reported neoplasm adverse events (combined) should not be viewed by the Division as a safety concern. Please also address the following:
 - a. The appropriateness of pooling different neoplasms in conducting analyses of reported rates.
 - b. Tobacco use history in the patients with reported neoplasm adverse events versus the general study population.

Sponsor stated that history of tobacco use was not captured systematically in the clinical studies. There was no check box in the CRFs. Sponsor will nonetheless attempt to determine the tobacco use status in patients with reported neoplasms.

- c. Compliance with taking study medication in patients with reported neoplasm adverse events versus the general study population.
- d. Mammograms in the patients with reported neoplasm adverse events.

The Sponsor will make efforts to determine mammography results in the three patients diagnosed with breast cancer.

- e. Potential for ascertainment bias (including method of case elicitation) in reported neoplasm adverse events.

You might also consider:

- a. Analyzing the existing subject biological samples for tumor markers.

Although it is not a requirement, the Sponsor was encouraged to consider the idea of analyzing existing serum samples for selected biomarkers (e.g, PSA, CEA, etc) retrospectively in patients who developed neoplasms as well as in all subjects in the protocol to ascertain the possible presence of tumors at study entry and their response to mirabegron.

- b. Analyzing the reported adverse events for the presence of paraneoplastic syndrome signs or symptoms.

DRUP suggested that Sponsor could evaluate the data for the presence of paraneoplastic syndrome signs and symptoms as another way of ascertaining the presence of potential malignancy in patients in Study 178-CL-049.

If the neoplasm concern cannot be resolved using the currently available data, then longer term follow-up of all patients who completed the one year safety protocol would probably be necessary and appropriate.

The sponsor stated that the above comment was clear.

Question 11: Datasets

Astellas intends to submit the integrated summary datasets used to generate the integrated summaries of safety and efficacy. An appropriate data definition file will be provided for the integrated datasets.

In addition, individual study datasets will be provided in SDTM format for key pharmacokinetic studies and phase 2 and phase 3 clinical studies supporting the mirabegron NDA for the indication of OAB. SDTM datasets will not be provided for the phase 2 studies conducted in patients with type 2 diabetes mellitus. Analysis (ADaM) datasets will be provided for the primary phase 3 studies (178-CL-046, 178-CL-047 and 178-CL-074) and the long-term safety study conducted in North America and Europe (178-CL-049). The briefing document summarizes the datasets to be provided in the NDA submission [Section 6.3.1 and Attachment 9.1]. Annotated eCRFs will be provided for the SDTM datasets, and data definition files will be provided for all datasets.

Does the Agency agree with the proposed approach for submission of datasets in the mirabegron NDA?

Response: Yes, we agree with the approach, but you also need to provide AdAM datasets for ISS and ISE.

The Sponsor had no further questions. They agreed to provide ADaM datasets for ISS and ISE.

Question 12: Patient Narratives

In the mirabegron NDA, Astellas plans to provide patient narratives for patients who experienced the following adverse events during the clinical development program:

- All deaths
- All serious adverse events (SAEs)
- All adverse events that lead to study discontinuation
- Key TEAEs of interest for patients in the phase 3 studies conducted in Europe and North America (Studies 178-CL-046, 178-CL-047, 178-CL-074 and 178-CL-049) [See Section 6.3.2].

Is the Agency in agreement with the patient narrative plan for mirabegron?

Response: Yes.

The Sponsor had no further comments.

Question 13: Patient Perception of Intensity of Urgency Scale Questionnaire

As part of the Agency's comments during the Special Protocol Assessment of the phase 3 pivotal trials, and also at the End-of-Phase 2 meeting, the Agency commented that the Patient Perception of Intensity of Urgency Scale (PPIUS) may be used for inclusion criteria but not for claims of treatment benefit as a secondary endpoint. Additionally, the Agency further commented that for patient reported secondary endpoints, supporting materials would need to be submitted to demonstrate instrument validity and the statistical analysis plan would need to account for these endpoints. The PPIUS is a patient reported 5-level response instrument developed to measure the degree of urgency at each micturition or incontinence episode. Included in the briefing document is a Patient Reported Outcome (PRO) evidence document which contains the following elements: the rationale for including the PPIUS as a measure of urgency severity in Astellas' phase 3 studies in patients with OAB, the conceptual framework of the PPIUS, an endpoint model summarizing all endpoints included in the phase 3 studies, the development and content validity of the PPIUS, and the psychometric characteristics of the PPIUS [See Attachment 7]. In addition, the statistical analysis plan for study 178-CL-074 has been provided which specifies the urgency endpoints as key secondary endpoints included in the hierarchical testing procedure for multiplicity adjustment. Are the PRO evidence documents provided sufficient to support review of the PPIUS validation in the NDA?

Response: Yes, the PRO evidence documents are sufficient to support *review* of the PPIUS validation in the NDA. However, we have concerns regarding the content validity of the instrument and its ability to support labeling claims.

- Open-ended patient interviews, i.e., concept elicitation focus groups or individual interviews, for concept identification were not conducted as part of the development of

the PPIUS. No empirical evidence was provided that patients spontaneously refer to "urgency" as a symptom of OAB or use this terminology to describe "a complaint of a sudden compelling desire to pass urine which is difficult to defer".¹ The definition of urgency used in the PPIUS appears to have been derived solely from literature review and expert opinion. Cognitive debriefing interviews were conducted in a small number of subjects to assess comprehension and understanding of the PPIUS but not to elicit or identify concepts in OAB. The lack of appropriate qualitative research to define the important aspects of OAB in patients poses a review issue for the PPIUS.

- Input from OAB patients during the cognitive debriefing interviews serves to highlight issues with the content validity of the PPIUS. Two patients expressed difficulties understanding the definitions of "urge incontinence" and "incontinence" (e.g., issue with the term "involuntary") or the definitions of each grade of urgency severity in the PPIUS. Furthermore, some patients indicated that they did not know how to rate the severity of their urgency, as this was rapidly evolving before a micturition.
- On its face, the PPIUS measures two different concepts: "urinary urgency" and "urge incontinence." No evidence was provided demonstrating that these two concepts are part of a continuum. In fact, at least one patient in the cognitive debriefing interviews indicated that "urinary leakage" could occur prior to reaching severe urgency.
- The participants in the cognitive debriefing interviews may not be representative of the clinical trial population due to an over representation of patients older than 50 years of age (mean age was 61.6 [SD=13.5, range 37.0—75.0 years]) and of female gender (n = 11, 91.7%). In addition, the proportion of patients with dry versus wet OAB and patients with other lower urinary tract symptoms should be provided to adequately characterize the population (e.g., Is "urge incontinence" relevant for "dry" OAB patients?).
- In addition, we have concerns that the term "urgency" and its definition in the PPIUS may have been introduced to subjects in the cognitive debriefing interviews and in the clinical studies.

The Sponsor acknowledged that the above comments are clear and they had no further questions.

NDA Structure and Format

Question 14: Pregnancy and Lactation Labeling

Astellas intends to format the Pregnancy section of the mirabegron label as per the proposed rule for Pregnancy and Lactation Labeling issued by the FDA in 2008. In this regard, the pregnancy labeling section will be formatted with separate Pregnancy and Lactation sections, with no pregnancy category provided in the label text. A proposed draft package insert for mirabegron is provided in Attachment 1. Does the Agency agree that the mirabegron label should be formatted according to the new proposed rule for Pregnancy labeling?

Response: No. Until the new Pregnancy and Lactation Labeling Rule becomes final, Pregnancy Categories must be used. The label should be formatted according to the Physicians Labeling Rule with all pregnancy data under section 8.1 and lactation under 8.3.

The Sponsor acknowledged that the comment is clear and had no further questions.

Question 15: Electronic Case Report Forms

As presented in Section 6.3.1.5 of the briefing document, Astellas plans to submit electronic case report tabulations for the individual studies, in accordance with the specifications provided in the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model and Implementation Guide. Does the Agency agree with this approach?

Response: Yes, we agree.

The Sponsor had no further questions.

Question 16: Electronic Common Technical Document Format

Astellas intends to provide a sample electronic common technical document (eCTD) submission from the mirabegron NDA for testing to CDER's regulatory review support staff in the Office of Business Process Support before submission of the mirabegron NDA. An eSubmission meeting may be requested to discuss the sample eCTD, if needed. Does the Agency have any additional recommendations with respect to ensuring successful filing of an eCTD-formatted NDA for mirabegron?

Response: In addition to what you have proposed, please also submit the following datasets to support the clinical pharmacology and pharmacometrics analysis:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- If applicable, a model development decision tree and/or table which gives an overview of modeling steps.
- Specify the food intake status of the study subjects included in the modeling.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot

should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

The Sponsor had no further questions. The comments are clear.

Additional Division of Scientific Investigation (DSI) Comment

In order to assist the Division and DSI with selecting clinical trial investigative sites for inspection, we request that the original NDA contain the specific information shown in the 2 attachments.

Dr. Blay explained that DSI is currently developing risk-based tools for site selection. He stated that the information requested is for those clinical study sites used in the pivotal efficacy studies.

Additional Comment from Study Endpoint and Labeling Development (SEALD):

The Sponsor was reminded to comply with regulatory requirement for the content and format of the PI in the NDA submission. Below is the website for New Content and Format Requirements for Prescription Information (PI):

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that were identified requiring further discussion.

4.0 ACTION ITEMS

Astellas Pharma plans to submit their NDA by 3rd Quarter 2011.

5.0 ATTACHMENTS AND HANDOUTS - None

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

/s/

MARK S HIRSCH
12/02/2010



IND 069416

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Astellas Pharma Global Development, Inc.
Three Parkway North
Deerfield, IL 60015-2548

ATTENTION: Judy Kannenberg
Associate Director, Regulatory Affairs

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND), submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Mirabegron Tablets, 25 mg, 50 mg, and 100 mg.

We also refer to your February 15, 2010, correspondence, received February 16, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated February 15, 2010. In order to initiate the review of the alternate proprietary name, (b) (4), submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Meredith Alpert, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-69416

ORIG-1

ASTELLAS
PHARMA GLOBAL
DEVELOPMENT
INC

YM178

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

/s/

CAROL A HOLQUIST
08/12/2010



IND 69,416

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Judy Kannenberg
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM178 (mirabegron).

We also refer to the Type B meeting between representatives of your firm and the FDA on March 1, 2010. The purpose of the meeting was to discuss a proposed Chemistry, Manufacturing, and Controls (CMC) data package to support a New Drug Application (NDA).

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Astellas Pharma Global Development, Inc.
Application Number:	IND 69,416
Product Name:	Mirabegron (YM178)
Meeting Requestor:	Judy Kannenberg, RAC Associate Director, Regulatory Affairs
Meeting Type:	Type B Pre-NDA Teleconference
Meeting Category:	Chemistry, Manufacturing and Controls (CMC)
Meeting Date and Time:	Monday, March 1, 2010, 11:00 AM – 12:00 PM EST
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	February 4, 2010
Meeting Chair:	Donna Christner, Ph.D.
Meeting Recorder:	Jeannie David, M.S.

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Pharmaceutical Science/Office of New Drug Quality Assessment (ONDQA)

Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader
Rao Puttagunta, Ph.D.	Review Chemist
Donna Christner, Ph.D.	Pharmaceutical Assessment Lead
Jeannie David, M.S.	Regulatory Health Project Manager

Division of Reproductive and Urologic Products (DRUP)

Eric Andreasen, Ph.D.	Pharmacology/Toxicology Reviewer
Roger Wiederhorn, M.D.	Clinical Division Team Leader

EXTERNAL PARTICIPANTS:ASTELLAS PHARMA GLOBAL DEVELOPMENT, INC.

John DeMay	Senior Director, Pharmaceutical Technical Mgmt
Reena Patil, Ph.D.	Assistant Director, Pharmaceutical Technical Mgmt
Marlowe Schneidkraut, Ph.D., DABT	Associate Director, Toxicology
Thomas Davey	Senior Manager, Regulatory Affairs
Donald Raineri, Pharm.D.	Senior Director, Regulatory Affairs
Judy Kannenberg, RAC	Associate Director, Regulatory Affairs
Allam Fakhoury, Pharm.D.	Associate Director, Project Management
Ton Kos, Ph.D.	Senior Director, Global Dvt Project Leader
Marcel Van Gelderen, Ph.D.	Director, Clinical Pharmacology

BACKGROUND

Astellas Pharma Global Development, Inc. (Astellas) requested a Type B Pre-NDA Chemistry, Manufacturing, and Controls (CMC) meeting, letter dated January 15, 2010, to discuss pre-NDA CMC topics related to mirabegron (YM178) for intended for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency (IND 69,416). It is anticipated that Astellas will submit an NDA in late 2010 or early 2011. An End of Phase 2 meeting between Astellas and the FDA was held on November 14, 2007 (FDA Meeting Minutes dated December 11, 2007), in which the Agency raised concerns about the acceptability of the proposed drug substance starting materials and the proposed drug product dissolution method.

The FDA's preliminary responses to Astellas Pharma Global Development, Inc.'s questions in the CMC briefing package received February 4, 2010, and official minutes captured during the teleconference on March 1, 2010, are provided below.

Sponsor Questions and FDA Response:**Question 1:**

At the End of Phase 2 meeting in November 2007, Astellas proposed (b) (4) as the starting materials for mirabegron (YM178). The Division commented at the meeting and in the official FDA meeting minutes that the submitted information for (b) (4) was not adequate to support its designation as a starting material for mirabegron.

The Division agreed with the designation of (b) (4) as a starting material, but provided recommendations for the submission of adequate controls and manufacturing information for (b) (4) in an IND amendment or in the NDA.

Astellas proposes to incorporate adequate controls on the materials used to prepare (b) (4) to ensure consistent quality and safety. Full GMP controls for mirabegron will begin with the starting materials, (b) (4). A full description

of (b) (4) and the proposed acceptance criteria for (b) (4) and an analysis of the formation and fate of impurities arising from the (b) (4) are provided in the briefing document in section 2.3.S.2.3.

A) Does the Division agree that (b) (4) can be considered as a starting material for the GMP synthesis of mirabegron?

FDA Response:

Your proposal to consider (b) (4) as a starting material is reasonable based on the submitted supporting information. We recommend that you include the complete CMC information on the proposed starting materials (b) (4) in the NDA or in a DMF with the appropriate Letter of Authorization.

If there is any change in the manufacturing process for the proposed starting materials or a new manufacturer is introduced after the NDA is approved, you should notify the FDA via a supplement rather than an annual report.

Any related substance in the 'starting materials' exceeding the identification threshold should be included as a specified impurity in the drug substance specification.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

B) Does the Division agree that the proposed acceptance criteria in section 2.3.S.2.3.1 and the impurity information in section 2.3.S.3.2.3 for (b) (4) provide adequate control of their quality for use in the (b) (4) of mirabegron?

FDA Response:

We agree.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

C) Does the Division have any comments related to the proposed acceptance criteria in section 2.3.S.2.3.2 for the following materials:

(b) (4)

(b) (4)

(b) (4)

FDA Response:

The proposed acceptance criteria seem acceptable at this time.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

D) Does the Division have any other comments related to the information provided in support of the designation of [REDACTED] (b) (4) as starting materials?

FDA Response:

We have no further comments at this time.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

Question 2:

The mirabegron drug substance produced by the current process exhibits a consistent particle size with a cumulative [REDACTED] (b) (4) diameter of approximately [REDACTED] (b) (4).

In the OCAS formulation, the drug release rate is governed by [REDACTED] (b) (4)
[REDACTED]

To evaluate the potential impact of changes in the drug substance particle size, drug substance batches with cumulative [REDACTED] (b) (4) particle diameters ranging from [REDACTED] (b) (4) were prepared and used to manufacture drug product. The dissolution profiles from these drug product batches were similar, with differences of 5% or less at each time point.

The modifications to the drug substance [REDACTED] (b) (4)
[REDACTED] batches were significantly outside of the normal operating parameters. To obtain drug substance [REDACTED] (b) (4)
[REDACTED].

Details on the modifications [REDACTED] (b) (4) and the dissolution data from the different particle size batches are provided in section 2.3.S.4.5.

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

[REDACTED]

FDA Response:

The evaluation of the impact that particle size may have on the dissolution rate of the drug product was conducted using (b) (4), which is extremely high and may have limited discriminating power. Therefore, we have concerns regarding the validity of the results from this study, which showed lack of influence of the particle size on the dissolution profile of the tested batches. Overall, we consider that the dissolution testing with a (b) (4) is not acceptable and we suggest that you repeat the dissolution testing using your proposed USP Apparatus 1 (basket – (b) (4)), but with a speed of 100 rpm. (b) (4)

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

Question 3:

During the End of Phase 2 meeting, the mirabegron dissolution conditions which use (b) (4) were discussed. (b) (4) is outside of the range allowed by the USP in Section <1092>. The Division did not agree that the data provided supported the use of the proposed conditions. The Division recommended that Astellas investigate either the use of different mesh sizes for the USP apparatus 1 (basket) method or the use of (b) (4). The Division indicated that additional data with supporting justification would be needed to determine if the (b) (4) method could be acceptable.

Astellas has evaluated the USP apparatus 1 method as recommended by the Division and has determined that both the (b) (4) and the basket method, using a (b) (4) mesh size basket at (b) (4), produce acceptable dissolution results for mirabegron OCAS tablets. Data comparing the (b) (4) and basket methods are presented in Section 2.3.P.5.6

Does the Division agree that the USP apparatus 1 basket method is acceptable for determining the dissolution profile of mirabegron OCAS tablets?

FDA Response:

Yes, we agree that USP Apparatus 1 (basket – (b) (4) mesh size) is acceptable for evaluating the dissolution profile of your product. However, the provided dissolution data showed that 100 rpm will be a more appropriate speed for the evaluation of your product. Therefore, we recommend that you use 100 rpm as the speed of rotation for any further dissolution testing of your product. Also, we recommend that you collect complete dissolution profile data (i.e., 2, 4, 6, 8, and 10 hours).

Additionally, your proposed acceptance criteria for the dissolution test (pages 26-27 of 54) are not acceptable. We recommend that you collect complete dissolution profile data using the new test (100 rpm) from clinical and stability batches and these data be used for the setting of the specification-sampling time points and specification-ranges.

Meeting Discussion:

Astellas requested clarification on the FDA’s recommendation to use 100 rpm as the paddle speed of rotation for dissolution testing. The FDA responded that upon re-analysis of the data from testing at paddle speeds of 100, (b) (4) showed little difference between (b) (4) in dissolution profiles for unacceptable batches, while a clear difference was apparent with 100 rpm paddle speed. The FDA concluded therefore that paddle speeds of either (b) (4) would not be able to differentiate unacceptable batches, and that 100 rpm would be appropriate.

Astellas inquired that they have proposed 2 dissolution testing methods with a 100 rpm paddle speed: (b) (4), the other using a 40 mesh size basket, and asked the Agency if the 100 rpm paddle speed with 40 mesh size basket would be acceptable (Figure 4, p. 105 of the briefing package). The FDA indicated that the 40 mesh size basket may be acceptable, but requested additional time to evaluate this information (i.e., dissolution data generated using USP Apparatus 1 (basket), 40 mesh screen and (b) (4) screen at 100 rpm paddle speed). Please note, FDA Post-Meeting Comment below.

With respect to the 5-timepoint sampling requested for the dissolution profile data, Astellas asked the Agency if the type of data provided on p. 105 of the briefing package was adequate. The FDA replied that the timepoints were unusual, with respect to fractions, but generally acceptable.

Astellas agreed to submit the requested evaluation and justification for acceptance criteria, and asked if it would be acceptable to provide only 3-timepoint sampling for release (early, mid, late). The FDA recommended that 5-timepoint sampling would be to build a complete dissolution profile prior to selection of the specification-sampling timepoints and specification-ranges. However, the specification itself can be based on only 3 timepoints.

Question 4:

In the OCAS formulation, the drug release rate is governed (b) (4)

(b) (4)

(b) (4)

(b) (4)
(b) (4). Astellas proposes to monitor the dissolution rate during release and stability, (b) (4).

Does the Division agree that monitoring the dissolution rate directly on stability is sufficient and that a shelf life acceptance criterion for (b) (4) is not needed for mirabegron OCAS tablets?

FDA Response:

At this time, since part of your justification is based on dissolution results collected at too high a speed, it is premature to delete the test for (b) (4). Request deletion of (b) (4) testing in the NDA with full justification and the data, including updated dissolution testing, to support the request.

Meeting Discussion:

Astellas asked if providing the updated dissolution testing discussed in Question 3. would be sufficient for deletion of the shelf life acceptance criterion for (b) (4). The FDA stated that this would be a review issue.

The FDA re-iterated that future specifications should be based on complete dissolution profile data from clinical and stability batches. Astellas agreed to collect data from clinical and stability batches, and will provide what they can for 5-point dissolution profile data. The FDA advised Astellas to clearly describe the data made available in the NDA.

Question 5:

Astellas has not observed any drug product impurities or degradation products that exceed the ICH threshold for identification (b) (4) based on a 100 mg mirabegron OCAS tablet). Unknown drug product impurities or degradation products have been observed at levels less than (b) (4) at release, and under normal storage conditions. Following the draft FDA Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, no evaluation of structural activity has been performed for these unidentified materials.

Does the Division agree that a structural evaluation of these low level drug product impurities or degradation products is not required?

FDA Response: *Yes. However, specification limits of 1.5 µg/day should be set for all known or theoretical genotoxic impurities in the drug substance. Unknown impurities related to in the drug product below the specification limits of (b) (4) based on a maximal 100 mg mirabegron dose do not need to be identified or qualified. Provide impurity profile comparisons and HPLC chromatograms of the preclinical, clinical and stability batches for evaluation in the NDA.*

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

Question 6:

Potential changes in the color of the tablet film-coating of the commercial formulation may be desired to improve tablet differentiation. Since the modified release characteristics of mirabegron OCAS tablets are based (b) (4)

(b) (4) should not have any detectable impact on formulation quality or performance. Anticipating that such a change would involve (b) (4)

(b) (4) Astellas would consider the change to be classified as a Components and Composition Non-Release Controlling Level 1 change as per the SUPAC-MR guidance. (b) (4)

The dissolution data comparing film-coated to non-coated tablets presented in section 2.3.P.2.2 of the briefing document indicates that the film-coating on the OCAS tablet does not result in a significant change in the dissolution profile. As a result, (b) (4)

(b) (4) not be expected to result in a detectable change in the dissolution profile.

Does the Division agree that this type of change in mirabegron OCAS tablets could be classified as a SUPAC-MR Level 1 change?

FDA Response:

Yes, we agree that a change in the color of the tablet film-coating could be classified as SUPAC-MR Level 1 change. We suggest that you repeat the dissolution testing comparing the film-coated and non-coated tablets with Apparatus 1 (basket – (b) (4)) at 100 rpm.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

Question 7:

Astellas will be including primary stability data for three batches of each tablet strength in the mirabegron NDA. The tablets used in the primary stability studies were produced at the proposed commercial batch size, at the proposed commercial site, and using the proposed commercial equipment. It is anticipated that a minimum of 18 months of long term stability data will be included in the NDA

The tablets in the primary stability batches are identical to the proposed commercial tablet except for the commercial tablet debossing. Data will be included in the NDA to demonstrate that the debossing has no impact on the stability of the tablets.

Astellas would like to submit an update to the stability data sections during the NDA review period. The stability update would be submitted no later than the 120 day safety update.

Information on the design of the stability studies and the primary stability batches is included in section 2.3.P.8.1 of the briefing document.

Does the Division agree that the proposed stability package will be adequate to support the NDA and that a stability update can be submitted no later than the 120 day safety update?

FDA Response:

We agree that the proposed stability package should be adequate to set an expiration dating period and that the stability update can be submitted no later than the 120 day safety update. We recommend that you investigate the dissolution test using rotation speeds of [REDACTED]^{(b) (4)} and 100 rpm for the current stability batches, and submit the comparative dissolution data in the NDA.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

Question 8:

Astellas plans to include one executed batch record for each dosage strength in the mirabegron NDA. These batch records will be selected from batches used in the primary stability studies.

Does the Division agree that the submission of a single representative batch record for each dosage strength will be adequate to support the NDA?

FDA Response:

We agree.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

Question 9:

Astellas intends to submit the mirabegron NDA electronically using the eCTD format. A single Drug Product section will be submitted containing all of the proposed drug product dosage strengths.

Does the Division agree that all proposed dosage strengths can be included in a single Drug Product section in the NDA?

FDA Response:

We agree.

Meeting Discussion:

Astellas acknowledged receipt of the FDA Response provided. No further discussion was requested.

FDA POST-MEETING COMMENT:

FDA considers that Astellas' request of conducting the dissolution testing of their product with the 40 mesh size basket at 100 rpm paddle speed is acceptable.

ACTION ITEMS:

There are no further action items other than those recorded in the meeting discussion sections above.

CONCURRENCE:

{See appended electronic signature page}

Jeannie David, M.S.
Regulatory Project Manager
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Donna Christner, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-69416	GI-1	ASTELLAS PHARMA GLOBAL DEVELOPMENT INC	YM178

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

/s/

JEANNIE C DAVID
03/17/2010

DONNA F CHRISTNER
03/17/2010



IND 069416

MEETING MINUTES

Astellas Pharma
Attention: Judy Kannenberg
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM178 (mirabegron).

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2009. The purpose of the meeting was to discuss 1) metabolite safety testing, 2) the results of thorough QT study 178-CL-037 and the design of QT study 178-CL-077, and 3) the conduct of a long-term safety study 178-CL-075 evaluating the use of mirabegron in males with bladder outlet obstruction at risk for urinary retention.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Mercier, Chief, Project Management Staff at (301) 796-0957.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance Meeting

Meeting Date and Time: December 8, 2009
11:00 – 12:30 PM, EST

Meeting Location: White Oak, Building 22
Conference Room 1313

Application Number: 069416
Product Name: YM178 (mirabegron)
Indication: Overactive Bladder (OAB)
Sponsor/Applicant Name: Astellas Pharma

Meeting Chair: Mark Hirsch, M.D.
Meeting Recorder: Jennifer Mercier

FDA ATTENDEES

George Benson, M.D. – Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D. – Medical Team Leader, DRUP
Roger Wiederhorn, M.D. – Medical Officer, DRUP
Doanh Tran, Ph.D. - Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Mahboob Sobhan, Ph.D. – Biometrics Team Leader, Division of Biometrics III (DBIII)
Lynnda Reid, Ph.D. – Pharmacology/Toxicology Supervisor, DRUP
Eric Andreasen, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Jennifer Mercier – Chief, Project Management Staff, DRUP

SPONSOR ATTENDEES

Astellas Pharma Global Development, Inc.

Peter Boerrigter, M.D. - Medical Science Director
Nancy Martin, M.D., PharmD, FCP - Medical Director, Medical Sciences
Marcel Van Gelderen, Ph.D. - Director, Clinical Pharmacology
Marlowe Schneidkraut, Ph.D., DABT - Associate Director, Toxicology
Mary Beth Blauwet, DrPH - Associate Director, Biostatistics
Misun Lee, Ph.D. - Senior Manager, Biostatistics
Donald Raineri, PharmD - Senior Director, Regulatory Affairs
Judy Kannenberg - Associate Director, Regulatory Affairs
Kenji Yasukawa, Ph.D. – Vice President, Head Global Therapeutic Area Urology
Ton Kos, Ph.D. - Senior Director, Global Development Project Leader

Allam Fakhoury, PharmD - Associate Director, Project Management

External Consultants to Astellas Pharma:

(b) (4)

BACKGROUND

Mirabegron is a beta 3-adrenergic receptor agonist currently under development for the treatment of OAB. Phase 3 studies are underway for the OAB indication. The Sponsor now seeks to conduct an additional, large, Phase 3 study in men with OAB and bladder outlet obstruction at risk for urinary retention (b) (4)

The Sponsor also plans to conduct a second thorough QT study. Finally, the Sponsor wishes to discuss the Agency's requirement for safety testing of mirabegron metabolites.

DISCUSSION

Question 1. Does the Division agree that Astellas can proceed with an additional long-term safety study in male OAB patients at risk for urinary retention based on the safety demonstrated by the urodynamic study?

Division's Response: Yes. We agree that Astellas can proceed with an additional long-term safety study in male OAB patients at risk for urinary retention based on the safety demonstrated by the urodynamics study.

Nonetheless, we continue to have concerns regarding the potential for BPH progression in obstructed males taking YM178, based upon the observation of dose-related increases in PVR in Study 060 which increased over time. References from the literature appear to support our concern (Roehrborn, CG; BJU Int. 2006 Apr; 97 Suppl 2:7-11 and BJU Int. 2008 Mar; 101 Suppl 3:17-21). Increases in PVR in Study 075 will be a review issue.

In addition, we have concerns that it may not be feasible to exclude all medical therapy for BPH in patients with OAB and BPH at risk of urinary retention. If patients were to use medications intended for BPH, we have concerns related to potential risks of interactions (e.g., between alpha-1 adrenergic antagonists and YM178, a beta-3 adrenergic agonist).

Additional discussion during the meeting:

- The urodynamic study showed a dose-related increase in PVR. The mean increase in residual urine observed at the high dose was comparable to the mean increase in average voided volume observed with anticholinergic therapy in the treatment of OAB. This outcome alone supports the Division's concern regarding use of mirabegron in male OAB patients with bladder outlet obstruction at risk for urinary retention.
- The Sponsor stated that a 30 mL change in the PVR would not impact the manner in which a patient was treated clinically. For an individual patient, the Division agreed, and

commented that a PVR of over 150 mL might be considered clinically meaningful. A PVR reaching 300 cc would clearly raise concerns.

- Despite the observed effect of mirabegron on bladder storage, the Division agreed that the planned study could proceed, to assess the effect of the mirabegron on urinary retention, the need for BPH-related surgery, and an increase of IPSS ≥ 4 points (symptomatic progression) in this target population.
- The Division also stated a concern that it may not be feasible to withhold effective medical therapy (alpha blocker drugs) in men with moderate and severe BPH related symptoms. The Division expressed a concern that if alpha blockers were to be given, the potential pharmacodynamic interaction of alpha blockers and a beta 3 adrenergic agonist is unknown. The Division indicated that this concern should be addressed, preferably with a pharmacodynamic drug interaction study.
- The sponsor stated that in their Phase 3 program they did not contraindicate the concomitant use of YM178 and alpha blockers, and they were aware that some patients in Phase 3 had taken both alpha blockers and mirabegron. Therefore, they stated that some relevant safety information could be derived from the ongoing Phase 3 studies.
- The Sponsor proposed to allow only those patients who fail in the proposed study to be given alpha blockers. For example, a patient with an increase in IPSS of at least 4 points, would achieve an endpoint in the study, then could be “rescued” with alpha blocker therapy. The Division stated that the Sponsor could make such a proposal in the final study protocol.

Question 2. The proposed primary endpoint for study 178-CL-075 is a combined endpoint of acute urinary retention (AUR) or meeting criteria for BPH-related surgery as defined in the protocol synopsis. Does the Division agree with a combined primary endpoint and the proposed definition for the endpoint?

Division’s Response: No. In addition to the proposed primary endpoint (acute urinary retention [AUR] and meeting the criteria for BPH-related surgery), we recommend adding an additional criterion: a four point or greater increase in the IPSS (“symptomatic progression”). Symptomatic progression is the most prevalent clinical event in men with LUTS suggestive of BPH, and should increase the number of “progression events” captured in this study.

Additional discussion during the meeting:

- The Sponsor agreed with the addition of a third criterion (four point or greater increase in the IPSS).
- The Division stated the 4-point increase in IPSS should be confirmed on 2 observations, but IPSS need be administered just once at screening and once at baseline.

Question 3. Does the Division have any comments on the design of the 178-CL-075 long-term safety study in males, including the following?

Division’s Response: Yes, we have comments about each of the elements:

- *Inclusion/exclusion criteria:*

To define the target population (men with overactive bladder and BPH at risk of urinary retention), we recommend the following inclusion criteria:

- Enlarged prostate (>30 gm by ultrasound)
- International Prostate Symptom Score (IPSS) > 12 points
- Maximum urinary flow rate (Qmax) 3 mL/sec – 12 mL/sec (as you currently recommend).
- Urinary frequency, defined as >8 micturitions per day
- Presence of urinary urgency or urge urinary incontinence, at least 1 episode per day.

You propose the use of the Patient Perception of Intensity of Urgency Scale (PPIUS) to include subjects with severe urgency (Grade 3) or urge incontinence (Grade 4). We find this acceptable for purpose of subject inclusion, but not for claims of product benefit, such as reduction in urinary urgency.

- *Study duration:*

We are requesting a lower relative risk, which will require adding patients and/or increasing the duration of the study (e.g., to at least two years). See our comments in the next two sections.

- *Safety margin*

The proposed relative risk of (b) (4) allows YM178 to be (b) (4) worse than placebo, which is unacceptable. (b) (4)
(b) (4), YM178 should be no more than 20% worse than placebo to be considered non-inferior.

We remind you that even if the study meets its primary objective of demonstrating statistical non-inferiority, clinical events will be reviewed individually to determine whether they raise concerns.

- *Sample size*

The sample size should be re-analyzed based upon our recommendations for changes to the primary endpoint, safety margin, and duration of treatment. The protocol would also need to restate the hypothesis in terms of the risk ratio with lower margin as well as the upper limit of the 95% CI for the risk ratio at which YM178 will be considered noninferior to placebo.

Additional discussion during the meeting:

- *Inclusion/exclusion criteria:*
 - The Division stated that the recommended inclusion/exclusion criteria provided in the preliminary comments were key inclusion/exclusion criteria, but not all the criteria.
 - The Sponsor stated their concern that ultrasound was not needed to determine prostate size. The Sponsor believes there is too much variability when using ultrasound for this purpose. The Division stated that ultrasound is not required. The Division thought that by enriching the enrolled population with patients with ultrasound-documented prostate enlargement, the study would more rapidly

accrue progression events. Sponsor should make a proposal in the final study protocol.

- The Sponsor agreed with the recommended IPSS and maximum urinary flow rate criteria provided in the preliminary comments.
 - The Sponsor asked for clarification about the recommended urinary frequency and urgency criteria. The Division stated that the OAB criteria (urinary frequency, urgency, and urge incontinence) need to be well defined. The Division recommended use of a 3-day diary to capture urinary frequency, urgency and urge incontinence at baseline. The Sponsor may use the criteria and procedures used in their original Phase 3 OAB studies and propose these in the final protocol.
- Safety margin
 - The Sponsor noted that the recommended relative risk of 1.2 would require a very large number of patients.

○ [REDACTED] (b) (4)

Question 4. Astellas believes that the results of the urodynamic study, combined with the results of the phase 3 studies and the proposed 178-CL-075 long-term safety study, should be adequate to support the mirabegron labeling [REDACTED] (b) (4)
Does the Division agree with this approach?

Division's Response: If you incorporate our recommendations (especially in regard to adjusting the relative risk and sample size) and address the other concerns we have raised, then your approach appears reasonable. The concern about increases of PVR will be a review issue. [REDACTED] (b) (4)

Additional discussion is required in regard to timing of the submission of the data from Study 075. It would appear that an efficacy supplement, submitted after review of the original NDA for YM178, would be appropriate.

Additional discussion during the meeting:

- No additional discussion.

Question 5. The Division recommended the conduct of a long-term safety study in this population during the Special Protocol Assessment (SPA) review of study protocols 178-CL-046 and 178-CL-047 (February 2008). To continue this process, Astellas proposes to utilize the SPA mechanism to facilitate review of the final 178-CL-075 study protocol. While it is recognized

that study 178-CL-075 is primarily a long-term safety study, this large phase 3 protocol of approximately 2200 patients and a duration of 1 year also includes secondary efficacy endpoints

(b) (4). Does the Division agree with utilizing the SPA review process for study protocol 178-CL-075?

Division's Response: No. Although this study, 178-CL-075, is primarily a long-term safety study, which includes secondary efficacy endpoints, we do not agree with utilizing the SPA review process in this case. In order to qualify for a SPA, the clinical trial must form the primary basis of an efficacy claim.

Additional discussion during the meeting:

- No additional discussion.

Questions for Written Comment

Question 6: Does the Division concur with the conclusions Astellas has determined from QT study 178-CL-037?

Division's Response: The Division is unable to provide a response to this question at this time, because your October 19, 2009 submission (S-0184), containing results from Study 178-CL-037, is currently under consultative review by IRT-QT.

Although we do not yet have the consultative report from IRT-QT, the Division wishes to express concern related to the findings from the subgroup analysis and re-analyses of Study 037. It would be appropriate to discuss how you will address this specific concern in your NDA as soon as possible, but no later than at the Pre-NDA meeting.

Additional discussion during the meeting:

The Division expressed serious concern in regard to the apparent positive results of the original TQT study. QT prolongation observed at two times the maximum, to-be-marketed dose in males and females, and at the maximum, to-be-marketed dose in females was concerning and would be a major NDA safety review issue. The Division urged the Sponsor to address this issue prior to NDA submission and to ensure that it was a topic of discussion at a Pre-NDA meeting. The Sponsor noted that additional nonclinical studies were underway to better understand the results from the human TQT study. The Division acknowledged this and indicated that patch clamp studies may be informative in understanding potential drug-drug interactions and which ion channels may be perturbed by YM178 or its metabolites.

Question 7: Does the Division or the IRT-QT have any comments or recommendations for the design of the second QT study 178-CL-077?

Division's Response: The Division is unable to provide a response to this question at this time, because your October 19, 2009 submission (S-0184), containing the protocol for Study 178-CL-077, is currently under consultative review by IRT-QT.

Question 8: The results of study 178-CL-037 will be included in the original NDA for mirabegron; Astellas is proposing to include the results of the second QT study 178-CL-077 in the 120-day safety update to the NDA, not in the original application. Is the Division in agreement with this submission?

Division's Response: No. The full study report for Study 178-CL-077 should be submitted with the original NDA.

Additional general discussion of QT during the meeting:

- The Division reminded Sponsor that IRT-QT is currently reviewing the QT submission. They have planned a tentative completion date of January 22, 2010.
- The Division reminded Sponsor that the apparent positive QT study has raised concerns for the Division. The Sponsor needs to address the QT issue prior to a Pre-NDA meeting. This is a major safety concern.
- The Sponsor acknowledged the Division's concern and stated that they shared the same concern. The Sponsor indicated that they are pursuing several approaches (e.g., degree of change in heart rate, metabolite concentration) in an attempt to determine what caused the apparent positive QT signal.
- The Division stated that once IRT-QT had completed their review of the submission, the Division would issue a detailed regulatory letter with their findings and would be willing to meet with the Sponsor for further discussion if needed.

Question 9: Astellas has identified 2 major metabolites of mirabegron defined as 10% of the total drug related exposure (ICH M3 (R2), "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals", June 11, 2009). Both are phase II metabolites (glucuronides) and neither is pharmacologically active. Astellas has characterized the systemic exposures at steady state for these metabolites in rats, mice, rabbits and monkeys. Results revealed that both of the major metabolites are generated in monkeys at systemic exposures comparable to that observed in humans. Therefore, no further safety testing of these metabolites is warranted. Does the Division agree that no further safety testing of these metabolites is required?

Division's Response:

It is premature to respond to this question with a definitive answer as the study reports have not been submitted for review. However we concur with the threshold levels for characterization of metabolites in the current ICH M3 (R2) guidance [metabolite(s) observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies]. As presented in the meeting package it appears that the metabolites were either less than 10% of the drug-related exposure in humans, or the levels in humans were not significantly greater than that in the toxicology studies of at least one species. At this time and pending review, we do not anticipate requests for further nonclinical study of the metabolites.

When the study reports are submitted, please address the following points:

1. There is a serious safety concern regarding elevated exposure to YM178 during pregnancy. Rabbits in the embryo-fetal toxicity study (178-TX-016) achieved exposures to YM178 that were six times that observed in the metabolism study in non-pregnant rabbits (Appendix 3, 178-ME-097) at similar oral doses. This will need to be addressed given the observed embryo-fetal toxicities in rabbits (cardiomegaly and dilated aorta). Even though this appears to be a species specific finding (not observed in rats) the affect that pregnancy has on pharmacokinetics in humans is unknown.
2. It should be noted whether the pharmacokinetic data of metabolites in humans was at steady state (178-CL-037).
3. The apparent discrepancy in the source of the data for Table 20 and Appendix 3 in the meeting package should also be clarified.

Additional discussion during the meeting:

- The Sponsor inquired about the rationale for the Division's concern regarding the differential pharmacokinetic response in pregnant versus non-pregnant rabbits. The Division noted the 6-fold difference in rabbits in the embryo-fetal toxicity study compared to non-pregnant rabbits was unexpected. Further, the Division stated that increased exposure during pregnancy in rabbits is a concern since we will not have clinical pharmacokinetic data from pregnant women, and we currently do not understand if pregnancy itself significantly increases systemic exposure. The Division noted that this same finding was not observed in rats. The Division stated that this discrepancy will need to be addressed. Without data to refute this finding, it will be a major review issue. The Sponsor indicated that they would further investigate this issue and it could be due to differences in analytical techniques.

Additional Nonclinical Request:

In order to complete our review of the carcinogenicity studies, we will need the recent historical control data for neoplasms from the laboratory that conducted the carcinogenicity studies. Additionally, to aid the statistical review, the data should be submitted electronically. Data formatting specifications and guidances are attached to the meeting minutes. (See attachment)

ACTION ITEMS

- The sponsor will submit a proposed protocol for the long-term safety study.
- Meeting minutes will be sent to the sponsor within 30 days.

ATTACHMENTS AND HANDOUTS

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies (The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 02/05/2008

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 02/05/2008

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2006 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm> under the title of the above guidance document. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can also be found at the above FDA website under the title of this document (or directly at <http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf>). At this time, we are only requesting the tumor dataset in the format described on page 7 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the current draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at <http://www.fda.gov/cder/guidance/815dft.pdf>. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 5238, Building 22, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

(Attachment A)

Cover page of "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications"

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2006
Electronic Submissions

Revision 1

(Attachment B)

Data format table on page 7 (APPENDIX 1) of the associated document "Study Data Specifications"

Tumor Dataset For Statistical Analysis^{1,2} (tumor.xpt)				
Variable	Label	Type	Codes	Comments
STUDYNUM	Study number	char		³
ANIMLNUM	Animal number	char		1,3
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		3,4
TUMORNAM	Tumor name	char		3,4
ORGANCOD	Organ/tissue code	char		3,5
ORGANNAM	Organ/tissue name	char		3,5
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	⁴
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	⁴
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

¹ Each animal in the study should have at least one record even if it does not have a tumor.

² Additional variables, as appropriate, can be added to the bottom of this dataset.

³ ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

⁴ A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unuseable or not examined.

⁵ Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail link.lin@fda.hhs.gov or link@cder.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-69416

GI-1

ASTELLAS
PHARMA GLOBAL
DEVELOPMENT
INC

YM178

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

/s/

MARK S HIRSCH
01/05/2010



IND 069416

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Astellas Pharma Global Development, Inc.
Three Parkway North
Deerfield, Illinois 60015-2548

ATTENTION: Ms. Judy Kannenberg
Associate Director, Regulatory Affairs

Dear Ms. Kannenberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Mirabegron Tablets, 50 mg.

We also refer to your June 18, 2009, correspondence, received June 19, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reasons.

1.



2.

3.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Meredith Alpert at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-69416

ORIG-1

ASTELLAS
PHARMA GLOBAL
DEVELOPMENT
INC

YM178

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

/s/

CAROL A HOLQUIST
12/16/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 69,416

Astellas Pharma US, Inc.
Attention: Donald Raineri, PharmD
Senior Director, Regulatory Affairs
Three Parkway north
Deerfield, IL 60015-2548

Dear Dr. Raineri:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM178.

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2007. The purpose of the meeting was to discuss (a) the safety of proceeding to phase 3, (b) the design of the phase 3 studies, (c) the overall clinical development program for the treatment of overactive bladder, and (d) the adequacy of the proposed technical information to support a marketing application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 14, 2004
TIME: 1:00 PM – 2:30 PM
LOCATION: CDER WO 1417
APPLICATION: IND 69,416
DRUG NAME: YM178
TYPE OF MEETING: EOP2

MEETING CHAIR: Mark Hirsch, M.D.

MEETING RECORDER: Karl Stiller

FDA ATTENDEES: (Title and Office/Division)

From the Division of Reproductive and Urologic Products:

George Benson, M.D., Medical Team Leader
Mark Hirsch, M.D., Medical Team Leader
Suresh Kaul, M.D., Medical Officer
Roger Wiederhorn, M.D., Medical Officer
Chong M. Kim, M.D., Medical Officer
Lynnda L Reid, Ph.D., Pharmacology Supervisor
Eric Andreasen, Ph.D., Pharmacologist
Karl Stiller, Regulatory Health Project Manager

From the Division of Biometrics III:

Mahboob Sobhan, Ph.D., Statistician, Team Leader

From the Office of Clinical Pharmacology:

Doanh Tran, Ph.D., Clinical Pharmacology Reviewer

From the Office of New Drug Quality Assessment:

Donna Christner, Ph.D., Pharmaceutical Assessment Lead
Rao Puttagunta, Ph.D., Chemistry Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Judy Kannenberg, Assistant Director, Regulatory Affairs
Marlowe Schneidkraut, Ph.D., D.A.B.T., Assistant Director, Toxicology
Bill Fitzsimmons, Pharm.D., Senior V.P., Research and Development
Allam Fakhoury, Pharm.D., Associate Director, Clinical Studies
Marianne Bovenhoff, MSc., MBA, Project Leader
Peter Boerrigter, M.D., Medical Director
Marcel Van Gelderen, Ph.D., Director, Clinical Pharmacology
Marloes Schaddelee, Ph.D., Sr. Clinical Pharmacokineticist

Ted Drogendijk, MSc., Sr. Biostatistician
Jeff Colledge, MR PharmS., Principal Scientist
Takeo Sugawara, Ph.D., Global Project Leader

BACKGROUND:

On October 15, 2007, Astellas Pharma US, Inc. submitted a briefing package with the following questions for the Division of Reproductive and Urologic Products (DRUP). DRUP provided a written response to the Sponsor's questions on November 8, 2007. The November 8, 2007, responses appear below. Additional meeting discussion is shown in bold italicized font after each response.

MEETING OBJECTIVES:

The objective of this End-of-Phase 2 meeting was to further discuss DRUP's responses.

DISCUSSION POINTS:

Chemistry, Manufacturing and Controls

Question 1: *Astellas proposes two compounds as starting materials for the (b) (4) of YM178. The (b) (4) is depicted in Module 2.3, Drug Substance, of the briefing document. Astellas believes that the designation of compounds (b) (4) as starting materials for the (b) (4) of YM178 is in compliance with FDA guidance and does not have the potential to adversely affect the quality of the drug substance produced.*

Does the Division recognize (b) (4) as starting materials for the manufacture of YM178?

FDA Response: No. The submitted information is not adequate to determine that the proposed designation of the starting materials is acceptable.

1. It is not clear whether the submitted suppliers will manufacture the proposed starting materials exclusively for the sponsor or they also manufacture them for non-pharmaceutical use. Refer to "Guideline for Submitting Supporting Information in Drug Applications for the Manufacture of Drug Substance (1987)".
2. It was not adequately explained how the sponsor will ensure that any future changes in the manufacturing process or the supplier for the proposed starting materials will not adversely affect the quality of the drug substance.
3. (b) (4): The acceptance criterion for individual unspecified impurities should be tightened to NMT (b) (4) in the proposed specification. Any impurity present at higher level should be identified and/or qualified, and included as a specified impurity.
4. (b) (4): The submitted specification is incomplete. It should include acceptance criteria for individual specified and unspecified impurities.

5. The starting material specifications should also include acceptance criteria for residual solvents.

Meeting Discussion for Point 1: *The Sponsor stated that the listed suppliers will manufacture (b) (4) for pharmaceutical purposes only, and (b) (4) will be manufactured on a commercial scale using the Sponsor's manufacturing process.*

Meeting Discussion for Point 2: *The Sponsor stated that any changes to the manufacturing process of either (b) (4) will require control procedures and contracts in place to ensure that specifications are met. DRUP stated that future changes in the manufacturing procedure could result in changes in the impurity profile of the proposed starting materials.*

In response to the meeting discussion for Points 1 and 2, DRUP agreed to re-consider the acceptability of the proposed starting materials and provide a response in the minutes.

Post Meeting Response: *At this time, we do not have enough information to determine if (b) (4) should be classified as a starting material because it is not commercially available. (b) (4) adequate controls should be established for this starting material, based on levels and safety of the impurities. A protocol for acceptance testing of the starting material before its use in the manufacture of the drug substance should be established. A full description of the starting material (b) (4) and controls should be provided for evaluation either in an Amendment to the IND or in the NDA.*

We agree that (b) (4) can be designated as a starting material because it is commercially available. (b) (4), the same advice concerning adequate controls and the manufacturing information for (b) (4) applies.

Meeting Discussion for Point 3: *The Sponsor stated that a commitment to identify and qualify unspecified impurities (b) (4) should apply to the drug substance rather than to the starting materials. DRUP asked that the Sponsor provide additional information to support this request in their NDA.*

Post Meeting Response: *The Sponsor should provide historical data on impurity levels in both (b) (4) and in the drug substance in order to demonstrate that the impurities in (b) (4) are not carried over to the drug substance at levels above the qualification limits, unless these levels in the drug substance are adequately qualified. The drug substance specification should also reflect the controls to address the potential carry-over of the impurities from the (b) (4). Refer to the ICH Guidance Q3A(R2) for information on identification and qualification of impurities and degradation products.*

Meeting Discussion for Points 4 and 5: *The Sponsor stated that they accept DRUP's comments.*

Question 2: *As described in Module 2.3, Drug Product, of the briefing document, the USP dissolution (b) (4), with a rotation speed of (b) (4), has been utilized consistently throughout the development process of YM178 OCAS tablets. The rotation speed was chosen to (b) (4) when dissolution is performed. Astellas believes the (b) (4) speed is acceptable to reduce variability in the obtained dissolution rates. Based on the information provided in Module 2.3 of the briefing document, does the Division concur with the proposed rotation speed of (b) (4) for the dissolution testing of YM178 tablets?*

FDA Response: No. The submitted data at 100 rpm appears to be sufficient to support the use of 100 rpm paddle rotation speed for dissolution testing. The submitted data for the “batch with target dissolution profile” would pass L₂ USP dissolution criteria for extended release dosage forms.

Meeting Discussion: *The Sponsor stated that their process was developed using (b) (4) because of problems encountered with (b) (4). s. They stated that the (b) (4) paddle speed is justified because it shows robustness, is discriminatory, holds unreliability to < 10%, and removes anomalies. DRUP stated that there will be further internal discussion with the dissolution group on the issue and will include comments in the minutes. DRUP also suggested that the Sponsor investigate the use of different basket mesh sizes or the use of (b) (4). The Sponsor stated that they have not yet tried different mesh sizes, and are reluctant to use (b) (4) because the (b) (4) is the standardized method and is available globally.*

Post Meeting Response: *While your explanation is duly noted, more data is needed to make a final determination if (b) (4) is acceptable. Additional data and appropriate justification should be provided in the NDA and the final determination will be made during the NDA review.*

Question 3: *Astellas believes that the physical, chemical and stability properties of YM178 tablets have been sufficiently characterized to support initiation of the proposed phase 3 studies. See Modules 2.3.S and 2.3.P of this briefing document for further information.*

Does the Division concur?

FDA Response: Yes. However, the drug product specification will be evaluated in greater detail when the NDA is submitted.

Meeting Discussion: *The Sponsor asked if they may use the (b) (4) paddle speed for Phase III. DRUP agreed that this is acceptable.*

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

Question 4: *Astellas believes that the results of the nonclinical studies conducted to date as well as the proposed studies planned with YM178, as outlined in Module 2.4 (Section 1.1, Table 1), are adequate to support the proposed clinical development plan and the NDA package.*

Does the Division concur?

FDA Response: No. There are several outstanding study reports that have yet to be submitted. For example, the reports for the clinical and nonclinical studies intended to evaluate the metabolic profiles will need to be submitted and assessed and may require further safety evaluation.

Meeting Discussion: *Since several studies were referenced in the end of phase 2 package that had not been submitted to the FDA, a general request was made for submission of all completed nonclinical studies. The Sponsor was encouraged to initiate the nonclinical metabolite studies as soon as possible so that they can be compared to the metabolic profile in humans to assess the acceptability of the animal studies. DRUP requested that metabolite studies be conducted in mice, rats, dogs and rabbits. The Sponsor agreed to submit the studies to DRUP as they become available.*

Clinical Pharmacology and Pharmacokinetics

Question 5: *Results from the recently completed drug-drug interaction study (Study 178-CL-036) show that AUC and Cmax of YM178 increase by less than 2-fold in the presence of a strong inhibitor of CYP3A4 (See Module 2.5, Sections 3.1.3 and 3.1.7) indicating that YM178 is a weak substrate to CYP3A4 and that CYP3A4-mediated metabolism does not play a major role in the elimination of YM178.*

Study 178-CL-005 (See Module 2.5, Section 3.1.3) has shown that YM178 is a modest inhibitor of CYP2D6. In-vitro data suggest that inhibition may be time-dependent. Astellas plans to study the interaction in more detail in a one sequence 3-way crossover study comparing the pharmacokinetics of the CYP2D6 substrate desipramine in the absence and presence of YM178 and after a 10-day recovery period. Astellas believes that together these studies will adequately characterize the inhibitory activity of YM178 towards CYP2D6.

Does the Division concur that the role of CYP3A4 and CYP2D6 activity in the metabolism of YM178 has been adequately characterized?

FDA Response: We agree that the completed and planned studies should provide adequate characterization of the role of CYP3A4 and CYP2D6 activity in the metabolism of YM178. It is premature to conclude that YM178 is “a weak substrate to CYP3A4 and that CYP3A4-mediated metabolism does not play a major role in the elimination of YM178.” Additionally, the determination of CYP2D6 extensive vs. poor metabolizer status of subjects in study 178-CL-005 should be defined.

Meeting Discussion: *The Sponsor asked for further clarification of DRUP’s position. DRUP stated that the raw data has not been reviewed, and whether there is an induction potential of CYP3A4 has yet to be determined. It is not clear whether CYP3A4 is a minor pathway or if*

there is another compensatory pathway that minimizes the effect of CYP3A4 inhibition. With respect to CYP2D6, it is unclear how “extensive” vs. “poor metabolizer” was characterized. The Sponsor stated study 178-CL-005 was conducted in 8 poor and 8 extensive metabolizers of CYP2D6. CYP2D6 status was evaluated by genotyping and confirmed with phenotyping. The sponsor will submit the full report for study 178-CL-005.

Question 6: *Astellas believes that the planned, ongoing, and completed clinical pharmacology studies, as outlined in CTD Module 2.5 (Section 1.3) are sufficient for labeling purposes and adequate to support an NDA submission.*

Does the Division concur?

FDA Response: No. We have the following comments:

1. Additional in vivo studies may be recommended if the results of your in vitro evaluation of YM178 as a possible inducer of human Cytochrome P450 enzymes (Study 178-ME-074) indicate an induction potential.
2. We recommend that you characterize the pharmacokinetic profile of the major metabolites of YM178 (e.g., RB-3, RB-6, RB-9, RB-11, and H1) in humans.
3. You should consider examining the effect of CYP3A4 induction on the pharmacokinetics of YM178 and its metabolites. CYP3A4 induction may lead to an increase in exposure to metabolite(s) formed via the CYP3A4 pathway.

Meeting Discussion: The Sponsor stated that they will take DRUP’s recommendations into consideration. The Sponsor intends to conduct studies to identify and characterize metabolites with exposure greater than 10% of the parent compound. DRUP stated that this approach is acceptable; however, the determination of which metabolite(s) fits the 10% criterion should be made following review of the data. The sponsor stated that they plan to focus on the 5 metabolites identified in comment #2. DRUP indicated that those 5 metabolites are examples of potential major metabolites and recommended that other unidentified major metabolites are also characterized. The Sponsor agreed to submit the data for review.

Clinical Development

Question 7: *During the YM178 Pre-IND meeting held in December 2005 (See Section 4 of this Module), the Division expressed a number of potential clinical safety concerns, which have been addressed in CTD Module 2.5 and summarized in Section 1.2.5 of the overview of this Module. These concerns included:*

- *increased heart rate and systolic blood pressure*
- *palpitations, headache, dizziness, postural hypotension and syncope*
- *increases in serum transaminases*
- *borderline QT prolongation*
- *blurred vision*

- *ventricular tachycardia*
- *compliance with food instructions*
- *glucose control in diabetics*

Does the Division believe that these concerns have been adequately addressed to support the initiation of the proposed phase 3 studies?

FDA Response: Yes. Nonetheless, the potential for hepatotoxicity still remains a concern and needs to be assessed throughout the phase 3 studies.

In addition, a new potential clinical concern is the occurrence of hypertension. An increased incidence of hypertension was reported as a clinical adverse event in the 100mg/day group compared to lower dose groups and placebo in phase 2.

Meeting Discussion: No further discussion.

Question 8: *Does the Division have any comments on the design of the phase 3 studies, including the following:*

- *Study duration*

FDA Response: The study duration of 12 weeks of active therapy is acceptable.

Meeting Discussion: No further discussion.

- *Inclusion/exclusion criteria*

FDA Response: The currently preferred primary efficacy endpoint in Overactive Bladder (OAB) trials is incontinence episode frequency (with micturition frequency serving either as a critical secondary endpoint or as a co-primary endpoint). Therefore, with respect to the inclusion criteria, a sufficient number of patients *with incontinence* at baseline need to be included to achieve success for that primary endpoint.

We caution that your 4-point urgency scale may not be universally well-understood. Therefore, we advise you to supplement this with a lay term definition (e.g., “strong need to urinate immediately”) and the investigator’s impression of the symptoms.

Meeting Discussion: The Sponsor proposed urge incontinence episode frequency and micturition frequency as co-primary endpoints. The Division accepted the proposal. The Sponsor asked whether it would be acceptable to enroll 70% “wet OAB” patients and 30% “dry OAB” patients. DRUP stated that the number of “wet OAB” patients should be sufficient to demonstrate statistically and clinically significant differences from placebo for urge incontinence episode frequency. The Sponsor also asked if the proposed 5-point Urgency Scale adequately addressed DRUP’s concerns re: patient understanding. DRUP stated that the scale was acceptable for inclusion criteria, but not acceptable for claims of treatment benefit as a secondary endpoint. For such claims, validation of the instrument would need to be shown and the statistical plan would need to take the endpoint into consideration. The Sponsor asked how other products had received an indication that included the word “urgency”. DRUP

stated that the indication statement for OAB products will remain the same because of precedence. However, the lack of a validated instrument to substantiate the “urgency” endpoint poses the major hurdle in supporting stand-alone labeling claims for “urgency”.

- *Doses selected*

FDA Response: We agree with the doses selected for clinical development.

Meeting Discussion: No further discussion.

- *Safety monitoring*

FDA Response: Safety monitoring to the extent stated appears to be acceptable.

We note one Serious Adverse Event (SAE) of hypothyroidism requiring hospitalization in a treated patient in the phase 2 study. Additional information regarding this case will inform the need to monitor for thyroid effects in phase 3 studies.

Meeting Discussion: The Sponsor stated that the patient in question had serum TSH measured 2 months prior to the trial and that symptomatic hypothyroidism requiring hospitalization was reported only 10 days after starting study medication. DRUP requested that the Sponsor provide additional pre- and post-study information about the patient, e.g., Is the patient currently off thyroid medication?, Why was serum TSH checked in this patient 2 months prior to the investigation? The Sponsor agreed to submit the additional information.

- *Efficacy endpoints*

FDA Response: The currently preferred primary efficacy endpoint for OAB studies is incontinence episode frequency. Micturition frequency should serve as a critical secondary endpoint or as a co-primary endpoint.

If labeling claims are anticipated for the secondary endpoints, the pre-defined statistical analysis plan must account for this and the claims must come from validated patient-reported outcome (PRO) instruments. We know of no currently validated PRO for urgency. If claims are anticipated from the ICIQ-OAB questionnaire, the validation materials for this instrument should be submitted for our review. If claims are anticipated for [REDACTED]^{(b) (4)}, further discussion is required.

Meeting Discussion: No further discussion.

- *Assessment scales/tools*

FDA Response: See previous discussion of Efficacy Endpoints.

Meeting Discussion: No further discussion.

Question 9: As part of the phase 3 program, Astellas is planning to conduct a separate long-term, multi-center, randomized, double-blind, active-controlled safety study, 178-CL-049, to assess the safety of treatment with YM178 for up to 1 year. The study will recruit patients enrolled into the pivotal studies, as well as new patients. Patients from the pivotal studies will be allowed to enter the long-term study after a 4-week washout period. All patients will undergo a 2-week placebo-run-in period prior to receiving double-blind treatment. Astellas proposes to provide data in the NDA on at least 2500 patients, including 1500 patients exposed to YM178 with treatment duration of 3 months (750 patients in each YM178 dose group of 50 and 100 mg), 600 patients with treatment duration of 6 months (300 patients per YM178 dose group) and 400 patients with treatment duration of 12 months (200 patients per YM 178 dose group).

Does the Division agree to enroll patients who participated in the pivotal studies after a washout of 4 weeks into the long-term safety study?

FDA Response: The ICH recommendations for a New Molecular Entity (NME) for long-term safety are at least 100 patients treated *continuously* with the maximum approved to-be-marketed dose for 1 year and at least 300-600 patients for 6 months. If these requirements can still be met, then we do not object to the 4 week washout.

Meeting Discussion: *No further discussion.*

Does the Division have any further comments regarding the size of the proposed long-term safety database at the time of submission?

FDA Response: The size of the long-term safety database is acceptable.

Meeting Discussion: *No further discussion.*

Question 10: Astellas Study 178-CL-044 was a large randomized, double-blind, placebo and active controlled trial in patients with symptomatic OAB. The endpoints and treatment duration in Study 178-CL-044 are similar to those planned for phase 3.

Would the Division consider Study 178-CL-044, in addition to the studies proposed in the phase 3 development plan, as an additional adequate and well controlled study for registration of YM178?

FDA Response: Study 178-CL-044 could be submitted as a supportive study, but not as a replacement for either 178-CL-046 or 178-CL-047.

Meeting Discussion: *The Sponsor asked for additional clarification on DRUP's response. DRUP stated that the dose-ranging Study 178-CL-044 appeared to be underpowered due to the relatively small number of patients in each of the dose groups. In addition, the overall number of patients with "wet OAB" at baseline appeared to be small. Additionally, we note that the treatment effect size used for phase 3 study planning is larger than the treatment effect reported in phase 2. Therefore, based on these limitations, Study 178-CL-044 cannot be deemed an adequate replacement, but can be submitted as a supportive study.*

Question 11: *Astellas requests a deferment of the requirement to conduct clinical studies in pediatric patients until post-approval.*

Does the Division concur with this approach?

FDA Response: Yes.

Meeting Discussion: No further discussion.

Question 12: *Astellas has provided a draft Target Product Profile (TPP) in Section 3 of this Module to facilitate discussion regarding the proposed development program and potential labeling statements for YM178.*

[REDACTED] (b) (4)

Based on the data summarized in the briefing document and the proposed development program for YM178, does the Division agree with the proposed labeling statements identified in the TPP,

[REDACTED] (b) (4)

FDA Response: No. We do not agree with [REDACTED] (b) (4)

[REDACTED]

Meeting Discussion: [REDACTED] (b) (4)

[REDACTED]

DECISIONS (AGREEMENTS) REACHED:

See individual items above.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

See individual items above.

ACTION ITEMS:

See individual items above.

ATTACHMENTS/HANDOUTS:

None.

Linked Applications

Sponsor Name

Drug Name

IND 69416

ASTELLAS PHARMA INC YM178

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

/s/

MARK S HIRSCH

12/11/2007



Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION
ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2005

To: Donald L. Raineri, Pharm.D.
Senior Director, Regulatory Affairs

Company: Astellas Pharma US, Inc.

Fax number: (847) 317-7286

Phone number: (847) 405-1604

From: Jean Makie

Division of Division of Reproductive
and Urologic Drug Products

Fax number: 301-796-9897

Phone number: 301-796-0952

Subject: P-IND 69,416: Minutes for the 12/21/05 Pre-IND teleconference

NOTE:

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

P-IND 69,416
12/21/05 Pre-IND teleconference minutes

Pre-IND: 69,416 Type B Teleconference

Date: December 21, 2005 **Time:** 1:00-2:30 PM

Sponsor: Astellas Pharma, US

Drug: YM178 for overactive bladder [REDACTED] (b) (4)

FDA Participants:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Products(DRUP)

Suresh Kaul, M.D., Medical Reviewer, DRUP

Mahboob Sobhan,Ph.D., Biostatistics Reviewer Division of Biometrics2

Lynnda Reid, Ph.D., Pharmacology/Toxicology Supervisor, DRUP

Myong Jin Kim,Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUP

Jean Makie, M.S.,R.D., Sr. Project Manager, DRUP

Sponsor Attendees: Astellas Pharma Inc.,US

Sef Kurstjens, M.D., Ph.D., Sr. V.P., Research and Development

Abhijit Barve. M.D., Ph.D., Medical Director, Research and Development

Don Raineri, Pharm.D., Senior Director, Regulatory Affairs

Marilyn Bergland, B.S., Manager, Regulatory Affairs

Marlowe Schneidkraut, Ph.D., D.A.B.T., Assistant Director Toxicology.

Jeen Liu,Ph.D., Director, Biostatistics

Wolfram Nothaft, M.D., Director, Drug Development and Project Management

AstellasPharma, Inc., Japan

Takeo Sugawara, Ph.D., Global Project Manager

AstellasPharma, Europe

Marianne Bovenhoff, MSc., Local Project Leader, Europe

Arwin Ridder, MSc., Director, Clinical Research-Urology

Marcel Van Gelderen, Ph.D., Director, Exploratory Development Dept.

Dr. Iqbal Hussain, M.D., FRCS, Senior Medical Director

Jiuhong Zha, Ph.D., Manager Clinical Pharmacology Biopharmaceutical Sciences

Allam (Al) Fakhoury, Pharm.D., R.Ph., Assistant Director Clinical Studies

Background: On November 14, 2005, the Sponsor submitted a briefing package with the following questions for the Division. Preliminary draft responses to the questions provided in the Sponsor's briefing package were faxed by the Division to the Sponsor on December 19, 2005. Sponsor responses and discussions are also summarized below.

Nonclinical Pharmacology and Toxicology Program

Question 1: Nonclinical Pharmacology and Toxicology Program

Astellas believes that the currently conducted nonclinical studies, as outlined in Section 5 of this submission [End of Text Tables 1, 2 and 3], are adequate to support the proposed clinical development and registration of YM178.

Does the Division concur?

Division Response: No. The evidence is not convincing that a reassuring margin of safety exists between drug exposures associated with adverse effects in animals and those expected in clinical trials. We recommend that you submit information with the opening IND to demonstrate the differences between humans and animals in metabolism, metabolite profiles, possible toxic or reactive metabolites, distribution of radioactivity, and drug accumulation. In addition, we recommend that you also submit pharmacology data which demonstrates any species specificity, particularly with regard to cardiac effects. Findings in animals of particular concern include: cardiac arrhythmia, changes in vital signs, and increased serum liver function tests.

In regards to your reproductive and developmental toxicity program, the finding of dilated aortas in rabbit fetuses is of particular concern. Any additional information regarding the significance of this finding should be submitted. This finding should also be included in the Investigator's Brochure. Segment III reproductive studies should be submitted prior to submission of an NDA. We recommend that you select doses which

will define maternal and fetal toxicity as well as a no adverse effect level. Serious effects for which there are no demonstrated margins of safety may be a review issue for all reproductive studies and may affect the way in which the drug may be studied or marketed in women of reproductive potential.

Sponsor Response: The Sponsor acknowledged that safety margins for some animal findings were small. The Sponsor stated that completed Segment I and II reproductive and developmental studies were conducted at doses producing both maternal and fetal effects. Additionally, the Sponsor stated that the Segment III study will be initiated soon and agreed to submit the results for the Division's review when completed.

Division Response: We acknowledge ExecCAC review of carcinogenicity protocols.

Clinical Pharmacology

Question 2: Clinical Pharmacology – Drug-drug Interaction Studies

In vitro studies using liver microsomes suggested that the oxidative metabolism of YM178 was primarily mediated by CYP3A4, but a possible role of CYP2D6 could not be excluded. The clinical study 178-CL-005 demonstrated that in comparison with CYP2D6 extensive metabolizers, the increase in C_{max} and AUC in the poor metabolizers was minimal [see Section 5, End of Text Table 4.2]. Therefore the role of CYP2D6 in YM178 metabolism seemed not to be clinically relevant.

Astellas is planning to conduct a drug interaction study with ketoconazole (CYP3A4 inhibitor) to investigate potential interactions of concomitant use with YM178. Astellas believes this study will be adequate to assess the effect of CYP3A4 inhibition on the in vivo metabolism of YM178.

Does the Division concur?

Division Response:

We concur that a drug interaction study with ketoconazole will be adequate to assess the effect of CYP3A4 inhibition on the metabolism of YM178. Based on the results of this ketoconazole study, we may recommend an additional drug interaction study using a moderate inhibitor of CYP3A4.

We do not concur that the role of CYP2D6 in the YM178 metabolism is clinically irrelevant. You stated that the role of CYP2D6 in YM178 metabolism is not clinically relevant based on the exposure ratio of CYP2D6 extensive metabolizers (EMs) to poor metabolizers (PMs). However, your submission does not explain how you determined the status of CYP2D6 genotypes/phenotypes. Without this information, the Division cannot conclude that the exposure to YM178 is similar in EMs and PMs. Submit specific information regarding how EMs and PMs were identified in the report for this study. Based on this information, an additional 2D6 interaction study may be necessary.

Sponsor Response: The Sponsor clarified that the status of CYP2D6 phenotype for all patients in Study 178-CL-005 was determined using dextromethorphan as a probe drug. The phenotypic results were confirmed by genotyping of *3, *4, *5 and *6 alleles. The Sponsor agreed to submit all data to the IND for the Division's review.

Question 3: Clinical Pharmacology – Drug-drug Interaction Studies

Details of the drug interaction study with ketoconazole are located in Section 6 of this submission, Core Protocol 178-CL-036.

Does the Division have any comments on the protocol design (e.g., treatment duration, dose selection, dosage, inclusion/exclusion criteria)?

Division Response:

Ketoconazole 400 mg once daily is recommended. A drug interaction study with ketoconazole should be conducted with the highest (b) (4) YM178 dosage strength. Page 30 states that ketoconazole 200 mg twice daily will be given for 6 days but Page 32 states that ketoconazole will be administered for 7 days (days 1 through 7). Please clarify.

Additional Clinical Pharmacology Comments:

- Renal and hepatic impairment studies should be conducted.*
- A food effect study will be required if there is a formulation change in the modified release tablet.*
- A bridging study will be required if the to-be-marketed and clinical trial formulations are different.*
- Please submit your QT study protocol for our review prior to its initiation.*
- In general, the following should be addressed prior to NDA submission: mass balance, metabolism pathway, in-vitro metabolism studies, drug-drug interactions, dose-proportionality studies, analytical methods, bioavailability studies, single dose and multiple dose PK studies, effects of intrinsic and extrinsic factors, and food effect.*

Sponsor Response: The Sponsor clarified that the YM178 100 mg dose was selected based on clinical safety. The Sponsor understood that additional drug-drug interaction (DDI) study(ies) if the proposed highest clinical dose is greater than 100 mg.

Clinical Development

Question 4: Clinical Development – Indication

Astellas plans to submit a single IND for YM178 to evaluate patients with overactive bladder (OAB) (b) (4)

Does the Division concur?

Division Response: No, we do not concur with this strategy. We remain concerned about

(b) (4)
Extensive safety data will be necessary to resolve this major concern.

We recommend opening the IND for the traditional overactive bladder indication only
(b) (4) We specifically recommend opening the new IND with a modified and smaller version of the DRAGON protocol (see response to Question #6). *(b) (4)*

Question 5: Clinical Development – Initiation of Proposed Phase 2b Study

Astellas believes that the information gathered in clinical studies to date, as summarized in Section 5 of this submission, and the safety monitoring described in the phase 2 protocol support the initiation of the proposed phase 2b study [as found in Section 6] with YM178.

Does the Division concur?

Division Response: No, we do not concur. *(b) (4)*

(b) (4)
Based upon safety concerns, we recommend that the IND should be opened with a modified, smaller version of the DRAGON study (see response to Question #6).

Sponsor Response: The Sponsor acknowledged the Division’s clinical safety concerns and agreed to modify the DRAGON study as recommended.

Question 6: Clinical Development – Phase 2b Dose-Ranging Study (178-CL-044)

The first study to be conducted under the proposed IND is a phase 2b dose-ranging study in subjects with OAB. Details of the study are located in the draft protocol synopsis [see Section 6, Protocol 178-CL-044].

Does the Division have any comments on the design of this clinical protocol, in particular the proposed doses, study period, inclusion/exclusion criteria, schedule of assessments, and evaluation methodology?

Division Response:

We have the following recommendations for revisions to the DRAGON protocol to enhance safety:

1. *Reduce the proposed doses to 10mg, 25mg, 50mg, and 100mg. These doses may be further revised after review of the submitted nonclinical and clinical data when the IND is submitted.*
2. *Reduce the duration of the treatment period to 6 weeks.*
3. *Reduce the sample size. You might consider trend analyses rather than between-groups comparisons in order to lower sample size requirements.*
4. *Delete the tolterodine arm.*
5. *For a 6-week treatment period, assess LFTs and ECG at Weeks 2 and 6.*

Additional Discussion: The Division explained that the tolterodine arm was considered safe but unnecessary.

Question 7: Clinical Development – Clinical Development Plan

As part of the phase 3 program, Astellas is planning to conduct a long-term safety study. The study will be an open-label, multi-center study to assess the safety of treatment with YM178 for up to 1 year. Patients would be both directly recruited into the study and rolled-over from phase 2/3 studies. Astellas proposes to include data in the NDA on at least 600 patients with treatment duration of 6 months and at least 100 patients with treatment duration of 12 months.

Does the Division have any comments regarding the size of the proposed long-term safety database at the time of submission?

Division Response:

For an OAB-only indication, the proposed safety database appears acceptable. However, the final requirement for an OAB indication will be based on a review of the available safety information.

(b) (4)

Question 8: Clinical Development – Clinical Development Plan

Does the Division have any additional comments with respect to the proposed development program for YM178?

Division Response:

We have the following additional comments:

1. *During the development program, the following safety concerns will need to be addressed by human testing:*
 - a. *Increased heart rate and increased systolic blood pressure (seen at doses as low as 160mg IR).*
 - b. *Palpitations, headache, dizziness, and postural hypotension (also seen at 160mg IR), as well as syncope in 1 patient.*
 - c. *Increases in serum transaminases in 4 patients.*
 - d. *Borderline QT prolongation seen in 1 patient.*
 - e. *Blurred vision seen in 1 patient (at 240mg).*
 - f. *Ventricular tachycardia in dogs and monkeys. “Inconsistent” QT prolongation in monkeys.*
2. *Propose a means of evaluating the clinical relevance of the following nonclinical findings: hepatocyte necrosis in rats and dogs, heart lesions in dogs, and dilated aortas in rabbit fetus.*
3. *Compliance with food instructions (take with food) and its effect on adverse events will be a review issue.*
4. *Address whether YM-178 will affect glucose control in diabetics taking anti-glycemics.*
5. *In your IND, provide all available case report forms (CRFs) from the completed Phase 2 studies CL-003, CL-004, and CL-008.*

Additional Discussion: The Sponsor stated that they will submit the QT protocol to the Division for review and comments prior to conducting the study. Additionally, the Sponsor stated that no hypoglycemic events were observed at doses administered in completed studies and agreed to submit this data to the IND for the Division’s review. The Sponsor also agreed to monitor for hypoglycemic events in future OAB studies.

Additional CMC Comments

Please refer to the FDA Guidance for Industry: “Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-derived Products, November 1995” and “INDs for Phase 2 and Phase 3 studies: Chemistry, Manufacturing and Controls; May 2003” for the preparation of the CMC section (<http://www.fda.gov/cder/guidance/index.htm>).

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

/s/

Mark S. Hirsch
1/19/2006 11:34:35 AM



Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION
ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 5, 2006

To: Donald L. Raineri, Pharm.D.
Senior Director, Regulatory Affairs

Company: Astellas Pharma US, Inc.

Fax number: (847) 317-7286

Phone number: (847) 405-1604

From: Jean Makie

Division of Reproductive and Urologic
Products

Fax number: 301-796-9798

Phone number: 301-796-0952

Subject: IND 69,416: Serial 000_ 6/6/06 teleconference minutes

**Total no. of pages including
cover:**

NOTE:

Document to be mailed:	YES	<u>NO</u>
-------------------------------	-----	-----------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

IND 69,416
Serial 000: 6/6/06 teleconference Minutes

Teleconference Minutes

IND: 69,416

Date: June 6, 2006

Sponsor: Astellas Pharma, US

Time: 1:00-2:00 PM

Drug: YM178 for overactive bladder

FDA Participants:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Products (DRUP)

Roger Weiderhorn, M.D., Medical Reviewer, DRUP

Lynnda Reid, Ph.D., Pharmacology/Toxicology Supervisor, DRUP

Myong Jin Kim, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Office of Clinical Pharmacology (OCP) @ DRUP

Jean Makie, M.S.,R.D., Sr. Project Manager, DRUP

Sponsor Attendees: Astellas Pharma Inc., US

Donald Raineri, Pharm.D., Sr. Director, Regulatory Affairs

Iqbal Hussain, M.D., Sr. Medical Director, Medical Sciences

Masakazu (Sho) Andoh, M.E., Associate Director, Research Data Science

Jiuhong Zha, Ph.D., Manager, Biopharmaceutical Sciences

Marlowe Schneidkraut, Ph.D., D.A.B.T., Assistant Director, Toxicology

Marcel van Gelderen, Ph.D., Director, Clinical Pharmacology, Astellas Europe R&D

Marianne Bovenhoff, M.Sc., M.B.A., Transatlantic Project Leader, Astellas Europe R&D

Jim Keirns, Ph.D., Sr. Director, Biopharmaceutical Sciences

Background: The Sponsor submitted IND 69,416, serial 000, on May 9, 2006. The Division requested this teleconference to discuss our preliminary 30-Day Safety review

of their new IND. On June 5, 2006, the following requests for protocol revisions intended to resolve potential Clinical Hold safety concerns were faxed to the Sponsor for discussion during this teleconference.

1. Add a study procedure:

- Conduct orthostatic testing at Screening, as well as on Day -1 and pre-dose on Day 1 for each treatment period. Propose specific changes in blood pressure and pulse rate to define “baseline orthostasis” (for example, change in pulse rate with orthostatic maneuver of >20 bpm or to a level ≥ 120 bpm). (Note: Subjects should not be orthostatic at baseline)

Sponsor Response: The Sponsor agreed and will revise the protocol accordingly.

2. Revise eligibility criteria:

- Change inclusion criterion #2: “The subject is male or female 19 to ^(b)₍₄₎ 50 years of age, inconclusive”. (Note: Older subjects may tolerate increases in heart rate less well).

Sponsor Response: The Sponsor stated that they anticipated that a large part of the target population will be post-menopausal women, and, therefore, were concerned that the proposed 50 years of age limit may limit enrollment of this specific subgroup.

Division Response: The Division acknowledged this concern and proposed an upper limit of 55 years of age.

Sponsor Response: The Sponsor agreed and will revise the protocol accordingly.

- Change inclusion criterion #3: “The subject, if female, must be surgically sterile (must be documented), post-menopausal (defined as at least two years without menses) or must be using ^(b)₍₄₎ double-barrier contraception, IUD, or be in a stable relationship where the partner has had permanent sterilization.” (Note: All efforts should be made to avoid having pregnant females in this study).

Sponsor Response: The Sponsor asked if reference to ^(b)₍₄₎ could be removed, proposing the following change to inclusion criterion #3: “The subject, if female, must be surgically

sterile (must be documented), post-menopausal (defined as at least two years without menses) or must be using double-barrier contraception or a non-hormonal IUD.” All efforts would be made to avoid having pregnant females in the study.

Division Response: The Division agreed.

- Add an exclusion criterion: “The subject is taking any oral hormonal contraceptive”. (Note: Ketoconazole can substantially increase serum estrogen levels in subjects taking oral contraceptives).

Sponsor Response: The Sponsor agreed and will revise the protocol accordingly.

- Add an exclusion criterion: “The subject has a resting pulse < 50 bpm or > 90 bpm at Screening, on Day -1, or on Day 1, pre-dose.” (Note: Based upon potential increase in heart rate, subjects should have normal pulse rate at screening, and prior to dosing in each period).

Sponsor Response: The Sponsor agreed and will revise the protocol accordingly.

- Add an exclusion criterion: “The subject has baseline orthostasis (by pre-defined blood pressure and pulse criteria) at Screening, on Day -1, or on Day 1, pre-dose.” (Note: Same reason as above).

Sponsor Response: The Sponsor agreed and will revise the protocol accordingly.

- Add an exclusion criterion: “The subject is taking a potential inhibitor of CYP3A4 or CYP2D6.” (Note: Inhibitors of CYP3A4 and 2D6 may further increase serum YM178 levels).

Sponsor Response: The Sponsor agreed and will revise the protocol accordingly.

3. Add a stopping criterion:

- If the subject experiences hypotension or a medically significant increase in pulse rate after taking YM178 alone in Period 1, the subject should be discontinued from the trial (and not participate in Period 2). (Note: Subjects who do not tolerate YM178 alone in Period 1 should not proceed into Period 2).

Sponsor Response: The Sponsor agreed to exclude patients with symptomatic hypotension or medically significant increase in heart rate in Period 1 and will revise the protocol accordingly.

4. Lower the dose:

- The YM178 dose should be lowered to 50mg. (Note: We are concerned that when the 100mg dose is taken with ketoconazole, serum YM178 concentrations may be attained that have already been shown to induce clinically relevant increases in heart rate, tachycardia, palpitations and headache. We are particularly concerned about female subjects. A possible alternative to dose reduction is to exclude females entirely from the study.)

Sponsor Response: The Sponsor asked if it would be reasonable to start the study by first dosing male subjects (n=12) with 100 mg of YM178 in study Periods 1 and 2. If no significant safety concerns are observed, and if the mean C_{max} increases by < 50% in treated male subjects, the Sponsor proposed that female subjects will be dosed with 100 mg of YM178 in study Periods 1 and 2. If, however, mean C_{max} increases by > 50% or if significant safety concerns are observed in treated male subjects, the Sponsor proposed that female subjects will be dosed with 50 mg of YM178 in study Periods 1 and 2. The Sponsor estimates (a rough estimate) that the C_{max} was likely to increase by 20% after taking ketoconazole.

Division Response: The Division agreed with the Sponsor's proposal. It represents an adequate precaution for the potential risk in women.

Action Items:

- The Sponsor agreed to submit a general correspondence to their IND to confirm these agreements (received on June 7, 2006 via fax).
- The Sponsor will submit a revised protocol to their IND.
- The Division will continue their review of the Sponsor's serial #000 submission and will provide any further review comments, if applicable, via an Advice Letter.
- The Division will provide minutes of this teleconference within 30-days.

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

/s/

Mark S. Hirsch

7/5/2006 01:35:11 PM