CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204447 SUPPL # HFD # 130

Trade Name Brintellix

Generic Name vortioxetine

Applicant Name Takeda Pharmaceuticals USA Inc.

Approval Date, If Known

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?

5 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:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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: Hiren Patel, PharmD
Title: Senior Regulatory Project Manager, Division of Psychiatry Products
Date: September 4, 2013

Name of Office/Division Director signing form: Mitchell Mathis, MD
Title: Division Director (acting), Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

HIREN PATEL
09/30/2013

MITCHELL V Mathis
09/30/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204447 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Brintellix Established/Proper Name: vortioxetine Dosage Form: Tablets		Applicant: Takeda Pharmaceuticals USA Inc. Agent for Applicant (if applicable): N/A
RPM: Hiren Patel		Division: Division of Psychiatry Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 2, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 9/30/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	9/30/13
• Original applicant-proposed labeling	10/2/12
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	9/30/13
• Original applicant-proposed labeling	10/2/12
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	8/12/13 and 6/28/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptability Letter – 10/26/12 Name Review – 8/20/13; 10/26/12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 12/5/12 ☒ DMEPA 8/19/13; 5/16/13 ☒ DMPP/PLT (DRISK) 6/28/13 ☒ ODPD (DDMAC) 7/9/13 ☐ SEALD ☐ CSS ☒ Other reviews Maternal Health Team 8/19/13
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review – 11/29/12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 9/4/13 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Late Cycle Meeting Background Package – 6/20/13 Labeling PMR/PMC Discussion Comments – 6/14/13 Chemistry Discipline Review Letter – 6/7/13 Mid-Cycle Communication – 3/26/13 Filing Communication – 12/6/12 Filing Email – 11/30/12 NDA Acknowledgement – 10/9/12
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 6/28/12
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2/13/08
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Late-Cycle Meeting – 8/1/13 Type C Meeting – 4/2/10
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 9/30/13
Division Director Summary Review *(indicate date for each review)*	☐ None 9/16/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/20/13
PMR/PMC Development Templates *(6)*	☐ None 9/30/13
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader and Reviewer Review(s) *(indicate date for each review)*	Clinical Review - 6/5/13 Clinical Filing Review – 11/13/12
• Clinical review(s) *(indicate date for each review)*	See bullet above
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 18 of Clinical Review dated 6/5/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested OSI letter to investigator – 7/8/13 OSI Clinical Inspection Summary – 5/22/13 OSI letter to investigator – 5/14/13 OSI letter to investigator – 5/14/13 OSI letter to investigator – 5/14/13 OSI letter to investigator – 5/14/13 OSI letter to investigator – 5/7/13
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director, Team Leader, and Reviewer Review *(indicate date for each review)*	☐ None Statistical Review - 6/5/13 Statistical Filing Review – 11/13/12
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None See bullet above
Statistical Review(s) *(indicate date for each review)*	☐ None See bullets above
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology and Pharmacometrics Division Director, Team Leader, and Reviewer Review *(indicate date for each review)*	☐ None Clinical Pharmacology Review – 6/4/13 Clinical Pharmacology Filing Review – 11/15/12
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None See bullet above
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None See bullets above
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None 7/12/13

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 9/24/13
• Supervisory and Reviewer Review *(indicate date for each review)*	☐ None Nonclinical Review - 6/4/13 Nonclinical Filing Review – 11/13/12
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None See bullet above
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 5/1/13
❖ ECAC/CAC report/memo of meeting	☐ None 5/2/13 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 8/20/13
• Branch Chief, Team Leader, and Reviewer Review *(indicate date for each review)*	☐ None ONDQA Review - 5/29/13 ONDQA Initial Quality Assessment/Filing Review – 10/11/12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Biopharmaceutics Review – 7/1/13 Biopharmaceutics Review – 6/2/13 Biopharmaceutics Review – 4/8/13 Biopharmaceutics Filing Review – 11/14/12
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Microbiology Review – 5/1/13 Microbiology Filing Review – 11/8/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See pages 86 and 87 of Chemistry Review dated 5/29/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 7/23/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

HIREN PATEL
09/30/2013

PeRC PREA Subcommittee Meeting Minutes
September 4, 2013

PeRC Members Attending:
Lynne Yao
Robert "Skip" Nelson
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Tom Smith
Julia Pinto
Ethan Hausman
Peter Starke
Wiley Chambers
Andrew Mulberg
Andrew Mosholder
Colleen LoCicero
Dianne Murphy
Gregory Reaman
Dionna Green
Daiva Shetty
Lisa Kammerman
George Greeley
Jane Inglese

Guests Attending:
Robert Guidos
Richard Moscicki
Renan Bonnel (OPT)
Nichella Simms (PMHS)
Gilbert Burckart (OCP)
Courtney Suggs (OCP)
Richard Whitehead (DMEP)
Bradley McEvoy (OB)
Jaya Vaidyanathan (OCP)
Lokesh Jain (OCP)
David Carlson (DMEP)
Margaret Lin (DNP)
Hao Zhu (OCP)
Ellis Unger (ODE4)
Jing Zhang (DPP)
George Kordzakhia (DBI)
Linda Fossom (DPP)
Jenn Sellers (DPP)
Hiren Patel (DPP)
Joshua Lloyd (DAAAP)
Swati Patwardhan (DAAAP)
Juli Tomaino (DGIEP)
Anil Rajpal (DGIEP)
Nitin Mehrotra (OCP)
Karen Mahoney (DMEP)
Andre Jackson (OCP)
Sue-Chih Lee (PMTL)
Jian Wang (OCP)
Russel Fortney (DCRP)
Gail Moreschi (DCRP)
Shari Targum (DCRP)
Vicki Moyer (PMHS)
Amy Taylor (PMHS)
Melissa Tassinari (PMHS)

Agenda

10:00 NDA 204447 Brintellix (vortioxetine) Partial Waiver/Deferral/Plan
10:30 (b) (4)
11:00 NDA 21830 Asacol (mesalamine) Assessment
(b) (4)

Brintellix (vortioxetine) Partial Waiver/Deferral/Plan

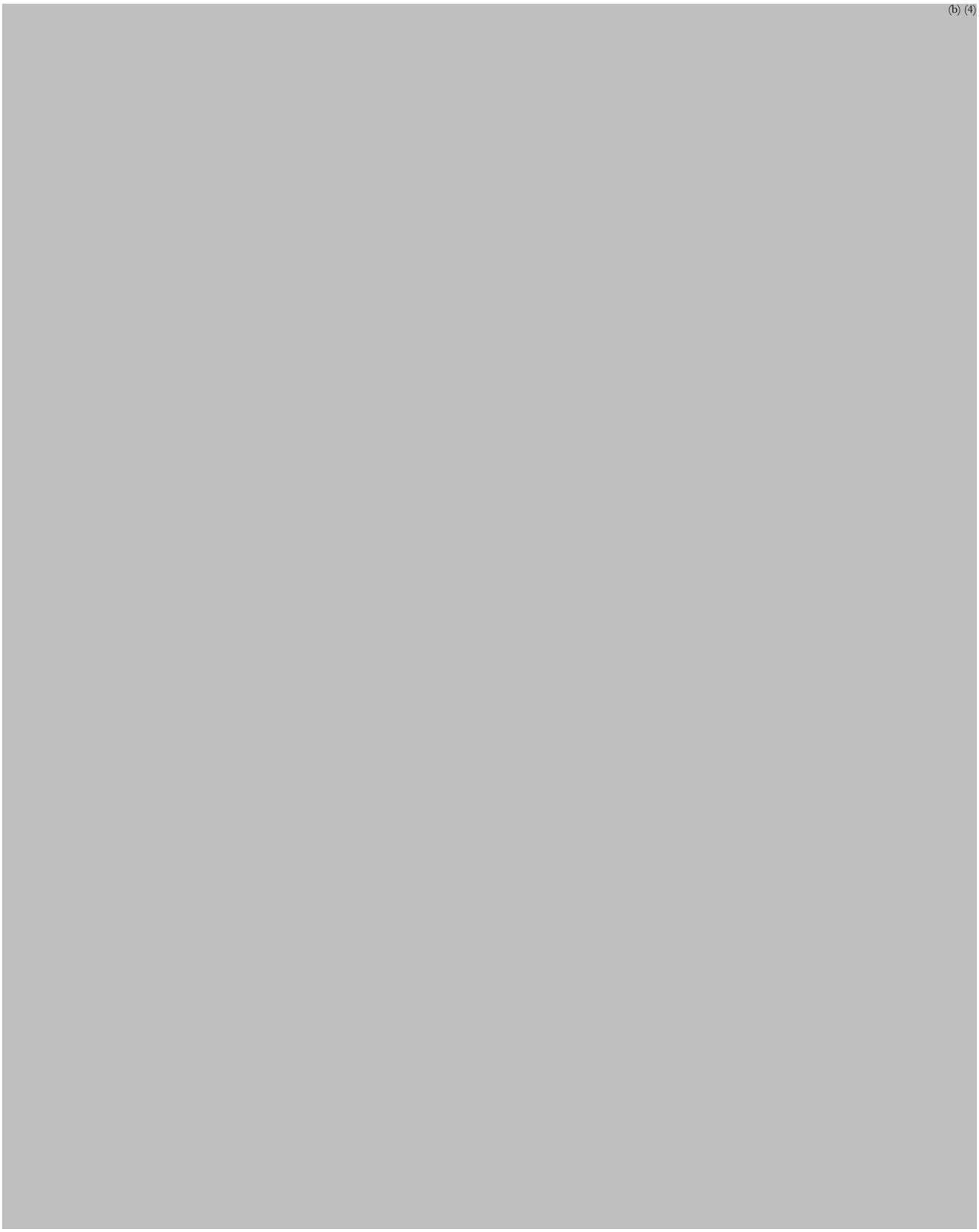
- NDA 204447 seeks marketing approval for Brintellix (vortioxetine) for the treatment of major depressive disorder (MDD).
- The application was submitted on October 2, 2012, and has a PDUFA goal date of October 2, 2013.
- The application triggers PREA as directed to a new active ingredient.
- A waiver is being requested for pediatric patients aged birth to six years because studies are impossible or highly impractical.
- *Division justification for waiver*: Studies in pediatric patients aged 0 to 6 years would be impossible or highly impractical due to the low prevalence of MDD in this age group.
- A deferral is being requested for pediatric patients aged 7 to 11 years and aged 12 to 17 years because adult studies have been completed and the product is ready for approval.
- The sponsor plans to conduct the following clinical studies:
    - Study 1 - Pharmacokinetics, Safety, Tolerability: Open-label study evaluating the pharmacokinetics and tolerability of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835 after multiple oral dosing of Lu AA21004 in child and adolescent patients with a DSM-IV diagnosis of Depressive and Anxiety Disorder. The study should consist of 2 populations: children aged 7-11 years and adolescents aged 12-17 years. There will be 4 dose cohorts (5, 10, 15 or 20 mg) within each population with patients being allocated to a cohort within their population.
    - Study 2 (12709A - SE) - Short-term Safety and Efficacy in children 7-11 years: double-blind, randomized, placebo-controlled, active-referenced (fluoxetine) study to test superiority of Lu AA21004 versus placebo in pediatric patients 7-11 years with Major Depressive Disorder (MDD). The dosing regimen will be based on the results from the pediatric PK study.
    - Study 3 (12710A - SE) - Short-term Safety and Efficacy in adolescents 12-17 years: double-blind, randomized, placebo-controlled, active-referenced (fluoxetine) study to test superiority of Lu AA21004 versus placebo in pediatric patients 12-17 years with Major Depressive Disorder (MDD). The dosing regimen will be based on the results from the pediatric PK study.
- The Division believes that the sponsor's proposal is adequate.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to 6 years because studies are impossible or highly impractical.

- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 7 to 17 years because the product is ready for approval in adults. The PeRC agreed to the proposed timelines for the deferred studies.

(b) (4)



Asacol (mesalamine) Assessment


(b) (4)

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/s/

JANE E INGLESE
09/19/2013

Patel, Hiren

From: Patel, Hiren
Sent: Friday, August 09, 2013 10:27 AM
To: 'Sambor, Joanna'
Subject: RE: NDA 204447 - LCM Meeting Minutes

Dear Joanna,

On face, we agree that the studies of vortioxetine administered to juvenile rats which you have already submitted to the NDA appear adequate to support use in children. Consequently, a study in juvenile rats will not be a PMR. We apologize for the confusion caused by our comment added to the minutes after the Late Cycle Meeting.

Regards,
Hiren

From: Sambor, Joanna [mailto:joanna.sambor@takeda.com]
Sent: Tuesday, August 06, 2013 10:03 AM
To: Patel, Hiren
Subject: RE: NDA 204447 - LCM Meeting Minutes

Dear Hiren,

Thank you for providing the minutes from the Late Cycle Meeting for NDA 204447. I would like to ask for clarification to the Post Meeting Note that was added on page 4 of the minutes.

> "Post-meeting Comment: To support the use of vortioxetine in children less than 12 years of age, you must conduct a (post-marketing) study to assess the safety of vortioxetine in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. The protocol should be submitted for our comments prior to initiation of the study. You should also include milestone dates."

In the NDA, 3 juvenile toxicity studies are included. The main juvenile toxicity study in rats is Study 12980, which includes evaluation of neurological/behavioral development and reproductive development. In this study, vortioxetine was administered to rats from day 21 to day 91 of age. The main study was preceded by a TK study (Study 12592) and a dose-range-finding study (Study 12685). The studies are also summarized in Module 2.6.6, Section 6.4.

Can you please advise as to whether these studies will address the study requested in the post-meeting comment?

Kind Regards,
Joanna

Joanna Sambor, MS
Director, Regulatory Strategy
Global Regulatory Affairs

Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-2948
(b) (6)

joanna.sambor@takeda.com
www.takeda.us

From: Patel, Hiren [mailto:Hiren.Patel@fda.hhs.gov]
Sent: Friday, August 02, 2013 9:58 AM
To: Sambor, Joanna
Subject: NDA 204447 - LCM Meeting Minutes

Hi Joanna,

Please find attached the LCM Meeting Minutes from our meeting on July 2, 2013. I am planning on sending you our edits to the vortioxetine labeling by the end of next week.

Thanks,
Hiren

Hiren D. Patel, Pharm.D., M.S., RAC
LCDR USPHS
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov

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/s/

HIREN PATEL
08/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

LATE-CYCLE MEETING MINUTES

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, M.S.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) dated October 2, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brintellix (vortioxetine) 5 mg, 10 mg, 15 mg, and 20 mg tablets.

We also refer to the late cycle meeting (LCM) between representatives of your firm and the FDA on July 2, 2013.

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

If you have any questions, call Hiren Patel, PharmD, Regulatory Project Manager at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Jing Zhang, MD
Medical Team Leader
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
Slides from Takeda

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 2, 2013; 9:00am-10:30am
Meeting Location: Building 22 Conference Room 1315

Application Number: NDA 204447
Product Name: Brintellix (vortioxetine)
Applicant Name: Takeda Pharmaceuticals USA, Inc.

Meeting Chair: Jing Zhang, MD
Meeting Recorder: Hiren Patel, PharmD, RAC

FDA ATTENDEES

Sandra Kweder, MD	Deputy Director, Office of New Drugs
Ellis Unger, MD	Director, Office of Drug Evaluation I
Robert Temple, MD	Acting Deputy Director, Office of Drug Evaluation I and Deputy Center Director for Clinical Science
Mitchell Mathis, MD	Division Director (acting), Division of Psychiatry Products (DPP)
Colleen Locicero, RPh	Associate Director for Regulatory Affairs, Office of Drug Evaluation I
Hiren Patel, PharmD, RAC	Senior Regulatory Project Manager, DPP
Jing Zhang, MD	Medical Team Leader, DPP
Jenn Sellers, MD	Medical Reviewer, DPP
Linda Fossom, PhD	Pharmacology/Toxicology Supervisor, DPP
Ramesh Sood, PhD	Acting Division Director, Office of New Drug Quality Assessment (ONDQA)
Wendy Wilson-Lee, PhD	Chemistry Reviewer, ONDQA
Houda Mahayni, PhD	Biopharmaceutics Reviewer, ONDQA
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Andre Jackson, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biometrics (OB)
George Kordzakhia, PhD	Biometrics Reviewer, OB
Simran Parihar, PharmD	Regulatory Project Manager, DPP
Reema Mehta, PharmD, MPH	Team Leader, Division of Risk Management
John Metcalfe, PhD	Senior Microbiology Reviewer, Office of Pharmaceutical Science
Somya Dunn, MD	Risk Management Analyst, Division of Risk Management
Sam H. Haidar, Ph.D., RPh	Chief, Bioequivalence Branch, Office of Scientific Investigations

Paul C. Brown, PhD	ODE Associate Director for Pharm/Tox, Office of New Drugs IO
Irene Z. Chan, PharmD, BCPS	Team Leader, Division of Medication Error Prevention and Analysis
Loretta Holmes, BSN, PharmD	Safety Evaluator, Division of Medication Error Prevention and Analysis
Laurelle Cascio, PharmD	Safety Evaluator, Division of Pharmacovigilance I
Li Zhang, Ph.D	Reviewer, Division of Pharmacometrics, OCP
Kim Taylor, MBA, MPH	Operations Research Analyst, Office of Strategic Programs
Jacqueline M. Major, PhD, MS	Epidemiologist, Division of Epidemiology-I (DEPI-I)
Teshara G. Bouie	Regulatory Health Project Manager, Office of New Drug Quality Assessment
Tammie Howard RN, MSN	Regulatory Reviewer, Pediatric and Maternal Health Staff, Maternal Health Team

(b) (4)

APPLICANT ATTENDEES

Albena Patroneva, MD	Executive Medical Director, Clinical Sciences, Takeda
Stephen Brannan, MD, CNS	Therapeutic Area Head, Clinical Sciences, Takeda
Atul Mahableshwarkar, MD	Senior Medical Director, Clinical Sciences, Takeda
Marianne Dragheim, MD	Chief Specialist, ICR Mood & Anxiety Disorders, Lundbeck
Michael Serenko, MD	Medical Director, Pharmacovigilance, Takeda
Karen Asin, PhD	Senior Fellow, Toxicology, Takeda
Grace Chen, PhD	Principal Scientist, Clinical Pharmacology, Takeda
Frank Ogrinc, PhD	Associate Director Statistics, Analytical Science, Takeda
Kevin Fletcher, Principal Pharmaceutical Scientist	CMC Strategy and Program Management, Takeda
Shuyen Huang, PhD	Associate Director, Regulatory Strategy CMC, Takeda
Binita Kwankin	Global Development Head, Regulatory Affairs, Takeda
Eric Floyd, MS, MBA, PhD	Vice President, US Regulatory Affairs, Lundbeck
Michael Cronquist Christensen, MSc, MPA, DrPH,	Senior Regulatory Strategy Leader, Lundbeck
Joanna Sambor, MS	Director Regulatory Strategy, Takeda
Laura Schiavoni, MBA, RAC	Senior Associate, Regulatory Strategy, Takeda

1.0 BACKGROUND

NDA 204447 was submitted on October 2, 2012 for Brintellix (vortioxetine).
Proposed indication(s): Treatment of Major Depressive Disorder
PDUFA goal date: October 2, 2013
FDA issued a Background Package in preparation for this meeting on June 20, 2013.

2.0 DISCUSSION

1. Introductory Comments

    a. Introductions, ground rules, objectives of the meeting.

Discussion: *The meeting started at 9:00am (EST) with 1) introductions of attendees from FDA and Takeda; 2) ground rules; and 3) objectives of the meeting. We stated that the purpose of the Late-Cycle meeting was to discuss any substantive review issues that had been identified to date. We noted that many of the review issues that were identified in the background package had been resolved and therefore the additional available time would be allocated to discussing other agenda items including Postmarketing Requirements/Postmarketing Commitments (PMC) and labeling.*

2. Discussion of Substantive Review Issues

Chemistry/Nonclinical

a) Drug substance DMF supporting the NDA remains deficient.

Chemistry

b) Packaging site comparability protocol is inadequate
c) Alternate drug product manufacturing site comparability protocol is inadequate.
d) Lot number and expiration date needed on immediate container labels.
e) Proposed Structured Product Labeling elements are inadequate.

Discussion:

Chemistry

We are reviewing your submitted amendment and have determined that the major DMF deficiency has been resolved; however, we have not yet evaluated the responses to the minor DMF issues. All remaining chemistry issues identified above have been adequately addressed. The facilities inspections are pending.

Biopharmaceutics

We acknowledge that your justification to use Case B instead of Case C for the comparative dissolution testing in support of the alternate manufacturing site that is proposed in the comparability protocol in your amendment dated June 20, 2013, is acceptable. There are no other Biopharmaceutics issues pending.

3. Postmarketing Requirements/Postmarketing Commitments

Clinical Pharmacology

a) An in vivo study in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.

b) In vitro determination of vortioxetine and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

Clinical

c) Pediatric studies: as a PREA requirement you will need to conduct two multi-center, double-blind, placebo-controlled pediatric studies in children and adolescents (7 to 17 years old) in the treatment of major depressive disorder. At least one of these studies must be a fixed-dose study.
d) A relapse prevention study in the United States (US): since only vortioxetine 20 mg/day demonstrated efficacy in the US and the relapse prevention study (11985A) was a non-US study, you will need to conduct a relapse prevention study to further characterize the dose response relationship of vortioxetine in the United States. This study should be a fixed dose study and the dose choice should cover the approved dose range.

Discussion:

Clinical Pharmacology

You agreed to conduct all clinical pharmacology related PMC studies and you will be providing a proposal on milestone dates (Final protocol submission, trial completion date, and final report submission). Additionally, we notified you that all results based on data generated by (b) (4) *will be removed from the current label due to the pending OSI inspection issues.*

Clinical

We acknowledge that a pediatric plan was submitted on August 26, 2011 under IND 76307 and that it included two pediatric studies: one in children ages 7 to 11 years old and the other in adolescents ages 12 to 17 years. The proposed plan is acceptable.

A relapse prevention study in the US is necessary considering that only vortioxetine 20 mg/day demonstrated efficacy in the US and the relapse prevention study (11985A) was a non-US study. Additionally, conducting a relapse prevention study that includes 20 mg and lower doses will answer the question of whether vortioxetine 20 mg/day is necessary for maintenance treatment in the US.

You provided the following major arguments against the requirement of a relapse prevention study:

a) *The totality of data across the dose range of 5 to 20 mg including within US subgroup demonstrated statistically significant and/or a clinical meaningful difference. You stated that in the positive 316 US study, 10 mg separated from placebo on change from Baseline in MADRS Total Score at Week 4 and 6. Although separation was not statistically significant at Week 8 ($p=0.058$), the difference from placebo was a clinically relevant -2.2 points. The elderly study (12541A) demonstrated in US subjects (~57 US subjects/arm) that vortioxetine 5 mg separated from placebo on the MADRS total by -3.6 points, $p<0.05$ (MMRM).*

b) *The two ongoing studies, LUAA21004_202 and LUAA21004_318 include a significant amount of US subjects and will provide more dose-related efficacy data in the US. Study LuAA21004_202 is an 8 week, flexible dose (10 to 20 mg), double-*

blind, and placebo controlled study in 600 subjects with cognitive dysfunction and MDD. Around 50% of study subjects will be recruited from the US.
Study LuAAS21004_318 is an 8 week, flexible dose (10 to 20 mg), double-blind, active-controlled study evaluating the efficacy of LuAA21004 on SSRI- induced sexual dysfunction (SD). All 440 subjects are recruited from the US and Canada.

c) *The reason for regional difference is unclear.*

We noted that not all of the results presented by you were based on the pre-specified primary endpoint with the pre-specified primary analysis. For example the data from the elderly study (12541A) was based on neither the pre-specified primary endpoint HAM-D-24 nor the pre-specified analysis ANCOVA, LOCF. The efficacy result from 5 mg did not support efficacy in the US subjects. Study LuAA21004-318 doesn't have a placebo arm (escitalopram 10 to 20 mg serves as an active control), and the efficacy data from this study is uninterpretable. Therefore, we encourage you to submit a justification document for us to review.

Post-meeting Comment:
To support the use of vortioxetine in children less than 12 years of age, you must conduct a (post-marketing) study to assess the safety of vortioxetine in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. The protocol should be submitted for our comments prior to initiation of the study. You should also include milestone dates.

4. Major Labeling Issues

Discussion:
Clinical Studies

Active Reference: In our Labeling PMR/PMC Discussion Comments letter dated June 14, 2013, we recommended including the efficacy data from the active comparators in the product label. You expressed that this would lead to unfair comparisons because the active comparators were included for the purpose of assay sensitivity only and the doses of vortioxetine used in these studies are not equivalent to doses used with active comparators. You also stated that there was a bias against vortioxetine because subjects who had a history of lack of response to previous adequate treatment with duloxetine/venlafaxine for any MDD episode were excluded from the studies. We indicated that we would consider removing active comparators' data from the label.

Regional Effect: In our Labeling PMR/PMC Discussion Comments letter dated June 14, 2013, we recommended 1) identifying pivotal studies as US or non-US studies, and 2) including the statement, "In all US studies, only the 20 mg dose was superior to placebo." You agreed to the first recommendation and objected to the second recommendation because there were concerns about unintended consequences of the statement, "some patients may benefit from a lower dose and this information will not be communicated to the physician." We agreed to revisit the corresponding labeling language.

(b) (4)

Time Course Plot: We requested that you provide plots of treatment effect over time for potential inclusion in the label. Such information can be useful to health care providers (HCPs) and patients.

We also mentioned that the (b) (4) *should be removed throughout section 14.*

Clinical Pharmacology

Mechanism of Action: We acknowledge that in addition to inhibition of the serotonin reuptake transporter, vortioxetine binds with moderate to high affinity at several serotonin receptors; however, there appears to be inadequate evidence, aside from in vitro binding/activity data, to support the activity at these other receptors as part of its mechanism of antidepressant action. You would need to demonstrate that the activity at these receptors contributes to the clinical efficacy of vortioxetine.

You asked for our basis for including receptors as part of the mechanism of action. We explained that relevant (in vitro) binding affinity/activity is important. However, because vortioxetine has very high affinity for and inhibitory activity at the serotonin reuptake transporter, an activity that is accepted as the mechanism of action for several antidepressants, attributing its antidepressant action to activities at other serotonin receptors would be expected to be difficult. Furthermore, the actual mechanism(s) underlying depression in humans is not known and there isn't a model for depression in animals that reliably predicts antidepressant efficacy in humans. In summary, in vitro is not in vivo and in vivo data (behavioral or neurochemical) from animals (rats) are not convincing evidence for antidepressant efficacy in humans.

We reiterated that we cannot include activities at specific receptors as part of the mechanism of action (section 12.1) without strong evidence that those activities contribute to the clinical efficacy. You indicated that a document justifying the inclusion of activities at some (few) receptors in the mechanism of action section of labeling would be submitted and we agreed to consider your rationale.

Dosage and Administration

Discontinuing Treatment: You referred to the Rosenbaum paper which studied withdrawal symptoms associated with fluoxetine, sertraline and paroxetine and argued that sertraline and paroxetine are associated with much more withdrawal symptoms compared to

vortioxetine. We agreed that there is a difference in the severity and frequency of withdrawal symptoms between some SSRIs/SNRIs and LuAA21004 regarding withdrawal symptoms. We do not think discontinuation syndrome should be included in the Warning & Precaution section of vortioxetine label. However, in your DESS analysis, 6 symptoms occurred in 5% and twice placebo at the end of the 1st week of discontinuation of vortioxetine 15 mg group and two symptoms occurred >4% and twice placebo in the 20 mg group. It is necessary to inform the health care providers (HCPs) and patients about these potential withdrawal symptoms after abrupt discontinuation of vortioxetine at higher doses. We noted that in the vortioxetine20 mg group not one of the 6 withdrawal symptoms mentioned in our Labeling PMR/PMC Discussion Comments letter dated June 14, 2013 met the criteria of 5% and twice placebo and therefore the corresponding labeling language will need to be modified.

Adverse Reactions

Treatment Emergent Sexual Dysfunction Adverse Events: In our Labeling PMR/PMC Discussion Comments letter dated June 14, 2013, we recommended deleting Table 3 (b) (4) *You disagreed with our recommendation and proposed an alternative table. Your alternative table did not provide clinically meaningful information. It is well known that SSRIs/SNRIs cause sexual dysfunction and the spontaneous report of sexual dysfunction related adverse events is under reported.* (b) (4) *You stated that in the duloxetine package insert, no female-specific AEs with regards to sexual dysfunction were noted in >2% of females treated with duloxetine. Therefore, duloxetine was not expected to demonstrate assay sensitivity for sexual dysfunction events in women. You offered to retain the modified table and have the collapsed summary data underneath it. We will review the supportive data and proposed changes before making any decision.*

(b) (4)

(b) (4)

Warnings and Precautions

Suicidality Language: In our Labeling PMR/PMC Discussion Comments Letter dated June 14, 2013 , we recommended deleting specific suicidality data from vortioxetine in the Warning and Precaution section of the label. You requested that these data be reinstated. We indicated that the language in section 5.1 is standard language for all SSRIs/SNRIs. We have not allowed sponsors to include their drug specific suicidalilty data in this section. (b) (4)

(b) (4)

5. Review Plans

Discussion: *We are on schedule to take an action on NDA 204447 by October 2, 2013.*

6. Wrap-up and Action Items

Discussion: *The clinical site inspections were completed and the results are acceptable.*

We plan on discussing the labeling items that were covered and will be providing you with our labeling revisions. You will be submitting justification documents with respect to our requests for a postmarketing relapse prevention study and revisions to draft labeling.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

JING ZHANG
08/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 76307

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Joanna Sambor, MS
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Sambor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for vortioxetine (Lu AA21004).

We also refer to the meeting between representatives of your firm and the FDA on June 22, 2012. The purpose of the meeting was to discuss the components of the planned vortioxetine NDA submission.

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

If you have any questions, call Hiren Patel, Regulatory Project Manager at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
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:	B
Meeting Category:	Pre-NDA (Pre-Submission)
Meeting Date and Time:	June 22, 2012; 3:00pm (EST)
Meeting Location:	Building 22 Conference Room 1313
Application Number:	IND 76307
Product Name:	Vortioxetine (Lu AA21004)
Indication:	Treatment of Major Depressive Disorder
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Thomas Laughren, MD

FDA ATTENDEES

Ellis Unger, MD	Acting Director, Office of Drug Evaluation I
Thomas Laughren, MD	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, MD	Deputy Division Director, DPP
Jing Zhang, MD	Medical Team Leader, DPP
Jenn Sellers, MD	Medical Officer, DPP
Linda Fossom, PhD	Pharmacology/Toxicology Supervisor, DPP
Antonia Dow, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Andre Jackson, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biometrics
Charles Bonapace, PharmD	Reviewer, Office of Scientific Investigations, Division of Bioequivalence & Good Laboratory Practice Compliance
Hiren Patel, PharmD, RAC	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Stephen Brannan, MD	PDD Therapeutic Area Head, Clinical Sciences, Takeda
Atul Mahableshwarkar, MD	Senior Medical Director, Clinical Sciences, Takeda
Marianne Dragheim, MD	Chief Specialist, ICR Mood & Anxiety Disorders, Lundbeck
Michael Serenko, MD	Medical Director, Pharmacovigilance, Takeda
Mitch Friedman, PhD, DABT	Director Toxicology, Biological Science, Takeda

Grace Chen, PhD	Principal Scientist, Clinical Pharmacology, Exploratory and Translational Development, Takeda
Frank Ogrinc, PhD	Associate Director Statistics, Analytical Science, Takeda
Eric Floyd, MS, MBA, PhD	Vice President, US Regulatory Affairs, Lundbeck
Stephanie Sommer, PhD	Regulatory Strategy Leader, Lundbeck
Joanna Sambor, MS	Associate Director Regulatory Strategy, Takeda

1.0 BACKGROUND

Lu AA21004 has been co-developed by Takeda Global Research & Development Center, Inc. (TGRD) and H. Lundbeck A/S (Lundbeck) for the treatment of MDD.

Lu AA21004 belongs to a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. The mechanism of action of Lu AA21004 is thought to be related to its multimodal activity, which is a combination of 2 pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter.

In vitro studies indicate that Lu AA21004 is an antagonist at 5-hydroxytryptamine type 3 (5-HT3), 5-hydroxytryptamine type 7 (5-HT7), and 5-hydroxytryptamine type 1D (5-HT1D) receptors, a partial agonist at 5-hydroxytryptamine type 1B (5-HT1B) receptor, an agonist at 5-hydroxytryptamine type 1A (5-HT1A) receptor, and an inhibitor of the 5-hydroxytryptamine transporter (5-HTT).

Lu AA21004 was initially being developed for MDD and generalized anxiety disorder (GAD) at doses up to 10 mg. The results of an initial phase 3 program did not demonstrate consistent efficacy in the United States, therefore a revised phase 3 program evaluating doses up to 20 mg was initiated in MDD only. The results from 3 of the 4 new studies are now available and global submissions to seek marketing authorization for Lu AA21004 in MDD are planned in 2012. A US NDA is planned for submission on October 1, 2012.

The following studies will be included in the NDA filing: 31 completed clinical pharmacology studies, 10 completed phase 2/3 short-term MDD studies (11492A, 11984A, 305, 13267A, 315, 316, 317, 303, 304, and 12541A, the dedicated elderly study), 1 MDD relapse prevention study (11985A), 4 phase 3 short-term GAD studies (308, 309, 310, and 311), and 1 GAD relapse-prevention study (12473A). Completed data from 3 open-label extension studies will also be provided (Studies 11492C, 11984B, and 301). In addition, interim safety data from 2 ongoing open-label extension studies will be included (Studies 314 and 13267B). A total of 14 additional studies are on going and will not be included in the NDA submission, but the safety data from these studies, as listings of serious adverse events (SAEs), will be included in the NDA.
The MDD indication will be supported by the data from subjects in 10 completed phase 2/3 placebo-controlled studies and one relapse prevention study in MDD. The sponsor claims that six (6) short-term studies in adults (11492A, 305, 13267A, 315 [US], 316 [US], and 12541A [some US subjects]) and the relapse-prevention study (Study 11985A) are positive (Table 6.a).

The intent of this meeting is to:

- Confirm that FDA agrees with the studies the sponsor considers adequate and well controlled in establishing the effectiveness and safety of the drug within the intended dose range.

- Acquaint FDA reviewers with the general information to be submitted in the NDA.

- Discuss the presentation of the data in the NDA to facilitate FDA's review.

- Have a common understanding with FDA regarding implications of an NDA submission early during the implementation of the Prescription Drug User Fee Act (PDUFA V).

2. DISCUSSION

2.1 Questions Pertaining to PDUFA V

Question 1: Does FDA agree with the sponsor's understanding regarding the elimination of the 120-day safety update?

Company Position: The sponsor is aware that the Pre-Submission meeting is to be scheduled prior to implementation of PDUFA V. Assuming the law will be in place at the time of the NDA, the sponsor would like to work with FDA to discuss and have a common understanding of the concepts of PDUFA V. The sponsor has the following understanding of the proposed goals and procedures for the Center for Drug Evaluation and Research (CDER) to apply during review of New Molecular Entities:

Pre-Submission Meeting: The sponsor understands that the Pre-Submission (pre-NDA) meeting will be attended by the FDA review team including appropriate senior FDA staff. The agreement and discussions will be summarized at the conclusion of the meeting and reflected in FDA meeting minutes.

Day 74 Letter: The sponsor understands that the planned review timeline included in the Day 74 letter for applications submitted under PDUFA V will include the planned date for the internal midcycle review meeting. The letter will also include preliminary plans on whether to hold an Advisory Committee (AC) meeting to discuss the application.

Mid-Cycle Review Interaction: The sponsor understands the FDA Regulatory Project Manager (RPM), and other appropriate members of the FDA review team (eg, Cross Discipline Team Leader [CDTL]), will call the applicant, generally within 2 weeks following FDA's internal midcycle review meeting, to provide the applicant with an update on the status of the review of the application. The update should include any significant issues identified by the review team to date, any information requests, information regarding major safety concerns, and preliminary review team thoughts regarding risk management, proposed date(s) for the late-cycle meeting, updates regarding plans for the AC meeting (if an AC meeting is anticipated), and other projected milestones dates for the remainder of the review cycle.

Late Cycle Meeting: The sponsor understands that for all applications submitted under PDUFA V, a meeting will be held between the FDA review team and the applicant to discuss the status of the review of the application late in the review cycle. FDA

representatives at the late-cycle meeting are expected to include the signatory authority for the application, review team members from appropriate disciplines, and appropriate team leaders and/or supervisors from disciplines for which substantive issues have been identified in the review to date. Additionally, the sponsor understands that the timing of this meeting will vary depending upon whether there will be an AC meeting scheduled for Lu AA21004.

Inspections: The sponsor understands that FDA's goal is to complete all Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and Good Manufacturing Practice (GMP) inspections for applications submitted under PDUFA V within 10 months of the date of original receipt for standard applications. This will allow 2 months at the end of the review cycle to attempt to address any deficiencies identified by the inspections.

FDA Response to Question 1: *We do not agree with your understanding regarding the elimination of the 120-day safety update. An application is not considered "incomplete" solely because the 120-day safety update is not included at the time of submission. The 120-day safety update is required as described in 21 CFR 314.50(d)(5)(vi)(b).*

Discussion: *We reiterated our position and stated that the 120-day safety update will still be required under PDUFA V. The sponsor agreed and will update the MDD open-label pool with additional data from ongoing long-term studies 314 and 13267B and the cut-off date will be September 30, 2012. We have no objection to the sponsor's plan. Regarding the content of the safety update, we clarified that we are only interested in deaths, serious adverse events, and discontinuations due to adverse events because of the open-label nature of these studies.*

Question 2: Does FDA agree with the sponsor's understanding of the proposed goals and procedures for CDER to apply to applications submitted under PDUFA V?

FDA Response to Question 2: *Please refer to question 3.*

Discussion: *There was no further discussion.*

Question 3: Does FDA have additional guidance for the sponsor with respect to PDUFA V?

FDA Response to Question 3: *The division agrees with your understanding of the proposed goals and procedures, as described in the current goals letter, for CDER to apply to applications submitted under PDUFA V. We note, however, that the final legislation has not passed.*

The division would like to provide the following additional information (again, as per the current goals letter) pertaining to Pre-Submission Meetings and Inspections for applications in "the Program" under PDUFA V:

Pre-Submission Meeting: At the pre-NDA/BLA meeting, the FDA and applicant will agree on the content of a complete application for the proposed indication(s), including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. At the meeting, the FDA and applicant may also reach agreement on submission of a limited number of application components not later than 30 calendar days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. These agreements will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

Inspections: All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Discussion: *There was no further discussion.*

2.2 Nonclinical

Question 4: Does FDA agree that the completed nonclinical data package for Lu AA21004 supports the filing of the Lu AA21004 NDA for the proposed indication?

FDA Response to Question 4: *Yes, on face the completed nonclinical package—including the chronic toxicology and carcinogenicity studies and the genotoxicity and reproductive and developmental toxicity batteries—supports filing.*

Discussion: *There was no further discussion.*

2.3 Clinical – Biopharmaceutics and Pharmacology

Question 5: Does FDA agree that the completed clinical pharmacology data package supports the filing of the Lu AA21004 NDA for the proposed indication?

FDA Response to Question 5: *Yes, the studies listed in Table 7a cover the essential areas for Clinical Pharmacology.*

Table 7.a Overview of Clinical Pharmacology Studies in the Lu AA21004 Development Program

Study	Type of Study	Dose Route of Administration (a)
Single- and Multiple-Dose PK Studies		
10272	PK in men	10, 20, 30, 50, or 75 mg
10467	PK in young women (SD and MD), young men (MD), and elderly men and women (SD and MD)	SD: 20 or 60 mg MD: 2.5, 5, 10, 20, 40, or 60 mg
Japanese Single- and Multiple-Dose PK Studies		
CPII-001	PK in Japanese men (SD and MD) and women (MD)	SD: 2.5, 5, 10, 20, or 40 mg MD: 5, 10, or 20 mg (men); 5 or 10 mg (women)
CPH-002	Relative bioavailability enteric-coated formulation	10, 20, 30 mg
CPH-003	PK in Japanese elderly subjects	10 mg
Mass Balance Study		
10477	Mass balance in healthy men	50 mg
Absolute and Relative Bioavailability Studies		
10982	Absolute bioavailability	4 or 9 mg IV or 20 mg PO
106	Food effect and relative bioavailability	10 mg
123	Food effect and relative bioavailability	20 mg
13921A	Relative bioavailability	20 mg
13138A	Relative bioavailability, enteric-coated formulation	20 and 30 mg
13119A	Food effect and relative bioavailability, enteric-coated formulation	20 and 30 mg
Intrinsic Factor Studies		
111	Effect of gender, age, and race	10 mg
114	Effect of hepatic impairment	10 mg
112	Effect of renal impairment	10 mg
Extrinsic Factor Studies—Cytochrome P450 Interaction Studies		
117	DDI (buproprion)	10 mg
115	DDI (rifampicin)	20 mg
103	DDI (ketoconazole and fluconazole)	10 mg
11826A	DDI (omeprazole)	10 mg
101	DDI (Indiana cocktail)	10 mg
102	DDI (oral contraceptives)	10 mg
109	DDI (warfarin)	10 mg
113	DDI (diazepam)	10 mg
Extrinsic Factor Studies—Other Interaction Studies		
110	DDI (ethanol)	20 and 40 mg
116	DDI (aspirin)	10 mg
118	DDI (lithium)	10 mg

Footnotes are on last table page.

Additional Office of Clinical Pharmacology Comments
Please complete the review tool in Appendix 1 and submit it with the NDA.

We request you consider using "forest plots" instead of the text and/or table to present the changes in drug PK within Sections 7 (Drug Interactions) and 8 (Use in Specific Populations) of the labeling. The SAS code to make the forest plot is provided in

Appendix 2 for your reference [See attached SAS code].

Please provide a table for the original PK information in Sections 7 and 8 of labeling that is associated with forest plots in the format below.

Factor (e.g. age, gender, renal impairment, inhibitors of CYP3A4, etc	Type (e.g. female under gender, and mild under renal impairment, etc)	Moiety	PK (Cmax and AUC)	Geometric Mean Ratio*	90% CI		Recommendation
					Lratio	Uratio	

*Change relative to the reference

Using forest plots in drug labeling may communicate more effectively intrinsic and extrinsic factors effects on pharmacokinetics than using texts. For information on the use of forest plots in drug labeling please refer to the following article: Essential Pharmacokinetic Information for Drug Dosage Decisions: A Concise Visual Presentation in the Drug Label, Clinical Pharmacology and Therapeutics, Sep;90(3):471-4. 10.1038/clpt.2011.149.

Discussion: *We agree with the sponsor's proposal to submit the completed "Review Aid"document with the 120-day safety update. Forest plots will be included in Sections 7 and 8 of labeling. The sponsor's proposed format is acceptable; however, we will be reviewing study reports to confirm the reported values. The sponsor proposed to include the PK summary table with Module 2.5.3 and noted that source data for the table will be summarized within Module 2.7.2. We agreed with the proposal.*

Question 6: Does FDA agree with the plan for population PK and population PK/pharmacodynamic analyses?

Company Position: Two separate population pharmacokinetic (PK) analyses will be performed based upon the pooled Lu AA21004 plasma concentration data collected in phase 1 (26 studies in healthy subjects) and phase 2/3 studies (12 studies conducted in subjects with MDD and Generalized Anxiety Disorder [GAD]), respectively. These analyses will be performed to develop a population PK model for Lu AA21004 and to identify the sources of variability (subject demographic, baseline clinical laboratory values, and concomitant medications) associated with the PK parameters of Lu AA21004. In addition, exploratory PK/pharmacodynamic (PD) analyses will also be performed to evaluate the relationship between Cav (area under the concentration-time curve

[AUC]/24) and the change from Baseline in MADRS total score (ΔMADRS) or nausea rate, respectively in patients with MDD.

All data sets and control streams that will be used for the population PK and PK/PD analyses will be submitted in the NDA following the guidance listed with the Department of Pharmacometrics at FDA.

FDA Response to Question 6: *The presented plan seems to be adequate. However, the use of only subjects with observed end of treatment MADRS total scores being included in this analysis needs to be modified, i.e., no last observation carried forward LOCF imputation. We recommend that you use MMRM for the analysis and use all MADRS total score values from week 1 to weeks 6 or 8.*

Discussion: *The sponsor proposed using MMRM analysis in addition to completer's analysis to explore PK/PD relationships and we agreed. For PK/PD analysis, the sponsor agreed to use MMRM analysis including all MADRS score values from week 1 to weeks 6 or 8. We agreed that the MADRS score observed at various visits can be linked to steady state exposures.*

Question 7: Does FDA agree with the submission proposal for 3 Japanese phase 1 studies?

FDA Response to Question 7: *The studies are Single Dose and Multiple Dose studies in men, women, elderly and relative BA for an enteric coated formulation. Most of these studies have also been done in Caucasians. Since these have been designated as supportive studies by the sponsor they can be used in the population pharmacokinetic analysis and coded to determine if there is a race effect.*

Discussion: *There was no further discussion.*

2.4 Clinical – Efficacy

Question 8: Does the FDA agree that the phase 2/3 studies, subject to review of data, are adequate to support the NDA filing and will support the proposed indication?

Company Position: There will be 11 completed phase 2/3 placebo-controlled studies in MDD subjects included in the NDA (11492A, 11984A, 305, 13267A, 315, 316, 317, 303, 304, 12541A, and 11985A). Six short-term studies in adults are positive (11492A, 305, 13267A, 315, 316, and 12541A, the dedicated elderly study). One study is ongoing (317) and will be included in the NDA. Study 11984A is considered supportive for efficacy and 2 studies (303 and 304) are considered failed or negative. In addition, 1 relapse-prevention study (Study 11985A) is also positive. Table 6.a summarizes the positive and supportive studies that will be included in the NDA.

Table 6.a: Phase 2/3 MDD Studies Supporting the Efficacy of Lu AA21004

Study No./ Region	Study Design	IMP Doses (mg)	Brief Description of Results
11492A ex-US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, active-reference (VLF), fixed-dose	Lu AA21004 5, 10 VLF 225 PBO	Positive
11984A ex-US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, active-reference (DUL), fixed-dose	Lu AA21004 2.5, 5, and 10 DUL 60 PBO	Failed (both Lu AA21004 and active reference did not separate from placebo), supportive for clinical effect at 5 and 10 mg
305 ex-US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, fixed-dose	Lu AA21004 1, 5, 10 PBO	Positive
13267A ex-US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, active-reference (DUL), fixed-dose	Lu AA21004 15, 20 DUL 60 PBO	Positive
315 US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, active-reference (DUL), fixed dose	Lu AA21004 15, 20 DUL 60 PBO	Positive
316 US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, fixed-dose	Lu AA21004 10, 20 PBO	Positive at 20 mg, supportive for clinical effect at 10 mg
317 US	Efficacy and safety Randomized, double-blind, parallel-group, PBO-controlled, fixed-dose	Lu AA21004 10, 15 PBO	Ongoing, will be submitted with the NDA
12541A Elderly Study US + ex-US	Efficacy and safety in elderly Randomized, double-blind, parallel-group, PBO-controlled, active-reference (DUL), fixed-dose	Lu AA21004 5 DUL 60 PBO	Positive for elderly, including US subjects
11985A ex-US MDD Relapse-prevention	Relapse-prevention Open-label, flexible-dose followed by randomized, double-blind, parallel-group, PBO-controlled, fixed-dose	Lu AA21004 5, 10	Positive for maintenance

PBO=placebo, VLF=Venlafaxine, DUL=Duloxetine, MMRM=mixed model for repeated measures.

As discussed at the Type C Meeting (30 March 2010), the requirement to demonstrate efficacy in the US population has been met, specifically in Studies 315, 316 and 12541A. The efficacy data from the third phase 3 study in the US (Study 317) will be included in the NDA. The safety data from this study (317) will be included in the integrated analysis of safety. As Study 317 is the only phase 3 study that utilized central rater methodology, the sponsor is currently evaluating whether this study should be integrated in the meta analysis of efficacy.

FDA Response to Question 8: *Results from the phase 2/3 studies you have conducted should provide sufficient data to support filing an NDA submission for Lu AA21004 in the treatment of MDD.*

Discussion: *There was no further discussion.*

Question 9: Based upon the totality of the available clinical efficacy data from US and ex-US clinical studies, the sponsor proposes that the recommended starting dose be 10 mg once daily and the therapeutic dose range be 5 to 20 mg. This recommendation is irrespective of the outcome of the 1 remaining phase 3 study to be included in the NDA (Study 317) as the dose range is supported by the completed studies. Does the FDA have any comments with regards to the proposed dosing recommendation?

Company Position: The sponsor recognizes that the FDA will require a full review of the NDA. However, initial comments on the proposed dosing recommendation are welcome. Efficacy results per dose from the completed MDD studies are summarized in **Table 6.b.**

Table 6.b: Efficacy Summary of Completed MDD Studies

	Lu AA21004				Active Reference (a)
Study (Phase, Region)	5 mg	10 mg	15 mg	20 mg	
11492A (Phase 2, ex-US)	+	+	N/A	N/A	+
11984A (Phase 3, ex-US)	Supportive	Supportive	N/A	N/A	Supportive
305 (Phase 3, ex-US)	Supportive	+	N/A	N/A	N/A
13267A (Phase 3, ex-US)	N/A	N/A	+	+	+
315 (Phase 3, US)	N/A	N/A	—	+	+
316 (Phase 3, US)	N/A	Supportive	N/A	+	N/A
317 (Phase 3, US)	N/A	Pending Data	Pending Data	N/A	N/A
303 (Phase 3, US)	—	N/A	N/A	N/A	N/A
304 (Phase 3, US)	—	N/A	N/A	N/A	+
12541A (Phase 3, US and ex-US)	+	N/A	N/A	N/A	+
11985A (Phase 3, ex-US)	+	+	N/A	N/A	N/A

(a) Venlafaxine 225 mg for 11492A; duloxetine 60 mg for 304, 11984A, 13267A, and 315.

The sponsor proposes that the recommended starting dose should be 10 mg. As deemed necessary by treating physicians based upon individual patient response, the dose may be escalated to 15 or 20 mg or reduced to 5 mg.

FDA Response to Question 9: *Whether or not the data you plan to submit would support an approval, and if so, what the starting and target doses for treatment would be matters of review, and we have no comment at this time.*

Discussion: *There was no further discussion.*

2.5 Clinical – Clinical Safety

Question 10: Does FDA agree that the long-term exposure data and safety data from ongoing studies support the filing of the NDA for the proposed indication?

Company Position: At the time of NDA submission, it is anticipated that more than 7800 subjects across phase 1-3 MDD or GAD studies will have been exposed to Lu AA21004, including more than 2000 subjects exposed for 6 months and 1100 subjects for 12 months. For subjects with MDD, it is anticipated that approximately 5000 subjects will have been exposed to Lu AA21004, including approximately 1500 subjects exposed for 6 months and approximately 770 subjects for 12 months across the dose range of 5 to 20 mg. Of these, it is anticipated that approximately 400 subjects will have been exposed for 6 months and at least 100 subjects for 12 months on the highest doses of 15 to 20 mg.

For the ongoing open-label safety extension studies supporting the NDA, safety data in the clinical database as of 04 May 2012 will be provided. This data set will contain standard safety variables (eg, adverse events [AEs], SAEs, laboratory results, vital signs, electrocardiogram [ECG] results, and Columbia-Suicide Severity Rating Scale [C-SSRS]) from the 2 ongoing open-label studies. Additionally, listings of blinded SAEs and CIOMS from ongoing double-blind studies will be provided.

FDA Response to Question 10: *The safety data in the proposed submission should be sufficient for filing.*

Discussion: *There was no further discussion.*

Question 11: Does FDA agree that the proposed data cut-off date and content for inclusion of safety data from the ongoing studies in the NDA are acceptable?

FDA Response to Question 11: *Yes.*

Discussion: *There was no further discussion.*

Question 12: Does FDA agree with the proposed presentation of GAD safety data?

Company Position: A phase 3 program in subjects with GAD has been conducted with Lu AA21004. At this time, the sponsor is not seeking an indication for GAD; however, for completeness of safety assessment, 5 completed phase 3 GAD studies will be included in the NDA and as part of the Integrated Analysis of Safety (IAS). The 4 short-term GAD studies (308, 309, 310, and 311) will be grouped together in the Short-term GAD Studies Group in the IAS, and they also will be grouped with 10 short-term MDD studies (11492A, 11984A, 305, 13267A, 315, 316, 317, 303, 304, and 12541A) to form the Short-term MDD/GAD Studies Group. The GAD relapse-prevention study 12473A will be summarized separately. The GAD data will be analyzed according to the IAS statistical analysis plan as submitted on 13 February 2012, S/N 212.

FDA Response to Question 12: *Yes.*

Discussion: *There was no further discussion.*

Question 13: Does FDA agree with the approach for inclusion of narratives in the NDA?

Company Position: The sponsor plans to include narratives for all deaths, other SAEs, and AEs that led to study discontinuation in the NDA. Narratives for deaths and other SAEs will be provided in the Council for International Organization of Medical Sciences report (CIOMS) format. Narratives for AEs that led to study discontinuation will be provided in program-assisted narratives (PANs) format.

FDA Response to Question 13: *Yes.*

Discussion: *There was no further discussion.*

Question 14: Does FDA agree that the planned inclusion of CRFs are adequate and acceptable for FDA review?

Company Position: Case report forms (CRFs) will be submitted for deaths, SAEs, and adverse events that led to study discontinuations, and no patient profiles will be submitted.

FDA Response to Question 14: *Yes.*

Discussion: *There was no further discussion.*

Question 15: Does FDA agree that, based on the presentation of safety data in this document, a REMS is not considered necessary for Lu AA21004 and that the antidepressant Medication Guide can be part of approved labeling?

Company Position: The sponsor is aware of the antidepressant Medication Guide and intends to include a Medication Guide for Lu AA21004 as part of labeling. The sponsor is also aware of the Guidance for Industry: "Medication Guides- Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) November 2011" and the recent release of the REMS requirement for vilazodone on 29 June 2011 stating that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meet the standard in 21 CFR 208.1. No risks have been identified in the Lu AA21004 data that warrant a REMS. Therefore, the sponsor does not intend to submit a REMS in the NDA and considers the Medication Guide to be part of approved labeling.

FDA Response to Question 15: *Based on the summary safety data that you provided, it appears a REMS may not be necessary. A decision on this question would, however, be a matter of NDA review. We have no objection to your proposal to include a Medication Guide for Lu AA21004 as part of labeling.*

Discussion: *There was no further discussion.*

2.6 Regulatory Administrative Questions

Question 16: Does FDA agree with the sponsor's plan for providing financial disclosure information in the NDA?

Company Position: The Lu AA21004 NDA will include financial disclosure information for all Lu AA21004 studies that meet the definition of covered study under 21 CFR 54, including phase 2 and 3 randomized controlled trials. Financial disclosures or certifications will not be included for phase 1 studies or phase 3 open-label multicenter studies, as these studies are not considered covered studies per the regulations.

FDA Response to Question 16: *Yes.*

Discussion: *There was no further discussion.*

Question 17: Does FDA expect to receive summary level clinical site datasets in the NDA according to the pilot program, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions"? If so, does FDA agree with the sponsor's plan for providing this information in the NDA?

Company Position: The sponsor is prepared to provide summary level clinical site datasets in the NDA if FDA requests this information. The sponsor will include the following efficacy studies: 11492A, 11984A, 305, 13267A, 315, 316, 317, 303, 304, 12541A, and 11985A. The primary endpoint in these studies has been either MADRS or HAM-D24. MADRS has been included in all studies as a secondary endpoint, if not the

primary endpoint. The sponsor proposes to include only MADRS data for a consistent presentation of efficacy data across studies and clinical sites. Additionally, the following variables will also be included: IND, TRIAL, SITEID, ARM, ENROLL, SCREEN, DISCONT, ENDPOINT, ENDPTYPE, TRTEFFR, TRTEFFV, SITEEFFE, SITEEFFV, CENSOR, NSAE, SAE, DEATH, PROTVIOL, FINLDISC, LASTNAME, FRSTNAME, PHONE, FAX, EMAIL, COUNTRY, STATE, CITY, POSTAL, STREET.

FDA Response to Question 17: *The sponsor's plan as described in the briefing document is consistent with FDA's expectations for receiving summary level clinical site data in support of good clinical practice inspections. Please note, of the pivotal (phase 2/3) studies, the three negative studies need not be included. The document in Appendix 3 provides additional specificity about content and format in preparing this information for the positive pivotal studies.*

Discussion: *The sponsor proposed submitting within 30 calendar days after the submission of the original application, Section II of the Pre-NDA information request document provided by the Office of Scientific Investigations in Appendix 3 entitled, "Request for Subject Level Data Listings by Site."*

Post-meeting Note: *We agree with the sponsor's proposal to submit Section II of Appendix 3 within 30 calendar days after the submission of the original application for vortioxetine.*

Question 18: Does FDA confirm that the issue of scientific misconduct by (b) (4) will not prevent FDA from initiating the review of the NDA?

Company Position: GLP compliance is claimed for the affected nonclinical GLP studies with an exclusion of the bioanalytical study phases. All reports of the affected nonclinical studies have been amended with regard to this case. It is the sponsor's intention to include in the NDA a transparent and full explanation of how the bioanalytical data came to be compromised and a detailed description of the remedial actions taken in the form of a stand-alone report as well as a description in relevant sections of Module 2. In the view of the sponsor, the data package is deemed adequate for the purpose of initiating the review of the NDA.

FDA Response to Question 18:

Nonclinical
Based on our understanding at this time, the issue of scientific misconduct will most likely not prevent initiation of the review of the pharmacology/toxicology sections of the NDA.

Office of Clinical Pharmacology
On face, the issue of scientific misconduct will not prevent initiation of the review of the NDA. It is noted that assay misconduct will be a concern. Based upon your initial report,

certain studies are not impacted. However, the acceptance of studies that have been impacted by analytical misconduct will be a review issue. We acknowledge that you plan to include details of the remedy program in the NDA submission. We recommend that your PK reports should include and exclude all misconduct subjects. In your PK dataset, you should also include the information on (1) analytical center, (2) identified deficiencies, and (3) acceptability following your remedial actions. Additional information may be needed during the review process.

Discussion: *On face, we agreed with the sponsor's understanding of misconduct subjects as described in Appendix 4, slides 10-12. We stated that original and corrected data will be reviewed in depth and we may have additional information requests. The sponsor agreed to our recommendations for their Phase 1 popPK analysis and the popPK dataset for all Phase 1 studies.*

Question 19: Does FDA have specific guidance as to the information to be submitted in the NDA to adequately review this issue of scientific misconduct?

Company Position: A case of misconduct occurred at a contract research organization (b) (4) which conducted the bioanalysis of samples derived from several nonclinical and clinical studies for the development of Lu AA21004. The nonclinical and clinical studies were conducted at other locations and thus there is no relation to the misconduct.

The issue of scientific misconduct was first identified and reported to the sponsor by (b) (4) in February 2009. The sponsor and (b) (4) have undertaken an investigation to assess the impact of the deficiencies on the bioanalyses of the nonclincal and clinical studies and subsequently implemented a remedial action program. Based on the assessment and the outcome of the remedial actin program including retrospective evaluation, recalculation and reprocessing of data, the sponsor considers the bioanalytical data reliable and the study conclusions for the nonclinical and clinical studies adequate for the purpose of the NDA. Furthermore, based on the investigation, the sponsor has concluded that the identified deficiencies do not affect the safety of patients in any of the completed or ongoing studies.

On 23 February 2012, the sponsor received feedback from FDA regarding the case of misconduct by (b) (4) (submitted on 01 February 2012, S/N 211) stating that the scientific and compliance impact of the scientific misconduct will be a review issue. It is the sponsor's intention to include in the NDA a transparent and full explanation of how the bioanalytical data came to be compromised and a detailed description of the remedial actions taken in the form of a stand-alone report.

FDA Response to Question 19:

Nonclinical

We ask that you identify the 10 toxicology studies that were affected and the deficiencies that arose from the misconduct at the contract research organization (b) (4). In addition, provide the full report of the investigation and the remedial work that was conducted to address the deficiencies.

Office of Clinical Pharmacology
You will need to clarify which dosage form will be used in the clinical studies and which doses you intend to market. We also refer you to our comments in Question 18.

Discussion: *The sponsor confirmed that the IR formulation IV will be the commercial formulation with tablet strengths 5, 10, 15 and 20 mg.*

2.7 General Comments

FDA Office of Biometrics: *For those efficacy studies to support the proposed indication, please provide the following in your future NDA submission:*

(a) a list of correspondence history related to this program, including IND number(s) with serial numbers and submission dates of the protocols, SAPs, and amendments.
(b) all raw as well as derived variables in .xpt format;
(c) the SAS programs that produced all efficacy results;
(d) the SAS programs by which the derived variables were produced from the raw variables.

Discussion: *In general, the sponsor agreed to provide the information as requested above. The sponsor pointed out that for some trials the dataset was developed by Takeda, and for others the dataset was developed by Lundbeck. For Takeda-developed datasets, the sponsor initially proposed to provide only analysis programs that produce tables/listings/graphs from ADaM data, but not the analysis programs that produce ADaM data from SDTM data. We requested that the sponsor at least provide the analysis programs that derived the primary and key secondary variables based on the raw variables. The sponsor agreed.*

Additional Comments:
The sponsor is encouraged to submit the detailed remedial program and analytical and PK reports with amendments as soon as possible. Relevant information can be submitted under the IND.

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of

Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

5.0 ATTACHMENTS AND HANDOUTS

Takeda Global Research & Development Center, Inc. presented slides during the Pre-NDA meeting. The slide deck is attached in Appendix 4.

Appendix 1

CLINICAL PHARMACOLOGY SUMMARY REQUEST	
IND:	Letter Date:
Drug Substance:	Sponsor:
Drug Product:	

Dear Sponsor,

We request you to provide the **Clinical Pharmacology Summary** as review aid according to the format provided below. This review aid will allow us to perform the regulatory review more efficiently and in a timely manner. Should you have any questions please contact us via the Regulatory Project Manager for this submission. Thank you.

Regards

Psychiatry Clinical Pharmacology Team
Division of Clinical Pharmacology – 1
Office of Clinical Pharmacology, CDER, FDA.

CLINICAL PHARMACOLOGY SUMMARY

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for

all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable.
Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active

moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for $\geq$ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites

constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.10 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.12 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly

from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.13 Is there evidence for a circadian rhythm of the PK?

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Body Weight

2.6.2.3 Elderly

2.6.2.4 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC and Cmax of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.7 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC and Cmax of parent drug and relevant metabolites in the different hepatic function sub-groups assessed

by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity

reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of

interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product

demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence

of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe theindiidual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.8.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20°$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

Applicable to therapeutic proteins only

2.9.5.5 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.7 What is the performance of the neutralizing assay(s)?

Appendix 2

Supplementary material

Sample SAS code to create forest plots

```
Data covariateplot;
input Factor $1-23 constant PK $27-31 ratio lratio uratio Recommendation $48-66 codel;
cards;
CYP3A4 Inhibitors:       0  .    .    .    .          .          0   .
Ketoconazole             0 Cmax 1.38 1.20 1.59 Maximum dose: 20mg 1
                         0 AUC  1.51 1.36 1.68         .          2   .
Ethanol:                 0 Cmax 1.00 0.91 1.10 No dose adjustment 3   .
     .                   0 AUC  1.04 0.97 1.13         .          4   .
;
run;
proc print;run;

proc template;
define statgraph ForestPlot;
dynamic _pct;
begingraph / designwidth=660px designheight=350px;
entrytitle "Impact of other drugs on Vilazodone Pharmacokinetics(PK)" / pad=(bottom=5px);
layout lattice / columns=4 columngutter=0 columnweights=(.28 .10 .38 .24);
layout overlay / walldisplay=none border=false yaxisopts=(offsetmin=_pct offsetmax=_pct)
y2axisopts=(reverse=true type=discrete display=none offsetmin=_pct offsetmax=_pct)
xaxisopts=(display=none offsetmin=0 offsetmax=0);
entry halign=left "   Change due to" /location=outside valign=top;
scatterplot y=codel x=constant / yaxis=y2 markercharacter=Factor markerattrs=(size=0)
markercharacterattrs=(weight=bold);
scatterplot y=codel x=constant / yaxis=y2 markercharacter=type markerattrs=(size=0);
endlayout;

layout overlay / walldisplay=none border=false yaxisopts=(offsetmin=_pct offsetmax=_pct)
y2axisopts=(reverse=true type=discrete display=none offsetmin=_pct offsetmax=_pct)
xaxisopts=(display=none offsetmin=0 offsetmax=0);
entry halign=left "     PK" / textattrs=GraphLabelText location=outside valign=top;
scatterplot y=codel x=constant / yaxis=y2 markercharacter=PK markerattrs=(size=0);
endlayout;

layout overlay / walldisplay=none
yaxisopts=(display=none reverse=true offsetmin=_pct offsetmax=_pct
linearopts=(integer=true)) xaxisopts=(type=linear linearopts=(viewmin=0.5 viewmax=2)
offsetmin=0 offsetmax=0 label="Change relative to reference" labelattrs=(size=4px));
entry "Fold Change and 90% CI" / location=outside valign=top textattrs=GraphLabelText;
scatterplot x=ratio y=codel /xerrorlower=lratio xerrorupper=uratio
markerattrs=(color=orange symbol=diamondfilled size=4pct);
referenceline x=1 / lineattrs=(pattern=solid);

endlayout;

layout overlay / walldisplay=none border=false yaxisopts=(reverse=true type=discrete
display=none offsetmin=_pct offsetmax=_pct) xaxisopts=(display=none offsetmin=0
offsetmax=0);
entry  "Recommendation" / location=outside valign=top textattrs=GraphLabelText;
scatterplot y=codel x=constant / markercharacter=Recommendation
markercharacterattrs=GraphDataText;
endlayout;

endlayout;
endgraph;
end;
run;

proc template;
define Style foreststyle;
parent = styles.Journal2;
style GraphFonts from GraphFonts
      "Fonts used in graph styles" /
         'GraphTitleFont' = ("<MTserif>, <MTserif>",12pt)
         'GraphFootnoteFont' = ("<MTserif>, <MTserif>",12pt)
```

```
        'GraphLabelFont' = ("<MTserif>, <MTserif>",12pt)
        'GraphUnicodeFont' = ("<MTserif-unicode>",12pt)
        'GraphValueFont' = ("<MTserif>, <MTserif>",12pt)
        'GraphDataFont' = ("<MTserif>, <MTserif>",12pt)
        'GraphAnnoFont' = ("<MTserif>, <MTserif>",12pt);

  end;
run;

title;
options nodate nonumber;

ods listing close;
ods html gpath ='C:\…\Forestplot'
image_dpi=250 style=foreststyle file='forestplot.html' path='.';

ods graphics / reset imagename="Figure1" imagefmt=png noborder;
proc sgrender data=covariateplot template=ForestPlot;
run;

ods html close;
ods listing;
```

Appendix 3

NDA Information and Format: OSI Request to Sponsor

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate clinical investigator and sponsor/monitor/CRO inspections. The dataset requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number and principal investigator name
   b. Site location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   c. Current location of principal investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Name, address and contact information of all CROs in the clinical trials
   b. Physical location of study documents (location of inspection): (1) trial master file; (2) source documents generated by CROs; (3) sponsor/monitor files (e.g., monitoring master file, files for drug accountability, SAE, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if provided elsewhere in submission, please provide a link to the requested information).
5. For each pivotal trial provide original protocol and all amendments (if provided elsewhere in submission, please provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing of subject screened and reason for subjects not meeting eligibility requirements

b. Subject listing for treatment assignment (randomization)

c. Subject listing of drop-outs and subjects that discontinued with date and reason

d. Evaluable subjects/ non-evaluable subjects and reason not evaluable

e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

f. By subject listing, of AEs, SAEs, deaths and dates

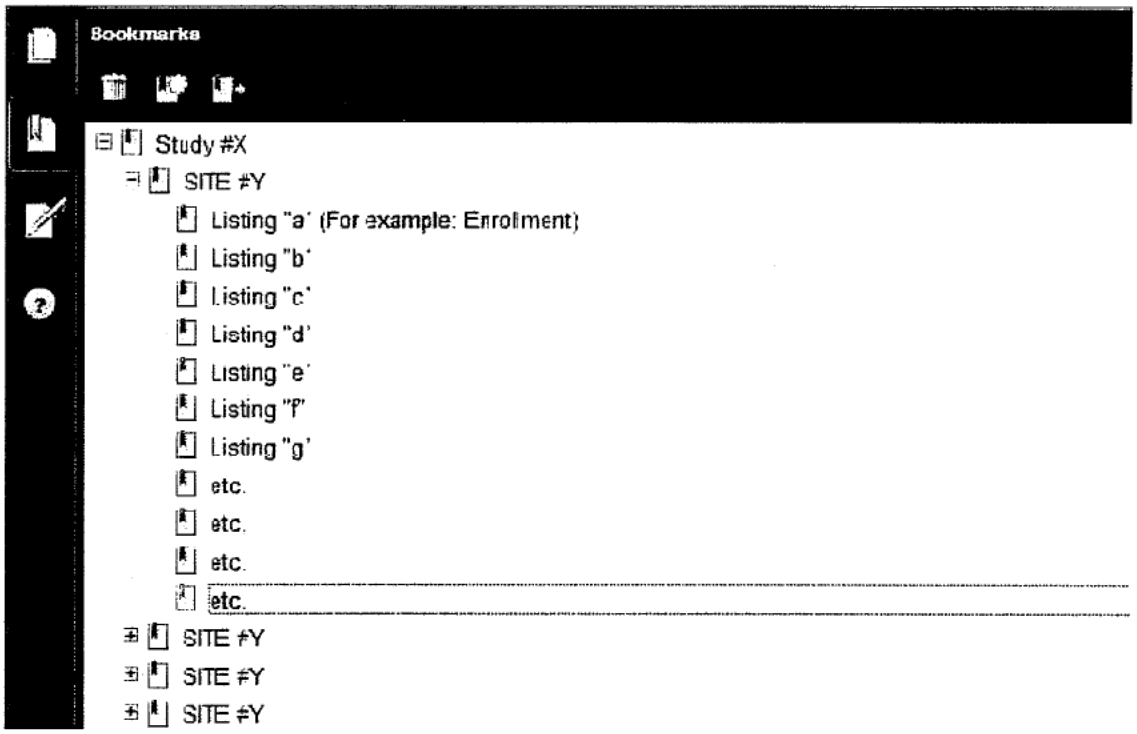
g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal trials)

j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the format shown below:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Inspection Planning in NDA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy:

- Treatment Efficacy Result (TRTEFFR) – efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on result reporting)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies with a time-to-event primary endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

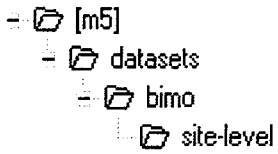
Attachment 2

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."

OSI 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 (Line listings, by site)	.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.

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

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

Appendix 4

June 22, 2012

The Sponsor would like to clarify and confirm the expectation regarding submission of the 120-day safety update

The Sponsor has the understanding that the regulation will be rewritten upon approval of PDUFA V, and the requirement as described currently in 21 CFR 314.50(d)(5)(vi)(b) will be eliminated

If we misunderstood and/or the requirement remains, the Sponsor will submit the safety update and would like to confirm the content (next slide)

Update MDD open-label pool with additional data from ongoing long-term studies 314 and 13267B

Use data in clinical database as of September 30, 2012

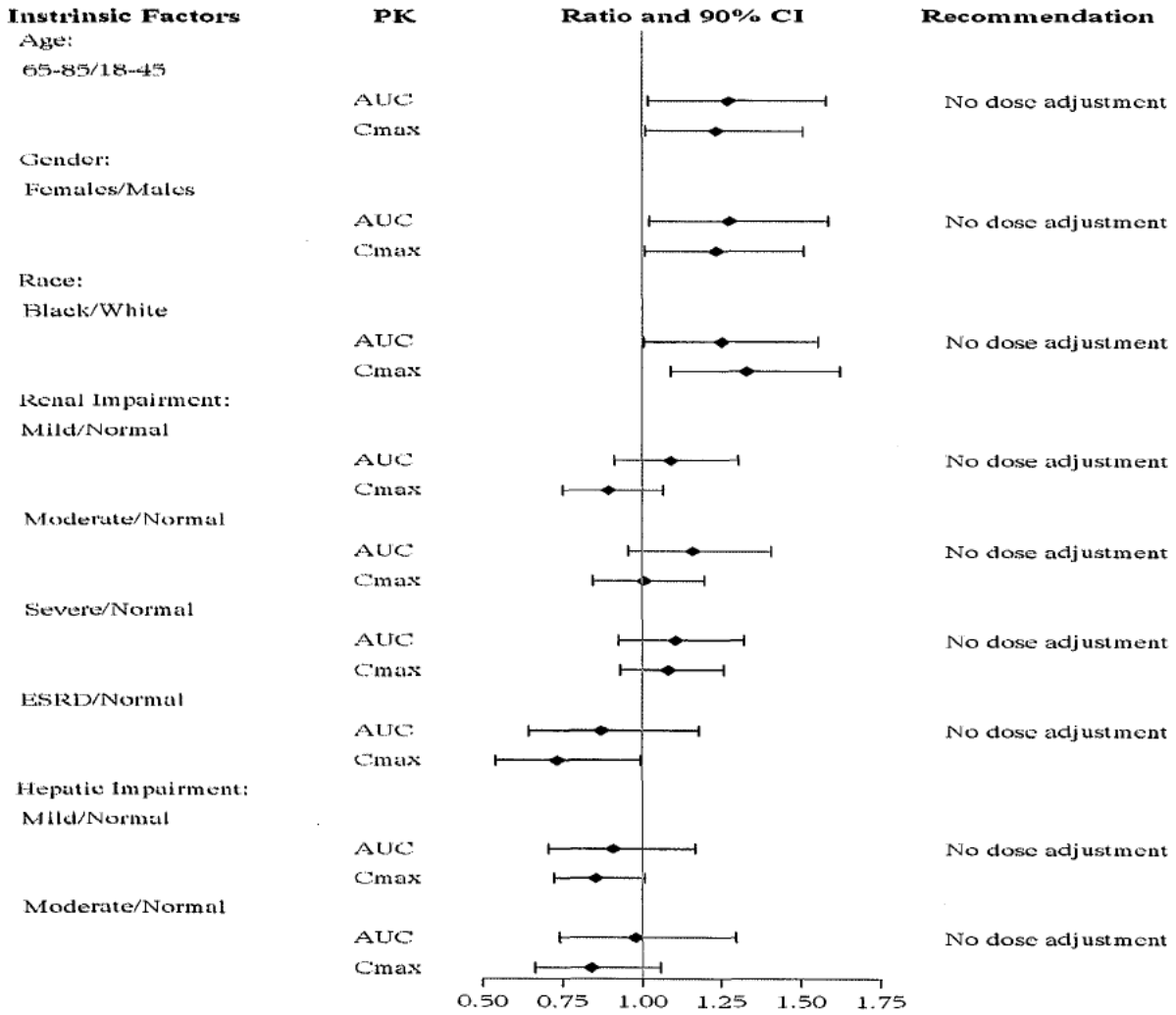
Data summaries will mirror those for NDA and will also include NDA results to allow for comparison to updated results

Listings of SAEs and CIOMS reports will be provided for other ongoing studies as in NDA

Table 7.f in briefing document identifies ongoing studies

The Sponsor would like to clarify the expectation for timeline for submission of the "Clinical Pharmacology Summary" review aid, considering completion of Modules 2.7.1 and 2.7.2

The Sponsor confirms that forest plots will be included in Sections 7 and 8 of labeling (see next slides)


Instrinsic Factors
PK
Ratio and 90% CI
Recommendation
Age:
65-85/18-45
AUC
Cmax
No dose adjustment
Gender:
Females/Males
AUC
Cmax
No dose adjustment
Race:
Black/White
AUC
Cmax
No dose adjustment
Renal Impairment:
Mild/Normal
AUC
Cmax
No dose adjustment
Moderate/Normal
AUC
Cmax
No dose adjustment
Severe/Normal
AUC
Cmax
No dose adjustment
ESRD/Normal
AUC
Cmax
No dose adjustment
Hepatic Impairment:
Mild/Normal
AUC
Cmax
No dose adjustment
Moderate/Normal
AUC
Cmax
No dose adjustment
0.50 0.75 1.00 1.25 1.50 1.75

The Sponsor would like to clarify/confirm the proper location of the requested PK table within the NDA

The Sponsor proposes to include this PK summary table within Module 2.5.3 and source data for the table will be summarized within Module 2.7.2

The Sponsor would like to clarify the request to include and exclude all misconduct subjects in the PK reports

The Sponsor would like to clarify the requested information to be included in the PK datasets

The Sponsor confirms that the IR formulation IV will be the commercial formulation with tablet strengths 5, 10, 15 and 20mg

- Bioequivalence has been established across the formulations used throughout the clinical development program, including the intended commercial formulation

Completed Clinical Studies in NDA

	# in NDA	# with BA Samples	# with BA by (b) (4)	# with (b) (4) Deficiencies	# with Compromised Samples
All	50	44	29	12	2
Phase I	31	31	20	7	2
Phase II/III	19	13	9	5	0

A detailed description of the investigation, remedial actions, and outcome will be provided in the NDA

Clinical Studies with Compromised BA Samples

PET Study [10985]:

Deficiency: Lu AA21004 BA samples in 2 batches (2 subjects, 41 samples each) were rejected due to integration deficiency

Remedy: All bioanalytical/PK data from these 2 subjects were excluded in the CSR amendment and the Phase I popPK analysis

PET Study [12260A]:

Deficiencies: 2 Lu AA21004 BA samples (2 subjects, 1 sample each) were annotated in the BA report stating that the accuracy of the results cannot be confirmed due to reinjection deficiencies

Remedy: CSR was not amended since the 2 BA samples only constituted 1/38 samples per subject or approximately 0.1% of the total BA samples in this study

The overall study conclusions are considered valid

Phase 1 popPK analysis (final model) will be conducted including and excluding the compromised data from the "misconduct subjects" in the 2 PET Studies

Is this consistent with FDA's expectation?

The analytical center, deficiencies identified and acceptablity following the remedy actions will be included in the popPK dataset for all Phase 1 studies

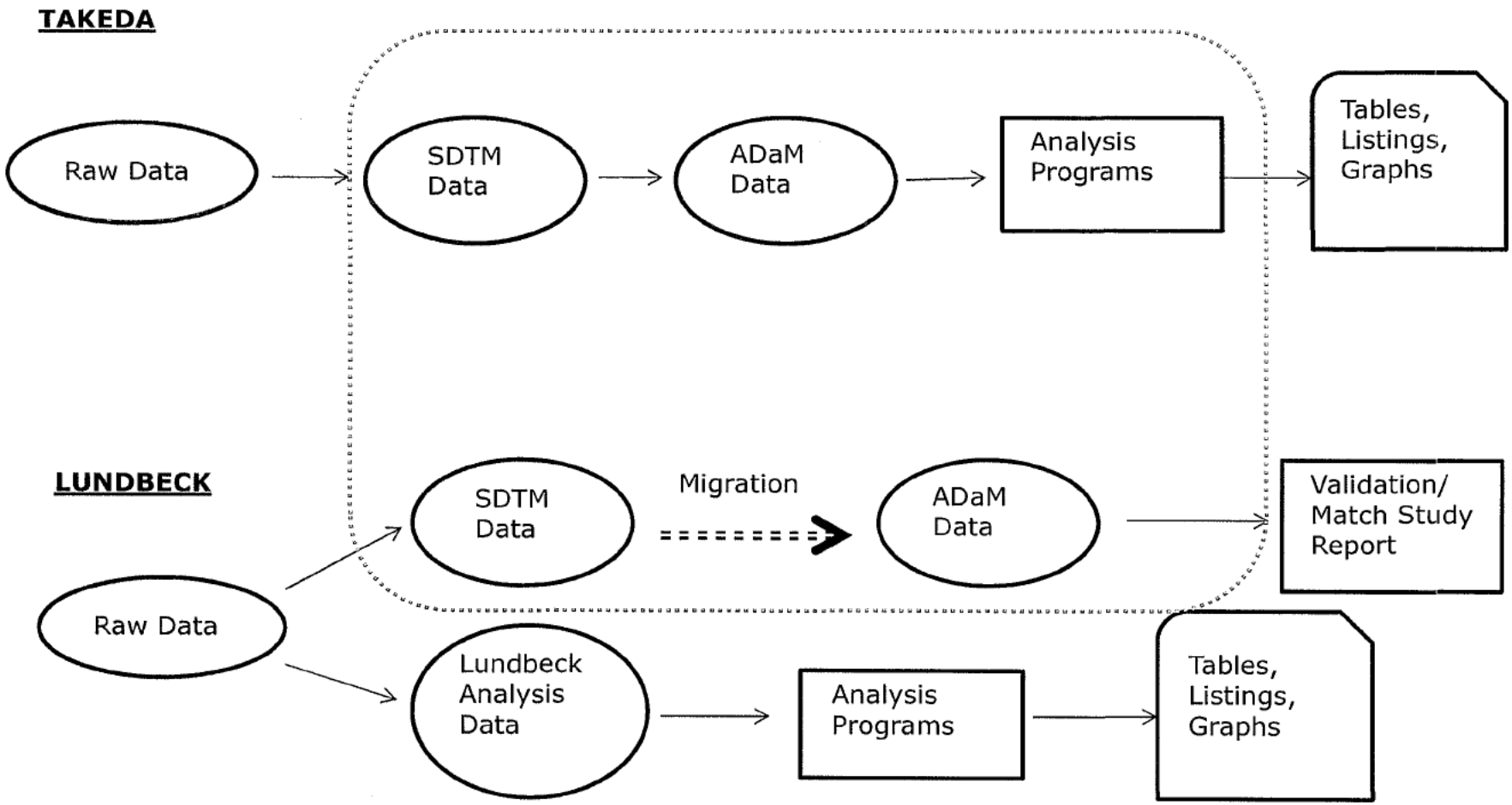
Is this consistent with FDA's expectation?

The Sponsor would like to clarify the recommendation for MMRM analysis

The Sponsor would like to clarify the request for correspondence history and confirm the location within the NDA for this information

- The Sponsor proposes to submit this information in tabular format as General Correspondence to the NDA

The Sponsor would like to clarify FDA's request for SAS programs due to the differences in analysis datasets between Lundbeck and Takeda (next slide)


TAKEDA
Raw Data
SDTM Data
ADaM Data
Analysis Programs
Tables, Listings, Graphs
LUNDBECK
Raw Data
SDTM Data
Migration
ADaM Data
Validation/ Match Study Report
Lundbeck Analysis Data
Analysis Programs
Tables, Listings, Graphs

The IAE SAP was reviewed by FDA in Feb 2012 and FDA feedback was provided

The Sponsor would like to clarify the following regarding presentation of data within Module 2.7.3:

The IAE will include analyses for two sets of studies – All Studies and Positive/Supportive Studies – for evaluating effects in subgroups

Because the meta-analyses for combining studies is based on MMRM analyses of the data within each study, Study 11984A was included as a supportive study. That study had positive results based on the pre-specified secondary analysis using MMRM

Only two efficacy studies are excluded from the Positive/Supportive group of studies – Study 303 and Study 304

Within 2.7.3, the discussion and presentation of effects in subgroups will be based upon the group of Positive/Supportive studies

Is this consistent with FDA's expectation?

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/s/

THOMAS P LAUGHREN
06/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

LATE CYCLE MEETING
BACKGROUND PACKAGE

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, M.S.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brintellix (vortioxetine) 5 mg, 10 mg, 15 mg, and 20 mg tablets.

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for July 2, 2013. Attached is our background package, including our agenda for this meeting.

If you have any questions, call Hiren Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: July 2, 2013; 9:00am-10:30am (EST)
Meeting Location: Building 22, Room 1315

Application Number: NDA 204447
Product Name: Brintellix (vortioxetine)
Indication: Treatment of Major Depressive Disorder
Sponsor/Applicant Name: Takeda Pharmaceuticals USA, Inc.

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this background package prior to this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

OVERVIEW OF ISSUES IDENTIFIED TO DATE

In addition to the contents of this background document, please also refer to the following Discipline Review (DR) letters already provided to you:

Chemistry – June 7, 2013

The current substantive review issues are as follows:

Chemistry/Nonclinical:
The drug substance DMF supporting your NDA remains deficient. We recommend that you contact the DMF holder to ensure that all deficiencies are addressed in a timely fashion.

Chemistry:
The remaining CMC issues are related to your comparability protocols for the new drug product packaging and manufacturing sites, and the CMC related labeling issues as provided in the Agency communication dated June 7, 2013.

Biopharmaceutics:
Submit the information communicated in the Discipline Review Letter dated June 7, 2013, which requests the submission of multi-point comparative dissolution profiles in 5 media for the proposed and current manufacturing sites.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

We have not identified the need for REMS or other risk management actions at this time.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
    - Introductions, ground rules, objectives of the meeting.

2. Discussion of Substantive Review Issue(s) – 25 minutes

   Each issue will be introduced by FDA and followed by a discussion.

   Chemistry/Nonclinical
    - Drug substance DMF supporting the NDA remains deficient.

   Chemistry
    - Packaging site comparability protocol is inadequate.
    - Alternate drug product manufacturing site comparability protocol is inadequate.
    - Lot number and expiration date needed on immediate container labels.
    - Proposed Structured Product Labeling elements are inadequate.

3. Postmarketing Requirements/Postmarketing Commitments – 20 minutes

   Clinical Pharmacology
    1. An in vivo study in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.

    2. In vitro determination of vortioxetine and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

   Clinical
    3. Pediatric studies: as a PREA requirement you will need to conduct two multi-center, double-blind, placebo-controlled pediatric studies in children and adolescents (7 to 17 years old) in the treatment of major depressive disorder. At least one of these studies must be a fixed-dose study.

    4. A relapse prevention study in the US: since only Lu AA21004 20 mg/day demonstrated efficacy in the US and the relapse prevention study (11985A) was a non-US study, you will need to conduct a relapse prevention study to further characterize the dose response relationship of Lu AA21004 in the United States. This study should be a fixed dose study and the dose choice should cover the approved dose range.

4. Major labeling issues – 35 minutes

5. Wrap up and Action Items – 5 minutes

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/s/

JING ZHANG
06/20/2013

MITCHELL V Mathis
06/20/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Friday, June 14, 2013 10:04 AM
To: joanna.sambor@takeda.com
Cc: Patel, Hiren
Subject: NDA 204447

Hi Joanna,

In regards to your NDA above, we have the following comments.

1. The proposed acceptance criterion of Q= (b) (4) at 30 min is acceptable. Your commitment to review and evaluate the dissolution acceptance criterion for the ongoing stability studies and commercial batches for one year after the approval of the NDA is not
necessary. Your proposed acceptance criterion of Q= (b) (4) at 30 min is supported by the bioequivalence data submitted on May 31, 2013.

2. The comparability protocol for an additional manufacturing site is acceptable provided that you submit the information communicated in the Discipline Review Letter dated June 7, 2013, which requests the submission of multi-point comparative dissolution profiles in 5 media for the proposed and current manufacturing sites.

Regards,

Teshara G. Bouie, MSA, OTR/L
CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
06/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

LABELING PMR/PMC DISCUSSION COMMENTS

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, M.S.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your October 2, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (vortioxetine) 5 mg, 10 mg, 15 mg, and 20 mg tablets.

We also refer to our December 6, 2012, letter in which we notified you of our target date of June 14, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On January 24, 2013, we received your January 24, 2013 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

Additionally, we are recommending the following postmarketing requirements/commitments:

Clinical Pharmacology

1. An in vivo study in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.

2. In vitro determination of vortioxetine and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

Clinical

3. Pediatric studies: as a PREA requirement you will need to conduct two multi-center, double-blind, placebo-controlled pediatric studies in children and adolescents (7 to 17 years old) in the treatment of major depressive disorder. At least one of these studies must be a fixed-dose study.

4. A relapse prevention study in the US: since only Lu AA21004 20 mg/day demonstrated efficacy in the US and the relapse prevention study (11985A) was a non-US study, you will need to conduct a relapse prevention study to further characterize the dose response relationship of Lu AA21004 in the United States. This

study should be a fixed dose study and the dose choice should cover the approved dose range.

If you have any questions, email me, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

LCDR Hiren D. Patel, Pharm.D., M.S., RAC
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

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

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/s/

HIREN PATEL
06/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

DISCIPLINE REVIEW LETTER

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, MS Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your October 2, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vortioxetine Tablets.

We also refer to your amendment dated May 31, 2013. Please note, this amendment is currently under review and is not subject to this letter.

We have reviewed the Chemistry, Manufacturing, and Controls section of your submission and have identified the following deficiencies:

Drug Substance

1. The submission references DMF (b) (4) for drug substance chemistry, manufacturing, and controls information. Our review found DMF (b) (4) deficient. The DMF holder was notified of the deficiencies.

Comparability Protocols

2. The proposed reporting category is not acceptable for the packaging site comparability protocol. The normal reporting category for this change is a "Changes Being Effected in 30 days (CBE-30) " supplement. Our current approach to reducing reporting category is a one-step reduction. As such, we recommend a CBE-0 reporting category for this change. Revise the protocol to clarify if the (b) (4). facility will be an alternative primary packaging site or replace the packaging site(s) included in the original submission. Although the proposed (b) (4) site may have a satisfactory compliance at this time, the compliance status at the time of implementation is unknown. Revise the protocol to include the following commitment statement – "The move to (b) (4) site will not be implemented if there is an unsatisfactory cGMP inspection for this site at the time of implementation." The revision should also include a commitment to include the drug product annual batches packaged at the new site in the long-term stability program. Revise the stability protocol to include testing at Month 18. Provide a revised packaging site comparability protocol.

3. The proposed reporting category is not acceptable for the alternate drug product manufacturer comparability protocol. We recommend a CBE 30 reporting category for this change based on the fact that the compliance status of the new site will need to be determined at the time of the site change. In addition, the potential for process parameters outside of the approved ranges at the new site will need to be evaluated prior to the site change. Include descriptions of the analytical procedures and the associated acceptance criteria used as part of the process validation in the protocol. Referencing the validation protocol alone is not sufficient to allow for full evaluation of the proposed protocol. The stability testing supporting the site change should be conducted in the blister packaging and the bottle packaging that represents the extremes in terms of (b) (4) . Include a commitment to not distribute any drug product that is deemed non-equivalent. Provide a revised comparability protocol for review.

   Submit multi-point dissolution profiles comparisons (with *f2* statistical testing) in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5 (five separate profiles) for the proposed and current manufacturing sites. Adequate sampling should be performed (e.g. at 5, 15, 30, 45, 60, and 120 minutes) until either (b) (4) of drug from the drug product is dissolved or an asymptote is reached. A (b) (4) may be used with appropriate justification.

Labeling

4. Revise the immediate container labels to include the lot number and expiration date as required by 21 CFR 201.18 and 201.17, respectively. Provide updated carton and container labels with the required lot and expiration date as well as the agreed upon removal of the (b) (4) special handling statement.

5. The proposed structured product labeling (SPL) data elements are not acceptable. Revise the data element describing the denominator for all strengths. The use of (b) (4) Revise the data element terms describing tablet shape and tablet flavor. The use of a (b) (4) data element is not acceptable as the tablet formulation does not contain (b) (4) . The use of (b) (4) to describe the tablet shape may be confusing and does not accurately reflect the almond shape of the tablets. The use of "TEAR" or "OVAL" to describe the tablet shape may be more appropriate. Provide updated SPL data element tables.

If you have any questions, call Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
06/07/2013

Patel, Hiren

From: Patel, Hiren
Sent: Thursday, June 06, 2013 3:02 PM
To: Sambor, Joanna (joanna.sambor@takeda.com)
Subject: NDA 204447

Dear Joanna,

We have the following labeling recommendations at this time for vortioxetine:

A. General Comment for all Labels and Labeling

The graphic above the letter "i" is distracting and interferes with the readability of the name. Remove the graphic or, alternatively, consider relocating it away from the proprietary name, established name, and strength.

B. Retail Container Label (500-count)

The "child-resistant" statement is located in the center of the principal display panel of the 500-count retail container labels and is too prominent in this location. Exchange the locations of the "child-resistant" statement and the Medication Guide (MG) statement. Additionally, debold the font of the "child-resistant" statement and revise the text to appear in title case.

C. Retail Container Labels and Professional Sample Bottle Labels

The statement of strength lacks prominence on the retail container labels and professional sample bottle labels because there does not appear to be sufficient color contrast between the statement of strength and the white background. Increase the size of the statement of strength, increase the point weight of the text, or darken the hue to ensure there is sufficient contrast between the statement of strength and background color.

D. Professional Sample Blister Card

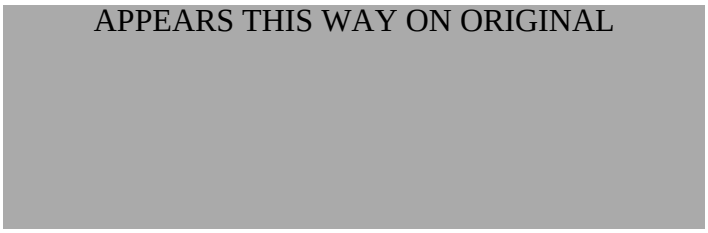
1. The directions for tablet removal lack clarity. Revise the directions to read "To remove tablet, push the tablet through the foil backing from this side" or use similar verbiage.
2. The directions for tablet removal lacks prominence on the inside right panel. Move the "To remove tablet…" statement to where the (b) (4) is currently located. The (b) (4) should be removed since it is duplicative information that is already listed on the inside left panel. Additionally, relocate the "Store in original container" statement to the bottom of the inside right panel.
3. Revise the statement of strength to read "XX mg per tablet" on all panels.
4. The net quantity statement, "One sample unit contains...", is not optimally worded for clarity. Revise the statement to read "Contains 7 tablets".

E. Professional Samples: Blister Cards, Sample Bottles and their Respective Carton Labeling

1. We note the NDC identification codes on the blister carton labeling and blister cards are identical. This is inappropriate because four blister cards are packaged in each carton. Therefore, revise the NDC identification code for the carton labeling.
2. We note the NDC identification codes on the sample bottle carton labeling and sample bottles are identical. This is inappropriate because four sample bottles are packaged in each carton. Therefore, revise the NDC identification code for the carton labeling.

F. Professional Sample Carton Labeling for the 7-count Bottles
The Brintellix website address is too prominent. On the top flap of the carton for the 7-count bottle, exchange the locations of the website address and the MG statement. Additionally, decrease the font size of the website address. Consider relocating the website address to a side or back panel.

Regards,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/s/

HIREN PATEL
06/06/2013

Executive CAC
Date of Meeting: April 30, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Karen Davis Bruno, Ph.D., DMEP, Alternate Member
Linda Fossom, Ph.D., DPP, Supervisor
Antonia Dow, Ph.D., DPP, Presenting Reviewer

Author of Draft: Antonia Dow

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA 204-447
Drug Name: Vortioxetine
Sponsor: Takeda Pharmaceuticals, Inc

Background: This NDA is for the use of vortioxetine in major depressive disorder. Vortioxetine is a selective serotonin reuptake inhibitor (SSRI) with additional serotonin receptor activity (antagonist at 5-HT3, 5-HT7, and 5-HT1D; partial agonist at 5-HT1B; agonist at 5-HT1A). However,, the effect of the additional serotonin receptor activity on vortioxetine's antidepressant effects are unknown.

Vortioxetine was negative for mutagenicity in the Ames assay and for clastogenicity in the *in vitro* chromosome aberration assay and in the *in vivo* rat micronucleus assay.

Protocols for the 2-year mouse and rat carcinogenicity studies were presented to the Executive CAC on January 16, 2007. The doses used in mice and female rats were those recommended by the Exec CAC, with the high dose based upon AUC. The doses used in male rats were those recommended by the Exec CAC, with the high dose based on MTD for renal pathology in the 26-week rat general toxicology study.

Mouse Carcinogenicity Study: Male and female CD-1 mice were dosed orally (by gavage, in 15% hydroxypropyl-β-cyclodextrin) at 0, 5, 15, or 50 mg/kg/day and 0, 10, 30, or 100 mg/kg/day, respectively, for at least 102 weeks. The exposures (AUC_{0-24}) at the high dose were approximately 20X and 13 – 22X the MRHD of 20 mg/day for male and female mice, respectively. AUC values for mice were based on interpolated data from shorter toxicity studies, because PK was not assessed in the carcinogenicity study.

No biologically relevant, drug-related increases in neoplasms were seen in mice administered vortioxetine. The incidence of hepatocellular adenomas was numerically increased for males at the HD but did not reach statistical significance for a common tumor. Non-neoplastic findings of hepatotoxicity and the presence of crystalline material in the hepatic bile ducts were seen in HD males.

Rat Carcinogenicity Study: Male and female Wistar rats were dosed orally (by gavage, in 10% hydroxypropyl-β-cyclodextrin and 4.4% glucose monohydrate) at 0 (water), 0 (vehicle), 2, 7, or 20 mg/kg/bid and 0 (water), 0 (vehicle), 5, 15, or 40 mg/kg/bid, respectively, for 104 weeks. The exposures (AUC_{0-24}) at the high dose were approximately 3 – 7X and 15X the MRHD of 20 mg/day for male and female rats, respectively. AUC values for rats were based on data from shorter toxicity studies, because PK was not assessed in the carcinogenicity study. Increased premature mortality was seen at the high dose in females due to blockage of the common bile duct by crystals.

The incidence of polypoid adenomas of the rectum was statistically significantly increased (trend and pairwise) in high dose females at exposures 15X the exposures at the MRHD of 20 mg/day (Table 1). The incidence of hemangiomas in the mesenteric lymph node was numerically increased for mid and high dose males compared to vehicle; although, not significant for pairwise comparison (Table 1). However, the increased incidence of combined hemangiomas and hemangiosarcomas at all sites was not statistically significant. The incidence of hepatocellular adenomas was numerically increased for males and females at the high dose but did not reach statistical significance for a common tumor. Non-neoplastic findings of hepatotoxicity and crystalline material in the hepatic bile ducts were seen in high dose males and mid and high dose females.

Table 1: Statistical results for neoplasms in the rectum of female and mesenteric lymph node of male rats compared to vehicle (10% hydroxypropyl-β-cyclodextrin and 4.4% glucose monohydrate)

Organ	Tumor	n=55/group					Trend test p-value	Pairwise Test (V vs. HD) p-value
		W	V	LD	MD	HD		
Rectum (female)	polypoid adenoma	0	0	0	1	4	0.0034	0.0448
Mesenteric lymph node (male)	hemangioma	3	6	6	13	15	0.004	0.0163
	hemangiosarcoma	0	0	0	0	0	--	--
	all sites hemangioma + hemangiosarcoma	4	7	9	13	15	0.0180	0.0313

W = Water Control; V = Vehicle Control

[Data from Dr. Jackson's statistical analysis]

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol. The Committee noted the increased premature mortality of high dose female rats, but considered that survival was adequate and sufficient numbers of rats were exposed for a sustained amount of time for an adequate assessment of carcinogenicity.

- The Committee concurred that the polypoid adenomas of the rectum in high dose females were drug related.

For both the rat and mouse studies, the possible confounding effect of hydroxypropyl-β-cyclodextrin on the liver is not known.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DPP
/Linda Fossom, DPP
/Antonia Dow, DPP
/Hiren Patel, DPP
/Adele Seifried, OND IO

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/s/

ADELE S SEIFRIED
05/02/2013

DAVID JACOBSON KRAM
05/02/2013

Patel, Hiren

From Sambor, Joanna (TGRD) [joanna.sambor@takeda.com]
Sent Wednesday, April 10, 2013 10 04 AM
To Patel, Hiren
Subject RE: NDA 204447 - clarification on response to information request

Hiren,

Thank you for the response.

Joanna

From: Patel, Hiren [mailto:Hiren.Patel@fda hhs.gov]
Sent: Tuesday, April 09, 2013 7:24 PM
To: Sambor, Joanna (TGRD)
Subject: RE: NDA 204447 - clarification on response to information request

Joanna,

We agree with your proposal to submit 24 months of stability data in support of a 36 month drug product expiration. We also agree that the post-approval stability protocols will not need to be updated based on the new proposed expiration.

Regards,
Hiren

Hiren D. Patel, Pharm.D., M.S., RAC
LCDR USPHS
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov

From: Sambor, Joanna (TGRD) [mailto:joanna sambor@takeda.com]
Sent: Thursday, April 04, 2013 2:53 PM
To: Patel, Hiren
Subject: NDA 204447 - clarification on response to information request

Dear Hiren,

As requested at the mid-cycle teleconference, we are working on providing a rolling response to the Mar 5, 2013 CMC Information Request. The first response is expected shortly. We are also preparing responses to the new IRs from the mid-cycle teleconference that were communicated in the Mar 26, 2013 letter. We do have one question/proposal for our response to the following information request from the Mar 26 letter:

FDA Request:

The proposed drug product expiration dating period is (b) (4). However, the proposed post-approval stability protocols for the Takeda process qualification batches, the Lundbeck commercial-scale batches, and the annual stability batches do not include testing at (b) (4). Revise these post-approval protocols to include testing at (b) (4) to confirm the proposed drug product expiration. The scheduled testing at (b) (4) should include samples for all tablet strengths and packaging configurations included in the stability program.

Takeda Proposal:
At this time, 24 month stability data is available. Would it be valuable to FDA to receive the 24 month stability data in response to the Information Request and concurrently change the requested product expiration dating period to 36 months? If so, the post-approval stability protocols already include testing at 36 months. If this submission would result in a change to the NDA review time, then this change would be made post-approval.

Please let me know if you have any questions and thank you for your guidance,
Joanna

Joanna Sambor, MS
Associate Director, Regulatory Strategy
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-2948
(b) (6)
joanna.sambor@takeda com
www.tgrd.com

###
The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and

###

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/s/

HIREN PATEL
04/10/2013

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Wednesday, March 06, 2013 11:40 AM
To: Sambor, Joanna (TGRD)
Cc: Patel, Hiren; Grewal, Renmeet
Subject: NDA204447- Clinical Information Request

Importance: High

Dear Joanna,

Please refer to the maintenance study 11985A in your original NDA 204447.
At the End of Phase II Meeting held on February 5, 2008, we expressed the rationale for requiring responders to be stabilized for at least 12 weeks before randomization.In this trial, patients were eligible for randomization as long as they stayed in remission state for the last two visits (Weeks 10 and 12) of the open-label phase. To explore the actual stabilization durations, please provide the following information:

- For each patient obtain the stabilization duration (i.e., the number of consecutive weeks the patient remained in remission immediately prior to randomization). Submit the SAS program that generated this variable (stabilization duration) and a .xpt data set that contains this variable. Summarize the outcome of this variable

Please respond to this information request no later than COB Monday, March 11,2013.

Sincerely,
Rimmy

Renmeet Grewal, Pharm.D., RAC, CDR USPHS
Team Leader, Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

RENMEET GREWAL
03/07/2013

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Wednesday, March 06, 2013 4:38 PM
To: Sambor, Joanna (TGRD)
Cc: Patel, Hiren
Subject: Request Mean Changes for Vital Signs: NDA 204447 Vortioxetine/Takeda/ Treatment of MDD

Dear Joanna,
Please see the information request below from our clinical team:

Please summarize the mean changes from Baseline to Final visit (endpoint) for vital sign variables in MDD short-term pool and the MDD/GAD short-term pool. Please use the format of the following table. Please respond to this request no later than Monday, March 11, 2013.

Table: Mean Change (SD) from Baseline to Final Visit (Endpoint) for Vital Signs Variables in MDD Short-Term Pool

Parameter (Units)	Placebo (N=)	LuAA21004 (mg)					Duloxetine (N=)
		5 (N=)	10 (N=)	15 (N=)	20 (N=)	Total (a) (N=)	
SBP, standing (mmHg)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
DBP, standing (mmHg)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
Pulse, standing (bpm)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
SBP, supine (mmHg)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
DBP, supine (mmHg)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
Pulse, supine (bpm)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
SBP, orthostatic (mmHg)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)
Weight (kg)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)	Mean Change (SD)

Total (a): also include doses: 1mg and 2.5mg
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure
SD: standard deviation

Sincerely,
Rimmy

Renmeet Grewal, Pharm.D., RAC, CDR USPHS

Team Leader, Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

RENMEET GREWAL
03/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

INFORMATION REQUEST

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, MS
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vortioxetine Tablets.

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 NDA.

Drug Substance

1. The submission references DMF (b) (4) for drug substance chemistry, manufacturing, and controls information. Our review found DMF (b) (4) deficient. The DMF holder was notified of the deficiencies.

Drug Product

2. The excipient selection information provided in the submission does not address the potential impact of different grades of hydroxypropyl cellulose, microcrystalline cellulose, and mannitol on drug product manufacturing or quality. Different grades of these excipients exhibit different material attributes such as viscosity, moisture content, and particle size distribution. Either update the drug product composition and excipient specification information to include the specified technical grades for hydroxypropyl cellulose, microcrystalline cellulose, and mannitol or provide data demonstrating that differences in technical grades for these excipients do not impact drug product manufacturing or quality.

3. The submission indicates that the (b) (4) of Lu AA21004 HBr (b) (4) are expected to occur under processing and storage. It is unclear if this evaluation of crystal form stability included an assessment of the potential for the formulation excipients to contribute to form changes. For example, several of the formulation excipients are hygroscopic (hydroxypropyl cellulose, microcrystalline cellulose, sodium starch glycolate, hypromellose, and PEG) and

may promote changes in polymorphic or hydrate form. Comment on the potential for the tablet core and film-coat excipients to promote the formation of undesired polymorphs, hydrates, or solvates of Lu AA21004 HBr and propose appropriate controls, if needed.

4. Based on our assessment, we consider the potential for Lu AA21004 HBr polymorph conversion to be a high risk material attribute. (b) (4) (b) (4) (b) (4) Either provide data demonstrating that the manufacturing processes do not promote changes in Lu AA21004 HBR polymorph, hydrate, or solvate form or update the proposed regulatory drug product specification to include appropriate tests to monitor these attributes.

5. The manufacturing process description for the Lundbeck site indicates that magnesium stearate (b) (4) (b) (4) However, the Lundbeck process development report does not address why this process step is needed at Lundbeck, especially since it is not required at the Takeda site. Provide the process development information that supports the inclusion of this process step in the commercial manufacturing process.

6. The Takeda process development report indicates that content uniformity and related substances were evaluated as response variables using step-wise linear regression during the (b) (4) optimization study. However, the report lacks the results from the statistical analysis for these two response variables. Either provide the step-wise linear regression results for content uniformity and related substances or comment on why (b) (4) do not have a statistically significant impact on these response variables.

7. The batch formulas for the Lundbeck site indicate the amount of magnesium stearate (b) (4) (b) (4) The Lundbeck master batch records do not specify the amount of magnesium stearate added either. Update the batch formulas and any other relevant sections (e.g. description and composition) of the submission to include the actual amount of magnesium stearate (b) (4) (b) (4) .

8. The submission lacks a description of the final drug product packaging. Based on our assessment, we consider the final packaging operation to be a critical unit operation due to the inclusion of processing steps such as (b) (4) (b) (4) at the Lundbeck site. In order to evaluate the adequacy of your packaging control strategy provide a complete description of the packaging process (b) (4) as described in the packaging design space proposed in Section P.7 of the submission). You can

either revise the manufacturing process description in Section P.3.3. or include a master batch record for packaging.

9. The proposed regulatory drug product specification does not identify the tests performed during stability testing. Section P.8 of the submission did not include a separate stability specification. Revise the proposed regulatory drug product specification to include a designation of the tests performed as part of the drug product stability testing. Confirm that all specification tests are performed on the finished, film-coated tablet.

10. The container closure information provided in the submission did not include references to relevant CFR regulations or supplier information for the bulk packaging components. Update Section P.7 of the submission to include this information.

11. Although the calculated headspace is the same for the proposed 7-count, 45 cc HDPE bottle and the 14-count, 45 cc HDPE bottle presentations, (b) (4) . Comment on the impact (b) (4) for drug product packaged in the 7-count, 45 cc HDPE bottle compared to the 14-count, 45 cc HDPE bottle.

12. The proposed packaging design space appears reasonable. However, comment on how changes in drug product contact surface will be evaluated and reported to the Agency in light of the proposed packaging design space. It is not clear based on the information included in the submission if any changes in container closure system made based on this design space will be reported to the Agency as required by 21 CFR 314.70. The implementation of a design space does not obviate the requirement to report changes to the application. Additionally, it is unclear if changes to the design space will be reported to the Agency. The Agency recognizes that changes to low criticality parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.

13. The inclusion of stability protocols to support post-approval changes in Section 3.2.P.8.2 is not appropriate. Any stability protocols supporting proposed comparability protocols should be included in the comparability protocol for consideration. Update Section 3.2.P.8.2 of the submission to remove the post approval change stability protocols. Update any proposed comparability protocols to include supporting stability protocols.

14. The executed batch records for the registration stability batches were not translated into English. As such, we cannot determine the amount of magnesium stearate added to these batches (b) (4) . Specify the amount of magnesium stearate added (b) (4) for all registration stability batches. If different amounts were used based on final packaging presentation, indicate these differences in the response.

15. Our evaluation of the registration stability data noted trends in water content at both accelerated and long-term conditions. Conduct a statistical analysis of the (b) (4) results for all tablet strengths in the blister at long-term conditions. Comment on the (b) (4)

[redacted] during storage or exposure of the drug product to elevated humidities to promote changes in Lu AA21004 polymorph, hydrate, or solvate form.

16. The formulation contains two hygroscopic polymers – hydroxypropyl cellulose, polyethylene glycol, and hypromellose. As the proposed post-approval drug product stability specification does not include a control [redacted], comment on the [redacted] proposed shelf life to affect [redacted] these polymers and thus, impact drug product dissolution and [redacted] over the proposed shelf life.

17. The proposed drug product storage statement includes instructions to [redacted] Based on the photostability study results, [redacted] In addition, the instruction [redacted] contradicts the assertion that the stability results demonstrate that changes [redacted] do not negatively impact drug product quality. Explain why these special storage instructions are proposed for the drug product storage statement.

Information Request

As noted in the May 27, 2010 Type C Meeting Background Materials and agreed upon in the June 23, 2010 preliminary responses, provide the three months of stability data from the Takeda site process validation batches. If additional time points are ready for submission, provide these results as well.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
03/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

METHODS VALIDATION
MATERIALS RECEIVED

Takeda Global Research Development Center Inc.
Attention: Joanna Sambor, Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015
FAX: (224) 554-7870

Dear Joanna Sambor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vortioxetine Tablets, 5 mg, 10 mg, 15 mg, and 20 mg and to our October 23, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 11, 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 (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

FILING COMMUNICATION

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, MS
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) dated and received October 2, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for vortioxetine hydrobromide 5 mg, 10 mg, 15 mg, and 20 mg tablets.

We also refer to your amendments(s) dated:

October 3, 2012	October 26, 2012
October 15, 2012 (2)	November 8, 2012
October 19, 2012	November 16, 2012

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is October 2, 2013.

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, mid-cycle, 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 June 14, 2013. In addition, the planned date for our internal mid-cycle review meeting is February 26, 2012. We are not currently planning to hold an advisory committee meeting to discuss this application.

Labeling

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

(b) (4)

We request that you resubmit labeling that addresses this issue within 3 weeks from the date of this letter. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a waiver or deferral has been obtained. A pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to: 1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and 2) support dosing and administration for each pediatric subpopulation for which the product has been assessed to be safe and effective.

We acknowledge receipt of your request for a partial waiver of pediatric studies for pediatric patients 0 to 6 years for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge your request for a partial deferral for pediatric patients 7 to 17 years; however, it is not complete. Within 30 days of the date of this letter, you will need to provide:

1. The certification required by FDCA Section 505B(a)(3) and (4).
2. A pediatric plan, which is a statement of intent which outlines the Pediatric Studies (PK/PD, efficacy and safety) that you plan to conduct. It must include a timeline for submission of studies (protocol, initiate studies, submit studies) and address development of age appropriate formulation. Furthermore, it should address under what grounds you are requesting deferral of pediatric studies.

Once we have reviewed your request, we will notify you if the partial deferral request is denied.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Psychiatry Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Hiren Patel, Regulatory Project Manager, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
12/06/2012

Patel, Hiren

From: Patel, Hiren
Sent: Friday, November 30, 2012 10:39 AM
To: 'Sambor, Joanna (TGRD)'
Subject: NDA 204447

Dear Joanna,

Reference is made to NDA 204447 received on October 2, 2012. Please note that your New Drug Application has been filed and we will be issuing a 74-day letter.

Regards,
Hiren

Hiren D. Patel, Pharm.D., M.S., RAC
LCDR USPHS
Regulatory Health Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-2087
Email: hiren.patel@fda.hhs.gov

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/s/

HIREN PATEL
11/30/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204447
IND 076307

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Takeda Pharmaceuticals USA, Inc.
One Takada Parkway
Deerfield, IL 60015

ATTENTION: Joanna Sambor, MS
Associate Director, Regulatory Affairs

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) dated and, received October 2, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and also your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vortioxetine Tablets 5 mg, 10 mg, 15 mg, and 20 mg.

We also refer to your requests for review of your proposed proprietary name "Brintellix" submitted under NDA 204447, dated and received October 3, 2012; and under IND 076307, dated and received May 10, 2012. We have completed our review of the proposed proprietary name, Brintellix and have concluded that it is acceptable.

The proposed proprietary name, Brintellix, 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. Additionally, if **any** of the proposed product characteristics as stated in your October 3, 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 Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Hiren Patel, at (301) 796-2087.

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

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/s/

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
10/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

REQUEST FOR METHODS VALIDATION MATERIALS

Takeda Global Research Development Center Inc.
Attention: Joanna Sambor
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Joanna Sambor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vortioxetine tablets, 5 mg, 10 mg, 15 mg, and 20 mg.

We will be performing methods validation studies on Vortioxetine tablets, 5 mg and 20 mg, as described in NDA 204447.

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

Method, current version

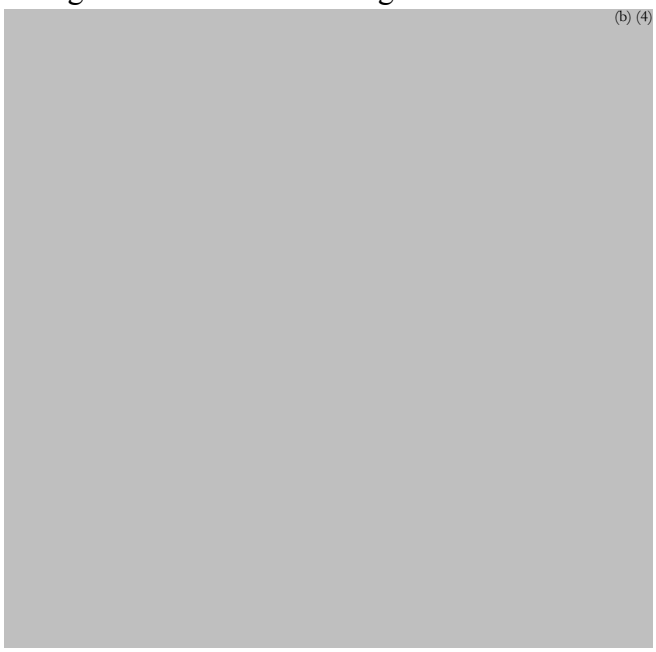
Analytical Procedure, Identification, Assay and Impurities by HPLC, Lu AA21004 hydrobromide Method No. 826-METH-331
Analytical Procedure, Determination of impurities, GC Lu AA21004 hydrobromide, Method No. 826-METH-401
Analytical Procedure, Assay and Degradation Products, Lu AA21004 Tablets Method No. LuAA21004-18067
Analytical Procedure, Content Uniformity, Lu AA21004 Tablets Method No. LuAA21004-18068
Analytical Procedure, Dissolution, Lu AA21004 Tablets Method No. LuAA21004-18069

Equipment

1 (b) (4) HPLC column
1 (b) (4) capillary column (b) (4)
1 (b) (4) HPLC column
1 HPLC column

Samples and Reference Standards

50 Vortioxetine 5 mg tablets
50 Vortioxetine 20 mg tablets
1 g Lu AA21004-HBr drug reference standard
1 g Lu AA21004-HBr drug substance



Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
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 (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

NDA ACKNOWLEDGMENT

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, MS
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

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: vortioxetine hydrobromide 5 mg, 10 mg, 15 mg, and 20 mg tablets

Date of Application: October 1, 2012

Date of Receipt: October 2, 2012

Our Reference Number: NDA 204447

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 December 1, 2012, 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).

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 Psychiatry 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.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

LCDR Hiren D. Patel, Pharm.D., M.S., RAC
Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
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/

HIREN PATEL
10/09/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 76307

Takeda Global Research & Development Center, Inc.
Attention: Joanna Sambor, M.S.
Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Ms. Sambor:

Please refer to your Investigational New Drug Application (IND) file for Lu AA21004.

We also refer to the meeting between representatives of your firm and the FDA on March 30, 2010. The purpose of the meeting was to discuss the development of Lu AA21004 for the treatment of major depressive disorder.

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, contact Hiren D. Patel, Pharm.D., Regulatory Project Manager, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	March 30, 2010
TIME:	2:00PM – 3:30PM
LOCATION:	White Oak CDER Bldg 22, Room 1309
APPLICATION:	IND 76307
DRUG NAME:	Lu AA21004
TYPE OF MEETING:	Type C Face to Face Meeting
MEETING CHAIR:	Thomas Laughren, M.D.

FDA ATTENDEES:

Thomas Laughren, M.D.	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Division Director, DPP
Jing Zhang, M.D.	Medical Team Leader, DPP
Jenn Sellers, M.D.	Medical Reviewer, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Team Leader, DPP
Raman Baweja, Ph.D.	Clinical Pharmacology Team Leader
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Peiling Yang, Ph.D.	Biometrics Team Leader
George Kordzakhia, Ph.D.	Biometrics Reviewer
Hao Zhu, Ph.D.	QT-IRT Scientific Lead
Michael Sauers	DDMAC Group Leader
Amy Toscano, Pharm.D.	DDMAC Reviewer
Hiren D. Patel, Pharm.D., M.S.	Regulatory Project Manager, DPP

Takeda Global Research & Development Center, Inc. Attendees:

Stephen Brannan, M.D.	Executive Medical Director, Clinical Sciences, TGRD
Atul Mahableshwarkar, M.D.	Senior Medical Director, Clinical Sciences, TGRD
Marianne Dragheim, M.D.	Senior Specialist, ICR Mood & Anxiety Disorders, Lundbeck
Michael Serenko, M.D.	Associate Medical Director, Pharmacovigilance, TGRD
Mitch Friedman, PhD, DABT	Director of Toxicology, Nonclinical Safety and Efficacy, TGRD
Ying Wang, M.D., Ph.D.	Principle Clinical Pharmacologist, Clinical Pharmacology, TGRD
Frank Ogrinc, Ph.D.	Associate Director, Analytical Sciences, TGRD
Binita Kwankin	Director, Regulatory Affairs, TGRD
Iman Barilero, Ph.D.	Divisional Director, Regulatory Development Strategy, Lundbeck

Eva Boge, MSc	Regulatory Strategy Leader, Regulatory Development Strategy, Lundbeck
Una Ortell	Director, Regulatory Promotion and Advertising
Joanna Sambor, M.S.	Manager, Regulatory Affairs, TGRD

Background:

Lu AA21004 is under development by Takeda Global Research & Development Center, Inc. and H. Lundbeck A/S for the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD). Lu AA21004 is a bis-arylsulfanyl amine. The sponsor suggests that its in vitro profile shows that the compound combines: potent inhibition of the 5-HT transporter; antagonism at 5-HT3, 5-HT1B, and 5-HT7; and 5-HT1A receptor partial agonism.

As of Dec, 2009, several MDD studies have been completed: a short-term phase 2 POC study; 4 short-term phase 3 efficacy studies in adults; and 1 maintenance study in adults. Four short-term efficacy studies in adults with GAD have also been completed. Additional studies ongoing include: a short-term efficacy study in elderly adults with MDD; 2 longer-term safety studies in adults with MDD; and a maintenance study in GAD. The sponsor has concluded, based on the results from these studies, that efficacy has not been consistently demonstrated in either MDD or GAD in a dose range of 1 to 10 mg/day. They have also concluded that the 5-10 mg/day dose range was well-tolerated. Apparently the non-US studies were in part suggestive of efficacy for MDD in the 5-10 mg/day dose range, however, the US studies were not. The maintenance study in adults in a 5-10 mg/day dose range was apparently supportive of a maintenance effect. Similarly, the 3 US GAD studies were not supportive of efficacy in the 5-10 mg/day dose range, however, the one non-US study was supportive. The sponsor has therefore concluded that it will be necessary to conduct additional studies at higher doses, and they seek confirmation from FDA on their plans to explore doses in a range of 10-20 mg/day.

The sponsor is planning 4 additional short-term MDD studies: 3 in the US (15 and 20; 10 and 20; and 10 and 15), and 1 non-US (15 and 20).

Questions from the sponsor:

CLINICAL EFFICACY AND SAFETY QUESTIONS

Assessment of Current MDD Phase 3 Dataset and Approval Requirements:

Question 1: The sponsors' assessment of the current data is that higher doses need to be evaluated to show consistent efficacy in MDD in the United States. Does FDA agree?

> ***Preliminary Comments:*** *Based on the summary data you have provided, we agree that there does not appear to be persuasive evidence of efficacy for either MDD or GAD in the 1-10 mg/day dose range. We have no objection to your proposal to conduct additional studies in a dose range of 10 to 20 mg/day.*

Discussion at Meeting: *No further discussion.*

Question 2: The Lu AA21004 program is a global development program to support registration in the United Sates and Europe. The phase 2 and 3 studies are therefore conducted globally. The Sponsors would like to understand FDA's position on the acceptability of ex-US data to support US registration in the scenario where the ex-US studies may be positive and the US studies are negative or failed.

Preliminary Comments: *We would need at least some positive data from US studies. An application without such data would not be filed.*

Discussion at Meeting: *No further discussion.*

Indication:

Question 3: Does FDA agree that the current data package together with data from future studies, can support the following indication statement: "1.0 - Lu AA21004 is indicated for the treatment of Major Depressive Disorder (MDD)"?

Preliminary Comments: *On face, the proposed program should be able to provide evidence of efficacy for MDD. Whether or not it would be sufficient would be a matter for review.*

Discussion at Meeting: *No further discussion.*

Dose:

Question 4: The sponsors intend to include doses of 10, 15, and 20 mg/day in the 4 new phase 3 studies.

4a: Does FDA agree that doses of 10 to 20 mg are appropriate for phase 3 evaluation and eventual registration based on the pharmacological profile (see Sections 7.1 and 10.1) and currently available human efficacy and safety data (see Sections 7.0 and 8.0)?

4b: Assuming efficacy is demonstrated, does FDA agree that the clinical development plan (CDP) is structured appropriately to support a dosage and administration recommendation to start dosing for Lu AA21004 at 10 mg/day, with an increase up to 20 mg/day in patients with insufficient response at a 10 mg dose? Please refer to the Target Product Profile (TPP) for the proposed label text.

4c: Does FDA agree that the CDP, which includes abrupt discontinuation of Lu AA21004 and assessment of discontinuation symptoms at Weeks 1 and 2 after the last dose in most short-term studies and the relapse prevention study, will support the discontinuation statement in the Dosage and Administration section of the label as described in the TPP?

Preliminary Comments: *We have no objection to your proposed program for MDD. It is premature to discuss labeling prior to conduct of the proposed studies, and to submission and review of the data. Regarding discontinuation symptoms, we can discuss at the meeting optimal approaches to assessing for such symptoms. It is not sufficient to assess only at weekly intervals. These assessments must be more frequent, and can often be done by phone.*

Discussion at Meeting: *Since Lu AA21004 has a very long half-life, the sponsor argued against the need for more frequent than weekly assessments for discontinuation symptoms after stopping the drug. We agreed to consider this argument, but strongly recommended that they use some direct form of inquiry, preferably a formal assessment using a reliable tool for assessing discontinuation symptoms, rather than relying on spontaneous report.*

Exposure Requirements:

Question 5: Please refer to Section 9.2.8 for information pertaining to the current and projected subject exposure from the prior and new phase 2 and 3 programs.
5a: Assuming efficacy is demonstrated across the dose range of 10 to 20 mg, does FDA agree that the projected total, 6-month, and 1-year exposure across the dose range of 10 to 20 mg will support a future NDA?

5b: If 10 mg does not demonstrate efficacy in the future studies, and assuming efficacy is demonstrated across the dose range of 15 to 20 mg, will the projected total, 6-month and 1-year exposure at 15 to 20 mg be adequate to support a future NDA?

Preliminary Comments: *It's difficult to interpret your projections based on what you have provided. The bottom line is that you will need a minimum of 1500 total exposed to relevant doses of Lu AA21004, including 300-600 for 6 months and at least 100 for 12 months. Relevant doses are those for which efficacy has been demonstrated.*

Discussion at Meeting: *No further discussion.*

Analyses for Assessment of Sexual Dysfunction:

Question 6:
6a: Does FDA agree that presentation of the conclusions of the pooled analyses (shift analysis) can be included in the label, Section 6 Adverse Events—Effects on Sexual Function, as described in the TPP?

6b: Does FDA agree that the pooled analyses can include data from both the MDD and GAD studies and from studies where the active dose of Lu AA21004 did not demonstrate primary efficacy when compared to placebo in the prior and new program?

6c: Does FDA agree that the pooled analyses can include data from all doses studied in the prior and new program, even if the dose is not intended for registration?

6d: Does FDA agree that a noninferiority margin of 10 percentage points versus placebo is appropriate for this pooled analysis (shift analysis)?

6e: The sponsors' understanding of FDA's comments at the EOP2 meeting regarding inclusion of sexual dysfunction noninferiority and superiority data within the label was that the active comparator would serve as an active reference within the clinical study from an efficacy perspective, but that the pooled analyses would evaluate superiority of Lu AA21004 over the active reference on the sexual dysfunction analyses. Does FDA concur?

Preliminary Comments: *We have comments on several aspects of your proposal:*

[1] Subgroup Analysis:

- *Your trials were not designed for subgroup analysis, i.e.,patients were not randomized within each stratum ("normal" vs. "abnormal" at baseline). The purpose of randomization is to maximize the balance with respect to observed and unobserved potential prognostic factors and patent characteristics between treatment groups. If patients are not randomized within each stratum ("normal" vs. "abnormal" status), imbalance could occur between treatment groups in the targeted subgroup with respect to potential prognostic factors, and this outcome is even more likely if the sample size in the targeted subgroup turns out to be small. Thus, the interpretability of a treatment comparison within each subgroup may be a concern, whatever statistical model is used. Please refer to Cui et al. (Journal of Biopharmaceutical Statistics 2002; 12(3): 347-358).*

- *Since patients who are assigned to the "abnormal" status at baseline could still experience symptom worsening after receiving drugs, it is unclear what the rationale would be for considering only the "normal" subgroup. In addition, the suitability of the definition of "normal" status needs to be justified. If ASEX is not suitable for assessing for change in a more diverse population, and is useful only for a "shift" analysis, we advise that you consider "change from baseline" for another instrument, e.g., the CSFQ score, as a primary sexual dysfunction endpoint for all patients.*

[2] Assay Sensitivity: To demonstrate assay sensitivity for sexual dysfunction, it would be sufficient to show that the active reference significantly worsened the sexual dysfunction compared to either placebo or Lu AA21004. In general, it should be easier to achieve this goal with a comparison to placebo.

[3] Non-Inferiority (NI) Margin: We do not agree to your proposed NI margin. If you still decide to use the shift analysis, the NI margin should be chosen as a certain percentage of worsening by the active reference (relative to placebo). To be more specific, you will need to demonstrate that the worsening magnitude by Lu AA21004 (i.e., the difference in proportions of patients whose status become "abnormal" between the placebo arm and the Lu AA21004 arm, denoted by d) is at most 20% of the worsening magnitude by an active reference (i.e., active reference – placebo,*

denoted by d), i.e., demonstrate that d < d/5 based on a two-sided 95% confidence interval.*

[4] Analysis with all doses pooled: It is problematic to pool all LU AA21004 doses together in analysis because the severity of adverse events generally depends on dose levels. For example, the 20 mg dose may cause severe sexual dysfunction while 1 mg may not cause any. Thus, analysis with all doses pooled may lead to a bias in favor of your drug. To ensure an adequate control of the type I error rate, we advise you to pre-specify a sequential testing order (such as from the high to the low dose, or the reverse order) to compare each potentially effective dose with placebo. In any case, the only comparisons of interest will be for those doses of your drug that are shown to be effective.

[5] Trial Considerations and Analysis Plan: As we advised at the EOP2 meeting that you need to have a detailed plan prospectively. This includes, but is not limited to what trials are to be included and what endpoint and analysis model are to be used. Trials to be included should be similar in design, such as duration, assessment schedule, etc. Under this scenario, we have no objection to pooling trials from both MDD and GAD indications given that "trial/study" is included as a factor in the statistical model. In order to reduce a selection bias, you should consider all eligible trials in the clinical development program whether or not efficacy is demonstrated. We advise you to have a thorough plan on this before conducting any future trials that may be included in such a meta-analysis. Retrospective selection of the primary endpoint or analysis can inflate the false positive error rate.

[6] Logistic Regression Model: Because of the strong assumption imposed in a logistic regression model, extensive model diagnostics are required for assessment of goodness-of-fit or a lack of fit of the fitted model. We do not recommend using a model with a treatment by status interaction term in place of stratified randomization by status. In this case, the inference on the treatment effect on sexual dysfunction for the "normal" subgroup is solely model based (and depends on the interaction term) and is unverifiable by a permutation test.

Discussion at Meeting:

Subgroup Analysis:

- *The sponsor acknowledged our concerns about possible imbalance with focus on a subgroup for which there was no stratification, and they agreed to include stratification based on normal vs abnormal in future trials.*
- *The sponsor argued that current thinking regarding assessment of drug-induced sexual dysfunction proposes looking at change from normal to abnormal, and that further change in patients who are already abnormal at baseline would be hard to detect and unlikely to contribute much to any observed effect. They indicated that even the author of the CSFQ has advocated for such shift analyses. Apparently there are no shift criteria for defining worsening in patients who are abnormal at baseline. We agreed to further consider their arguments once they submit a more complete package on this issue as part of a future protocol submission.*

Assay Sensitivity: The sponsor indicated an interest in showing that Lu A21004 is statistically superior to duloxetine, in order to support a claim of superiority to this drug. We emphasized that we felt a more reasonable goal would be to show that Lu AA21004 is neutral with regard to sexual dysfunction and noted again that they only needed to show that duloxetine is worse than placebo to accomplish assay sensitivity. Supporting a claim of superiority to duloxetine for Lu AA21004 would be far more difficult, since this would require a comparison of the dose response curves for Lu AA21004 and duloxetine, i.e., we would want them to compare the safety of these two compounds at equi-effective doses. This would require multi-arm studies and would be very difficult to accomplish. Thus, we strongly discouraged such a goal.

Non-Inferiority (NI) Margin: The sponsor continued to argue for their proposed NI margin based on data derived from earlier studies and FDA's recent NI guidance. They felt that our proposed margin was exceedingly conservative and would be difficult to achieve. We suggested that they put together a strong argument for their proposed approach and include this with their initial full protocol, and we will consider it further.

Doses to be included in Meta-Analysis: The sponsor agreed to limit the analyses to doses shown to be effective for Lu AA21004.

Logistic Regression Model: We reiterated our concerns about this model and recommended that they consider alternatives.

Adequacy of CDP to Support Proposed Claims:

Question 7: Clinical studies

7a: Depressed patients with high level of anxiety symptoms—In the proposed phase 3 MDD studies the sponsors have predefined the change from Baseline on the MADRS total score in the population with high anxiety scores (HAM-A total score ≥20 at Baseline) as a key secondary endpoint, which has been included as part of an analysis plan adjusted for multiplicity. Does FDA agree that the analysis plan is acceptable to support a claim in the Clinical Studies section of the label, as described in the TPP?

7b: Anxiety symptoms in depressed patients—In the proposed phase 3 MDD studies the sponsors have predefined the change from Baseline on the HAM-A total score as a key secondary endpoint, which has been included as part of an analysis plan adjusted for multiplicity. Does FDA agree that the analysis plan is acceptable to support a claim in the Clinical Studies section of the label, as described in the TPP?

7c: The proposed phase 3 studies will include 1 PRO endpoint as a key secondary endpoint, the Sheehan Disability Scale (SDS). Additional exploratory PRO endpoints will be included in some of the proposed phase 3 studies. A separate dossier including supporting documentation for PROs to be included in the CDP (eg, validation of instruments, analysis plan) has been submitted to the IND for consult by Agency staff with expertise in PROs. After review of this supporting documentation, and assuming positive data, does FDA agree that the analysis plan is acceptable to support a claim in the Clinical Studies section of the label, as described in the TPP

Preliminary Comments: *We do not agree with your proposal to carve out a subgroup of depressed patients with higher levels of anxiety symptoms at baseline. Although the STAR-D findings are of theoretical interest, "anxious depression" is not yet a widely recognized and well-accepted subtype of depression, and your proposed analyses are only of exploratory interest. While it is of some interest that such a subtype has been proposed for DSM-V, this concept is years away from establishment as a recognized entity. Similarly, we do not agree with your proposal to add the HAM-A as a secondary outcome. Anxiety symptoms are part of the depressive syndrome and of course it would be expected that anxiety symptoms would improve along with other aspects of the MDD syndrome. Thus, we would consider such an endpoint redundant with the primary measure of depression.*

The SDS is acceptable as a key secondary endpoint to assess the functional domain. However, not all key secondary endpoints you proposed in appendices are acceptable for potential labeling inclusion. We will provide you the feedback when you submit the individual protocols.

Discussion at Meeting: *We again explained our concern that focusing on a subgroup of patients with prominent anxiety at baseline is not supported by current established diagnostic categories, and did not agree to this as a key secondary analysis, for purposes of labeling. They agreed that such analyses would be exploratory, and also agreed that they would not add HAM-A as a key secondary endpoint for purposes of labeling.*

Question 8: Response and Remission Rates

As the Division considers remission/response redundant to the primary efficacy endpoints for inclusion in the label, the sponsors seek acknowledgement from the Division of Drug Marketing, Advertising, and Communications (DDMAC) that should these endpoints not appear in the label, the sponsors can promote these endpoints. This is predicated on the results of the secondary endpoints of response and remission, as defined in the TPP, being predefined, positive, replicated, and supportive of the primary endpoint.

Preliminary Comments: *DDMAC does not make comments on individual claims or on hypothetical promotional pieces. However, when evaluating promotional materials, DDMAC generally consults with the division to determine whether claims and presentations contained therein are supported by substantial evidence. While claims and presentations that are not included in labeling may be acceptable to use in promotion, they would still be held to the same standard of evidence as would claims for inclusion in product labeling. In this instance, we have already alerted DDMAC that we would likely object to the promotion referred to above. However, should you seek DDMAC's advice on any proposed promotional materials, please submit them after the NDA is submitted for FDA review. For specific information on how to request advisory comments from DDMAC on proposed promotional materials, please refer to our website.*

Discussion at Meeting: *We expressed our concerns about the arbitrary nature of the definitions for these constructs, and would not commit to accepting them even for purposes of promotion. They argued that an abundance of literature support their practical value in predicting outcome. We indicated that they could always make arguments based on new evidence and we would of course consider such arguments at some future time.*

Statistical Analyses Methods:

Question 9: The sponsors will use mixed model repeated measures (MMRM) as the primary statistical analysis for future studies for the efficacy assessments MADRS, HAM-A, and other scales (see Section 9.2.9). Does FDA agree with this approach?

Preliminary Comments: *In principle, we have no objection to MMRM as the primary analysis. Since the purpose of this meeting is to seek guidance on some key issues, given such a short period of time, we are unable to review in detail the protocol synopses as well as SAP for all proposed trials in the appendices. You will need to pre-specify detailed sensitivity analysis to explore the scenario when the mechanism of missing data is not "completely at random".*

Discussion at Meeting: *No further comment.*

Question 10: To control the 2-sided type I error over all the efficacy endpoints that are intended to support potential claims in each of the Lu AA21004 doses in a study, the Bonferroni correction will be used within a study with a prespecified hierarchy containing the primary endpoint and the key secondary endpoints for statistical testings. The hierarchy will be tested separately for each of the 2 doses per study using the Bonferroni-corrected alpha level 0.025 (see Section 9.2.9.1). Does FDA agree with this approach?

Preliminary Comments: *Yes. In case you are interested in a more powerful but more complex procedure, you might want to refer to Bretz et al. (Statistics in Medicine 2009; 28:586-604) because your proposal is a specific case of the graphical testing approach.*

Discussion at Meeting: *No further comment.*

CLINICAL PHARMACOLOGY QUESTIONS

Clinical Pharmacology Development Program:

Question 11: A comprehensive clinical pharmacology program has been conducted with Lu AA21004. The principal dose within this program has been 10 mg. Based on the available results obtained from the in vitro and in vivo studies the Sponsors contend that the data from the current clinical pharmacology program will support a potential target therapeutic dose of up to

20 mg once daily. Does the FDA agree that the clinical pharmacology program does not need to be repeated with the higher dose?

Preliminary Comments: *The current Clinical Pharmacology program on the 10 mg dose may be sufficient but it will remain a review issue depending on the outcome of your current drug-interaction studies on the 10 mg dose and whether the drug exhibits linear pharmacokinetics at the doses studied.*

The firm should clarify which dosage form was used in the Clinical Studies. This information is requested since several of the Clinical Pharmacology studies used more than one dosage form (e.g., L13119A- a 20 mg IR tablet, a 20 mg gastro-resistant EC1 capsule and a 30 mg gastro-resistant EC1 capsule).

Sponsor's Response: *The Immediate Release (IR) formulation has been and is intended to be the formulation for development and commercialization. An enteric coated (EC) formulation was used as an exploratory formulation in only two Phase 1 studies and this formulation will not be pursued at this time.*

Discussion at Meeting: *No further comment.*

Question 12: Does FDA agree with the Sponsors' interpretation that QTcNi (simple linear regression model), which was the predefined primary endpoint in the QTc study (T104), is an inappropriate endpoint and QTcF is the appropriate endpoint for study T104?

Preliminary Comments:

QT Interdisciplinary Review Team Comments:

No. You should use the predefined primary endpoint (QTcNi) in the QT study report. However, we will consider both QTcNi and QTcF when we review your study report.

Discussion at Meeting: *The sponsor presented data that they feel support the use of the QTcF, and we agreed to review these arguments. They indicated that they would be submitting the results of their thorough QT study in July, 2010, and will include these additional data and arguments as part of that package.*

Question 13: Does FDA agree that multiple doses of 40 mg QD of Lu AA21004 used as the supra-therapeutic dose in the QTc study (T104) will cover the highest clinical dose of 20 mg QD?

Preliminary Comments:

QT Interdisciplinary Review Team Comments:

Your rationale for using 40 mg QD as the supra-therapeutic dose in the QTc study (T104) appears to be reasonable. However, we will defer our final conclusion until after we review your study report.

Discussion at Meeting: *No further discussion.*

Mechanism of Action:

Question 14: Does FDA agree that the available nonclinical data support the text to be included in the Mechanism of Action section of the label, as described in the TPP?

Preliminary Comments: *It is premature to discuss labeling at this time. The adequacy of studies to support labeling claims will be a matter of review when your NDA is submitted.*

Discussion at Meeting: *No further discussion.*

Nonclinical Question - Dose:

Question 15: The sponsors intend to include doses of 10, 15, and 20 mg in 4 new phase 3 studies. Please refer to Section 10.2.1 for the nonclinical toxicology safety margin for these doses. Does FDA agree that the nonclinical safety and toxicology package supports study of doses up to 20 mg in phase 3 studies?

Preliminary Comments: *Yes.*

Discussion at Meeting: *No further discussion.*

Additional Comments:

We recommend that you perform periodic ECG monitoring for the ongoing and future clinical trials until we review your thorough QT study report. The suggested time points should be at baseline, around T_{max} of Lu AA21004 at steady state, and periodically thereafter as clinically indicated.

Discussion at Meeting: *The sponsor argued against the need for trying to obtain ECGs at Tmax, given the long half-life of the drug and the flat time-concentration curve. We agreed to consider such arguments and their proposed monitoring plan in the protocols to be submitted, along with the CSR for the thorough QT study.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-76307	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	LU AA21004

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

/s/

THOMAS P LAUGHREN
04/02/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 76,307

Takeda Global Research & Development Center, Inc.
Attention: Joanna Sambor, M.S.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LuAA21004.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2008. The purpose of the meeting was an End of Phase II discussion.

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 me at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 5, 2008
TIME: 3:00pm
LOCATION: White Oak, Bldg 21, Room 1313
APPLICATION: IND 76,307
DRUG NAME: LuAA 21044
TYPE OF MEETING: End of Phase II meeting

MEETING CHAIR: Thomas Laughren, M.D.

MEETING RECORDER: Renmeet Grewal, Pharm.D.

FDA ATTENDEES:
- Thomas Laughren, M.D., Director, Division of Psychiatry Products
- Mitchell Mathis, M.D., Deputy Director, Division of Psychiatry Products
- Gwen Zornberg, M.D., Medical Team Leader, Division of Psychiatry Products
- Karen Brugge, M.D., Medical Reviewer, Division of Psychiatry Products
- Peiling Yang, Ph.D., Team Leader; Office of Biostatistics
- George Kordzakhia, Statistics reviewer, Office of Biostatistics
- Linda Fossom, Ph.D., Pharm / Tox Reviewer, Division of Psychiatry Products
- Barry Rosloff, Ph.D., Pharm / Tox Team Leader, Division of Psychairtry Products
- Raman Baweja, Ph.D., Team Leader, Office of Clinical Pharmacology
- Thomas Oliver, Ph.D., PAL, Office of New Drug Quality Assessment

Sponsor Participants:
- Mick Roebel, Regulatory Affairs, Takeda
- Joanna Sambor, Regulatory Affairs, Takeda
- Iman Barilero, Regulatory Development Strategy, Lundbeck
- Eva Bøge, Regulatory Development Projects, Lundbeck
- Sandeep Patil, Clinical Sciences, Takeda
- Stephen Sainati, Clinical Sciences, Takeda
- Marianne Dragheim, ICR Mood & Anxiety Disorders, Lundbeck
- Sissel Vorstrup, ICR Psychiatry & Neurology, Lundbeck
- Torsten Meldgaard Madsen, ICR Mood & Anxiety Disorders, Lundbeck
- Nicholas Moore, Behavioral Pharmacology, Lundbeck
- Karina Bernholm, Toxicology, Lundbeck
- Lars Dalgaard, Metabolism, Lundbeck
- Frank Ogrinc, Biostatistics and Data Management, Takeda
- Henrik Loft, Biostatistics, Lundbeck
- Ying Wang, Clinical Pharmacology, Takeda

BACKGROUND:

Background: Lu AA21004 is under development by Takeda Global Research & Development Center, Inc. and H. Lundbeck A/S for the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD). The compound has just entered phase III of clinical development. Lu AA21004 belongs to a new chemical class of psychotropics, the bis-aryl-sulfanyl amines. The *in vitro* profile shows that the compound combines potent inhibition of the 5-HT transporter (5-HTT) and 5-HT1A receptor partial agonism with high affinity for the 5-HT3 receptor. The purpose of this meeting is to present the results of the phase II clinical trial with Lu AA21004 and to discuss and obtain agreement on the proposed phase III clinical trial program designed to demonstrate the efficacy and safety of Lu AA21004 in the treatment of MDD and GAD.

A phase II Proof of Concept (PoC) study (Study 11492A) in MDD (patients with a MADRSscore ≥30) has just been completed. This study was an international, multi-centre, 6-week, randomised, double-blind, placebo-controlled, active referenced, parallel-group, fixed-dose (Lu AA21004 5 mg/day and 10 mg/day, venlafaxine XR 225 mg/day) study in 426 patients with MDD, evaluating efficacy and safety. Preliminary results demonstrate significant improvement on the primary efficacy endpoint of both 5 and 10 mg LuAA21004 compared with placebo. Lu AA21004 apparently was well-tolerated in this study.

Additional planned MDD trials include the following:

- 11984A: This is a randomized, double-blind, 8-week, fixed-dose (2.5, 5, and 10 mg/day), placebo-controlled, active-referenced (duloxetine 60 mg/day), parallel-group study with a planned sample size of 660 MDD patients with a baseline MADRS ≥26.
- 303: This is a randomized, double-blind, 6-week, fixed-dose (5 mg/day), placebo-controlled, parallel-group study with a planned sample size of 600 MDD patients with a baseline MADRS ≥30.
- 306: This is a randomized, double-blind, 6-week, fixed-dose (10 mg/day), placebo-controlled, parallel-group study with a planned sample size of 600 MDD patients with a baseline MADRS ≥30.
- 304: This is a randomized, double-blind, 8-week, fixed-dose (2.5 and 5 mg/day), placebo-controlled, active-referenced (duloxetine 60 mg/day), parallel-group study with a planned sample size of 480 MDD patients with a baseline MADRS ≥22.
- 305: This is a randomized, double-blind, 8-week, fixed-dose (1 and 5 mg/day), placebo-controlled, parallel-group study with a planned sample size of 360 MDD patients with a baseline MADRS ≥26.
- 307: This is a randomized, double-blind, 10-week, fixed-dose (2.5 and 5 mg/day), placebo-controlled, parallel-group study with a planned sample size of 360 elderly MDD patients with a baseline MADRS ≥26.
- 11985A: This is a randomized withdrawal study. Remitters from a 12-week, open-label flexible-dose (5 and 10 mg/day) phase in MDD patients would be randomized to continue on their same dose of Lu AA21004 or placebo, with up to 64 weeks of observation for relapse. It is expected that 250 patients would be randomized.
- In addition, it is expected that longer-term safety data would be available from over 1000 patients from open-label continuations from the shorter-term trials.

The sponsor plans to collect data on "sustained response" in several of its MDD studies in order to support a claim of "early sustained response." "Response" would be defined as a ≥ 20% decrease in HAMD24. "Sustained response" for any individual patient would be declared if the response criterion is met at week 1 and at least 2 additional visits (2, 4, and 6 weeks). The hypothesis testing strategy would involve the following sequence: mean change from baseline in HAMD24 at week 6; mean change from baseline in HAMD24 at week 1; proportions of patients meeting sustained response criterion. All three null hypotheses would have to be rejected.

The sponsor is also planning 4 short-term studies in GAD, as follows:

- 308: This is a randomized, double-blind, 8-week, fixed-dose (2.5, 5, and 10 mg/day), placebo-controlled, active-referenced (duloxetine 60 mg/day), parallel-group study with a planned sample size of 625 GAD patients with a baseline HAMA ≥20.
- 309; 310; 311: These would be 3 identical randomized, double-blind, 8-week, fixed-dose (5 mg/day), placebo-controlled, parallel-group studies with a planned sample size of 300 GAD patients with a baseline HAMA ≥20.

The sponsor plans on including several PRO measures in its trials, including the SF-36, and intends to seek inclusion of positive findings from such instruments in labeling.

Before initiation of a full phase III program, the sponsors would like to consult the FDA with regard to:

- The clinical development program
- The clinical endpoints
- The clinical/statistical assessment and regulatory aspects of early sustained response
- The indications based on the proposed clinical program

Questions:

Question 1. Assuming positive efficacy results and a beneficial safety profile for Lu AA21004 from the studies outlined below, does the Agency agree that the proposed program (efficacy endpoints, doses used, patient population studied, using LOCF as the primary statistical approach, safety evaluations planned, etc.) and patient exposure (approximately 2800, 950, and 800 patients for short-term, 6-month, and 12-month exposure, respectively) is adequate to support an indication for use of Lu AA21004 in the treatment of MDD at doses of 2.5, 5, and 10 mg?

Preliminary Comments: *On face, the proposed program appears to be adequate to support an MDD filing. However, whether or not this program would be sufficient would of course be a matter of review. It is our understanding that your proposed program (including both your POC trial and all planned phase 3 trials) would provide for multiple comparisons with placebo for different doses as follows:*

-5 mg: 6 comparisons
-10 mg: 3 comparisons
-2.5 mg: 3 comparisons
-1 mg: 1 comparision

These studies should provide sufficient data to reach a conclusion about antidepressant efficacy for this compound, and also about dosing advice for labeling. You might consider fewer trials with more dose groups per trial, since this should provide better data on dose response. You might also consider including older and younger patients in the same trial to allow for comparisons of safety and efficacy across the age spectrum. The dosing range that would be supported by the results of this program would be a matter of review based on the evidence available in the application.

Regarding patient exposure, it would be important that ICH criteria would be met for the relevant doses from the standpoint of efficacy. It would be helpful to have an update on any additional findings regarding possible effects on prolactin and cortisol, and also on any significant rashes. There are 2 additional safety issues you need to be aware of. There has been concern about the possibility of suicidality as an adverse effect of antidepressants, so it will be necessary for you to include an approach that goes beyond spontaneous reporting to better assess for suicidality in the conduct of your trials. One available instrument is the Columbia-Suicide Severity Rating Scale (C-SSRS), and this would be an acceptable approach. We would be willing to consider others as well. There has also been concern about the possibility of sexual dysfunction as an adverse effect of antidepressants, so it will be necessary for you to include an approach that goes beyond spontaneous reporting to better assess for sexual dysfunction as well in the conduct of your trials. There are several available instruments for assessing for sexual dysfunction.

Sponsors Comments:

The Sponsors would like to discuss the dose range.

Regarding age spectrum the Sponsors acknowledge the comment and will ensure that the ICH requirements (at least 100 elderly patients) are fulfilled.

The projected exposure by dose will be presented at the meeting.

Prolactin and Cortisol:

There are no additional investigations regarding possible effects on serum levels of prolactin and cortisol to date. Serum levels of prolactin and cortisol were only evaluated in two completed SD (Study 10272) and MD (Study 10467) studies in healthy young men. This information has been communicated to the FDA in the initial IND application.

Rash:

In addition to the cases of rash that have been described in the Briefing Document from the PoC study (pg 44-45), three additional adverse events have been observed in the Long-term Safety Study (Study 11492C, as of 3 Feb 2008), all had normal relevant laboratory values.

- *Patient 3814 (Lu AA21004 10 mg group in Study 11492A), a 22 year old woman reported mild eczema on Day 7 in Study 11492A (as described in the Briefing*

Document, pg 44-45) lasting for 6 days. She had an ongoing medical history of unspecific dermatitis, confirmed by a dermatologist. In the extension study, 11492C, the patient reported a new event of "Cutaneous eruption" on Day 5 lasting for 13 days, and "Dermatitis left ear" on Day 55 lasting for 11 days, both of mild intensity. She was later withdrawn on Day 83 due to a protocol violation

- *Patient 3765 (venlafaxine group in Study 11492A), a 52 year old woman reported "Skin irritation, no rash" on Day 9 lasting for 8 days of mild intensity, and "Rash" on Day 90 lasting for 35 days of moderate intensity. She is continuing in the study on Lu AA21004 10 mg.*
- *Patient 4020 (venlafaxine group in Study 11492A), a 57 year old man reported "Worsening rash on lower limbs" on Day 77 and ongoing of moderate intensity. He was withdrawn on Day 115 from the study due to lack of efficacy*

Overall from the clinical studies in MDD to date, mild to moderate rash were reported by 7 patients.

Suicidality assessment:

The FDA has requested that the Sponsors in their development programme in major depressive disorder include the Columbia-Suicide Severity Rating Scale (C-SSRS).

The sponsors propose to implement the C-SSRS in studies 301, 303, 304, 305, 306, 307, not yet submitted to the IND, as prospective collection of suicidal ideation and suicidality. In the current program, we utilize the following criteria and wording to capture suicidal ideation and suicidality:

- *Exclusion criteria: The patient has a significant risk of suicide according to the investigator's opinion or has a score >= 5 on item 10 (suicidal thoughts) of the MADRS or has made a suicide attempt in the previous 6 months.*
- *Withdrawal criteria: the patient has a significant risk of suicide according to investigator's opinion or has a score >=5 on item 10 (suicidal thoughts) of the MADRS Ethical rationale:*

The selection criteria in the study exclude the participation of patients at high risk for suicide. Throughout the study, indicators of suicidal risk will be assessed both by rating scale assessment and by investigator's clinical judgement, and the patient will be withdrawn from the study in case of such risk.

The Sponsors have two placebo-controlled studies currently ongoing in Europe, the dose-finding study and the relapse prevention study, as well as two open-label extension studies. For these studies, the C-SSRS scale will not be implemented, but the exclusion and withdrawal criteria defined above are utilized.

For the entire clinical development plan, data on suicidality will be analyzed per the procedure proposed by Kelly et al in the C-CASA. The PoC data has been analyzed according to this procedure and there were no findings of relevance.

Will implementation of the C-SSRS also be requested in the GAD programme?

Sexual dysfunction:

The Sponsors propose to implement scales to assess treatment emergent sexual adverse events, e.g. the Changes in Sexual Functioning Questionaire (CFSQ), Arizona Sexual Experience Scale (ASEX) or Derogatis Interview for Sexual Functioning (DISF). We propose to implement one of these scales in one of the clinical studies in each of the MDD and GAD programmes.

Discussion at Meeting:

We reiterated our preference for fewer studies than planned with more dose groups per study, in order to better understand dose response. They maintained their preference for more studies with fewer dose arms per study. Their explanation for their preference seemed to be that it is difficult to show dose response for depression trials. Ultimately, we disagreed on what would be an optimal approach, nevertheless, we indicated that their proposed program should generate useful data for achieving some understanding of dose response.

We talked at some length about our suggestion to include elderly and non-elderly adults in the same trial. Since submitting the briefing package, the sponsor had decided to conduct the elderly subsequent to filing an initial application and, thus, indicated their preference not to follow our advice. They indicated that they would have safety data on at least 100 elderly adults for the initial filing. We indicated that this plan would be acceptable.

Regarding the sponsor's update on prolactin, cortisol, and rash, and their view that serious rash was not likely to be a problem with this drug, we indicated that we would further discuss this matter internally and get back to them with additional advice, if indicated.

We indicated that their plan to use the C-SSRS for all future MDD studies would be acceptable. They indicated that they were having some difficulty accessing the C-SSRS, and we promised to try to help them gain access. We also indicated that they should plan on using the C-SSRS in all planned GAD studies.

We indicated that any of the 3 proposed sexual function scales would be acceptable for assessing sexual dysfunction. However, we strongly advised them to use a specific instrument in all of their trials. We suggested that, if they were able to show superiority to an active comparator (assuming the comparator were used in an optimal manner) and show non-inferiority to placebo for their drug, they may be able to add such findings to labeling. However, we advised that they would need to plan for this prospectively and should propose an analysis plan, e.g., a meta-analysis, **to accomplish this goal.**

Question 2: Assuming a positive outcome of the relapse prevention study (Study 11985A), would this study support an indication claim in the labeling as provided below?

(b) (4)

(b) (4) *The exact labeling language supported by a positive study would be a matter or policy and review at the time the application was submitted.*

Sponsors Comments:

The Sponsors wish to discuss the design of the Relapse Prevention trial at the EoP2 meeting.

Discussion at Meeting: *The sponsor objected to the requirement for a 12 week period of stable "response" prior to randomization, arguing that the EMEA did not require such an extended responder phase. They cited recent FDA labeling which did not seem to make this requirement. We noted that language for* (b) (4) *claims that have recently been approved would be based on studies done 5 or more years ago, before our more recent policy change on this matter. We provided the rationale for this requirement and indicated that, for studies planned at the current time, we would insist on 12 weeks as a minimum stabilization period. We indicated that we would accept a reasonably flexible definition of "stable responder," e.g., it would be permissible for patients to have slight excursions outside threshold criteria.*

Post-Meeting Note: *The sponsor asked for clarification that FDA will accept positive short-term trials, without a successful randomized withdrawal study, as support for a claim of efficacy in the treatment of MDD.*

Response: Yes.

Question 3: Would it be acceptable to the Agency to have different scales (MADRS and HAM-D24) to assess the primary endpoint in the MDD development program?

Preliminary Comments: *We don't object to these instruments as bases for the primary endpoints in these trials. However, it would be helpful for you to provide the rationale for these different choices. We would also want to see the version of the HAM-D24 that you would propose to use.*

Sponsors Comments:

The Sponsors have the following rationale for using both the MADRS and the HAM-D_{24} in the development programme:

Both the MADRS and the HAM-D_{24} scales were included in the PoC study, and the MADRS was used as primary endpoint. Both scales are well-known scales for assessment of efficacy in MDD studies and one of the Sponsors has extensive experience with these scales. MADRS has been chosen as primary endpoint in the already initiated EU studies (11984A, 11985A). The HAM-D_{24} explores more detailed depression symptoms than the MADRS, and was seen in the PoC study to be more sensitive than the MADRS to early drug-placebo difference. The HAM-D_{24} is going to be used in all subsequent studies.

The version that the Sponsors will apply is included in CRF format.

Discussion at Meeting: *We accepted the sponsor's rationale for choosing these instruments.*

Question 4: Assuming that the pre-defined early sustained response is demonstrated with Lu AA21004 starting at Week 1, does the Agency agree that the proposed studies, one comparing 5 mg with placebo and the other comparing 10 mg with placebo, will support a labeling statement in the clinical section as provided below?

(b) (4)

Preliminary Comments: *There is no agreement on "response," and a* (b) (4) *in HAMD24 seems particularly weak. As an alternative, we suggest that you plan to test for mean change from baseline on the HAMD24 beginning at week 6, and then work backward sequentially, testing at each previous week (i.e., 5, 4, 3, 2, and 1). Testing would stop at the point significance is lost. You would of course need to have HAMD24 assessments at least weekly. We are considering permitting such findings to be included in labeling in support of language in labeling suggesting that an antidepressant effect was seen as early as week X and was maintained throughout the remainder of the trial (where X would be the earliest week at which statistical significance was still maintained). Although we have not yet confirmed this as a policy, this would be your best hope of obtaining any language in labeling regarding early onset of effect. It would be challenging, however, to develop hypothesis testing strategies to adjust for multiple doses and timepoints, and perhaps key secondary endpoint, e.g., PROs. We would be happy to provide further feedback on this issue as you develop more complete protocols and SAPs.*

Sponsors Comments:

Based on the preliminary comments received from FDA, the study design and analyses for the proposed studies will be modified.

It is still planned that two studies will be conducted for establishing the early effects of Lu AA21004 versus placebo – one study will compare the 5 mg dose to Placebo and one study will compare the 10 mg dose to Placebo. The revisions below apply to each study.

The highlights of changes are:

1. *Visits at weeks 3 and 5 will be added. Thus, post-baseline study visits will be at Weeks 1, 2, 3, 4, 5, and 6.*
2. *Statistical testing will be specified in the SAP as recommended by FDA – sequential tests from Week 6 and working backwards to Week 1. Statistical testing will stop when a non-significant test is found and the earliest effect will be established at the earliest statistically significant study week.*
3. *The sample size for the study could be based on the statistical comparison at Week 1.*
4. *According to the results from the PoC study, the expected difference from placebo at Week 1 will be near 1.5 points for the HAM-D_{24} scale with a maximum standard deviation of 6.0 points at the Week 1 visit.*
5. *Setting the statistical power based on Week 1, there will be at least 85% power with N= 289 subjects per group; thus, N= 300 subjects per group will be enrolled in each treatment group.*
6. *The overall power of the sequential tests will also be investigated and will be described in the SAP.*

Discussion at Meeting: *We objected to the sponsor's proposed plan, since it appeared to us that they were simply overpowering the study to show a difference from placebo at week 1 that was not clinically meaningful. This is the criticism that is typically targeted at this approach. We argued that, in their POC study, they had been able to show a 5 unit difference (on the HAMD-24) with a sample of only 100 patients per group. Thus, we argued that 100 patients per group should be an adequate sample size if their drug has a meaningful effect at week 1. They countered that the smaller observed effect at week 1 was a predictor of a clinically meaningful effect later in the trial. We were unable to agree on an approach to showing early response, however, we indicated that we would be willing to consider a more detailed argument for their proposed approach. They may submit this as an SPA.*

Question 5: **Assuming positive efficacy results and a beneficial safety profile for Lu AA21004 from the studies outlined below, does the Agency agree that the proposed program (efficacy endpoints, doses used, patient population studied, using LOCF as the primary statistical approach, safety evaluations planned, etc.) and patient exposure (approximately 800 patients exposed short term) is adequate to support an indication for the use of Lu AA21004 in treatment (b) (4)? Would the Agency grant this dosing range based on one study including all three doses and three studies investigating 5 mg?**

Preliminary Comments: *Although this program would provide 4 comparisons with placebo for the 5 mg dose, it would provide only 1 comparison for each of the 2.5 and 10 mg doses. It would be difficult to reach conclusions about the efficacy of these other doses with this limited program. We would recommend at least 1 additional comparison with placebo for each of the 2.5 and 10 mg doses. A second study with all 3 doses would accomplish this goal.*

Sponsors Comments:

We acknowledge the comment and propose to replace one Lu AA21004 5 mg clinical study with a new study that compares Lu AA21004 2.5 mg and 10 mg to placebo. This will give overall 2 comparisons of 2.5 mg and 10 mg with placebo and 3 comparisons of 5 mg with placebo. In total, there will be four short-term placebo-controlled studies in GAD:

- *Dose finding study: 2.5, 5, 10 mg*
- *One short-term study: 2.5, 10 mg*
- *Two short-term studies: 5 mg*

Discussion at Meeting: *We indicated that this proposed set of studies should be able to generate some useful information about dose response.*

Question 6: The Sponsors intend to bridge to the long-term safety data obtained in the MDD population and therefore do not plan to conduct long-term safety studies in the GAD population. Is this approach acceptable to the Agency?

Preliminary Comments: *Yes.*

Sponsors Comments: *The Sponsors acknowledge the comment. No further discussion is requested.*

Discussion at Meeting: *There was no further discussion.*

Question 7: The Sponsors intend to submit data supporting that Lu AA21004 is indicated for the treatment of (b) (4) MDD (b) (4). Is the Agency in agreement with this approach?

Preliminary Comments: *Yes.*

Sponsors Comments: *The Sponsors acknowledge the comment. No further discussion is requested.*

Discussion at Meeting: *There was no further discussion.*

Question 8: The Sponsors intend to include relevant Patient Reported Outcome measures (PROs) in the planned clinical trials. The data analysis of those will follow the Draft Guidance issued by FDA. Assuming that the pre-defined analysis for the PROs is successful, does the Agency agree that this will support a labeling statement in the clinical section as provided below, using the example of SF-36?

(b) (4)

Preliminary Comments: *We may permit certain PRO data in labeling, depending on the instruments used and the results. We recommend that you submit full documentation on the specific PRO instruments you intend to use so that we can assess their acceptability. We will likely consult with agency staff with expertise in such instruments.*

Sponsors Comments:

The Sponsors acknowledge the FDA's comment and, after the EoP2 meeting, will submit the full documentation for the PROs suggested for the Clinical Development Programme.

At the meeting the Sponsors would like to discuss the statistical approach for PROs. The Sponsors propose the following analysis plan for PROs:

- *If there is a statistically significant finding for the primary efficacy analysis, then testing will proceed for the pre-specified PRO measures.*
- *The PRO measures will be pre-specified as secondary endpoints for the study.*
- *PRO measures will be set as part of a separate hierarchical testing plan in the study SAP, using alpha = 0.05.*
- *Significant findings for the PRO measures included in this pre-specified testing plan can be used as significant findings from the study, along with efficacy.*

Discussion at Meeting: *We reiterated that we would want to assess each PRO measure for validity and relevance, and have our consultant experts consider each as well. We indicated that replication would be needed, and also cautioned them to pay close attention to multiplicity adjustment for hypothesis testing, especially when there were different outcomes, doses, and time points for analysis.*

Question 9: Does the Agency agree that the proposed pharmacokinetic and drug-drug interaction studies appear adequate for the approvability of Lu AA21004 for use in the MDD (b) (4) populations?

Preliminary Comments:
COMPANY POSITION
Lu AA21 004 has been evaluated in the following 5 clinical pharmacology studies:
- Single Ascending Dose Study (Study 10272)

- Multiple Ascending Dose Study (Study 10467)
- Absorption, Metabolism, and Elimination Study (Study 10477)
- Multiple Dose PET Study (Study 10985)
- Omeprazole Interaction Study (Study 1 1826A)

FDA RESPONSE
1. The studies seem to be appropriate but their approvability is a matter for review when the NDA is submitted.
2. The sponsor should elucidate the human metabolic pathway scheme for the drug. Both active and major metabolites should be identified. Further, the relative contribution of each biotransformation pathway for the drug should be ascertained. Mass balance details should be provided in the NDA.

COMPANY POSITION
The planned clinical pharmacology studies for the development of Lu AA21004 are as follows:
-Pharmacokinetics, Safety and Tolerability in Healthy Subjects

-Food Effect and Bioavailability/Bioequivalence Study

- Open-label, randomized, single-dose, 3-period crossover study to evaluate the effect of food on pharmacokinetics of Formulation 3 and to compare bioavailability/bioequivalence of Formulation 1 versus Formulation 3 in 24 healthy subjects

-Absolute bioavailability study

- Open-label, randomized, crossover study to investigate the absorption process in the context of absolute bioavailability in approximately 12 healthy subjects

FDA RESPONSE
1. Some of the data to which the firm refers had been previously submitted on April 4, 2007 with the opening IND. The studies seem to be appropriate but their approvability is a matter for review when the NDA is submitted.
2. The sponsor should make appropriate BE links between their to-be-marketed formulations and clinical formulations.

COMPANY POSITION
Pharmacodynamic Effects in Healthy Subjects

QT/QTc Study (LuAA21004_104

- Double-blind, randomised, placebo- and positive-controlled, 4-arm parallel-group study with multiple doses of Lu AA21 004 10 mg, 40 mg or placebo, for 14 days, or multiple doses of placebo for 13 days plus a single dose of moxifloxacin 400 mg for 1 day in approximately 340 healthy adult male subjects (85 per treatment arm)

FDA RESPONSE
The QTc study will be reviewed at the Center level, therefore OCP has no comments on the study design.

COMPANY POSITION
Intrinsic Factors (Special Populations):

Age, Gender, Race Study
- A randomised, single-blind, placebo-controlled, parallel group study with single and multiple doses of Lu AA2l 004 or placebo in 64 healthy adult subjects. (Ratio of randomization for active drug to placebo is 3: 1). The study will enroll 8 white young women, 8 white young men, 8 white elderly women, 8 white elderly men, 8 black young women, 8 black young men, 8 black elderly women and 8 black elderly men)

Renal Impairment Study
- Open-label, single-sequence study in patients with mild, moderate, and severe renal impairment or patients on hemodialysis and their healthy matched control subjects, single and multiple doses of Lu AA21004 for 14 days in approximately 48 subjects

Hepatic Impairment Study
- Open-label, single-sequence study in patients with mild and moderate hepatic impairment and their healthy matched control subjects, single and multiple doses of Lu AA21004 for 14 days in approximately 32 subjects

FDA RESPONSE
There are guidances on the FDA website with information on the conduct of these studies to which the firm should refer. These studies appear to be adequate but their approvability is a matter for review when the NDA is submitted.

COMPANY POSITION

Extrinsic Factors

Indiana Cocktail DDI Study (LuAA21004_101)
- Open-label, single-sequence study with single doses of caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, and midazolam 4 mg on Day 1, washout for 4 days, following multiple doses of Lu AA21 004 10 mg for 14 days; then co-administration of Lu AA21 004 10 mg plus drug cocktail probes of caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, and midazolam 4 mg for 1 day in 24 healthy subjects

Ketoconazole/Fluconazole DDI Study (LuAA21004_103)
- Open-label, randomised, single-sequence, parallel-group study with a single dose of Lu AA21004 10 mg, 14 days washout, following multiple doses of ketoconazole 400 mg, or fluconazole 200 mg for 6 days, then co-administration of Lu AA21 004 10 mg and ketoconazole 400 mg or fluconazole 200 mg for 1 day in 36 healthy subjects

Rifampin DDI Study

- Open-label, single-sequence study with a single dose of Lu AA21004, following multiple doses of rifampin, then co-administration of Lu AA21004 and rifampin for 1 day in approximately 20 healthy subjects

Comparison of PK profiles of Lu AA21004 and its Metabolites in CYP2D6 Poor Metabolisers versus Extensive Metabolisers

- Single-blind, placebo-controlled, single-sequence study with single and multiple doses of Lu AA21004 in approximately 24 subjects (approximately 12 CYP2D6 PMs and 12 CYP2D6 EMs)

Oral Contraceptive DDI Study (Lu AA21004_102)

- Randomised, single-blind, 2-period crossover study, multiple doses of Lu AA21004 10 mg + ethinyl estradiol 30 µg and levonorgestrel 150 µg for 21 days, multiple doses of placebo + ethinyl estradiol 30 µg and levonorgestrel 150 µg for 21 days, 35-day washout between the 2 treatments, in 28 healthy adult female subjects

Diazepam DDI Study

- Randomised, open-label, 3-arm, parallel-group drug-drug interaction study with multiple doses of Lu AA21004, multiple doses of diazepam, or multiple doses of Lu AA21004 + diazepam in approximately 72 healthy subjects (24 subjects per group)

Warfarin DDI Study

- Open-label, placebo-controlled, single-sequence study with warfarin 1 to 10 mg titration followed by multiple stable doses of warfarin + Lu AA21004 or placebo for 14 days in approximately 36 healthy subjects

Ethanol DDI Study

- Double-blind, randomised, 4-period crossover study with a single dose of Lu AA21004, ethanol 0.6 g/kg, placebo for Lu AA21004 or placebo for ethanol in approximately 24 healthy subjects

FDA RESPONSE

There are guidances on the FDA website with information on the conduct of drug-drug interaction studies which the firm should refer. These studies appear to be adequate but their approvability is a matter for review when the NDA is submitted.

Sponsors Comments: *The Sponsors acknowledge the comments to the proposed PK and DDI studies and would follow the directions for the NDA. No further discussion is requested.*

Discussion at Meeting: *No further discussion.*

Question 10: **Would the Agency agree with the study design and the selected doses for the QTc study described below (pg 20-22 of briefing package)?**

Preliminary Comments: *On face, the proposed study should be acceptable, however, once the full protocol is submitted, we will submit it to the QT Team for consult, and will provide feedback to you, as appropriate.*

Sponsors Comments: *The Sponsors acknowledge the comments and will send the protocol as soon as available after the EoP2 meeting for review by QT Team. No further discussion is requested.*

Discussion at Meeting: *No further discussion.*

Question 11: Does the Agency agree that the non-clinical safety of Lu AA21004 and its metabolites is adequately covered by the safety studies that have been or are being conducted by the Sponsors and that no further studies are required based on the information provided below (pg 22-23 of briefing package)?

Preliminary Comments: *We agree that the studies you have completed and submitted for review (safety pharmacology, general repeated-dose toxicology in rats (up to 6 months duration) and dogs (up to one year duration), embryo-fetal developmental studies in rats and rabbits, complete genotoxicity battery), in combination with the other standard studies you are conducting or plan to conduct (fertility study, which should be submitted prior to Phase III clinical testing; and a peri/post-natal developmental study and carcinogenicity studies, which should be submitted with the NDA), and the investigative/supportive studies you have proposed (e.g., to characterize the crystals seen in kidney/biliary system of rodents; mass-balance and metabolite profiling in dogs; plasma protein binding) appear on face adequate to support the development of Lu AA21004 as an antidepressant.*

Additionally, we appreciate that you have recognized and are addressing the need for animal coverage of major human metabolites so early in drug development. Your proposal to re-evaluate the need for further investigations based on the results of your currently-proposed studies is appropriate. We agree that your proposed plan seems adequate at this time.

Sponsors Comments: *The Sponsors acknowledge the comments and for your information the fertility data has been submitted in IND sequence 0010 (submitted January 24, 2008). No further discussion is requested.*

Discussion at Meeting: *No further discussion.*

Question 12: The Sponsors anticipate that Lu AA21004 has no potential for abuse liability and therefore no additional studies are planned in this area. The Sponsors will, in addition to standard adverse events collection (including potential overdose cases throughout the clinical development plan, gather information on discontinuation symptoms. Does the Agency agree?

Preliminary Comments: *Yes.*

Sponsors Comments: *The Sponsors acknowledge the comment. No further discussion is requested.*

Discussion at Meeting: *No further discussion.*

Question 13: The Sponsors intend to work closely with both the FDA and EMEA (PDCO) in constructing a common pediatric development plan addressing both PWR and PIP requirements in order to assess the efficacy and safety of Lu AA21004 in children and adolescents. The Sponsors intend to ask both FDA and EMEA for a deferral of conducting pediatric clinical studies until after approval of the adult indications. Does FDA agree to this approach?

Preliminary Comments: *Yes.*

Sponsors Comments: *The Sponsors acknowledge that the deferral has been granted. Further, the Sponsors would like to explore FDA view regarding coordination of the global pediatric development plan as per the US PWR and the EU requirement for PIP.*

Discussion at Meeting: *We indicated that we would be willing to discuss with our pediatric group the sponsors problem of having a very different timetable for planning pediatric studies from the standpoint of European regulators and FDA. The sponsor asked if we would be willing to give informal feedback on plans for pediatric studies even in advance of submitting a PPSR. We indicated that we would consider providing such feedback.*

Additional Comments:
Tables and graphs in section 2 give concentrations in nmol/L. For the NDA all concentrations should be expressed as ng/ml or in other similar units.

Linked Applications	Sponsor Name	Drug Name
IND 76307	H LUNDBECK AS	LU AA21004

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/s/

THOMAS P LAUGHREN
02/13/2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

MID-CYCLE COMMUNICATIONS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

MID-CYCLE COMMUNICATION

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, M.S.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for vortioxetine tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 12, 2013. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, contact me at Hiren.Patel@fda.hhs.gov or (301) 796-2087.

Sincerely,

{See appended electronic signature page}

LCDR Hiren D. Patel, Pharm.D., M.S., RAC
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 12, 2013

Application Number: NDA 204447
Product Name: Vortioxetine Tablets
Indication: Major Depressive Disorder
Applicant Name: Takeda Pharmaceuticals USA, Inc.

Meeting Chair: Mitchell Mathis, M.D.
Meeting Recorder: Renmeet Grewal, Pharm.D., RAC

FDA ATTENDEES
Mitchell Mathis, M.D., Acting Division Director, Division of Psychiatry Products (DPP)
Jing Zhang, M.D., Clinical Team Leader, DPP
Jenn Sellers, M.D., Clinical Reviewer, DPP
Linda Fossom, Ph.D., Nonclinical Team Leader, DPP
Antonia Dow, Ph.D., Nonclinical Reviewer, DPP
Chhagan Tele, Ph.D., Office of New Drug Quality Assessment (ONDQA) Team Leader
Wendy Wilson, Ph.D., ONDQA Reviewer
Hao Zhu, Ph.D., Office of Clinical Pharmacology (OCP) Team Leader
Andre Jackson, Ph.D., OCP Reviewer
Peiling Yang, Ph.D., Biostatistics Team Leader
Houda Mahayni, Ph.D., ONDQA Biopharmaceutics Reviewer
Colleen Locicero, R.Ph., Associate Director Regulatory Affairs
Kimberly Taylor, Operations Research Analyst, Office of Planning and Informatics
(b) (4)

Renmeet Grewal, Pharm.D., RAC, Senior Regulatory Project Manager

APPLICANT ATTENDEES
Stephen Brannan, M.D., CNS Therapeutic Area Head, Clinical Sciences, Takeda
Atul Mahableshwarkar, M.D., Senior Medical Director, Clinical Sciences, Takeda
Marianne Dragheim, M.D., Chief Specialist, ICR Mood & Anxiety Disorders, Lundbeck
Paula Jacobsen, Principal Scientist, Clinical Sciences, Takeda
Michael Serenko, M.D., Medical Director, Pharmacovigilance, Takeda
Karen Asin, Ph.D., Senior Fellow, Toxicology, Takeda
Grace Chen, Ph.D., Principal Scientist, Clinical Pharmacology, Takeda
Frank Ogrinc, Ph.D., Associate Director Statistics, Analytical Science, Takeda
William Palo, M.S., Associate Director, Safety Statistics, Analytical Science, Takeda
Kevin Fletcher, Senior Pharmaceutical Scientist, CMC Strategy and Program Management, Takeda
Trupti Dixit, Ph.D., Associate Director, CMC Strategy and Program Management, Takeda

Shuyen Huang, Ph.D., Associate Director, Regulatory Strategy CMC, Takeda
Eric Floyd, M.S., MBA, Ph.D., Vice President, US Regulatory Affairs, Lundbeck
Michael Cronquist Christensen, M.Sc., MPA, DrPH, Senior Regulatory Strategy Leader, Lundbeck

Joanna Sambor, M.S., Associate Director Regulatory Strategy, Takeda
Christine Greenberg, Manager, Regulatory Strategy, Takeda
Hedley Stickell, M.S., Project Director, Strategic Project Management, Takeda
Martin Damm Olling, M.Sc., Senior Project Director, Lundbeck

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Office of New Drug Quality Assessment

1) The DMF referenced for the drug substance chemistry, manufacturing, and controls information is deficient. The DMF holder was notified of the deficiencies.
2) The submission lacks sufficient information to demonstrate that the drug product formulation, manufacturing process, and storage conditions do not promote changes in the drug substance polymorph, hydrate, or solvate form.
3) The drug product stability data does not adequately address the impact of increased water uptake during storage due to packaging changes or formulation excipients on the final drug product quality.

For detailed deficiencies, please refer to our Information Request letter dated March 5, 2013.

3.0 INFORMATION REQUESTS

Office of Clinical Pharmacology

1) Submit a full study report including assay information for the 5 mg tablet bioequivalence study. All datasets should also be submitted in *.xpt format.

Office of New Drug Quality Assessment

The following comments are new deficiencies that have been identified since our March 5, 2013 information request:

2) The descriptions of the drug product analytical procedures and validation do not specifically identify when system suitability criteria will be evaluated. Confirm that the system suitability criteria, especially the tailing factor criterion, will be evaluated during routine testing for the appropriate analytical procedures (e.g. HPLC methods).
3) The submission includes two new packaging configurations, i.e., 7-count 45 cc and 500-count 150 cc HDPE bottle presentations; these were not initially considered during design of the primary stability bracketing and matrixing applied for the Lundbeck primary stability batches. In addition, the packaging process for the Lundbeck site includes (b) (4) . Therefore, we do not consider any stability results for the 7-count 45 cc and 500-count 150 cc HDPE bottles from the Takeda site process qualification batches representative of the stability for these presentations at the Lundbeck site. Revise the Lundbeck commercial lots stability protocol to include testing of samples packaged in the 7-count 45 cc and 500-count HDPE bottles for the first three commercial batches to confirm the stability of drug product packaged in these presentations at the Lundbeck site.
4) The proposed drug product expiration dating period is (b) (4). However, the proposed post-approval stability protocols for the Takeda process qualification batches, the Lundbeck commercial-scale batches, and the annual stability batches do not include testing at (b) (4). Revise these post-approval protocols to include testing at (b) (4) to confirm the proposed drug product expiration. The scheduled testing at (b) (4) should include samples for all tablet strengths and packaging configurations included in the stability program.

Additionally, we refer you to our Information Request letter dated March 5, 2013 for our previous information requests.

Biopharmaceutics:

5) The dissolution data provided do not support your proposed acceptance criteria of NLT (b) (4) (Q) dissolved in 30 minutes. Therefore, implement an acceptance criterion of **Q =** (b) (4) **at 20 minutes** for the dissolution test and provide the updated specifications table for your drug product. Also update all relevant sections of your NDA.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We have not identified any major safety concerns at this point during the review and we do not propose any risk management plans at this time.

5.0 ADVISORY COMMITTEE MEETING

An advisory committee meeting is not anticipated at this time.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

1) We plan to issue any Discipline Review Letters by June 12, 2013.
2) We plan to communicate proposed labeling and if necessary, any postmarketing commitment requests by June 14, 2013 if major deficiencies are not identified during the review.
3) A Late-Cycle Meeting has been scheduled on July 2, 2013 from 9:00am-10:30am (EST).

4) We plan to send the Agency background package for the Late-Cycle Meeting by June 20, 2013.
5) We are on track with completing GCP and GMP inspections by August 2, 2013.
6) We plan to take an action by the October 2, 2013 PDUFA date.

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/s/

HIREN PATEL
03/26/2013