

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205422Orig1s000

205422Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # **NDA 205422/Orig-1 & 2**

SUPPL #

HFD #-130

Trade Name REXULTI

Generic Name Brexpiprazole

Applicant Name Otsuka Pharmaceutical Company, Ltd (OTSUKA)

Approval Date, If Known 07/10/15

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)

b) 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:

c) Did the applicant request exclusivity? YES NO

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

5 years

d) 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

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: CDR Kofi B. Ansah, Pharm.D., RAC
Title: Senior Regulatory Project Manager
Date: 07/10/15

Name of Office/Division Director signing form: CAPT Mitchell V. Mathis, M.D
Title: Director, 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/

KOFI B ANSAH
07/14/2015

MITCHELL V Mathis
07/14/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # NDA 205422/Original-1 & NDA 205422/Original-2 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: REXULTI Established/Proper Name: Brexpiprazole Dosage Form: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg		Applicant: Otsuka Pharmaceutical Company, Ltd (OTSUKA) Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Inc.
RPM: Kofi Ansah, Pharm.D., RAC		Division: Division of Psychiatry Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="text-align: center;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check:</p> <p><i>Note: 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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is 07/11/15 but Action Date: 07/10/15 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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., new listed drug, patent certification revised).

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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): Approval Letter-7/10/2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	11/24/2014
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	DMEPA Review – 3/19/2015 & 11/21/2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> None 9/23/2014 DMEPA: <input checked="" type="checkbox"/> None 6/22/2015; 3/19/2015 DMPP/PLT (DRISK): <input type="checkbox"/> None 6/23/2015 OPDP: <input checked="" type="checkbox"/> None 6/26/2015 SEALD: <input type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None 6/8/2015 Product Quality <input checked="" type="checkbox"/> None See Quality Review Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	RPM Filing Review – 9/23/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Label/SRPI Review – 9/23/2014 <input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>5/13/2015</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Yes
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 5/27/2014
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A 12/9/2014
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A 4/2/2015
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/10/15
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/28/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 7/10/15 (5 templates)
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	6/29/2015
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Review (6/28/2015)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 6/8/2015
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None DRISK 7/9/2015 & 3/19/2015 and CSS 6/8/2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 4/30/2015; 4/22/2015; 3/12/2015; 3/16/2015; 2/11/2015; 2/5/2015
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None but Quality Micro Review: 8/8/2014 – Filing Review & 12/2/2014 – Primary Review
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Primary- 6/25/2015 & 3/16/02015; Filing - 9/1/2014
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/18/2015 & 9/3/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 7/9/15
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 3/19/2015 -Primary & 9/3/2014 - Filing
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 12/29/2014
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 12/5/2014 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Addendum – 3/3/2015; Primary Review 2/26/2015; IQA & Filing Review – 9/23/2014
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None Micro 8/8/2014 & 12/2/2014; Biopharmaceutics - 2/25/2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Primary Review 2/26/2015 and IQA & Filing Review – 9/23/2014
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

KOFI B ANSAH
07/14/2015

From: Ansah, Kofi
To: David.Paul.A@FDA; Guinn.Patrick@FDA
Cc: Goldberger.David@FDA
Subject: RE: NDA 205422 REXULTI Labeling - Carton and Container Label
Date: Friday, July 10, 2015 5:37:00 PM

Dear Patrick,

Acknowledging receipt –Thank you.

Kofi.

From: David, Paul A
Sent: Friday, July 10, 2015 5:30 PM
To: Guinn, Patrick; Ansah, Kofi
Cc: Goldberger, David
Subject: RE: NDA 205422 REXULTI Labeling - Carton and Container Label

Perfect, we appreciate your cooperation.
Paul

CAP Paul A David R Ph Chief Regulatory Project Management Staff
Division of Psychiatry Products
10903 New Hampshire Avenue Building 22 Room 4100
Silver Spring MD 20993 0002
Phone: 301 796 1058

From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Friday, July 10, 2015 5:25 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: RE: NDA 205422 REXULTI Labeling - Carton and Container Label

Dear Kofi,

As we just discussed with you and Paul, please refer to the attachment that reflects the current revised labeling (carton and container label) which provides the following updates to make the carton and container labels consistent with the USPI.

- (b) (4)
- (b) (4)
- Revised Storage Statement to reflect the USP definition of Controlled Room Temperature

In addition, the labels are being provided as a single pdf file as requested.

Regards, Patrick.

From: Ansah, Kofi [<mailto:Kofi.Ansah@FDA>]
Sent: Friday, July 10, 2015 4:57 PM
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A
Subject: RE: NDA 205422 REXULTI Labeling - Carton and Container Label
Importance: High

Hi Patrick

We acknowledge receipt of the emails referenced below. Given that these changes are editorial changes, we are ok with your proposal to make the noted editorial changes below and provide the revised carton and container labels as part of the FPL.

Therefore, with that understanding, for this pending action; we will be attaching the Agreed-Upon USPI/MG and the Bottle & Bottle-Carton Labels you emailed to us on 6/12/15 (and formally submitted to the NDA on 6/15/15) to the action letter. Let us know if you agree, asap?

Best Regards,
Kofi.

Kofi Boadi Ansah, R.Ph., Pharm D., MBA, RAC
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA Center for Drug Evaluation and Research, Office of Drug Evaluation-1
10903 New Hampshire Avenue, White Oak Bldg 22, Room 112
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Phone: (301) 796-158
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Email: Kofi.Ansah@FDA

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From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Friday, July 10, 2015 4:21 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI Labeling - Carton and Container Label

Dear Kofi,

We provided an e-mail on June 22 (see below) indicating that the storage condition statement would be updated to reflect the USP definition of Controlled Room Temperature. In addition, the other item is the (b) (4) which is already noted in the USPI provided as Final Draft Labeling.

These changes affect the bottle labels and carton labels but not the Final Draft USPI provided this morning.

In the message we indicated that these revisions, from the labeling provided June 12 and acknowledged by FDA as acceptable on June 20, would be provided with the revised carton and container labels as part of the FPL.

Please let me know if you have any further questions.

Best Regards, Patrick.

From: Guinn, Patrick
Sent: Monday, June 22, 2015 7:39 PM
To: kofi.ansah@FDA; paul.david@FDA
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI Labeling - Storage Statement Revision

Dear Kofi,

The Storage Statement in the USPI was modified by FDA (March 26 labeling comments) to reflect the USP definition of **Controlled Room Temperature— A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77° F).**

Brex USPI
16.2 Storage

Store PRODUCT tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

However, this revision was not noted by FDA in the comments for the carton and container labels and we inadvertently did not incorporate it into the label revisions that were submitted on June 12.

In order to be consistent across the labeling components (USPI, carton, and container), we have now implemented this revision to the storage statement on the carton and container labels (printed on the side panel) to reflect the language in the USPI. We will provide you with the revised carton and container labels as part of the FPL.

Please let me know if you have any questions.

Regards, Patrick.

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

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

/s/

KOFI B ANSAH
07/10/2015

From: [Ansah Kofi](#)
To: [Guinn Patrick](#)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](#); [David, Paul A](#)
Subject: FDA draft Label (USPI & MG) for Agreement -- NDA 205422 REXULTI (brexpiprazole) (OPC-34712)
Date: Thursday, July 09, 2015 8:06:00 PM
Attachments: [final FDA draft-LABEL \(PI-MG\) Brexpi \(v.07-09-15\).docx](#)
Importance: High

Dear Patrick,

Based on your response to our 07/08/15 Labeling comments/edits that we received today, we are providing you our proposed/ final draft Label (USPI & MG) for your review – Please find attached. Kindly let us know as soon as possible, if we have agreement on this Label by 09:00 am EDT tomorrow; July 10, 2015.

Note: Again, please confirm the label conforms to the requirements listed on this FDA website. To help you, the Agency provides a 42-item checklist (scroll down to Selected Requirements of Prescribing Information (SRPI)

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

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KOFI B ANSAH
07/10/2015

From: Ansah, Kofi
To: [Guinn, Patrick \(Patrick.Guinn@otsuka-us.com\)](mailto:Patrick.Guinn@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com); [David, Paul A](mailto:David.Paul.A)
Subject: Additional FDA Labeling Edits/Comments -- NDA 205422/Brexpiprazole (OPC-34712)
Date: Wednesday, July 08, 2015 10:59:00 PM
Attachments: [07-08-15 FDA edits draft-LABEL \(PI-MG\) Brexpiprazole \(v.07-03-15\) \[MARKED-UP\].docx](#)
Importance: High

Dear Patrick,

Attached is the draft Label (as amended on 7/3/15) with our additional edits and comments with input from the signatory authority (i.e., we worked off your 7/3/15 response to our 7/1/15 edits). Please review our edits and comments to the USPI & MG and resubmit labeling that addresses our comments, as applicable. Please be sure to work off the word document (PI & MG) we have attached and track any edits/counter-proposal(s) you may have at this point (include your own comments as necessary).

Provide the requested labeling changes/information to us via email, as soon as possible; preferably by 1:00 pm EDT tomorrow (Thursday, July 9, 2015) -- But no later than 2:00 pm EDT. The resubmitted labeling will be used for further labeling discussions.

Note: Additionally, please ensure TOC matches FPI and again confirm that the label conforms to the requirements listed on this FDA website. To help you, the Agency provides a 42-item checklist (scroll down to Selected Requirements of Prescribing Information (SRPI).

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

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC
Commander, US Public Health Service
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From: [Ansah, Kofi](mailto:Ansah.Kofi)
To: Patrick.Guinn@otsuka-us.com; [David, Paul A](mailto:David.Paul.A)
Cc: David.Goldberger@otsuka-us.com
Subject: Re: Follow-up FDA Labeling Edits/Comments -- NDA 205422/Brexpiprazole (OPC-34712) - Sponsor's Response (03 July 2015)
Date: Saturday, July 04, 2015 1:24:19 PM

Hi Patrick,

Acknowledging receipt of your response to our 3rd round of Label comments/edits.

Thanks,
Kofi.

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Friday, July 03, 2015 02:45 PM Eastern Standard Time
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David <David.Goldberger@otsuka-us.com>; Guinn, Patrick <Patrick.Guinn@otsuka-us.com>
Subject: Follow-up FDA Labeling Edits/Comments -- NDA 205422/Brexpiprazole (OPC-34712) - Sponsor's Response (03 July 2015)

Dear Kofi,

Reference is made to the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) original NDA 205422 submitted on behalf of Otsuka Pharmaceutical Company, Ltd. (OPC) for OPC-34712 (brexpiprazole) for the treatment of adult schizophrenia and for the adjunctive treatment of Major Depressive Disorder (MDD) in adults, on July 11, 2014. Reference is also made to the edits and comments to the draft brexpiprazole label provided by the FDA on July 01, 2015.

As requested we are providing tracked edits and response comments for the USPI and Medication Guide as a single document (please see attachment).

For administrative purposes we want to note that the USPI and Medication will be provided as a single document utilizing a perforation to allow for separation of the documents in the packaged product.

Regards, Patrick.

Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.



Otsuka
2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277

(b) (6)

Email: Patrick.Guinn@otsuka-us.com

From: Ansah, Kofi
To: [Guinn, Patrick \(Patrick.Guinn@otsuka-us.com\)](mailto:Patrick.Guinn@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com); [David, Paul A](mailto:David.Paul.A)
Subject: RE: Follow-up FDA Labeling Edits/Comments -- NDA 205422/Brexipiprazole (OPC-34712)
Date: Wednesday, July 01, 2015 11:54:00 PM
Attachments: [07-01-15 FDA edits Sponsor's draft - PI Brexipiprazole \(v.06-02-15\)\[MARKED-UPI.docx](#)
[07-01-15 FDA edits draft - MG \(v.06-02-15\)\[CLEAN\].docx](#)
Importance: High

Dear Patrick,

Find attached your draft Label (as amended on 6/2/15) with our follow-up edits and comments (i.e., we worked off your 6/2/15 response to our 5/28/15 edits). Please review our edits and comments to the PI & MG and resubmit labeling that addresses our comments, as applicable.

Please be sure to work off (i.e., use) the word documents (PI & MG) we are sending you and track any edits/counter-proposal(s) you may have at this point (include your own comments as necessary).

Provide the requested labeling changes/information to me via email as soon as possible, preferably by end-of-day this Friday -- But no later than noon on Monday; July 6, 2015. The resubmitted labeling will be used for further labeling discussions and additional input by other team members & the signatory authority.

Note: Additionally, I would like to bring your attention the following website that compiles all of the labeling guidances. Please confirm the label conforms to the requirements listed on this FDA website. To help you, the Agency provides a 42-item checklist (scroll down to Selected Requirements of Prescribing Information (SRPI)).

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

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC
Commander, US Public Health Service

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/s/

KOFI B ANSAH
07/10/2015

From: Ansah, Kofi
To: "Guinn, Patrick"; David, Paul A
Cc: Goldberger, David
Subject: Sponsor's Additional Clarification -- NDA 205422 REXULTI (brexpiprazole) - PMR-PMCs
Date: Thursday, July 09, 2015 7:07:00 PM

Hi Patrick,

Noted -- Thank you for the confirmation – Best regards.

Kofi.

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Thursday, July 09, 2015 6:44 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: RE: Sponsor Additional Clarification -- RE: NDA 205422 REXULTI - PMR-PMCs

Dear Kofi,

I am confirming that there was a typo regarding Study-1 (Final Protocol Submission 331-10-233). FDA records are correct, the protocol was submitted on 31 March 2014 as IND 101871 SN0358.

Best Regards, Patrick.

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Thursday, July 09, 2015 6:00 PM
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A
Subject: Sponsor Additional Clarification -- RE: NDA 205422 REXULTI - PMR-PMCs

Dear Patrick,

The clarification you provided seems okay – Thanks.

Also, we note that for Study-1, there was a typo regarding "*Final Protocol Submission (331-10-233): 02/2014 (Submitted)*" as captured in my initial email below. Our records indicate the protocol was submitted March 2014 (i.e., 03/2014) not 02/2014. Can you please confirm?

Best Regards,
Kofi.

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Wednesday, July 08, 2015 4:45 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI - PMR-PMCs Sponsor Additional Clarification

Dear Kofi,

We are currently conducting a 26-week, placebo-controlled, long-term efficacy study in MDD using adjunctive REXULTI (Trial 14570A); similar to the short-term studies randomized patients will have less than a 50% reduction in MADRS total score during the 6 week prospective treatment period prior to the 26 week randomized phase. The primary endpoint of this study is sustained remission, i.e. the percent of patients in full remission (defined as a MADRS total score of ≤ 10) for at least 8 consecutive weeks during the randomized treatment period. The study plans to enroll over 2000 subjects and to randomize approximately 400 patients to REXULTI and 400 patients to placebo; we anticipate this study to complete in late 2016. We believe this study design will address the long-term treatment benefit of adjunctive REXULTI versus placebo with a clinically relevant outcome measure.

To the best of our knowledge, there have been no randomized withdrawal, relapse prevention studies conducted with adjunctive agents in MDD (the Seroquel relapse prevention study was with monotherapy). As such, it is difficult to estimate the study size and power that would be required to show a clinically relevant outcome.

We propose to discuss the design of the on-going study described above in a Type C Meeting (timelines outlined below) as well as FDA's thoughts on the design of a randomized withdrawal relapse prevention study.

As part of our PMC we commit to conduct the study that is agreed upon by FDA and the Sponsor (either the on-going study, or a randomized withdrawal relapse prevention study, or an alternative design).

Meeting Request: Aug 1, 2015
Briefing Package: Sep 15, 2015
Type C Meeting: Oct 15, 2015

Assuming that the ongoing study is not sufficient we would propose the following timelines.

(b) (4)


Please let us know if this additional information is sufficient.

Regards, Patrick.

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Wednesday, July 08, 2015 3:55 PM
To: Guinn, Patrick; David, Paul A
Cc: Goldberger, David
Subject: RE: NDA 205422 REXULTI - PMR-PMCs Sponsor Agreements

Hi Patrick,

We are requesting information regarding proposed study design & timelines for the study with further discussion post-action.

Regarding the Labeling Comments, we are still working on getting you something today.

Best Regards,
Kofi.

From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Wednesday, July 08, 2015 3:48 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: RE: NDA 205422 REXULTI - PMR-PMCs Sponsor Agreements

Dear Kofi,

In your message below, are you requesting information regarding study design, timelines for the study, or timelines for the meeting for discussion.

In addition, could you provide an update on anticipated timing of labeling comments.

Kind Regards, Patrick.

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Wednesday, July 08, 2015 3:44 PM
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A
Subject: RE: NDA 205422 REXULTI - PMR-PMCs Sponsor Agreements

Dear Patrick,

Thank you for your prompt response. We acknowledge your acceptance of these commitments and agreeing to conduct these studies. We also note that regarding Study 4, you intend to discuss with the Division the study design & timelines post-action. However, please kindly propose something for further discussion post-action.

Thanks,
Kofi.

From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Wednesday, July 08, 2015 2:56 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI - PMR-PMCs Sponsor Agreements

Dear Kofi,

Thank you for your communication. We formally accept the 5 PMC's listed below (please refer to our responses incorporated in your communication below).

As a point of reference we modified the description of Study #2 to reflect the study design in the PSP (26 week extension is double blind and active controlled).

Also for Study #4 we accept the commitment and would like to discuss with you the study design

and timelines.

Regards, Patrick.

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Wednesday, July 08, 2015 1:04 PM
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A
Subject: PMR-PMCs for NDA 205422/Brexpi

Dear Patrick:

Per our brief phone conversation earlier today, please find below the list PMR/PMCs and propose/provide the dates we need from you. Kindly respond to this request asap today – Thank you.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing brexpiprazole in the relevant pediatric population.

Final Protocol Submission (331-10-233): (b) (4)
Study/Trial Completion: 05/2016
Final Report Submission: 11/2016

2. Deferred pediatric study under PREA for the treatment of schizophrenia in children aged 13 to 17 years. Conduct a Phase 3, Efficacy: multicenter, randomized, double-blind **trial with two phases: Phase 1 - placebo- and active-controlled, short-term (6 weeks) study; Phase 2 – active-controlled long-term extension (26 weeks) study. Goal of both phases is** to obtain data on the efficacy and safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission (331-10-234): 06/2016
Study/Trial Completion: 12/2020
Final Report Submission: 06/2021

3. Deferred pediatric study under PREA for the treatment of (b) (4) schizophrenia in adolescents aged 13 to 17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (2 years) study to obtain data on the safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission (331-10-236): 06/2016
Study/Trial Completion: 12/2022

Final Report Submission:

06/2023

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING
REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

4. A placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients who require adjunctive treatment of major depressive disorder.
 - We agree to this postmarketing commitment (PMC) and would like to discuss with FDA an appropriate design, the draft protocol, and timelines. We propose to submit a meeting request post-approval to further discuss the details of the PMC.
5. A placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients with schizophrenia.

Final Protocol Submission: 09/2012

Trial Completion: 02/2015

Final Report Submission: 10/2015

Thanks,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

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/s/

KOFI B ANSAH
07/10/2015

From: Ansah, Kofi
To: ["Guinn, Patrick"](#)
Cc: [Goldberger, David](#); [David, Paul A](#)
Subject: Feedback on_Sponsor"s Response to FDA/DMEPA Comments -- NDA 205422 REXULTI (brexpiprazole)/Revisions to Draft Carton and Container Labels
Date: Saturday, June 20, 2015 11:39:00 AM

Hi Patrick,

Great – Noted – Thank you.

Best Regards,
Kofi.

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Saturday, June 20, 2015 11:19 AM
To: Ansah, Kofi
Cc: Goldberger, David; David, Paul A
Subject: RE: Feedback on_Sponsor's Response to FDA/DMEPA Comments -- NDA 205422 REXULTI (brexpiprazole)/Revisions to Draft Carton and Container Labels

Dear Kofi,

This is to acknowledge receipt of your message. This was formally submitted to the NDA on June 15, 2015, as sequence number 0033.

Best Regards, Patrick.

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

From: Ansah, Kofi [Kofi.Ansah@fda.hhs.gov]
Sent: Saturday, June 20, 2015 10:58 AM Eastern Standard Time
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A
Subject: Feedback on_Sponsor's Response to FDA/DMEPA Comments -- NDA 205422 REXULTI (brexpiprazole)/Revisions to Draft Carton and Container Labels

Dear Patrick,

DMEPA finds the labels/labeling you provided in your 6/12/15 email acceptable. If you haven't already done so, please kindly formally submit your response with the attachments to your NDA.

Note: My earlier email bounced back because I had tried to attach your 3 emails with attachments from 6/12/15. I am resending my email without the afore mentioned attachments -- Thank you.

Best Regards,
Kofi.

From: Ansah, Kofi
Sent: Monday, June 15, 2015 11:31 AM
To: 'Guinn, Patrick'; David, Paul A
Cc: Goldberger, David
Subject: RE: NDA 205422 REXULTI (brexpiprazole) - Response to FDA/DMEPA Comments - Revisions to Draft Carton and Container Labels E-mail #1

Hi Patrick,

Acknowledging receipt of this and the other two emails – Thank you. I have shared your emails with DMEPA and will let you know if they have any follow-up questions and/or when their review of your response(s) is done.

Best Regards,
Kofi.

From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Friday, June 12, 2015 9:38 PM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI (brexpiprazole) - Response to FDA/DMEPA Comments - Revisions to Draft Carton and Container Labels E-mail #1

Dear Kofi,

Please refer to the draft carton and container labels submitted to FDA on February 27, 2015 (SN0026) and the revised carton and container labels submitted to the FDA on June 04, 2015 (SN0029).

In addition, please refer to the DMEPA review comments on the carton and container labels received from the FDA on June 09, 2015.

Revised draft carton and container labels are being provided (see attached – due to size of files 3 separate e-mails will be provided) based on FDA comments.

- E-mail #1 includes Bottle label; (b) (4)
- E-mail #2 includes Carton (strengths 0.25mg; 0.5mg; and 1mg)
- E-mail #3 includes Carton (strengths 2mg; 3mg; and 4mg)

In addition, we have included below the comments made by DMEPA (bolded) and the sponsor's responses (in italics).

The revised draft carton and container labels as well as the sponsor's responses will be submitted through the ESG early next week.

FDA Comment 1: We are okay with the revisions to the container labels and carton labeling as proposed in SN0029. However, (b) (4)
we would like you to describe how the lot and expiration date will be presented.

Otsuka's Response: (b) (4)
(b) (4)
the lot and

expiry date will now be printed online.

A. All Container Labels and Carton Labeling

FDA Comment A1: Revise the dosage form “tablets” to the same font and font size as the active ingredient to ensure compliance with 21 CFR 201.10(g)(2).

Otsuka’s Response: The font and font size of the dosage form “tablets” has been changed to be the same as the “brexpiprazole” active ingredient on all container and carton labels. The font size of “brexpiprazole tablet” is at least one half the size of the tradename “REXULTI” as required by 21 CFR 201.10(g)(2).

FDA Comment A2: The statement of strength lacks prominence due to its small size. Additionally, the colored background area in the upper right triangle used to differentiate the strengths is too small in size, resulting in inadequate strength differentiation within the product line. Increase the font size of the statement of strength. Consider relocating the statement of strength to the lower right corner triangle and applying the colored background to that area, or use other means, in order to facilitate an increase in the font size and a larger colored background area.

Otsuka’s Response: The font size of the statement of strength (both numeric value and “mg”) has been increased from the original size. Additionally, the size of the upper right corner triangle has been increased from the original size in order to accommodate the larger font for the statement of strength and provide a larger colored background area to further increase differentiation between the strengths.

FDA Comment A3: The (b) (4) colors used to differentiate the 0.5 mg and 1 mg strengths are similar and do not provide sufficient differentiation between the two strengths. We recommend the use of a different color for one of the strengths (one that is not similar to those used to differentiate the other strengths). Additionally, the (b) (4) background used to provide differentiation for the 4 mg strength overlaps with the large (b) (4) main background on the principal display panel and thus does not provide sufficient differentiation. Consider using a colored background (one that is not similar to those used to differentiate the other strengths) for the 4 mg strength in order to improve its differentiation.

Otsuka’s Response: The color of the upper right corner triangles on each of the effected display panels has been changed as follows:

- 0.5 mg Strength - Changed to a dark orange
- 4 mg Strength - Changed to a light blue

These changes have been implemented in all applicable labeling. The upper right corner triangle for the 1 mg strength has been retained as yellow.

FDA Comment A4: The 1 mg statement of strength (b) (4) lacks sufficient contrast against the “yellow” background. Increase the contrast by using a dark font color (e.g., black) or by using other means.

Otsuka’s Response: To increase the contrast of the 1 mg statement of strength against the yellow background in the upper right corner triangle the text has been changed to a dark green on each of the effected display panels for all 1 mg labeling.

Additionally, to increase the contrast of the 2 mg statement of strength against the light green background in the upper right corner triangle, the text has been changed to a dark green on each effected display panel.

FDA Comment A5: The three middle digits of the NDC number are sequential from a lower to higher number starting with the lowest tablet strength (e.g., XXXXX-035-XX and XXXXX-036-XX). Similarity in product code numbers has led to selecting and dispensing of the wrong strength. To help minimize product selection errors, we recommend that you increase the prominence of the three middle digits by increasing their size in comparison to the remaining digits or put them in bold type (e.g., XXXXX-035-XX or XXXXX-036-XX).

Otsuka's Response: The size of the font for all of the NDC digits has been increased; additionally, for the three middle digits of the NDC numbers, bold type has been used and the font has been further increased in comparison to the remaining digits on all labeling.

FDA Comment A6: The statement (b) (4) which is located below the net quantity statement is redundant and contributes to clutter on the principal display panel. Consider deleting the statement since there is already a statement on the side panel that conveys the same information.

Otsuka's Response: The statement (b) (4) which was located below the net quantity statement, has been removed from the principle display panels on all labeling.

Additionally, the size of font for the net quantity statement has been increased and, in order to accommodate the changes in font size, the net quantity statement has been placed above the NDC number.

FDA Comment A7: The Medication Guide (MG) statement, as currently presented, does not state how the MG is provided as required per 21 CFR 208.24 (d). We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton. Place on the principal display panel in a prominent and conspicuous manner:

- a. "Dispense the enclosed Medication Guide to each patient" or
- b. "Dispense the accompanying Medication Guide to each patient.

Otsuka's Response: The statement "Dispense the accompanying Medication Guide to each patient" has been placed on the principal display panel on all labeling.



Regards, Patrick.

Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.



Otsuka
2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277

(b) (6)

Email: Patrick.Guinn@otsuka-us.com

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Tuesday, June 09, 2015 4:44 PM
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A
Subject: FDA/DMEPA Comments -- RE: NDA 205422 REXULTI (brexpiprazole) - Sequence 0029
Amendment: Revisions to Draft Carton and Container Labels
Importance: High

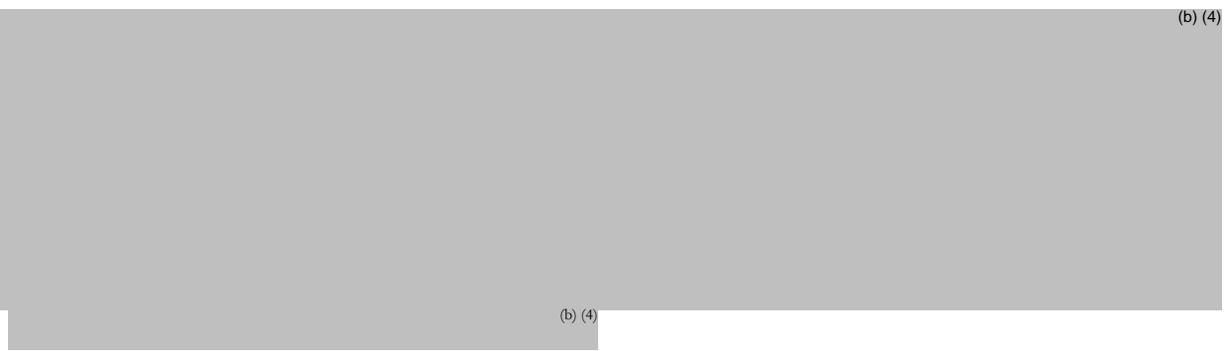
Dear Patrick,

We have completed our review of your Carton & Container labeling; including your revisions contained in SN0029 (dated 6/5/15). We are okay with the revisions to the container labels and carton labeling as proposed in SN0029. However, (b) (4) we would like you to describe how the lot and expiration date will be presented.

Additionally, DMEPA recommends the following be implemented prior to approval of this NDA:

A. All Container Labels and Carton Labeling

1. Revise the dosage form “tablets” to the same font and font size as the active ingredient to ensure compliance with 21 CFR 201.10(g)(2).
2. The statement of strength lacks prominence due to its small size. Additionally, the colored background area in the upper right triangle used to differentiate the strengths is too small in size, resulting in inadequate strength differentiation within the product line. Increase the font size of the statement of strength. Consider relocating the statement of strength to the lower right corner triangle and applying the colored background to that area, or use other means, in order to facilitate an increase in the font size and a larger colored background area.
3. The (b) (4) colors used to differentiate the 0.5 mg and 1 mg strengths are similar and do not provide sufficient differentiation between the two strengths. We recommend the use of a different color for one of the strengths (one that is not similar to those used to differentiate the other strengths). Additionally, the (b) (4) background used to provide differentiation for the 4 mg strength overlaps with the large (b) (4) main background on the principal display panel and thus does not provide sufficient differentiation. Consider using a colored background (one that is not similar to those used to differentiate the other strengths) for the 4 mg strength in order to improve its differentiation.
4. The 1 mg statement of strength (b) (4) lacks sufficient contrast against the “yellow” background. Increase the contrast by using a dark font color (e.g., black) or by using other means.
5. The three middle digits of the NDC number are sequential from a lower to higher number starting with the lowest tablet strength (e.g., XXXXX-035-XX and XXXXX-036-XX). Similarity in product code numbers has led to selecting and dispensing of the wrong strength. To help minimize product selection errors, we recommend that you increase the prominence of the three middle digits by increasing their size in comparison to the remaining digits or put them in bold type (e.g., XXXXX-035-XX or XXXXX-**036-XX**).¹
6. The statement (b) (4) which is located below the net quantity statement is redundant and contributes to clutter on the principal display panel. Consider deleting the statement since there is already a statement on the side panel that conveys the same information.
7. The Medication Guide (MG) statement, as currently presented, does not state how the MG is provided as required per 21 CFR 208.24 (d). We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton. Place on the principal display panel in a prominent and conspicuous manner:
 - a. “Dispense the enclosed Medication Guide to each patient” or
 - b. “Dispense the accompanying Medication Guide to each patient”



Note: ¹ See the FDA guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* available at: <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm349009.pdf>.

Best Regards,
Kofi.

From: Ansah, Kofi
Sent: Tuesday, June 09, 2015 12:07 PM
To: 'Guinn, Patrick'; David, Paul A
Cc: Goldberger, David
Subject: RE: NDA 205422 REXULTI (brexpiprazole) - Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels

Hi Patrick,

Here is to acknowledging receipt of your submission containing your revisions to the draft Carton & Container Labels (SN0029). We should have some comments to you by Friday.

Also, please note that there was some miscommunication and what DMEPA had meant to convey with our 5/11/15 email was that they had no additional information request regarding the draft Carton & Container Labels. But they do have some comments for you and will include those in our response to SN0029.

Thanks,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Friday, June 05, 2015 9:00 AM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI (brexpiprazole) - Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels
Importance: High

Dear Kofi,

Since there have been several amendments recently submitted for NDA 205422, I wanted to make you aware of the following submission as well.

To accommodate packaging sizes, the sponsor has modified the size of the label for the container bottle. As a result, a few minor revisions to the text and artwork were made to the bottle label and the carton label as outlined in the following Table.

Label Revisions from Previously Submitted Artwork to FDA	
Bottle	Carton
(b) (4)	

Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels was submitted to the Agency on June 4, 2015.

The submission included labeling (bottle as well as carton and container) for all strengths. A representative sample (1mg) is attached.

On 11 May 2015, we received an e-mail correspondence from you that DMEPA and OPQ/CMC had reviewed the carton and container labels and had no further comments and no additional information was required. Although we believe that the revisions made are relatively minor and continue to adhere to the labeling guidance regarding important content and information required for the principle display panel (PDP) and secondary display panels, we want to ensure that FDA is aware of these changes and that the changes are considered acceptable.

Would it be possible for you to provide me with a target date for communication from FDA regarding this matter?

Regards, Patrick.

Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.



Otsuka
2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277

(b) (6)

Email: Patrick.Guinn@otsuka-us.com

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/s/

KOFI B ANSAH
07/09/2015

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUSANNAH O'DONNELL
07/09/2015

From: Ansah, Kofi
To: ["Guinn, Patrick"](#)
Cc: ["Goldberger, David"; David, Paul A](#)
Subject: FDA/DMEPA Comments -- RE: NDA 205422 REXULTI (brexpiprazole) - Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels
Date: Tuesday, June 09, 2015 4:44:00 PM
Importance: High

Dear Patrick,

We have completed our review of your Carton & Container labeling; including your revisions contained in SN0029 (dated 6/5/15). We are okay with the revisions to the container labels and carton labeling as proposed in SN0029. However, (b) (4) we would like you to describe how the lot and expiration date will be presented.

Additionally, DMEPA recommends the following be implemented prior to approval of this NDA:

A. All Container Labels and Carton Labeling

1. Revise the dosage form “tablets” to the same font and font size as the active ingredient to ensure compliance with 21 CFR 201.10(g)(2).
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- carton. Place on the principal display panel in a prominent and conspicuous manner:
- a. "Dispense the enclosed Medication Guide to each patient" or
 - b. "Dispense the accompanying Medication Guide to each patient"

(b) (4)

(b) (4)

Note: ¹ See the FDA guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* available at: <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm349009.pdf>.

Best Regards,
Kofi.

From: Ansah, Kofi
Sent: Tuesday, June 09, 2015 12:07 PM
To: 'Guinn, Patrick'; David, Paul A
Cc: Goldberger, David
Subject: RE: NDA 205422 REXULTI (brexpiprazole) - Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels

Hi Patrick,

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Thanks,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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Email: Kofi.Ansah@fda.hhs.gov

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From: Guinn, Patrick [<mailto:Patrick.Guinn@otsuka-us.com>]
Sent: Friday, June 05, 2015 9:00 AM
To: Ansah, Kofi; David, Paul A
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 205422 REXULTI (brexpiprazole) - Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels
Importance: High

Dear Kofi,

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To accommodate packaging sizes, the sponsor has modified the size of the label for the container bottle. As a result, a few minor revisions to the text and artwork were made to the bottle label and the carton label as outlined in the following Table.

Label Revisions from Previously Submitted Artwork to FDA	
<i>Bottle</i>	<i>Carton</i>
(b) (4)	

Sequence 0029 Amendment: Revisions to Draft Carton and Container Labels was submitted to the Agency on June 4, 2015.

The submission included labeling (bottle as well as carton and container) for all strengths. A representative sample (1mg) is attached.

On 11 May 2015, we received an e-mail correspondence from you that DMEPA and OPQ/CMC had reviewed the carton and container labels and had no further comments and no additional information was required. Although we believe that the revisions made are relatively minor and continue to adhere to the labeling guidance regarding important content and information required for the principle display panel (PDP) and secondary display panels, we want to ensure that FDA is aware of these changes and that the changes are considered acceptable.

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Regards, Patrick.

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Otsuka Pharmaceutical Development & Commercialization, Inc.



2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277

(b) (6)

Email: Patrick.Guinn@otsuka-us.com

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/s/

KOFI B ANSAH
06/10/2015

From: Ansah, Kofi
To: [Guinn, Patrick \(Patrick.Guinn@otsuka-us.com\)](mailto:Patrick.Guinn@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com); [David, Paul A](#)
Subject: Follow-up FDA Labeling Edits/Comments -- NDA 205422/Brexiprazole (OPC-34712)
Date: Thursday, May 28, 2015 8:59:00 PM
Attachments: [05-28-15 FDA edits Sponsor's draft-LABEL Brexiprazole \(v.04-14-14\)IMARKED-UPI.docx](#)
[05-28-15 FDA edits Sponsor's draft-LABEL Brexiprazole \(v.04-14-14\)IMARKED-UPI.pdf](#)
Importance: High

Dear Patrick,

Find attached your draft Label (as amended on 4/14/14) with our follow-up edits and comments (i.e., we worked off your 4/14/15 response to our initial edits). Please review our edits and comments and resubmit labeling that addresses our comments, as applicable.

Please be sure to work off (i.e., use) the word document we are sending you and track any edits/counter-proposal(s) you may have at this point (include your own comments as necessary).

Provide the requested labeling changes/information to me via email preferably by end-of-day on Tuesday; June 2, 2015 -- But no later than The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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Email: Kofi.Ansah@fda.hhs.gov

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

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/s/

KOFI B ANSAH
06/02/2015

From: [Ansah, Kofi](#)
To: Patrick.Guinn@otsuka-us.com
Cc: David.Goldberger@otsuka-us.com; [David, Paul A](#); [Grewal, Renmeet](#)
Subject: Re: Info Request from CDER/PASE -- NDA 205422/OTSUKA/ Brexpiprazole (OPC-34712)
Date: Monday, June 01, 2015 11:42:25 PM

Dear Patrick,

Thank you for your email. We note that the age groups we are requesting are (40-65 and ≥ 65).

Best Regards,
Kofi.

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Monday, June 01, 2015 03:41 PM Eastern Standard Time
To: Ansah, Kofi
Cc: Goldberger, David <David.Goldberger@otsuka-us.com>; David, Paul A; Grewal, Renmeet; Guinn, Patrick <Patrick.Guinn@otsuka-us.com>
Subject: RE: Info Request from CDER/PASE -- NDA 205422/OTSUKA/ Brexpiprazole (OPC-34712)

Dear Kofi,

We would like clarification from you regarding the age group criteria that is listed in the spreadsheet in order to provide the most appropriate data that is required.

In the spreadsheet, the following categories are listed for age groups:

Age Group
<17 years
≥ 17 - <40 years
40- 65 years
≥ 75 years

Are these the age groups (40-65 and ≥ 75) that FDA is requesting or is this a typo?
Should it be

Age Group
<17 years
≥ 17 - <40 years
40- 65 years
> 65 years

OR

Age Group
<17 years
≥ 17 - <40 years
40- 64 years

≥ 65 years

Regards Patrick.

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Friday, May 29, 2015 11:45 AM
To: Guinn, Patrick
Cc: Goldberger, David; David, Paul A; Grewal, Renmeet
Subject: Info Request from CDER/PASE -- NDA 205422/OTSUKA/ Brexpiprazole (OPC-34712)
Importance: High

Dear Patrick,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, REXULTI (brexpiprazole), currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- “MORE INFORMATION” sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

We are requesting you submit this information for each proposed indication (i.e., submit 2 separate set of tables) as soon as possible but no later than 10 days from receipt of this email (i.e., by 6/8/15)

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
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Email: Kofi.Ansah@fda.hhs.gov

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Table 7.5.3-a. Subgroup Analysis of AEs, Safety Population (pooled pivotal trials; in addition to all TEAEs, pleas

Subgroup	Treatment		Control		Relative Risk***	95% LL
	x (%)**	Total, n	x (%)**	Total, n		
Any TEAEs*	40 (80.0)	50	45 (90.0)	50		
Sex						
Male	25 (83.3)	30	25 (100.0)	25		
Female	15 (75.0)	20	20 (80.0)	25		
Age Group						
<17 years						
>=17 - <40 years						
40- 65 years						
>=75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source:

*Designate per review, other options are SAEs or AEs of special interest (for instance, an HLT, SOC, or user-designi

** Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentag

***Designated per review, other options are Risk Difference, Hazard Ratios, etc

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/s/

KOFI B ANSAH
06/02/2015

From: Ansah, Kofi
To: [Guinn, Patrick \(Patrick.Guinn@otsuka-us.com\)](mailto:Patrick.Guinn@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com); [David, Paul A](#)
Subject: Clinical Information Request -- Follow-up FDA Labeling Edits/Comments - NDA 205422/Brexpiprazole (OPC-34712)
Date: Tuesday, June 02, 2015 2:08:00 PM

Dear Patrick,

We have the following information request and we'll appreciate it if you can provide your response right around the same time you respond to the Label edits/comments we sent you on 5/28. That is a response no later than 2:00 pm tomorrow will be helpful.

In reviewing Study 331-10-227, we note that there were a disproportionately high number of major protocol deviations due to concomitant medications in the 3 mg/day brexpiprazole+ADT group. Approximately 1/3 of those deviations were due to concomitant medications likely used to treat EPS (e.g., benztropine, biperiden, diphenhydramine). However, none of the subjects who received these medications have EPS-related AEs recorded in the AE database. Although it is possible that subjects who received diphenhydramine may have been experiencing seasonal allergies, an alternative explanation for the other medications is unlikely. Please review these protocol deviations and revise your AE tables as needed.

Although the protocol deviations were more balanced in the other three pivotal trials reviewed with this NDA submission, the discrepancy noted above calls the data from those trials into question as well. Please review any case in which a patient received prohibited anticholinergic medication or diphenhydramine for possible inclusion in the AE database as a case of EPS, as this may impact the data included in your product labeling. If you believe these protocol deviations should not be counted as EPS events, please provide your rationale along with the requested data.

Best Regards,
Kofi.

From: Ansah, Kofi
Sent: Thursday, May 28, 2015 9:01 PM
To: Guinn, Patrick (Patrick.Guinn@otsuka-us.com)
Cc: Goldberger, David (David.Goldberger@otsuka-us.com); David, Paul A
Subject: Follow-up FDA Labeling Edits/Comments -- NDA 205422/Brexpiprazole (OPC-34712)
Importance: High

Dear Patrick,

Find attached your draft Label (as amended on 4/14/14) with our follow-up edits and comments (i.e., we worked off your 4/14/15 response to our initial edits). Please review our edits and comments and resubmit labeling that addresses our comments, as applicable.

Please be sure to work off (i.e., use) the word document we are sending you and track any edits/counter-proposal(s) you may have at this point (include your own comments as necessary).

Provide the requested labeling changes/information to me via email preferably by end-of-day on Tuesday; June 2, 2015 -- But no later than The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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/s/

KOFI B ANSAH
06/02/2015

**PeRC Meeting Minutes
May 13, 2015**

PeRC Members Attending:

Lynne Yao

Robert "Skip" Nelson

Wiley Chambers

Rosemary Addy

George Greeley

Peter Starke

Daiva Shetty (Did not review [redacted] Non-responsive REXULTI)

Freda Cooner

Tom Smith

Karen Davis-Bruno

Daiva Shetty

Andrew Mulberg

Greg Reaman [redacted] Non-responsive

Adrienne Hornatko-Munoz

Andrew Mosholder [redacted] Non-responsive

Hari Cheryl Sachs

Julia Pinto

Shrikant Pagay

Lily Mulugeta

Kevin Krudys

Rachel Witten

Dianne Murphy

Maura O'Leary

Kristiana Brugger

Agenda

Non-responsive

11:30	NDA	205422	REXULTI (brexpiprazole) Partial Waiver/Deferral/Plan *w/Agreed iPSP	Adjunctive treatment of MDD Treatment of schizophrenia
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Non-responsive

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Non-responsive

REXULTI (brexpiprazole) Partial Waiver/Deferral/Plan

- Proposed Indication: Adjunctive treatment of MDD and Treatment of schizophrenia
- The Division noted that the plan is the same as the one agreed upon in the Agreed iPSP for this product.
- PeRC Recommendations:
 - The PeRC agreed with the plan for a partial waiver and deferral for this product.

Non-responsive

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/s/

GEORGE E GREELEY
05/26/2015



NDA 205422/Original-1
NDA 205422/Original-2

GENERAL ADVICE

Otsuka Pharmaceutical Company, Ltd.
Attention: Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
C/o Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Guinn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 2, 2015, and our March 23, 2015 letter containing our Background Information for the LCM.

The attached document provides the background for the issue raised in our LCM Background Package.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:

Amendment to Late-Cycle Meeting Background Package

Introduction

The information provided below has been extracted from the primary clinical review for NDA 205422. It is intended to provide some insight into our assessment as to whether or not Study 331-10-227 should be considered a positive trial.

Review of Relevant Regulatory History

Meetings

March 29, 2011: End of Phase 2 Meeting

At this meeting, both the schizophrenia and MDD development programs were addressed. Related to the MDD program, FDA informed the sponsor that Study 331-08-211 would not likely be considered a positive study (failed to demonstrate efficacy based on the pre-specified analysis), and that at least two positive studies, including at least one fixed-dose study, would be required to support an indication of adjunctive treatment of MDD. FDA further recommended studying fixed doses of 1 mg and 3 mg. Possible dose-dependent risks for akathisia, weight gain, and increased CPK concentration were noted, and FDA recommended that these be systematically assessed. FDA did acknowledge that, if positive, 331-09-222 might serve as a pivotal study if the sponsor could provide data from an adequate and well-controlled positive fixed-dose study. In response to FDA's recommendation, the sponsor proposed two fixed-dose studies: one with 1 mg and 3 mg doses, the other using only a 2 mg dose. FDA stated that this was acceptable, but recommended including all three doses in a single study. FDA agreed to the sponsor's proposed use of the Sheehan Disability Scale (SDS) as a key secondary endpoint, but viewed other proposed secondary endpoints (e.g., remission rate) as exploratory.

September 27, 2013: Written Response Only pre-NDA guidance on non-CMC issues.

In response to the sponsor's inquiry whether positive results from Studies 331-10-227 and 331-10-228 would be sufficient to support an indication for adjunctive treatment in MDD, FDA stated:

As previously stated in the EOP2 meeting, we would require at least one positive fixed-dose study to support an NDA application. Although this will be a matter for review, it appears that the two fixed-dose studies 227 and 228 would be sufficient to support an NDA application, if they are positive studies.

FDA further noted that efficacy data from the individual studies would be reviewed for the primary endpoint. The sponsor noted a plan to also include pooled data; FDA stated the pooled analyses could be submitted as supportive data, but that it was not clear how the information would be used.

May 12, 2014: Pre-NDA Meeting

FDA's preliminary comments note, "On face, only one study demonstrated the efficacy of

brexpiprazole as adjunctive therapy in MDD.” At the face-to-face meeting, the sponsor presented the data to support an indication for adjunctive treatment of MDD. At that time, the Division agreed that the data from the clinical trials support *filing*, but remained silent on the acceptability of the sponsor’s analyses, leaving the results up to interpretation as a potential review issue.

Key Protocol Submissions

In April of 2011, the sponsor submitted protocols for the proposed pivotal trials in both the schizophrenia and adjunctive MDD programs. FDA sent comments to the sponsor related to both development programs on May 19, 2011.

- MDD: FDA strongly discouraged the use of last observation carried forward (LOCF) approach for the primary analysis, recommended that the sponsor propose sensible sensitivity analyses in case the missing data mechanism is “missing not at random,” and recommended including the SDS at additional time points. Pertaining only to Study 331-10-227, FDA noted that the proposed hierarchical multiple testing procedure (Hochberg) is a non-separable procedure. Thus, the null hypothesis associated with the key secondary endpoint could only be tested if both null hypotheses associated with the primary endpoint were rejected.

The sponsor responded to the pivotal trial design comments on August 15. The sponsor made changes to the primary analyses and sensitivity analyses as advised but, regarding the Hochberg procedure, acknowledged our concerns but kept this procedure in the statistical plans.

In April, 2012, the sponsor submitted **Amendment 3**. This amendment provides the basis for the sponsor’s claim that Study 331-10-227 is a positive trial; however, this claim is based on analyses using the *per-protocol set*, rather than the *intent-to-treat set*. FDA sent an Information Request to the sponsor on May 4 seeking clarification on several points, to which the sponsor replied on May 11. Key among these:

FDA Comment #6: Clarify your analysis plan regarding subjects who have already been randomized based on the original response criteria. Will they be completely excluded from the final analysis, or will they be included in the final analysis?

Otsuka’s Response: The final analysis will be based on the intent-to-treat (ITT) principle to include all randomized subjects in the analysis as randomized. In addition, we will provide the analysis on the per protocol set (PPS) analysis, which will exclude those subjects who do not meet the new response criteria as supportive analysis. Statistical analysis will be done to examine the impact on study conclusions of these patients.

Review of Relevant Individual Trials Used to Support Efficacy

A brief summary of review issues pertinent to the late cycle meeting discussion is presented below. The overall efficacy review for adjunctive treatment of MDD considered both Studies 331-10-227 and 331-10-228.

Study 331-10-227: Adjunctive Treatment of Major Depressive Disorder

Study Design

Overview and Objective

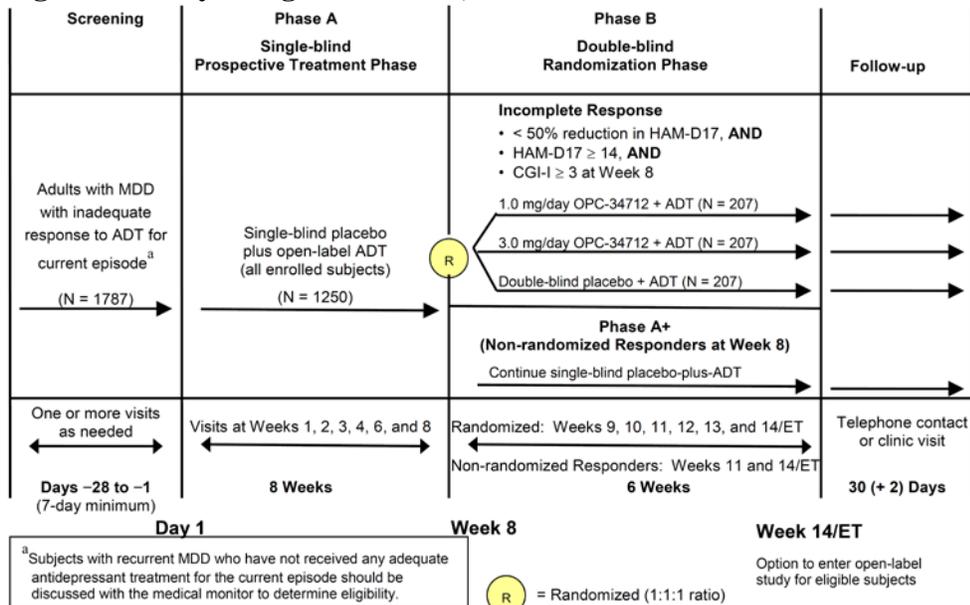
The primary objective of this study was to compare the efficacy of brexpiprazole (1 and 3 mg/day) to placebo as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in subjects who demonstrate an incomplete response after eight weeks of prospective treatment with the same assigned open-label ADT.

The secondary objective was to evaluate the safety and tolerability of brexpiprazole (1.0 and 3.0 mg/day) as adjunctive therapy to ADT in the proposed subject population with MDD.

Trial Design

Study 331-10-227 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial designed to assess the safety and efficacy of two fixed doses of brexpiprazole as adjunctive therapy to an assigned open-label ADT in depressed subjects who have demonstrated an incomplete response to prospective treatment with the same ADT. A schematic of the study design is presented in Figure 1, below.

Figure 1. Study Design Schematic, 331-10-227



(source: Study 331-10-227, original clinical trial protocol—April 8, 2011 version, Figure 3.1-1, page 33)

Phase B (Double-blind Randomization Phase): Phase B is the portion of the study on which the efficacy assessment is based. Subjects with an incomplete response at the end of Phase A were eligible to enter the 6-week Double-blind Randomization Phase (Phase B). In the original protocol, incomplete response was defined as < 50% reduction in depressive symptom severity between baseline and the Week 8 visit, as measured by the HAM-D17 Total Score; AND a HAM-D17 Total Score \geq 14 at the Week 8 visit; AND a Clinical Global Impression-Improvement (CGI-I) score \geq 3 at the Week 8 visit. Eligible subjects were randomized in a 1:1:1 ratio to one of the following double-blind treatment regimens:

- Adjunctive 1.0 mg/day brexpiprazole-plus-ADT
- Adjunctive 3.0 mg/day brexpiprazole-plus-ADT
- Continued placebo-plus-ADT

The dose of ADT was based on the final dosage of the assigned open-label ADT reached during Phase A. During Phase B, randomized subjects attended weekly visits at Weeks 9, 10, 11, 12, 13, and 14.

Subjects entering this phase have had both documented historical inadequate response to 1-3 antidepressants in the current episode, and prospectively established incomplete response to an additional antidepressant. Prior antidepressant trials were all of adequate dose and duration based on approved labeling for the given antidepressant. This trial design and the criteria for inadequate response are similar to those used to establish efficacy of other drugs for this indication.

- *Amendment 3:* On March 23, 2013, the sponsor submitted Amendment 3 to protocol 331-10-227 (and 331-10-228). The sponsor reported that blinded review of data from Trial 331-10-227 indicated that some subjects responded to ADT at earlier visits during the prospective phase, but did not meet criteria for response at the Week 8 visit, and thus were eligible for randomization at Week 8. The sponsor felt that these subjects should not be considered non-responders, given that they had previously demonstrated response during Phase A. With Amendment 3, subjects responding to ADT before Week 8 would also be considered responders and would not be eligible for randomization at the Week 8 visit. These subjects could be eligible to receive single-blind placebo-plus-ADT for an additional six weeks in Phase A+. The sponsor stated that, in order to reduce the potential for bias in the ratings, the trial sites would remain blinded to the details of the changes to the randomization criteria. At the time this amendment was implemented, 210 subjects had already been randomized. **Forty-two of them did not meet the Amendment 3 criteria.**
- The revised criteria for incomplete response are as follows:
 - < 50% reduction in HAM-D17 Total Score between baseline of Phase A and the Week 8 visit, AND
 - HAM-D17 Total Score \geq 14 at the Week 8 visit, AND
 - [New] < 50% reduction in Montgomery Åsberg Depression Rating Scale (MADRS) Total Score between baseline of Phase A and scheduled visits at Weeks 2, 4, 6, and 8, AND

- [Week 2, 4, and 6 criteria new] CGI-I score of ≥ 3 at scheduled visits at Weeks 2, 4, 6, and 8.

Dose selection: Dose selection for this trial was based on preliminary efficacy and safety data from Phase 1 and 2 trials, as well as discussion with FDA at the End of Phase 2 (EOP2) meeting. In a Phase 2 trial (Study 331-08-211) with a similar design, flexibly-dosed adjunctive brexpiprazole 1.5 ± 0.50 mg/day was numerically superior to adjunctive placebo with respect to the primary endpoint (change from Week 8 to Week 14 in Montgomery Asberg Depression Rating Scale [MADRS] Total Score). The effect of this dose did not reach statistical significance using the prespecified adjustment for multiple comparisons in the primary analyses. However, the sponsor noted that brexpiprazole had a “favorable profile with respect to movement disorders” in subjects with MDD at doses up to 3 mg/day. The sponsor also reported that brexpiprazole did not result in any consistent, clinically relevant changes in laboratory values, vital signs (blood pressure or heart rate), or electrocardiogram (ECG) parameters in the completed Phase 1 and 2 clinical trials in subjects with MDD; however, statistically significant increases in weight were observed relative to placebo. The sponsor further stated that, in patient trials, brexpiprazole had been well tolerated at multiple doses up to 4 mg/day in subjects with MDD who received concomitant ADT.

Based on this data, and FDA’s advice to conduct two Phase 3 trials with at least one fixed-dose trial, the sponsor chose to explore the dose range from 1 mg to 3 mg daily. Between this study and Study 331-10-228, doses of 1 mg, 2 mg, and 3 mg were evaluated; however, while the dose ranges of the trials overlapped, the actual doses did not.

Study Endpoints

The primary efficacy outcome variable was the change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the MADRS Total Score. For this trial, the MADRS was administered using the Structured Interview Guide for the MADRS (SIGMA) which provides detailed instructions for administration of this structured interview.

The key secondary efficacy variable is the change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit, LOCF) in Sheehan Disability Scale (SDS) Mean Score (the mean of 3 individual item scores). The SDS is commonly used as a secondary measure to assess impairment in functioning associated with MDD.

Statistical Analysis Plan

The original protocol defined the following analysis sets:

- Enrolled Sample: all subjects who signed an ICF for the trial and enrolled into Phase A.
- ADT Sample: all subjects who took at least one dose of antidepressant IMP.
- Randomized Sample: all subjects who were randomized in Phase B.
- Safety Sample: those randomized subjects in Phase B who received at least one dose of double-blind trial medication as indicated on the dosing record.

- Efficacy Sample: all subjects in the Safety Sample who have an end of Phase A (i.e., Week 8) value and at least one post-randomization efficacy evaluation for MADRS Total Score in Phase B.
- The Phase A+ Sample: all subjects who respond at the end of Phase A (are therefore not randomized), and who continue on ADT + single-blind placebo beyond Week 8.

The core dataset for all efficacy analyses was defined as the intent-to-treat (ITT) dataset, consisting of data from all randomized subjects. Hochberg's procedure was used to adjust for the multiple comparisons of the two brexpiprazole groups vs placebo and maintain the overall Type I error at 0.05 (two-tailed). For the two comparisons, if the larger of the two P-values was ≤ 0.05 and each comparison is in favor of brexpiprazole, both doses (1 mg and 3 mg) would be declared significantly better than placebo. If the larger P-value was > 0.05 , the smaller P-value would be compared to 0.025. If the smaller P-value was ≤ 0.025 and the corresponding comparison was in favor of brexpiprazole, the dose corresponding to the smaller P-value would be declared significantly better than placebo. In this case, using the ITT population, neither dose of brexpiprazole reached this $p < 0.025$ threshold.

The planned comparisons of the key secondary endpoint (SDS Mean Score) employed another Hochberg procedure at an alpha level of 0.05 (two-sided), and could only be considered if both null hypotheses for the primary endpoint (MADRS Total Score) were rejected. Because the null hypotheses (dose = placebo) were not rejected, the secondary endpoint is not considered positive despite reaching the $p < 0.05$ threshold.

Protocol Amendments

While the study was ongoing, the sponsor submitted Amendment 3 which amended the randomization criteria to redefine incomplete responders as those subjects who did not meet response criteria over the entire course of Phase A, and not solely at the end of Phase A. Protocol Amendment 3 added criteria based on the MADRS (Weeks 2, 4, 6, and 8) and CGI-I (Weeks 2, 4, and 6), in addition to the existing criteria for the HAM-D17 and CGI-I at Week 8, in order for a subject to be eligible for randomization into Phase B (see Trial Design, above, for details). When this change was implemented, 210 subjects had already been randomized into in Study 331-10-227.

The Efficacy Sample per Amendment 3 Criteria included all subjects in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. This sample was considered the "per protocol set" for the Phase 3 trials, as communicated in the correspondence with the FDA (IND 103, 958; Serial # 0148, dated May 15, 2012): "The final analysis will be based on the intent-to-treat (ITT) principle to include all randomized subjects in the analysis as randomized. In addition, we will provide the analysis on the per-protocol set (PPS) analysis, which will exclude those subjects who do not meet the new response criteria as supportive analysis."

Study Results

Patient Disposition

Approximately 1653 subjects were planned for enrollment into Phase A in order to randomize 660 subjects into Phase B. A total of 2310 subjects were screened for the trial, 1539 were enrolled into Phase A, and 1532 received at least one dose of sponsor-provided ADT. Of these, 255 subjects (16.6%) discontinued during Phase A, 677 subjects (44.2%) were randomized into Phase B (226 in the 1 mg/day brexpiprazole+ADT group, 230 in the 3 mg/day brexpiprazole+ADT group, and 221 in the placebo+ADT group), and 600 subjects (39.2%) continued treatment with placebo+ADT in Phase A+.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the change in MADRS Total Score from Baseline (End of Phase A) to Week 14 for the Efficacy Sample. The Efficacy Sample was the intent-to-treat (ITT) population. The 3 mg/day brexpiprazole+ADT group showed numerically greater improvement compared with the placebo+ADT group for the primary efficacy parameter (LS mean difference=-1.52, p=0.0327); however, the p-value for the primary Efficacy Sample did not meet the prespecified threshold of 0.025 using the Hochberg method to correct for multiplicity. The LS mean change for the 1 mg/day brexpiprazole+ADT group also showed a numerically greater improvement compared with the placebo+ADT group (LS mean difference=-1.19, p=0.0925). These results are presented in Table 1, below, and were confirmed by our statistical reviewer.

Based on the prespecified statistical plan, this is a negative trial.

Table 1: Primary Efficacy Analysis—Mean Change in MADRS Total Score, Study 331-10-227

Variable	1mg Brex+ADT	3mg Brex+ADT	Placebo+ADT
MADRS Total Score, MMRM	N=225	N=226	N=218
Mean (SD) End of Phase A	26.69 (5.61)	26.31 (5.24)	26.23 (5.27)
LS Mean (SE) Change At Week 14	-7.65 (0.50)	-7.98 (0.51)	-6.45 (0.51)
LS Mean Difference (95% CI)	-1.19 (-2.58, 0.20)	-1.52 (-2.92, -0.13)	-
P-value	0.0925	0.0327	-

(source: Study 331-10-227, Clinical Study Report, Table11.4.1.1.1-1, page 158)

- Analysis by population:** The sponsor also provided data using the Efficacy Sample per Amendment 3 Criteria (the per protocol set). As noted above, the sponsor is basing the assertion that this was a positive trial on this analysis, claiming that the analysis provides evidence for the treatment effect in the 3 mg/day brexpiprazole+ADT group. In fact, the proposed labeling includes these analyses rather than the prespecified ITT analyses.

Using the per protocol set, the 3 mg/day brexpiprazole+ADT group achieved a greater mean change compared with the placebo+ADT group at Week 14 (LS mean difference=-1.95), and the p-value met the Hochberg threshold (p=0.0079). The LS mean change for the 1 mg/day brexpiprazole+ADT group again showed numerically greater improvement compared with the placebo+ADT group at Week 14 (LS mean difference=-1.30, p=0.0737), and failed to reach the threshold of statistical significance.

Table 2: Per Protocol Analysis—Mean Change in MADRS Total Score, Amendment 3 Criteria, Study 331-10-227

Variable	1mg Brex+ADT	3mg Brex+ADT	Placebo+ADT
MADRS Total Score, MMRM	N=211	N=213	N=203
Mean (SD) End of Phase A	26.85 (5.61)	26.48 (5.29)	26.46 (5.20)
LS Mean (SE) Change At Week 14	-7.64 (0.52)	-8.29 (0.53)	-6.33 (0.53)
LS Mean Difference (95% CI)	-1.30 (-2.73, 0.13)	-1.95 (-3.39, -0.51)	-
P-value	0.0737	0.0079	-

(source: Study 331-10-227, Clinical Study Report, Table11.4.1.1.2-1, page 159)

Our statistical reviewer performed her own analysis for the per-protocol set. Her results were similar but not exactly the same as the sponsor's results. The LS mean differences in MADRS score were -1.29 (p=0.0770) and -1.93 (p=0.0085) for brexpiprazole 1 mg and 3 mg respectively, favoring brexpiprazole groups compared with placebo. The LS mean differences in SDS mean score were -0.45 (p=0.0258) and -0.44 (p=0.0311) for brexpiprazole 1 mg and 3 mg respectively. Our reviewer noted that, in her opinion, the Efficacy Sample should be used for the primary analysis as it preserves the randomization and is pre-specified as the primary efficacy set. I concur with that assessment.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint of mean change from baseline (end of Phase A) to Week 14 in SDS Mean Score was analyzed using MMRM model with heterogeneous toeplitz covariance structure (TOEPH). Both brexpiprazole+ADT dose groups showed greater improvement (p<0.05) than the placebo+ADT group for the change in SDS Mean Score, with LS mean differences of -0.49, (p=0.0091) and -0.37 (p=0.0474) for the 1 mg/day brexpiprazole+ADT group and 3 mg/day brexpiprazole group, respectively. However, because neither doses showed statistical significance for the primary endpoint, the pre-specified hierarchical testing procedure was terminated after evaluation of the primary endpoint. It is also worth noting that, despite small p-values, the magnitude of improvement in the brexpiprazole+ADT groups was quite small as well; the clinical relevance of this degree of change is questionable.

Table 3: Key Secondary Efficacy Analysis—Summary of Mean Change from Baseline to Week 14 in SDS Mean Score, Study 331-10-227

Variable	1mg Brex+ADT	3mg Brex+ADT	Placebo+ADT
SDS Mean Score, MMRM	N=218	N=212	N=208
Mean (SD) End of Phase A	5.92 (1.95)	5.76 (2.26)	5.61 (1.93)
LS Mean (SE) Change At Week 14	-1.33 (0.14)	-1.21 (0.13)	-0.84 (0.13)
LS Mean Difference (95% CI)	-0.49 (-0.87, -0.12)	-0.37 (-0.73, -0.00)	-
P-value	0.0091	0.0474	-

(source: Study 331-10-227, Clinical Study Report, Table11.4.1.2.1-1, page 169)

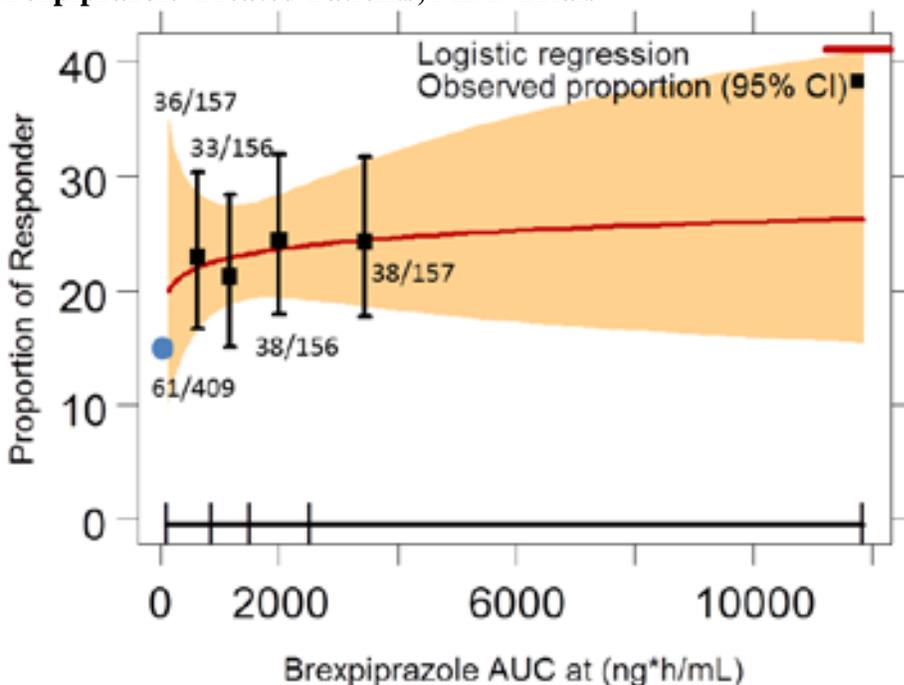
Dose/Dose Response

It is difficult to draw any meaningful conclusions regarding dose-response from this study. Of the two pivotal trials, this was the only one that included more than one brexpiprazole dose group. While the 3 mg/day group certainly fared better than the 1 mg/day group, neither was statistically better than placebo on the pre-specified analysis. Based on exposure-response modeling using data from both this trial and Study 331-10-228, OCP concluded that there was no significant increase in responder rate with the increase of brexpiprazole AUC in the MDD trials (see below).

Additional FDA Analyses Conducted on Individual Trial

- The sponsor stated that subjects who did not meet the revised criteria for incomplete response in Protocol Amendment 3 “were fundamentally dissimilar to those with a persistent inadequate response during this phase.” Our statistical reviewer performed the primary MMRM analysis with the additional variable “amend3” (meeting Amendment 3 criteria, yes vs no). The result was almost identical with that of the primary analysis. The p-value for the factor “amend3” was 0.34, suggesting that this factor does not significantly impact the analysis results.
- OCP evaluated the relationship between brexpiprazole exposure and clinical response. As shown in Figure 2, below, there was no significant increase in responder rate with the increase of brexpiprazole AUC in the MDD trials.

Figure 2: No Significant Increase of Responder^a Rate with the Increase of AUC in Brexpiprazole-Treated Patients, MDD Trials



^aResponse defined as $\geq 50\%$ reduction in MADRS total score at Week 14 from end of Phase A (Week 8). (source: OCP review, Figure 4)

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/s/

MITCHELL V Mathis
03/29/2015

From: Ansah, Kofi
To: [Guinn, Patrick \(Patrick.Guinn@otsuka-us.com\)](mailto:Patrick.Guinn@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com)
Subject: Initial FDA Labeling Edits/Comments -- NDA 205422/Brexpiprazole (OPC-34712)
Date: Friday, March 27, 2015 12:14:00 AM
Attachments: [03-26-15 FDA edits Sponsor's draft-LABEL Brexpiprazole \(v.10-14-14\)IMARKED-UP1.docx](#)
[03-26-15 FDA edits Sponsor's draft-LABEL Brexpiprazole \(v.10-14-14\)IMARKED-UP1.pdf](#)

Dear Patrick,

Find attached your draft Label (as amended on 10/14/14) with our initial round of edits and comments. Please review our edits and comments and resubmit labeling that addresses our comments.

Please be sure to work off (i.e., use) the word document we are sending you and track any edits/counter-proposal(s) you may have at this point (include your own comments as necessary). Also, as previously discussed, please integrate the labeling changes you provided in your Labeling amendment dated 2/27/15 (i.e., incorporating the REXULTI tradename & (b) (4))

Provide the requested labeling changes/information to me via email in by April 16, 2015. The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

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Email: Kofi.Ansah@fda.hhs.gov

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

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/s/

KOFI B ANSAH
03/27/2015

From: Ansah, Kofi
To: ["Guinn, Patrick"](#)
Cc: [Goldberger, David](#)
Subject: Follow-Up to LCM Background Package -- NDA 205422/OTSUKA/ Brexpiprazole (OPC-34712)
Date: Tuesday, March 24, 2015 6:28:00 PM
Attachments: [Foreign Visitor Data Request Form -- NDA 205422 Brexpiprazole.pdf](#)
Importance: High

Dear Patrick,

We have been able to reschedule the LCM as a face-to-face meeting. Please note the following details/changes:

Meeting Date and Time: April 2, 2015 (1:00 – 2:00 pm EDT)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, Maryland 20903

For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, as soon as possible. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: **CDR Kofi Ansah, x 6-4158; or Mr. Dave Berman, x 6-1044.**

Best Regards,
Kofi.

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Tuesday, March 24, 2015 10:56 AM
To: Ansah, Kofi
Cc: Goldberger, David; Guinn, Patrick
Subject: RE: LCM Background Package -- NDA 205422/OTSUKA/ Brexpiprazole (OPC-34712)

Dear Kofi,

Based on the feedback provided in the Late Cycle Review Meeting Background Package, we are requesting that the meeting scheduled for April 2, 2015, to be a Face-To-Face meeting instead of a teleconference.

In addition, we are requesting to have the following individuals present for the meeting.

- **Signatory Authority (ODE Director)? – Dr. Temple**
- **Division Director – Dr. Mathis**

- **Division Deputy Director – Dr. Farchione**
- **Cross-Discipline Team Leader (CDTL) – ??**
- **Review Discipline Team Leaders - ??**

Specific discussion points for the Face-to-Face Meeting will be provided shortly along with the potential attendees from Otsuka/Lundbeck.

Regards, Patrick.

Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.



Otsuka
2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277

(b) (6)

Email: Patrick.Guinn@otsuka-us.com

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Monday, March 23, 2015 9:52 PM
To: Guinn, Patrick
Cc: Goldberger, David
Subject: LCM Background Package -- NDA 205422/OTSUKA/ Brexpiprazole (OPC-34712)

Dear Patrick,

Please find attached our Background material for the LCM on 4/2/15. Expect our initial Label comments by Wednesday, 3/26/15, as discussed.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Otsuka Pharmaceutical Company, Ltd.
MEETING START DATE AND TIME	April 2, 2015; 1:00 pm EDT
MEETING ENDING DATE AND TIME	April 2, 2015; 2:00 pm EDT
PURPOSE OF MEETING	Late-Cycle Meeting (LCM)
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	FDA White Oak Campus, Bldg. 22, Room #1417 10903 New Hampshire Ave, Silver Spring MD 20993
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Kofi B. Ansah, Pharm.D., CDR US Public Health Service Project Manager, Division of Psychiatry Products FDA/ CDER, Office of Drug Evaluation-I 10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112 Silver Spring, MD 20993 - 0002 Phone: (301) 796-4158 Email: Kofi.Ansah@fda.hhs.gov
ESCORT INFORMATION (If different from Hosting Official)	(same as above)

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/s/

KOFI B ANSAH
03/24/2015



NDA 205422/Original-1
NDA 205422/Original-2

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Otsuka Pharmaceutical Company, Ltd.
Attention: Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
C/o Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Guinn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 2, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell Mathis, M.D.
CAPT USPHS
Director
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: April 2, 2015 (1:00 – 2:30 pm EDT)
Meeting Location: Teleconference

Application Number: NDA 205422/Original-1 and NDA 205422/Original-2
Product Name: Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg
Indication: Adjunctive Treatment of Major Depressive Disorder & Treatment of schizophrenia
Sponsor/Applicant Name: Otsuka Pharmaceutical Company, Ltd.

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 and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issue(s) have been identified to date:

Clinical - For the indication “Adjunctive Treatment of Major Depressive Disorder,” it is our view that you have submitted only one positive study to support this application.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LATE-CYCLE MEETING (LCM) AGENDA

1. Introductory Comments – 4 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 20 minutes

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

- As noted in the mid-cycle communication, it is our view that you have only submitted one positive study for the adjunctive treatment of MDD.

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

- Study in adolescents with schizophrenia

4. Major Labeling Issues – 25 minutes

- Information related to the Adjunctive Treatment of MDD will need to be removed from the label.

5. Review Plans – 1 minute

- We plan to complete our review and take action by July 10, 2015 or the PDUFA goal date.

6. Wrap-up and Action Items – 5 minutes

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/s/

MITCHELL V Mathis
03/23/2015

From: Ansah, Kofi
To: "[Parsi, Megan](#)"
Cc: [Goldberger, David](#); [Grewal, Renmeet](#); [Sohn, Ann J](#)
Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)
Date: Monday, January 26, 2015 12:16:00 PM

Hi Megan,

In principle, the Division is in agreement with the approach you have described below (in your December 17, 2014, email). Please formally submit an amended Pediatric Plan (to include your revised protocol) to your NDA as soon as possible. Also, please note that we will be seeking PeRC's input as part of the NDA review process and would communicate any additional comments they may have to you at that time.

Best Regards,
Kofi.

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

From: Parsi, Megan [<mailto:Megan.Parsi@otsuka-us.com>]
Sent: Wednesday, January 21, 2015 1:38 PM
To: Ansah, Kofi
Cc: Goldberger, David
Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Dear Kofi,

Hope all is well. As a gentle follow-up, could you please let me know if there are any updates regarding the FDA review of the proposals outlined in the email below in Dec 2014?

The Team is eager to hear back from the FDA so that we know how to proceed with the PK study. Please note that timelines for completion of this study as provided in the PSP would be impacted by timing of initiation of this study.

For the purpose of efficiency, to limit the number review cycles back and forth, and amendments to the protocol, we would be grateful to know if in principal. FDA is in agreement with the approach we have described. If so, we can follow-up with an official submission of this information, including a revised protocol.

Thank you for your assistance in advance.

Kind regards,
Megan

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

From: Parsi, Megan
Sent: Wednesday, January 07, 2015 11:45 AM
To: 'Ansah, Kofi'
Cc: Goldberger, David
Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Hi Kofi,

Could you please let me know if you have received any further input from your Team regarding our responses below on the PSP and the pediatric PK study protocol for study 331-10-233?

Would greatly appreciate any status update on this.

Many thanks
Megan

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

From: Parsi, Megan

Sent: Wednesday, December 17, 2014 2:59 PM

To: 'Ansah, Kofi'

Cc: Goldberger, David

Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Dear Kofi,

Please see below the additional information and clarifications we would like to provide to hopefully reach consensus and move forward with initiating the study:

In response to your email below dated December 9th, the key objective of the PK study 331-10-233 is to provide information on the PK characteristics in adolescents, thus generating data supporting dose decision for the future efficacy studies. Full safety/tolerability assessment will be determined by the subsequent planned short-term and long-term studies.

To clarify this point, Otsuka proposes to amend the protocol and the PSP as appropriate, modifying the study objectives as follows:

Primary objectives: To primarily evaluate the Pharmacokinetics of brexpiprazole, and its metabolite, in connection with a multiple oral dosing in adolescent patients, and to also assess the safety and tolerability of brexpiprazole used as a multi-dose regimen in this population

Secondary objective: To assess the efficacy of brexpiprazole

Therefore key focus of study 331-10-233 is PK; safety and tolerability information will be collected but are expected to be very limited due to the small number of patients exposed in a phase 1 PK study, with a very short treatment exposure and an open-label design.

With respect to your previous comment related to the use of a broad array of patient population (FDA email below dated Nov 10, 2014: "Thus, expanding the inclusion criteria to patients with a broad array of diagnoses is not acceptable"), we propose to limit the inclusion criteria to patients with schizophrenic and bipolar spectrum disorders. Based on information available from the literature, the PK characteristics are not expected to vary between schizophrenic and bipolar spectrum disorders. This is illustrated in similar PK studies conducted with other agents in an extended patient population to support dosing decisions for future studies (eg., lurasidone and aripiprazole). In addition, there is limited difference in tolerability and safety between these populations over a short time period within the proposed age-range. We acknowledge FDA's concern in using a broad population, and therefore, agree to remove patients with Tourette's disorder from the inclusion criteria. Neuroleptic naive patients will also be excluded from the study.

As an additional consideration to justify the proposal for the use of patients with schizophrenia and bipolar spectrum disorders, we would like to reiterate challenges with enrollment of patients with Schizophrenia only into the PK study. Given the prevalence of adolescents with schizophrenia is very low, and considering that the prevalence of schizophrenia at the lower age range of adolescents 13-14 is quite rare, the population will likely be skewed toward higher age group (16-17). Therefore, inclusion of a broader diagnosis will ensure better distribution of the patients across the entire studied age range (13-17 years). This enables generating sufficient data for the next phase of the pediatric clinical program.

Please let me know if you have any questions or comments. We will be happy to discuss further as needed.

Kind regards,
Megan

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

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Tuesday, December 09, 2014 6:30 PM
To: Parsi, Megan
Cc: Goldberger, David
Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Hi Megan,

As I mentioned in our brief telephone discussion, what are your specific concerns? We are assuming you want to find a middle ground on expanding your patient population. BUT, the primary issue is related to the fact that you listed safety/tolerability among the primary outcomes. If you decided that PK was primary and safety/tolerability were secondary, we don't see why you can't expand. After all, we don't expect PK to differ across populations. If you want more than that, we may need to have a discussion.

Best Regards,
Kofi.

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

From: Parsi, Megan [<mailto:Megan.Parsi@otsuka-us.com>]
Sent: Wednesday, November 12, 2014 8:52 AM
To: Ansah, Kofi
Cc: Goldberger, David
Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Dear Kofi,

I am resending this email as I received a note that it was not delivered properly. Apologies if you have received it already.....

Best regards,
Megan

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

From: Parsi, Megan
Sent: Monday, November 10, 2014 1:59 PM
To: 'Ansah, Kofi'; Goldberger, David
Subject: RE: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Dear Kofi,

Thank you for your response. We hope to have the opportunity to have a further discussion with you in an effort to better understand FDA's concern, and clarify the intended patient population.

Would you be available for a phone call this week?

I am at the Rockville office this week and available on my (b) (6).

Kind regards,
Megan

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

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Monday, November 10, 2014 8:41 AM
To: Parsi, Megan; Goldberger, David
Cc: Ansah, Kofi
Subject: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)

Dear Ms. Parsi:

We acknowledge receipt of your 8/22/14 submission containing your proposed amendment to the Agreed-iPSP.

We have completed our review of the afore mentioned submission and we do not agree with your proposed amendment to the agreed iPSP. Based on data from currently approved products, it is reasonable to assume that safety and tolerability will vary by patient population. Thus, expanding the inclusion criteria to patients with a broad array of diagnoses is not acceptable.

Please submit your pediatric plan (essentially the Agreed-iPSP) to your NDA 205422, if you haven't already done so – It would be presented to the PeRC for discussion under PREA during the PMR/PMC negotiation phase of the NDA review.

Thanks,
Kofi.

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/s/

KOFI B ANSAH
01/27/2015

From: Ansah, Kofi
To: [Parsi, Megan \(Megan.Parsi@otsuka-us.com\)](mailto:Megan.Parsi@otsuka-us.com); [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com); [Guinn, Patrick \(Patrick.Guinn@otsuka-us.com\)](mailto:Patrick.Guinn@otsuka-us.com)
Cc: [Chang, ShinYe](mailto:Chang.ShinYe); [Parihar, Simran](mailto:Parihar.Simran)
Subject: RE: Statistical Comments -- RE: Notification of Termination of An Investigator - Brexpiprazole (Ref: INDs (b) (4) 103958; 101871 & NDA 205422) Non-responsive
Date: Tuesday, January 13, 2015 9:55:00 AM

Megan,

One point of clarification; we note that you alerted us by email on 11/7/14 but your formal submission to the affected applications was on November 17, 2014.

Thanks,
Kofi.

From: Ansah, Kofi
Sent: Monday, January 12, 2015 11:25 AM
To: Parsi, Megan (Megan.Parsi@otsuka-us.com); Goldberger, David (David.Goldberger@otsuka-us.com); Guinn, Patrick (Patrick.Guinn@otsuka-us.com)
Cc: Chang, ShinYe; Parihar, Simran
Subject: Statistical Comments -- RE: Notification of Termination of An Investigator - Brexpiprazole and (Ref: INDs (b) (4) 103958; 101871 & NDA 205422) Non-responsive

Dear Megan,

We refer to your November 7, 2014 submission to INDs 101,871 (SN 435), 103,958 (SN 361), (b) (4) We acknowledge your notification of the GCP non-compliance at a certain study center and your decision of terminating these two principal investigators (i.e., Bernadette B. D'Souza, M.D. and Otto Dueno, M.D). We also appreciate the fact that you provided a list of affected studies, highlighting the submission history.

In principle, patients from the affected study center should still be included in the primary analysis set. However, you should also plan to run analyses by excluding these patients to explore the impact of the non-compliance violation on the efficacy outcome, which should be included in your future study reports. It will be a matter of future NDA review exactly which analysis set will be used to describe the efficacy outcome in the labeling.

Please contact the respective Regulatory Project Manager for your IND/application if you have any questions regarding these comments.

Thanks,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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From: Parsi, Megan [<mailto:Megan.Parsi@otsuka-us.com>]

Sent: Friday, November 07, 2014 5:16 PM

To: Ansah, Kofi; Chang, ShinYe; Parihar, Simran

Cc: Goldberger, David; Guinn, Patrick

Subject: Notification of Termination of An Investigator - Brexpiprazole Non-responsive

Dear All,

On behalf of my colleagues, I have attached for your reference, a copy of a notification letter to the FDA Office of Compliance regarding termination of an investigator (site), where several ongoing Brexpiprazole Non-responsive studies are conducted. Specifically, principal investigators, Bernadette B. D'Souza, M.D. and Otto Dueno, M.D., of Midwest Clinical Research Center, 1 Elizabeth Place, Suite G3, South Building, Dayton, OH 45417, USA, are being terminated from conducting the ongoing clinical trials for Otsuka and Lundbeck (Otsuka's partner for co-development of Non-responsive brexpiprazole). The studies have been submitted to the following INDs:

Non-responsive

Brexpiprazole (OPC-34712, Lu AF41156):

- (b) (4)
- IND MDD 103,958 (adjunctive treatment of patients with MDD)
- IND 101,871 (treatment of patients with Schizophrenia)

Please see the attached letter for a list of the ongoing studies. In addition, as noted therein, we plan to formally submit a similar notification to the appropriate existing applications.

Please let me know if you have any questions or comments.

Wishing you all a great weekend!

Best regards,
Megan

Director, Regulatory Affairs

Otsuka Pharmaceutical Development and Commercialization Inc.
508 Carnegie Center
Princeton, NJ USA 08540
Phone: 1-609-535-9660

(b) (6)

Fax: 1-609-535-9760

Email: megan.parsi@otsuka-us.com

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/s/

KOFI B ANSAH
01/13/2015



NDA 205422/Original-1
NDA 205422/Original-2

MID-CYCLE COMMUNICATION

Otsuka Pharmaceutical Company, Ltd.
Attention: Megan Parsi
Director, Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
508 Carnegie Center
Princeton, NJ 08540

Dear Ms. Parsi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg.

We also refer to the teleconference between representatives of your firm and the FDA on December 30, 2014. The purpose of the teleconference was to provide you 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 CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: December 30, 2014

Application Number: NDA 205422/Original-1 and NDA 205422/Original-2

Product Name: Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg

Indication: Adjunctive Treatment of Major Depressive Disorder & Treatment of schizophrenia

Applicant Name: Otsuka Pharmaceutical Company, Ltd.

Meeting Chair: Tiffany R. Farchione, M.D.

FDA ATTENDEES

Tiffany R. Farchione, M.D.	Deputy Director (acting), Division of Psychiatry Products (DPP)
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP
Violetta Klimek, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Olen Stephens, Ph.D.	Branch Chief,
Hao Zhu, Ph.D.	Clinical Pharmacology, Team Leader, OCP
Peiling Yang, Ph.D.	Biometrics Team Leader, DBI/OB
George Kordzakhia, Ph.D.	Biometrics Reviewer, DBI/OB
Xiang Ling, Ph.D.	Biometrics Reviewer, DBI/OB
Danny S. Gonzalez, Pharm.D., MS	Risk Management Analyst, Office of Surveillance and Epidemiology/ Division of Risk Management

APPLICANT ATTENDEES

Otsuka Pharmaceuticals Company, Ltd.:

George Chao, Ph.D.	Vice President, Biometrics
David Goldberger, R.Ph., RAC	Vice President, Global Regulatory Affairs
Timothy Goggin, Ph.D.	Vice President, Clinical Pharmacology
Mary Hobart, Ph.D.	Director, Clinical Management
June Li	Vice President, Biostatistics
Robert McQuade Ph.D.	Executive Vice President, Global Medical Affairs
John Ouyang	Director, Biostatistics
Megan Parsi	Director, Global Regulatory Affairs
Arash Raoufina, Ph.D.	Director, Clinical Pharmacology
Raymond Sanchez, M.D.	Senior Vice President, Global Clinical Development
Aleksandar Skuban M.D.	Director, Global Clinical Development

Mid-Cycle Communication

Haruhiko Sugino, Ph.D.
Henrietta Ukwu, M.D.
Peter Zhang

Director, Innovative Indications, Regulatory
Senior Vice President, Global Regulatory Affairs
Director, Biostatistics

H. Lundbeck A/S:

Iman Barilero, Ph.D.

Vice President, Regulatory Development Strategy
and Policy

Karim Benslimane

Regulatory Strategy Leader, Development Strategy
and Policy

Jacob Christophersen
Hans Eriksson, M.D.

Chief Project Director
Chief Medical Specialist, International Clinical
Research Psychiatry

Mette Krog Josiassen
Frank Larson

Senior Specialist, Biostatistics
Chief Specialist, Clinical & Quantitative
Pharmacology

Helle Birgitte Mengel
Allan Wehnert

Senior Vice President, Global Clinical Research
Group Senior VP R&D Project Strategy & Portfolio
Management

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

Clinical Pharmacology

- *Given our preliminary review of the dose/exposure-response relationships for both efficacy and safety, we think it may be beneficial for patients to receive adjusted doses under scenarios of significantly increased exposures (e.g., in specific patient populations and/or in patients receiving concomitant medications).*
- *With extensive hepatic metabolism and minimal urinary elimination, it is counter intuitive to notice that Brexpiprazole exposure in patients with severe renal dysfunction was*

Mid-Cycle Communication

significantly increased (i.e., 72% increase in mean AUC_{0-inf}) while its exposure was not affected by severe hepatic impairment. Please provide your thoughts for the observation.

- *As explained during the call, these two Clinical Pharmacology points are not significant/critical per se, but we do want to bring them to your attention.*

Clinical

- *With regard to the proposed indication of Adjunctive Treatment of Major Depressive Disorder, it is our view that you have submitted only one positive trial (331-10-228).*
- *For the schizophrenia indication, it appears you have one trial (331-10-231) in which both the 2mg and 4mg doses were statistically superior to placebo. However, in 331-10-230, only the 4mg dose was statistically superior.*

3.0 INFORMATION REQUESTS

There are no information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Safety review is ongoing -- We may have information requests in the coming months if concerns arise.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

1. We plan to issue any Discipline Review Letters by March 11, 2015
2. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and if necessary, any post-marketing commitment requests by March 23, 2015.
3. The Late-Cycle meeting is tentatively planned for **April 2, 2015** (from 1:00-2:30 pm EDT).
4. We plan to send the Agency Background Package for the Late-Cycle Meeting by March 23, 2015.
5. We plan to take an action by July 10, 2015 or the PDUFA goal date.

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/s/

MITCHELL V Mathis
01/01/2015



NDA 205422

**METHODS VALIDATION
MATERIALS RECEIVED**

Otsuka Pharmaceutical Company, Ltd
Attention: Yoshito Kihara
Medical Regulatory Affairs, CMC
224-18, Hiraishi Ebisuno, Kawauchi-cho
E-mail: Kihara.Yoshito@otsuka.jp

Dear Yoshito Kihara:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brexpiprazole tablets 0.25, 0.5, 1, 2, 3 and 4 mg and to our November 6, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 4, 2014, 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
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/15/2014

From: Ayalasomayajula, Vasantha
To: ["megan.parsi@otsuka-us.com"](mailto:megan.parsi@otsuka-us.com)
Cc: [Ayalasomayajula, Vasantha](#); [Makela, Cristina](#)
Subject: Correspondence on "Rexulti" Proprietary Name review request
Date: Tuesday, December 02, 2014 11:33:00 AM
Attachments: [NDA205422_Rexulti_Grantedletter.pdf](#)

Dear Megan,

As I mentioned to you earlier in our phone conversation please see attached an electronic copy of the Proprietary Name Granted letter that was sent via "mail" to the Otsuka Pharmaceuticals on 11/24/2014. Please let me know if you have any other questions as I am the project manager for this review.

Thanks a have a great day.

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

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/s/

VASANTHA S AYALASOMAYAJULA
12/07/2014

From: Ansah, Kofi
To: [Parsi, Megan \(Megan.Parsi@otsuka-us.com\)](mailto:Megan.Parsi@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com)
Subject: DMEPA Information Request - II -- NDA 205422/Brexipiprazole (OPC-34712)
Date: Friday, December 05, 2014 5:23:00 PM

Dear Megan,

Regarding your NDA currently under review, (b) (4)
(b) (4). To facilitate our review, DMEPA is requesting that you provide (b) (4)
Please respond to this request by COB,
Friday, December 12, 2014.

Additionally, given DMEPA's recent approval of your proposed Trade Name (REXULTI), we request that you integrate this TN into the most recent draft Label you submitted on 10/14/14 and resubmit. Please resubmit this revised draft Label as soon as possible (if you haven't already) but no later than Wednesday, December 10, 2014 – Thank you.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service
Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838
Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
12/06/2014

Executive CAC

Date of Meeting: December 2, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Karen Davis Bruno, Ph.D., OMPT, Alternate Member
Linda Fossom, Ph.D., DPP, Supervisor
Violetta Klimek, Ph.D., DPP, Presenting Reviewer

Author of Minutes: Violetta Klimek

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

NDA #: 205422

Drug Name: Brexpiprazole (OPC-331, OPC-34712)

Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Background: Brexpiprazole is a D₂ and 5HT_{1A} receptor partial agonist and 5HT_{2A} receptor antagonist, as well as partial agonist at D₃ receptor and α_{1/2} receptor antagonist. This NDA is for the use of brexpiprazole for the treatment of Schizophrenia and adjunctive treatment of Major Depressive Disorder.

Brexpiprazole was not genotoxic in a bacteria reverse mutation test with or without S9. A genotoxic signal was observed in the forward mutation test in mouse lymphoma cells after 3-hr exposure with S9 and in the chromosome aberration test in CHO cells after 3-hr treatment without S9. Positive responses observed in both tests were generally slight and occurred at the doses of moderate cytotoxicity, therefore these findings were considered to be inconclusive rather than positive. No genotoxicity was observed in two *in vivo* tests, the rat bone marrow micronucleus test and in the unscheduled DNA synthesis test.

Protocols for the 2-year carcinogenicity bioassays in mice and rats studies were presented to the Executive CAC on 10/20/09 (minutes dated 10/22/09). The doses of brexpiprazole used in both studies were those recommended by the Committee and a negative (water for injection) control, in addition to the vehicle (5% gum arabic) control, was included in both studies as recommended by the Committee.

The exposure to the test article during the study period was confirmed in TK groups of animals.

Mouse Carcinogenicity Study: Brexpiprazole was administered by oral gavage at doses of 0, 0, 0.75 (LD), 2 (MD), and 5 (HD) mg/kg/day to Crlj:CD1(ICR) mice (60/sex/group). These dose levels are 0.9- to 5.8-fold the oral MRHD (4 mg) on a body surface area basis. Dosing was planned for 104 weeks, but increasing mortality in both sexes, supported a decision (in agreement with the Division and Exec CAC) to terminate surviving males in week 91(negative control survivors decreased to n=20 [33% survival rate]) and surviving females in week 99 (LD group decreased to n= 15[25% survival rate]). The organs/tissues from all mice of all study groups were histologically examined.

In mammary glands of female mice, the incidences of animals with adenomas, adenocarcinomas, or adenosquamous carcinomas, combined, were increased in all dose groups without a dose-response relationship as shown in the following table excerpted from the FDA’s statistical review:

Sex	Organ Name	Tumor Name	Veh				P_Value			
			Cont	Low	Med	High	Dose Resp	VC vs. L	VC vs. M	VC vs. H
Female	Mammary gland	ADENOCARCINOMA	2	14	12	12	0.0568	<0.001*	0.0039*	0.0034*
		ADENOMA+ADENOCARCINOMA	3	14	12	13	0.0522	0.0023*	0.0104	0.0055*
		ADENOMA+ADENOCARCINOMA+CARCINOMA	3	16	23	16	0.0164	<0.001*	<0.001*	<0.001*
		CARCINOMA, ADENOSQUAMOUS	1	3	15	6	0.0673	0.2707	<0.001*	0.0500

Of note, the vehicle control was used by the FDA statistical reviewer for pairwise comparisons, however, the findings in the negative control group (4 adenocarcinomas and 1 adenosquamous carcinoma) did not affect the interpretation of data that mammary gland tumors observed in this study are test article-related.

Rat Carcinogenicity Study: Brexpiprazole was administered by oral gavage to Clr:CD(SD) SPF rats (60/sex/group) at 0, 0, 1, 3, 10 mg/kg (males) and 0, 0, 3, 10, 30 mg/kg (females) for 104 weeks. These doses are 2.3- to 68.6-fold the MRHD (4 mg) on a body surface area basis. The organs/tissues from all rats of all study groups were histologically examined.

No biologically relevant, drug-related increases in incidence of neoplasms at any dose level were observed in either male or female rats.

Executive CAC Recommendations and Conclusions

Mouse

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that the combined incidences of mammary gland neoplasms in females in all dose groups were drug related.

Rat

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DPP
/Linda Fossom, DPP
/Violetta Klimek, DPP
/Kofi Ansah, DPP
/Adele Seifried, OND IO

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/s/

ADELE S SEIFRIED
12/05/2014

ABIGAIL C JACOBS
12/05/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205422

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Commercialization Inc.
508 Carnegie Center
Princeton, NJ 08540

ATTENTION: David Goldberger, RPh, RAC
Vice-President, Global Regulatory Affairs, OPDC

Dear Mr. Goldberger:

Please refer to your New Drug Application (NDA) dated and received July 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brexpiprazole Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

We also refer to your correspondence, dated and received August 29, 2014, requesting review of your proposed proprietary name, Rexulti. We have completed our review of the proposed proprietary name, Rexulti, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your August 29, 2014, 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 Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact CDR Kofi Ansah, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4158.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/24/2014

From: [Ansah, Kofi](#)
To: Megan.Parsi@otsuka-us.com; David.Goldberger@otsuka.com
Cc: [Ansah, Kofi](#)
Subject: FDA Response -- RE: Status of FDA Review of iPSP and 233 Study Protocol -- IND 101,871 - Serial #421 - Brexpiprazole (OPC-34712)
Date: Monday, November 10, 2014 8:41:19 AM

Dear Ms. Parsi:

We acknowledge receipt of your 8/22/14 submission containing your proposed amendment to the Agreed-iPSP.

We have completed our review of the afore mentioned submission and we do not agree with your proposed amendment to the agreed iPSP. Based on data from currently approved products, it is reasonable to assume that safety and tolerability will vary by patient population. Thus, expanding the inclusion criteria to patients with a broad array of diagnoses is not acceptable.

Please submit your pediatric plan (essentially the Agreed-iPSP) to your NDA 205422, if you haven't already done so – It would be presented to the PeRC for discussion under PREA during the PMR/PMC negotiation phase of the NDA review.

Thanks,
Kofi.

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/s/

KOFI B ANSAH
11/13/2014



NDA 205422

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Otsuka Pharmaceutical Company, Ltd
Attention: Yoshito Kihara
Medical Regulatory Affairs, CMC
224-18, Hiraishi Ebisuno, Kawauchi-cho
E-mail: Kihara.Yoshito@otsuka.jp

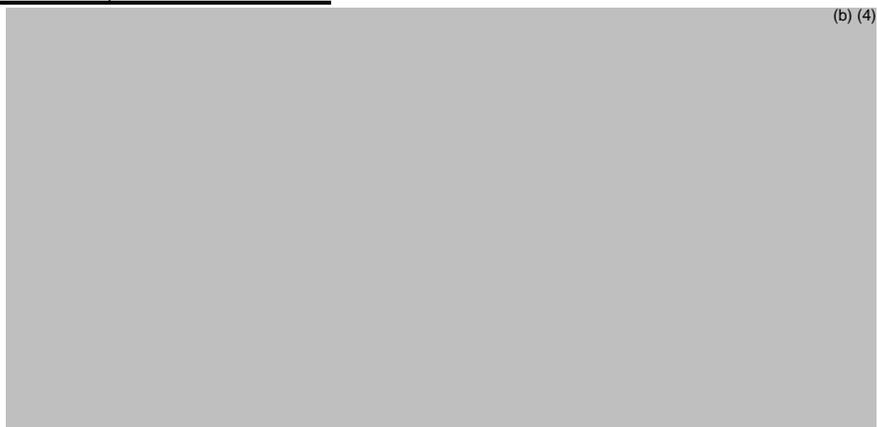
Dear Yoshito Kihara:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brexpiprazole tablets 0.25, 0.5, 1, 2, 3 and 4 mg.

We will be performing methods validation studies on Brexpiprazole tablets 0.25, 0.5, 1, 2, 3 and 4 mg, as described in NDA 205422.

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

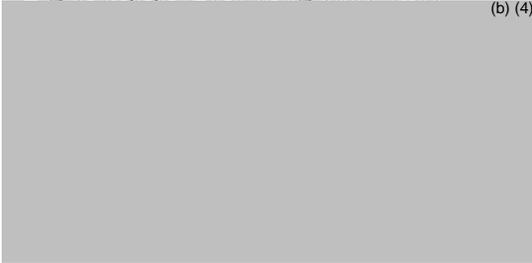
Method, current version



(b) (4)

Samples and Reference Standards

2 x 500 mg brexpiprazole reference standard
2 g brexpiprazole drug substance



100 tablets 0.25 mg/tablet brexpiprazole
100 tablets 1 mg/tablet brexpiprazole
100 tablets 4 mg/tablet brexpiprazole



Equipment

- 1 I (b) (4) C18 column 3 µm particle size 4.6 mm x 15 cm
- 1 pkg (b) (4) solid phase extraction columns
- 1 (b) (4) AQ column 3 µm particle size 4.6 mm x 15 cm
- 1 (b) (4) column 5 µm particle size 4.6 mm x 7.5 cm

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: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this e-mail. 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, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/06/2014

From: Ansah, Kofi
To: [Parsi, Megan \(Megan.Parsi@otsuka-us.com\)](mailto:Parsi.Megan@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:Goldberger.David@otsuka-us.com)
Subject: Clinical Pharmacology Information Request (revised) -- NDA 205422/Brexipiprazole (OPC-34712)
Date: Monday, October 27, 2014 12:09:00 PM
Importance: High

Dear Megan,

Regarding your NDA currently under review, we have the following information request from the Office of Clinical Pharmacology.

Please provide subject level genotype (e.g. A/A, A/G, G/G or 0, 1, 2) and haplotype (e.g. *1/*5) data for all subjects with CYP2D6 metabolizer status in your datasets (e.g. EM, PM, etc.), including appropriate identifiers to link to the source clinical trial datasets. Genotypes should be provided for all genotyped CYP2D6 variants. Additionally, please provide your classification system for determining metabolizer status based on genotyped SNPs and/or haplotypes and include a summary of CYP2D6 genotyping methods in addition to any relevant analytical validation or quality control summaries.

Please provide the requested information, as soon as possible, within 2 weeks of receiving this request (i.e., no later than 11/10/14).

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
10/27/2014

From: Ansah, Kofi
To: [Parsi, Megan \(Megan.Parsi@otsuka-us.com\)](mailto:Megan.Parsi@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com)
Subject: OSI Information Request -- NDA 205422/Brexpiprazole/Original-1 & Original-2
Date: Tuesday, October 07, 2014 3:31:00 PM
Importance: High

Dear Megan,

Regarding your NDA 205422 currently under review, we have the following information request from the Office of Scientific Investigations (OSI)/FDA

(OSI)/FDA requests that the following items be provided to facilitate development of sponsor/monitor/CRO inspection assignments. Please include the following information in a tabular format for Study 331-10-227, Study 331-10-228, Study 331-10-230, and Study 331-10-231:

- a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide copies of information previously provided.
- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

Please provide the requested information as soon as possible.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
10/07/2014



NDA 205422/Original-1
NDA 205422/Original-2

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Otsuka Pharmaceutical Company, Ltd.
Attention: Megan Parsi
Director, Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
508 Carnegie Center
Princeton, NJ 08540

Dear Ms. Parsi:

Please refer to your New Drug Application (NDA) dated and received July 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg.

We also refer to your amendment dated August 5, 2014.

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 July 11, 2015.

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 March 23, 2015. In addition, the planned date for our internal mid-cycle review meeting is December 9, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Biopharmaceutics

1. *Provide the PK parameter analysis datasets as SAS transport files for bioequivalence studies 209 and 243, preferably in stacked column format.*

Microbiology

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
 (b) (4)
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

HIGHLIGHTS (HL)

1. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. The HL is more than 1/2 page -- Request a waiver if you haven't already requested one.
2. Change the section heading; "Warning/Precautions" to Warnings and Precautions.

In addition, the following labeling issues were identified:

1. There seems to be 2 separate BW under the Full Prescribing Information (FPI).
2. The BW heading in the FPI does not match the BW in HL and they should be centered.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 14, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms to format items in regulations and guidances.

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

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

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

NDA 205422/Original-1 (Adjunctive treatment of major depressive disorder)

We reference the waiver granted on March 7, 2014, for the pediatric study requirement for this application.

NDA 205422/Original-2 (Treatment of schizophrenia)

We reference the partial waiver granted on April 24, 2014, for the pediatric study requirement for this application for pediatric patients 0 to 12 years old. We also reference the partial deferral granted on April 24, 2014, for the pediatric study requirement for this application for pediatric patients 13-17 years old.

Additionally, we note that you did not submit the certification(s) required by FDCA Section 505B(a)(3) and (4). We request that this be submitted.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

MITCHELL V Mathis
09/23/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205422/Original-1

NDA 205422/Original-2

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Communications, Inc.
508 Carnegie Center
Princeton, New Jersey 08540

ATTENTION: David Goldberger, RPh, RAC
Vice-President, Global Regulatory Affairs, OPDC

Dear Mr. Goldberger:

Please refer to your New Drug Application (NDA) dated and received July 11, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brexpiprazole Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

We also refer to your correspondence, dated and received on August 29, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). Therefore, (b) (4) is considered withdrawn as of August 29, 2014.

Finally, we refer to your correspondence, dated and received August 29, 2014, requesting review of your proposed proprietary name, Rexulti. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Therefore, the user fee goal date is November 27, 2014.

NDA 205422/Original-1

NDA 205422/Original-2

Page 2

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CAPT Louis Flowers, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3158. For any other information regarding this application, contact CDR Kofi Ansah, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4158.

Sincerely,

{See appended electronic signature page}

Captain Louis Flowers, PharmD, MS, CPH
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LOUIS R FLOWERS
09/04/2014

From: Ansah, Kofi
To: [Parsi, Megan \(Megan.Parsi@otsuka-us.com\)](mailto:Megan.Parsi@otsuka-us.com)
Cc: [Goldberger, David \(David.Goldberger@otsuka-us.com\)](mailto:David.Goldberger@otsuka-us.com)
Subject: Biometrics/Stats Information Request -- NDA 205422/Brexiprazole (OPC-34712)/ Adjunctive MDD Studies
Date: Thursday, August 28, 2014 5:42:00 PM
Importance: High

Dear Megan,

Regarding your NDA currently under review, we have the following statistical request with reference to the 2 adjunctive MDD studies submitted to NDA 205422/O-1. Please provide all necessary macro programs and format library files so that the SAS programs are executable to derive the analysis datasets from raw datasets and to duplicate the efficacy analysis results.

Please provide the requested information as soon as possible.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
08/28/2014



NDA 205422/Original-1
NDA 205422/Original-2

NDA ACKNOWLEDGMENT

Otsuka Pharmaceutical Company, Ltd.
Attention: Megan Parsi
Director, Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
1 University Square Drive, Suite 500
Princeton, New Jersey 08540

Dear Ms. Parsi:

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: OPC-34712 (brexpiprazole) Tablet 0.25, 0.5, 1, 2, 3, and 4 mg

Date of Application: July 11, 2014

Date of Receipt: July 11, 2014

Our Reference Number: NDA 205422

NDA 205422 provides for the use of OPC-34712 (brexpiprazole) Tablet for the following indications which, for administrative purposes, we have designated as follows:

- NDA 205422/Original-1 - Adjunctive treatment of Major Depressive Disorder
- NDA 205422/Original-2 - Treatment of Schizophrenia

All future submissions to your NDA should specify the NDA number and all Original numbers to which each submission pertains.

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 September 9, 2014, 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 and all pertinent Original numbers 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, 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 please email: Kofi.Ansah@fda.hhs.gov or call me at (301)796-4158.

Sincerely,

{See appended electronic signature page}

Kofi Ansah, Pharm.D., MBA, CDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

KOFI B ANSAH
08/20/2014

From: Ansah, Kofi
To: "[Parsi, Megan](#)"
Subject: Pharmtox Info Request (Datasets for Carcinogenicity Studies) -- NDA 205422 (brexpiprazole, aka OPC-34712)
Date: Tuesday, August 05, 2014 5:31:00 PM

Dear Megan,

Regarding your NDA currently under review, we found two carcinogenicity study reports in rat and mouse, respectively, but did not find any data set of either species. We need those datasets to continue our review -- Please help us locate the datasets or submit them to your NDA as soon as possible.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
08/05/2014



IND 101871
IND 103958

MEETING MINUTES

Otsuka Pharmaceutical Company, Ltd
C/O Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, RPh, RAC
VP, Global Regulatory Affairs
2440 Research Boulevard
Rockville, Maryland 20850

Dear Mr. Goldberger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OPC-34712 (brexpiprazole) oral tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 12, 2014. The purpose of the meeting was to discuss the planned NDA for brexpiprazole for use as adjunctive treatment in patients with major depressive disorder and for the treatment of patients with schizophrenia.

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 Shin-Ye Sandy Chang, Regulatory Project Manager at shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D
CAPT, USPHS
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

Meeting Date and Time: May 12, 2014 10:00 – 11:30AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 101871 & 103958
Product Name: OPC-34712 (brexpiprazole)
Indication: MDD, Schizophrenia
Sponsor/Applicant Name: Otsuka Pharmaceutical Development & Commercialization, Inc.

Meeting Chair: Mitchell Mathis, M.D.
Meeting Recorder: Shin-Ye Sandy Chang, Pharm.D.

FDA ATTENDEES

Mitchell Mathis, M.D., Division Director
Robert Levin, M.D., Medical Team Leader
Mark Ritter, M.D., Medical Reviewer
Linda Fossom, Ph.D., Pharmacology/Toxicology Supervisor
Violetta Klimek, Ph.D., Pharmacology/Toxicology Reviewer
Hao Zhu, Ph.D., Office of Clinical Pharmacology Reviewer
Huixia Zhang, Ph.D., Office of Clinical Pharmacology Reviewer
Xiaofeng Wang, Ph.D., Office of Clinical Pharmacology Reviewer
Peiling Yang, Ph.D., Biometrics Team Leader
Yeh-Fong Chen, Ph.D., Biometrics Reviewer
Shin-Ye Sandy Chang, Pharm.D., Regulatory Project manager
Loretta Holmes, BSN, PharmD, Safety Evaluator, Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA)

EASTERN RESEARCH GROUP ATTENDEES

Christopher A. Sese

SPONSOR ATTENDEES

Otsuka

Robert Berman, M.D., Global Clinical Development, CNS
George Chao, Ph.D., Vice President, Biometrics

David Goldberger, RPh, RAC, Vice President, Global Regulatory Affairs
Mary Hobart, Ph.D., Director, Clinical Management
Robert McQuade, Ph.D., Executive Vice President, Global Medical Affairs and Alliances
Megan Parsi, Director, Regulatory Affairs
Arash Raoufinia, Pharm.D., Director, Clinical Pharmacology
Aleksandar Skuban, M.D., Director, Global Clinical Development CNS
Takeshi Watanabe, Ph.D., Vice President, Global Pharmaceutical Business
Peter Zhang, Ph.D., Director, Biostatistics
Haruhiko Sugino, Ph.D., Director, Global Pharmaceutical Business

Lundbeck

Iman Barilero, Vice President, Regulatory Development Strategy and Policy
Karim Benslimane, Regulatory Strategy Leader, Regulatory Development Strategy and Policy
Raimund Buller, Director, International Clinical Research Psychiatry and Addictive Disorders
Hans Eriksson, Chief Medical Specialist, International Clinical Research Psychiatry
Anders Gersel Pedersen, Executive Vice President, Research and Development

1.0 BACKGROUND

Brexpiprazole (OPC-34712), an organic compound that was synthesized by Otsuka Pharmaceutical Co. Ltd., was selected for its partial agonistic activity at dopamine D2 receptor and antagonistic activity at serotonin 5-HT_{2A} receptors. OPC 34712 also has high binding affinities and acts as a partial agonist at dopamine D3 and serotonin 5-HT_{1A} receptors. Compared to aripiprazole, Brexpiprazole demonstrates slightly higher D2 affinity, lower intrinsic activity at D2 receptors, and higher affinity at the 5-HT_{2A} receptor.

Otsuka is planning to submit a New Drug Application for the dual indications of adjunctive treatment in patients with major depressive disorder (MDD) and for the treatment of patients with schizophrenia. The Division held an End-of-Phase 2 meeting with the sponsor on March 29, 2011 to discuss the clinical, non-clinical and pharmacokinetics program. On April 2, 2013, the Office of New Drug Quality Assessment I met with the sponsor to discuss the overall Chemistry, Manufacturing, and Controls (CMC) development program. A Pre-NDA CMC discussion was held on September 25, 2013 to discuss Otsuka's submission plans for brexpiprazole immediate release (IR) (b) (4) oral tablets. On April 27, 2013, the Division provided written response feedback on the proposed NDA for brexpiprazole.

The objectives of the meeting are as follows:

For the proposed indication of adjunctive therapy to antidepressants for the treatment of MDD in adult patients who had an inadequate response to antidepressant treatment:

- To obtain Division feedback on the proposed efficacy analyses of data from the trials conducted in subjects with MDD.
- To obtain Division agreement that the clinical data to be presented in the NDA are adequate to support filing of the brexpiprazole NDA.
- To obtain the Division's view on the patient description in the label

For the proposed indication of treatment of patients with schizophrenia:

- To obtain Division agreement that the clinical data to be presented in the NDA are adequate to support filing of the brexpiprazole NDA.
- To obtain agreement to items from previous regulatory interactions.

Regulatory History

Otsuka submitted IND 101,871 on 21 March 2008 for the treatment of schizophrenia. On 15 December 2008, the Otsuka submitted IND 103,958 for the adjunctive treatment of major depressive disorder. The following is a brief synopsis of the many correspondences between the Agency and sponsor regarding these two IND applications:

A. 29 March 2011: End of Phase 2 Meeting:

- For the Adjunctive MDD indication under IND 103,958:
 - Results from study 211, a completed 14 weeks (8 weeks single blind, 6 weeks of controlled adjunctive treatment), flexible dose (0.15mg-1.5mg \pm 0.5mg) demonstrated efficacy only for the 1.5mg flexible dosing arm, with the division noting that study would likely be considered a negative study for NDA purposes.
 - An additional flexible dose study with similar trial design as study 211 (study 222) using doses of 1 to 3 mg was ongoing, in addition to a 52 week open label study (study 212). However results from study 222 and 211 would not support an NDA application by themselves due to the flexible design of each trial.
 - A proposed flexible dose trial, trial 227, appeared to be acceptable to support efficacy, but only with an adequate, fixed, dose phase 3 study to also support efficacy.
 - The Agency recommended one fixed dose study with three fixed doses, however the sponsor proposed two separate studies (one with a 2mg fixed dose and another with 1 and 3mg fixed doses) in order to reduce a potential risk of a negative study with a study with increased treatment arms.
 - The Sheehan Disability Scale was agreed to be an acceptable key secondary endpoint
 - Based on results from study 211, a minimally effective dose was not yet demonstrated.
- For the Schizophrenia indication under IND 101,871:

- Results from a 6 week inpatient, flexible dose study (dose ranges of 0.25-6mg/day), with aripiprazole for assay sensitivity (study 203) failed to achieve efficacy on the primary endpoint, noting a large placebo effect. Retrospective analysis suggested that the study only had 30% power at the 5mg dosing arm to detect an effect, using an alpha of 0.05 and assuming no dropouts.
- Proposed protocols for two six-week, phase 3, fixed dose studies (studies 230 and 231) appeared to be adequate to support an NDA application, noting that the two studies; one using three fixed dosing arms of 1, 2 and 4mg/day and a second using only 2 and 4mg/day randomizing 180 patients to each treatment arm, would have 85% power to detect a 7 point difference in the PANSS total score assuming a p of <0.25 for multiple comparisons.
- The Positive and Negative Syndrome Scale (PANSS) total was score was agreed to be an acceptable primary endpoint for each schizophrenia trial.
- Either the CGI-S or Personal and Social Performance Scale (PSP) were determined to be acceptable key secondary endpoint.

B. 08 April 2011: New DRAFT protocols submitted to Agency under IND 101,871 and allowed to safely proceed:

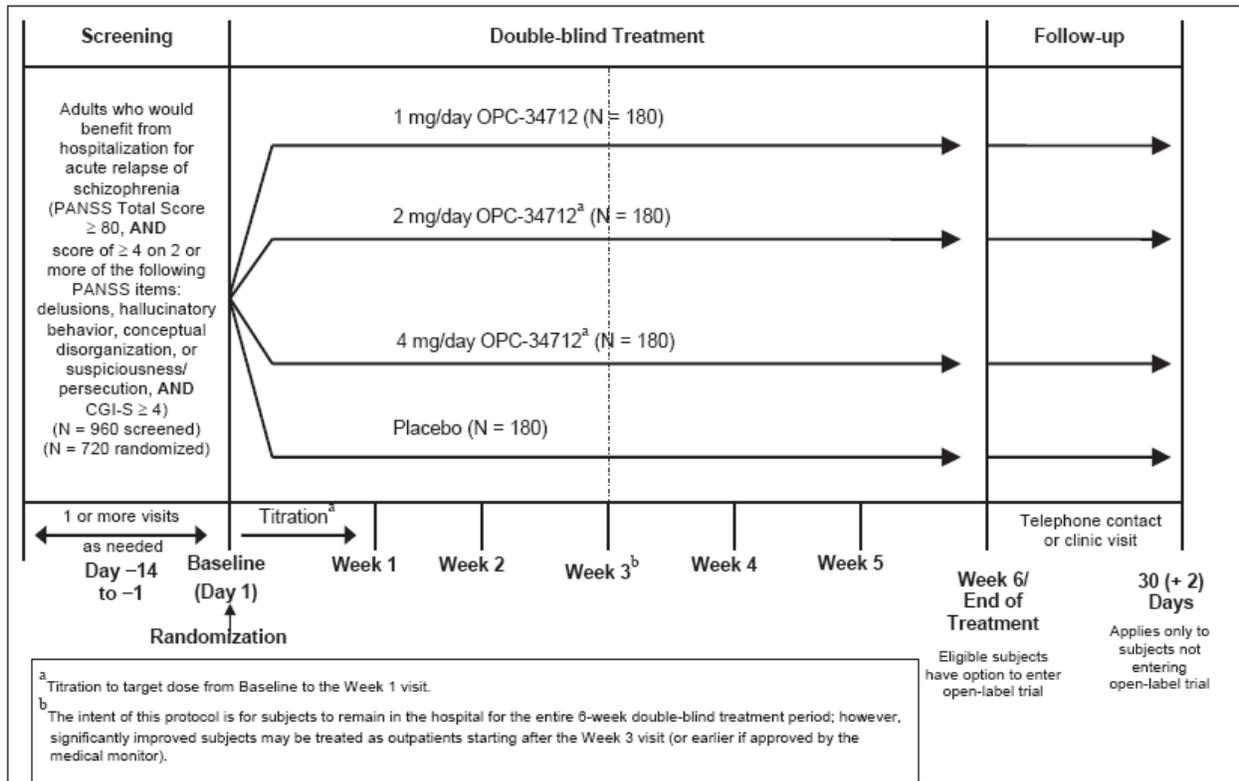
1. Study 230- Fixed dose phase three study using three fixed doses of BXP (1, 2 and 4mg/day) “A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of three fixed doses of OPC 34712 in the treatment of adults with acute schizophrenia.”

The primary objective of this study was to compare the efficacy of each of three fixed doses of OPC-34712 (1, 2 and 4mg/day) with placebo in the treatment of acute schizophrenia in adults.”

This was an inpatient, multicenter, randomized, double-blind, placebo of 720 patients with an acute relapse of schizophrenia (randomized 1:1:1:1) that was conducted in three phases: screening, 6-week double blind treatment phase and follow-up phase. The screening phase (up to 14 days) serves to:

- Allow of washout of prohibited medications
- Ensure subjects meet inclusion/exclusion criteria
- Establish a pretreatment baseline

A diagram of the study design is presented below:



The primary efficacy outcome is change from baseline to week 6/Early termination in the PANSS total score.

For the double-blind portion of the study, subjects who meet DSM-IV diagnosis of schizophrenia (confirmed with the MINI for psychotic disorders) and a positive and negative syndrome scale of the PANSS total score >80 , AND a score of at least 4 or greater of the following PANSS items:

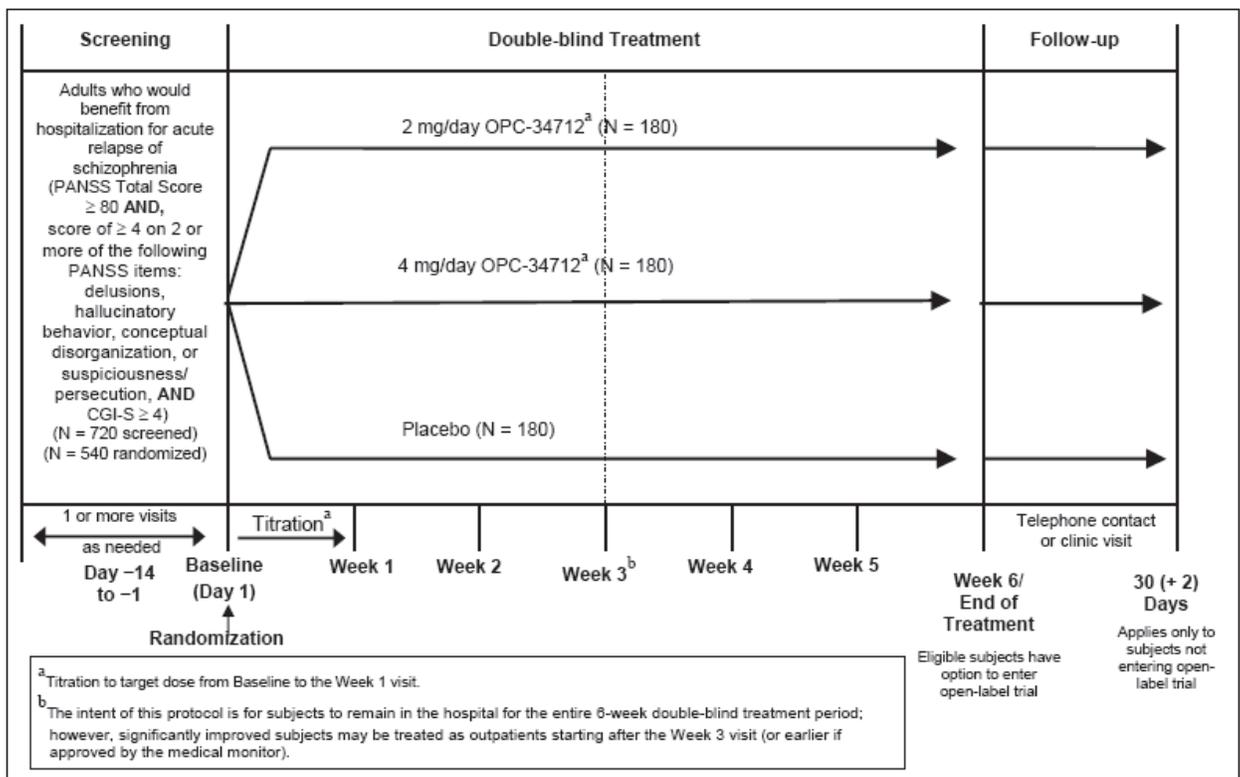
- Delusions
- Hallucinatory behavior
- Conceptual disorganization or
- Suspiciousness/persecution

AND a score of at least 4 or greater on the CGI-S scale were considered for enrollment.

Patients who have been hospitalized for 13 days or less or those outpatients who sign informed consent and then are immediately hospitalized are eligible to participate. All subjects are to remain in the hospital for the entire 6 weeks. However those patients who show significant improvement in symptoms after week 3 (based on investigator judgment) may be discharged to outpatient treatment provided all of the following conditions are met:

- A CGI-S at least 3 or less
 - No evidence of danger to self and others
 - Appropriate outpatient follow-up, including continued contact with study site staff to ensure continued safety of the subject
 - A reliable informant agrees to confirm adherence without outpatient study treatment.
2. Study 231- Fixed dose phase three study using two fixed doses of BXP (2 and 4mg/day) :
 “A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of two fixed doses of OPC 34712 in the treatment of adults with acute schizophrenia.” .

Of note, patient inclusion/exclusion and primary objective/endpoints were identical to study 230. For the fixed dose study 231, 540 patients aged 18-65 years old with an acute exacerbation of schizophrenia were randomized 1:1:1 to 2mg, 4mg of OPC-34712 respectively or placebo based on the following trial design:



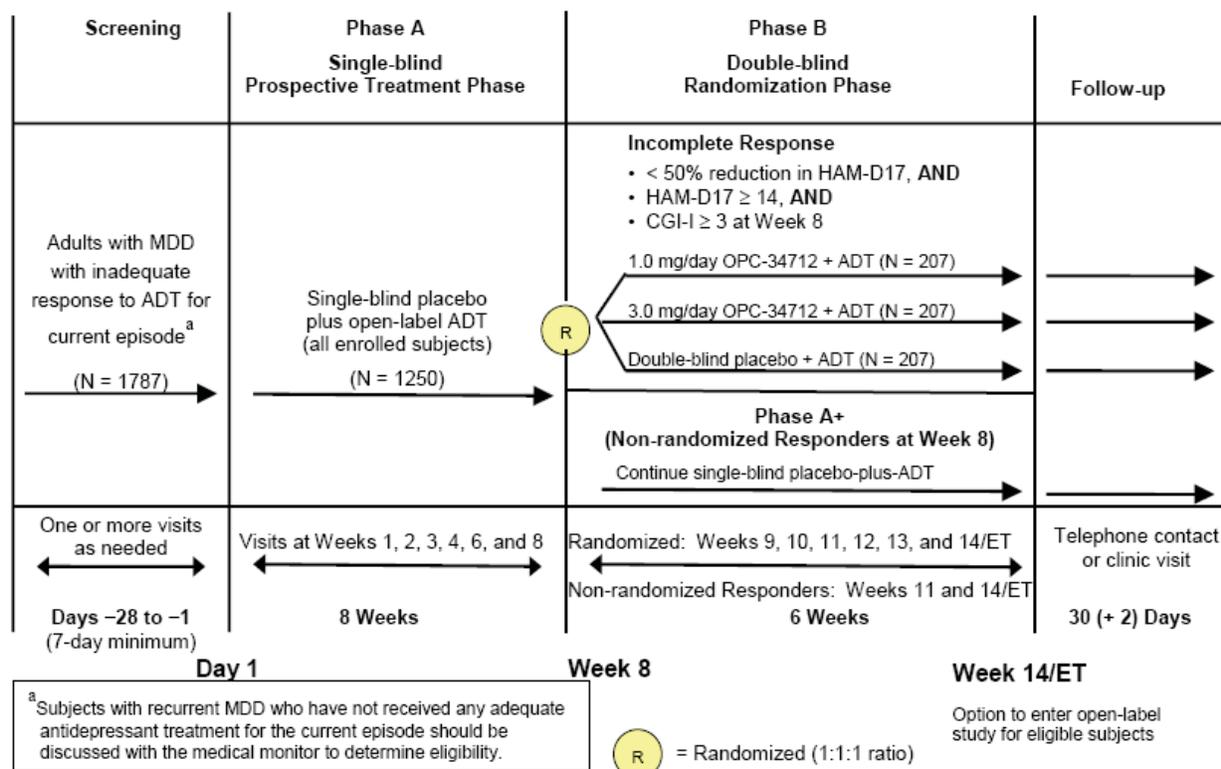
C. 08 April 2011: New protocols submitted to the Agency under IND 103,958:

1. Study 227- “A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of two fixed doses [1 and 3 mg/day] of OPC 34712 as adjunctive therapy in the treatment of adults with major depressive disorder.”

The primary objective of this study, as delineated by the sponsor was:

“To compare the efficacy of two fixed doses of OPC-34712 (1 and 3 mg/day) to placebo as adjunctive treatment to an assigned open-label ADT in patients who demonstrate an incomplete response after 8 weeks of prospective treatment with the same assigned open-label ADT.”

This was a multicenter, randomized, double-blind, placebo-controlled adjunctive therapy study in 621 patients with MDD (from an initial 1250 MDD patients initially entering single blind treatment in phase A) from 50 sites worldwide that will be conducted in four phases. A diagram of the study design is presented below with a more in-depth review of each phase presented after the diagram.



Screening Phase

As stated by the sponsor in the protocol: “Patients will enter a 7-28 day pre-treatment screening period to assess study eligibility criteria and to washout prohibited concomitant pharmacotherapy.”

Phase A-Single-blind Prospective Treatment phase

If patients meet the eligibility criteria for entry into the study at the end of screening, patients will then be enrolled into an eight week prospective treatment phase whereby all patients will receive:

- Investigator-determined, open label, marketed antidepressant therapy (ADT).

PLUS

- Single-blinded placebo concomitantly with the ADT selected from above as indicated in the dosing charts above.

The choice of ADT to be initiated in phase A made by the investigator was based on the following criteria:

- Patient will not receive ADT which has previously been reported with inadequate response or intolerability, unless clinically warranted and with consultation with medical monitor
- Patient will not be assigned to current ADT treatment regardless of different formulations that may exist
- Patients on citalopram will not be switched to escitalopram.
- No more than 4 out of 6 subjects should be assigned to any one ADT without permission of the medical monitor

Patients will be seen on-site at weeks 1, 2, 3, 4, 6 and 8 when an interim assessment of treatment response will take place on week 8 to identify which patients are identified as treatment responders or non-treatment responders.

A treatment responder is defined by the sponsor at the end of week 8 of phase A as those patients who:

- Had a $\geq 50\%$ reduction in the HAM-D17 total score at week 8 compared to baseline OR
- Had a CGI-I score < 3 at week 8.

Patient who meet the above criteria will NOT be randomized in double-blind fashion to OPC-34712 or placebo in phase B, but will attend visits at weeks 11 and 14 during the extension of treatment with placebo plus ADT. Dose adjustments to the ADT can occur between weeks 9 and 14. However the investigator choice of ADT cannot be changed until after week 14 (the end of the double blind period for phase B)

Phase B-Double-blind Randomization phase

Those patients that had an incomplete response due ADT plus single blind placebo at the end of week 8 of phase A, which is defined as:

- <50% reduction in the HAM-D17 total score at week 8 compared to baseline AND
- HAM-D17 score ≥ 14 AND
- CGI-I score ≥ 3 at week 8

will then enter a six-week double-blind randomization phase.

These patients will be randomized (1:1:1) in double-blind fashion to one of the following daily treatment regimens below:

1. Placebo + continued ADT treatment that was optimized under phase A or
2. OPC-34712 1mg + continued ADT treatment that was optimized under phase A or
3. OPC-34712 3mg + continued ADT treatment that was optimized under phase A

Dosing scheme for the OPC-34712 will be titrated in double-blind fashion according to the treatment arm assigned as follows:

Treatment Arm	Trial Visit					
	Week 8 ^a	Week 9 ^a	Week 10 ^a	Week 11 ^a	Week 12 ^a	Week 13 ^a
1.0 mg/day OPC-34712	0.5 mg/day	1.0 mg/day	1.0 mg/day	1.0 mg/day	1.0 mg/day	1.0 mg/day
3.0 mg/day OPC-34712	0.5 mg/day	1.0 mg/day	3.0 mg/day	3.0 mg/day	3.0 mg/day	3.0 mg/day
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

^aSubjects who experience dose-related tolerability issues will be withdrawn from the trial.

Patients who are unable to tolerate the assigned dose of OPC-34712 were withdrawn from the trial.

Patients will then return for onsite visits with staff every week (i.e. weeks 9, 10, 11, 12, 13 and 14).

Patients will be eligible to enter Phase A of this study provided that:

- They are aged 18-65, able to provide written consent and understand the study purpose, risks/benefits and compliance with the study procedures
- All subject have a current diagnosis of a major depressive episode (as defined by DSM-IV TR criteria and confirmed by the MINI) of at least 8 weeks in length that fulfill the following criteria:

- Have a reported history for the current depressive episode of inadequate response (defined as <50% reduction of depressive symptoms as measures by the ATRQ) to at least 1, but no more than three adequate antidepressant treatments (i.e. six weeks (three if combined treatment) in duration at the minimum dose specified in the ATRQ)
 - Must have had at least one trial with an antidepressant for at least 6 weeks at an adequate dose (as defined by the ATRQ) with the current episode (*see last bullet for exception*).
 - A chemically different ADT must be selected for phase A for all patients. Citalopram to escitalopram switches are not allowed.
 - Patients who experienced a partial response to any ADT (>50% symptom reduction on the ATRQ) during the current episode, the patient must have had an inadequate response to a subsequent ADT prior to study entry.
 - Patients who have not received adequate antidepressant treatment for their MDD and who still meet DSM-IV criteria for MDD may or may not be appropriate for inclusion into the trial—discussion with medical monitor is required.
- All subjects have a HAM-D17 total score of ≥ 18 at baseline
 - All subjects agree to discontinue all prohibited psychotropic medications at the time of informed consent

After completion of phase A, patients will be eligible to enter Phase B of this study provided that:

- HAM-D17 total scores at week 8 are ≥ 14 and
- HAM-D17 total scores at week 8 are less than 50% reduction from baseline AND

CGI-I score at week 8 > 3 .

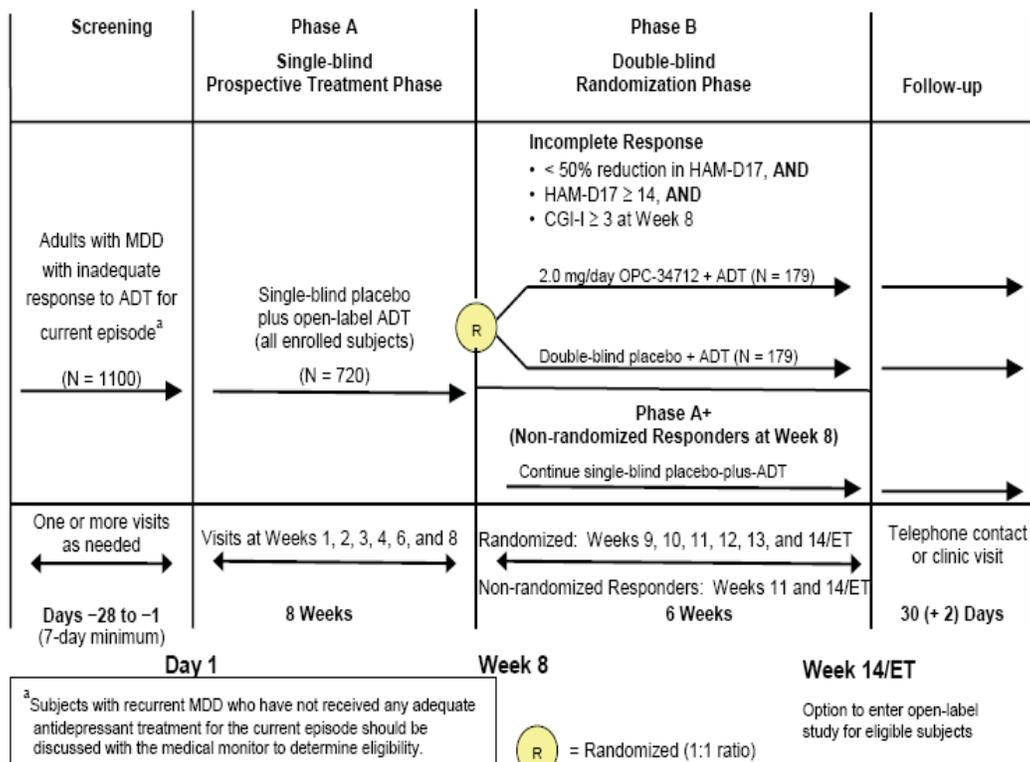
2. Study 228-“A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of the safety and efficacy of a fixed dose [2mg/day] of OPC 34712 as adjunctive therapy in the treatment of adults with major depressive disorder.”

As in Study 227 described above, Study 228 will be an inpatient, multicenter, randomized, double-blind, placebo of 358 with MDD (from an initial 720 MDD patients initially entering single blind treatment in phase A) from 50 sites worldwide that will be conducted in four phases. The only difference in study design between 227 and 228 is that study 228 is a two-arm fixed-

dose adjunctive treatment study (2mg OPC-34712), vs. the three-arm fixed adjunctive treatment study described above.

The primary and secondary objective and endpoints for study 228 are identical to study 227 above, with the exception of comparing efficacy of only the 2mg treatment arm vs. placebo as compared to the two dosing arms of study 227.

A diagram of the study design for study 228 is presented below:



Patients assigned to OPC 34712 will be dose titrated during week 1, achieving the final dose by week 2 as shown below:

Treatment Arm	Trial Visit					
	Week 8 ^a	Week 9 ^a	Week 10 ^a	Week 11 ^a	Week 12 ^a	Week 13 ^a
2.0 mg/day OPC-34712	0.5 mg/day	1.0 mg/day	2.0 mg/day	2.0 mg/day	2.0 mg/day	2.0 mg/day
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

^aSubjects who experience dose-related tolerability issues will be withdrawn from the trial.

Inclusion and exclusion criteria are identical to the criteria listed for study 227.

Efficacy and safety assessments, approaches to hypothesis testing and adverse event evaluations are identical, with the exception of having only one arm vs. two in study 227.

- D. 13 June 2011: The sponsor submitted ORIGINAL protocols for studies 230 and 231 under IND 101,871 after receiving comments from the Agency based on the draft 3 arm study designs. The sponsor instead proposed a four arm study with this submission for study 231 (0.25mg, 2mg, 4mg, and placebo) with a 1:2:2:2 randomization.
- E. 15 August 2011: Sponsor responds to statistical comments proposed by Agency to all four protocols.
- F. 02 April 2012: Protocol change #3 for IND 103,958- Sponsor submits a protocol change (PROTOCOL AMENDMENT 3) based on an analysis of blinded interim data from trials 227 and 228. Entry criteria for randomization into phase B double-blinded phase was changed such that patients who responded to antidepressant treatment early in phase A but were later found to not meet criteria for response at week 8 were NOT randomized into phase B. These patients were considered anti-depressant responders (even though they were not responding at week 8 and previously could be randomized to phase b prior to this protocol amendment. In addition, the primary statistical analysis was changed from an LOCF approach to an MMRM approach.
- G. 30 April 2013: Sponsor submits pre-NDA related questions to Agency for comment for IND 101,871 and IND 103,958. Agency responds on 13 Jun 2013.
- H. 08 Jul 2013: Agency responds to sponsor with regards to revised statistical analysis plan for study 228 under IND 103.958.
- I. 23 Aug 2013: Sponsor requested a type C meeting to discuss pre-NDA submission issues for both adjunctive MDD and schizophrenia clinical development programs. As data to support the schizophrenia clinical development program was not available, this meeting request was denied by the Agency.
- J. 11 Apr 2014: Sponsor requests a pre-NDA meeting for both Adjunctive MDD and schizophrenia programs as all clinical data is now available. Meeting is granted.

II. Results

A. IND 101,871 in Schizophrenia

Results from studies 230 and 231 demonstrated that 4mg/day of brexpiprazole treatment was statistically superior to treatment with placebo when mean change from baseline scores on the PANSS were compared between the two groups (primary endpoint). Although the 4mg dosing arm from both trials was statistically superior to placebo in studies 230 and 231, the 2mg dosing group was only statistically superior in one of two trials (trial 231). Doses lower than 2mg were

not statistically superior to placebo. Pooled data from both studies 231 and 230 did, however, demonstrate that both 2mg/day and 4mg/day of brexpiprazole treatment was statistically superior to placebo.

The results for the key secondary endpoint of mean change from baseline on the CGI-S scale mirrored the results obtained for the primary endpoint for both trials and for the 2mg and 4mg dosing arms, with only the 4mg dose demonstrating statistically superior results in both trials and only one of two trials demonstrating statistically superior results on mean change from baseline on CGI-S scores for the 2mg dosing arm. Pooled data from both studies 231 and 230 did, however, demonstrate that both the 2mg and 4mg/day brexpiprazole doses were statistically superior to placebo. Doses below 2mg were not shown to be statistically superior to placebo.

Treatment Group	N	Baseline Mean (SD)	LS Mean (SE)	LSM Difference	95% CI	P-Value
331-10-231						
Brex 0.25mg	87	93.61 (11.53)	-14.90 (2.23)	-2.89	(-8.27,2.49)	0.2910
Brex 2mg	180	95.85 (13.75)	-20.73 (1.55)	-8.72	(-13.1, -4.37)	<0.0001
Brex 4mg	178	94.70 (12.06)	-19.65 (1.54)	-7.64	(-12.0,-3.30)	0.0006
Ave Effect (2mg&4mg)				-8.18	(-12.0,-4.40)	<0.0001
Placebo	178	95.59 (11.46)	-12.01 (1.60)			
331-10-230						
Brex 1mg	117	93.17 (12.74)	-16.90 (1.86)	-3.37	(-8.06, 1.32)	0.1588
Brex 2mg	179	96.30 (12.91)	-16.61 (1.49)	-3.08	(-7.23, 1.07)	0.1448
Brex 4mg	181	94.99 (12.38)	-20.00 (1.48)	-6.47	(-10.6, -2.35)	0.0022

Average Effect (2mg&4mg)				-4.78	(-8.37,-1.18)	0.0093
Placebo	180	94.63 (12.84)	-13.53 (1.52)			
Pooled (230+231)						
Brex 2mg	359	96.08 (13.32)	-18.79 (1.07)	-5.46	(-8.46,-2.47)	0.0004
Brex 4mg	359	94.85 (12.20)	-20.01 (1.07)	-6.69	(-9.67, -3.70)	<0.0001
Placebo	358	95.16 (12.17)	-13.33 (1.10)			
203						
Brex 0.25mg	41	97.34 (8.46)	-12.41 (3.41)	4.88	(-3.09,12.85)	0.2288
Brex 1mg±0.5mg	88	96.24 (9.95)	-21.98 (2.19)	-4.69	(-10.8,1.39)	0.1299
Brex 2.5±0.5mg	90	95.89 (10.50)	-19.00 (2.25)	-1.72	(-7.89,4.46)	0.5841
Brex 5±1.0mg	92	97.80 (11.04)	-21.73 (2.19)	-4.45	(-10.5,1.63)	0.1508
Arip 15±5mg	50	97.12 (100.68)	-20.97 (2.93)	-3.68	(-10.9, 3.51)	0.3142
Placebo	93	97.51 (9.92)	-17.28 (2.19)			

B. IND 103,958 Adjunctive treatment of Major Depressive Disorder (MDD)

For the four (4) double-blind, placebo-controlled trials with brexpiprazole for the adjunctive treatment of depression, doses of 0.15mg to 3mg daily were adjunctively given for 6 weeks. Results from these trials demonstrated that only the 2mg and 3mg daily doses were statistically

superior to placebo treatment based on the mean change in MADRS total score from baseline (end of week 8 Phase A single-blind treatment with open label antidepressant) to week 14 of double blind treatment. Of note, randomization changed that occurred to these trials as a result of the adoption of protocol amendment 3 did not significantly affect the overall efficacy results.

Per Amendment 3 Criteria

Treatment Group	N	Baseline End of Phase A Mean (SD)	LS Mean Change End of Phase B (SE)	LSM Difference	95% CI	P-Value
331-10-228						
2mg Brex + ADT	175	26.87 (5.71)	-8.36 (0.64)	-3.21	(-4.87,-1.54)	0.0002
Placebo	178	27.32 (5.64)	-5.15 (0.63)			
331-10-227						
Brex 1mg +ADT	211	26.85 (5.61)	-7.64 (0.52)	-1.30	(-2.73,0.13)	0.0737
Brex 3mg +ADT	213	26.48 (5.29)	-8.29 (0.53)	-1.95	(-3.39,-0.51)	0.0079
Placebo +ADT	203	26.46 (5.20)	-6.33 (0.53)			
331-08-211						
Brex 0.15 +ADT	45	26.91 (6.14)	-5.17 (1.28)	-0.17	(-3.20,2.87)	0.9148
Brex 0.5 ±0.25mg +ADT	94	27.95 (5.89)	-5.20 (0.89)	-0.20	(-2.63,2.24)	0.8747
Brex 1.5 ±0.5mg	90	26.67 (5.26)	-8.28 (0.90)	-3.28	(-5.74,-0.82)	0.0092

+ADT						
Placebo +ADT	89	27.70 (6.76)	-5.00 (0.91)			
331-09-222						
Brex 1-3mg +ADT	158	26.62 (5.65)	-7.86 (0.66)	-1.45	(-3.24,0.33)	0.1099
Placebo +ADT	147	26.72 (5.85)	-6.41 (0.67)			

Original Protocol excluding amendment 3

Treatment Group	N	Baseline End of Phase A Mean (SD)	LS Mean Change End of Phase B (SE)	LSM Difference	95% CI	P-Value
331-10-228						
2mg Brex + ADT	187	26.61 (5.79)	-8.27 (0.61)	-3.12	(-4.70,- 1.54)	0.0001
Placebo	191	27.14 (5.60)	-5.15 (0.60)			
331-10-227						
Brex 1mg +ADT	225	26.69 (5.61)	-7.65 (0.50)	-1.19	(-2.58,0.20)	0.0925
Brex 3mg +ADT	226	26.31 (5.24)	-7.98 (0.51)	-1.52	(-2.92,- 0.13)	0.0327
Placebo +ADT	218	26.23 (5.27)	-6.45 (0.51)			
331-08-211						
Brex 0.15 +ADT	62	25.77 (6.24)	-6.91 (1.08)	-0.57	(-3.13,2.00)	0.6648

Brex 0.5 ±0.25mg +ADT	119	26.88 (5.97)	-6.65 (0.77)	-0.31	(-2.34,1.78)	0.7735
Brex 1.5 ±0.5mg +ADT	118	25.25 (5.88)	-8.69 (0.78)	-2.34	(-4.43,- 0.25)	0.0285
Placebo +ADT	126	26.21 (6.95)	-6.35 (0.75)			
331-09-222						
Brex 1-3mg +ADT	184	25.88 (5.82)	-7.99 (0.62)	-1.23	(-2.88,0.42)	0.1449
Placebo +ADT	181	26.00 (5.86)	-6.76 (0.61)			

Unlike results obtained from the primary endpoint analysis, the key secondary endpoint of mean change in the Sheehan Disability Scale (SDS) between baseline (end of phase A week 8) and end of phase B (week 14), brexpiprazole treatment demonstrated statistically superior effects in the dose ranges of 1 to 3mg/day compared to placebo. Randomization changes that occurred to these trials as a result of the adoption of protocol amendment 3 did not significantly affect the overall efficacy results.

Per Amendment 3 Criteria

Treatment Group	N	Baseline End of Phase A Mean (SD)	LS Mean Change End of Phase B (SE)	LSM Difference	95% CI	P-Value
331-10-228						
2mg Brex + ADT	167	6.03 (1.94)	-1.35 (0.17)	-0.46	(-0.88,- 0.03)	0.0349
Placebo +ADT	170	6.34 (2.15)	-0.89 (0.17)			
331-10-227						

Brex 1mg +ADT	204	5.95 (1.97)	-1.27 (0.15)	-0.49	(-0.89,- 0.09)	0.0158
Brex 3mg +ADT	201	5.81 (2.25)	-1.26 (0.15)	-0.48	(-0.88,- 0.08)	0.0191
Placebo +ADT	194	5.62 (1.90)	-0.78 (0.15)			
331-08-211						
Brex 0.15 +ADT	45	5.56 (2.53)	-0.65 (0.34)	-0.26	(-1.06,0.54)	0.5191
Brex 0.5 ±0.25mg +ADT	89	5.96 (2.37)	-0.67 (0.25)	-0.29	(-0.93,0.36)	0.3865
Brex 1.5 ±0.5mg +ADT	86	5.63 (2.37)	-1.17 (0.25)	-0.78	(-1.44,- 0.13)	0.0193
Placebo +ADT	85	5.74 (2.15)	-0.38 (0.26)			
331-09-222						
Brex 1-3mg +ADT	149	5.70 (2.13)	-0.90 (0.20)	-0.34	(-0.84,0.17)	0.1909
Placebo +ADT	139	5.70 (2.16)	-0.57 (0.20)			

Original Protocol excluding amendment 3

Treatment Group	N	Baseline End of Phase A Mean (SD)	LS Mean Change End of Phase B (SE)	LSM Difference	95% CI	P-Value
331-10-228						
2mg Brex +	179	5.97 (1.95)	-1.35 (0.17)	-0.45	(-0.86,-	0.0372

ADT					0.03)	
Placebo	181	6.32 (2.16)	-0.91 (0.17)			
331-10-227						
Brex 1mg +ADT	218	5.92 (1.95)	-1.33 (0.27)	-0.22	(-0.87,- 0.12)	0.0091
Brex 3mg +ADT	212	5.76 (2.26)	-1.21 (0.13)	-0.37	(-0.73,- 0.00)	0.0474
Placebo +ADT	208	5.61 (1.93)	-0.84 (0.13)			
331-08-211						
Brex 0.15 +ADT	61	5.43 (2.62)	-0.84 (0.27)	-0.22	(-0.86,0.42)	0.4954
Brex 0.5 ±0.25mg +ADT	111	5.48 (2.48)	-0.80 (0.21)	-0.19	(-0.73,0.35)	0.4902
Brex 1.5 ±0.5mg +ADT	113	5.24 (2.46)	-1.27 (0.20)	-0.66	(-1.20,- 0.12)	0.0161
Placebo +ADT	120	5.36 (2.33)	-0.61 (0.20)			
331-09-222						
Brex 1-3mg +ADT	174	5.44 (2.25)	-0.91 (0.19)	-0.22	(-0.69,0.26)	0.3778
Placebo +ADT	172	5.54 (2.21)	-0.69 (0.19)			

2.0 DISCUSSION

2.1. Efficacy - Major Depressive Disorder

Question 1: The MDD program evaluated brexpiprazole as adjunctive therapy to antidepressants for the treatment of MDD in adult patients who had a suboptimal response to at least 2 regimens of antidepressant treatment within the current depressive episode. The NDA submission for the MDD indication will include data from 4 short-term, adequate, well-controlled efficacy trials and 2 open-label, long-term extension trials (Table 3.2.2.1-1).

a) Does the Division agree with the approach used for the analysis of data supporting evidence of efficacy from the proposed clinical trials planned for inclusion in the NDA for brexpiprazole as adjunctive therapy for the treatment of patients with suboptimal response to antidepressants in MDD?

b) Does the Division agree that data from the proposed clinical trials are sufficient to support filing of the planned NDA for brexpiprazole as an adjunctive therapy for the treatment of patients with inadequate response to antidepressants in MDD?

FDA Response to Question 1: *On face, only one study demonstrated the efficacy of brexpiprazole as adjunctive therapy in MDD. Generally, one must have at least two positive studies for an indication. You may present a case for filing the application.*

Discussion: *Otsuka presented slides outlining the designs and efficacy results from the pivotal adjunctive MDD trials. The Division agreed that the data from the clinical trials support filing an NDA for the indication of adjunctive therapy in MDD.*

Question 2: The sponsor would like the Division's guidance on the acceptability to describe the brexpiprazole-studied population as (b) (4) in the clinical trials section of the prescribing information.

FDA Response to Question 2: *The study subjects were not a (b) (4) population. They had an inadequate, partial response to a single course of antidepressant treatment.*

Sponsor Response: All patients have demonstrated failure to respond to at least 2 (and up to 4) ADT treatments during the current episode

- Retrospective failure to respond to 1-3 prior antidepressant treatment courses within the current episode
 - <50% improvement, at an adequate dose and duration of at least 6 weeks, assessed with ATRQ questionnaire
- Prospective failure to respond during 8-week of antidepressant treatment
 - <50% improvement in depressive symptoms at every single visit during the prospective phase (Amendment 3 criteria)

The sponsor would like to understand the view of the Agency on other potential analyses that could be performed to further characterize the study population in terms of level of inadequate response in the clinical trials section of the PI

- Segmenting patients by level of prior response or non-response?

Discussion: *The Division reiterated that labeling would not include the term [REDACTED] (b) (4) [REDACTED]. The Division agreed that the labeling language in the Clinical Studies section should include an accurate description of the study population. We encouraged Otsuka to submit analyses to support a specific, accurate description of the study population.*

2.2. Efficacy – Schizophrenia

Question 3: The submission of the proposed application for the use of brexpiprazole for the treatment of patients with schizophrenia will be based on efficacy data from 2 double-blind, placebo-controlled, fixed-dose phase 3 trials of brexpiprazole for the treatment of adult subjects with acute exacerbation of schizophrenia.

Does the Division agree that data from the proposed clinical trials are sufficient to support filing of the planned NDA for brexpiprazole for the proposed indication of treatment of schizophrenia?

FDA Response to Question 3: *Although this will be a matter of review upon submission of the NDA, the summary of efficacy results appears to support the filing of the NDA for schizophrenia.*

Discussion: *No further discussion.*

2.3. Safety

Question 4: In the written response to request for advice from the FDA (dated 13 Jun 2013), the Division stated a preference to have an ISS for each indication included in the NDA. Otsuka agrees with the FDA's preferred approach and will provide two separate ISS. In the format of separate ISS for each indication, data from the clinical pharmacology and "All Brexpiprazole" treatment groups will be duplicated in each ISS. Below in 'Rationale' the presentation format and content for MDD and Schizophrenia indications is provided.

Could the Division confirm that Otsuka will provide separate ISSs for each indication as per the Agency's prior recommendation?

FDA Response to Question 4: *Yes, we request that you provide a separate ISS for each indication.*

Discussion: *No further discussion.*

Question 5: The safety cutoff date planned for both ISS is 31 Jan 2014 and the planned NDA submission is in June 2014.

Does the Division concur with the proposed data cutoff of 31 Jan 2014 for the ISS?

FDA Response to Question 5: *Yes, we concur.*

Discussion: *No further discussion.*

Question 6: For the 120-day safety update, the sponsor proposes to submit updated safety information from completed and ongoing trials using a data cut off of 31 May 2014. The update will include cumulative summaries of exposure, newly reported deaths, SAEs, and discontinuations due to AEs for both the completed and ongoing studies. As stated, the NDA is targeted for submission in June 2014.

Does the Division concur with the following?

a) The data cutoff date of 31 May 2014?

FDA Response to Question 6a: *Yes.*

Discussion: *No further discussion.*

b) The proposed cumulative summaries and data to be included in the 120-day safety update?

FDA Response to Question 6b: *Yes.*

Discussion: *No further discussion.*

2.4. Clinical Pharmacology

Question 7: Regarding the population PK/Pharmacodynamic analysis, in previous discussions with the Agency (Type C meeting written response dated 27 Sep 2013) it was agreed that, for the schizophrenia program, the pivotal phase 3 Trial 331-10-231 alone would provide sufficient efficacy and safety data to evaluate the exposure response presented in the initial NDA submission. The sponsor proposed to re-run the model with data from the second pivotal phase 3 Trial, 331-10-230, as a sensitivity analysis and provide updates to the exposure response in the 120-day safety update. The sponsor now proposes to include the data from both Trial 331-10-231 and Trial 331-10-230 in the population PK analysis and in the evaluation of exposure response that will be presented in the initial NDA submission; as such, no additional analysis will be conducted and no further updates will be provided in the 120-day safety update.

Does the Division concur that no update to the Population PK will be required in the 120-day update?

FDA Response to Question 7: *Yes, we agree.*

Discussion: *No further discussion.*

2.5. Regulatory and Administrative

Question 8: Based on the safety profile observed to date in the clinical development program for brexpiprazole, the sponsor proposes that a Risk Evaluation and Mitigation Strategy (REMS) is not required and does not plan to include a REMS in the proposed NDA.

Does the Division agree that a REMS is not required, based on the information provided?

FDA Response to Question 8: *We would make this decision during the course of the NDA review. Are there any specific safety concerns that we should discuss regarding the potential need for a REMS?*

Discussion: *The Division reiterated that we do not anticipate the need for a REMS at this time. This will be a review issue. Otsuka stated that they do not consider the cases of seizure to be related to treatment with brexpiprazole.*

Question 9: The sponsor requested evaluation of a proprietary name for brexpiprazole under the IND (IND 103,958 Serial No. 0274 and IND 101,871 Serial No. 0335). If the FDA finds the name currently under evaluation to be unacceptable, the sponsor would like the opportunity to submit an alternate proprietary name for evaluation to the NDA during the NDA review cycle.

Does the Division agree with the submission of the complete request for evaluation of the proprietary name after the initial NDA filing?

FDA Response to Question 9: *Yes.*

Discussion: *No further discussion.*

Additional Biometrics Comments: In your future NDA submission, please include the following items for efficacy studies:

- (a) all raw as well as derived variables in .xpt format;
- (b) the SAS programs that produced all efficacy results;

- (c) the SAS programs by which the derived variables were produced from the raw variables;
- (d) a list of IND numbers with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings;
- (e) minutes of DSMB meetings, if applicable.

Discussion: *No further discussion.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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.

A preliminary discussion on the need for a REMS was held and it was concluded that at this time, we have insufficient information to conclude whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks. The Agency noted that a final determination regarding the need for a REMS will be made during the review of the application.

- Major components of the application are expected to be submitted with the original [http://s7d2.scene7.com/is/image/Coach/51636_m1?\\$pd_full\\$](http://s7d2.scene7.com/is/image/Coach/51636_m1?pd_full) application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on September 25, 2013. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

4.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request 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.				

7.0 ATTACHMENTS AND HANDOUTS

Brexiprazole Type B Pre-NDA Meeting

May 12, 2014 (10:00 – 11:30AM)

Silver Spring, MD

Application Numbers: 101871 & 103958

Indication: MDD, Schizophrenia

Sponsor/Applicant Name: Otsuka Pharmaceutical Development & Commercialization, Inc.

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

/s/

MITCHELL V Mathis
05/27/2014



INDs 101,871 and 103,958

MEETING PRELIMINARY COMMENTS

Otsuka Pharmaceutical Company, Ltd.
c/o Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Yung-Ao Hsieh, Ph.D., Director, Regulatory Affairs CMC
2440 Research Boulevard
Rockville, Maryland 20850

Dear Dr. Hsieh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for for OPC-34712 Brexpiprazole.

We also refer to your July 12, 2013, correspondence, received July 12, 2013, requesting a meeting to discuss Otsuka's submission plans for brexpiprazole immediate release (IR) (b) (4) oral tablets.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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.
Acting Division Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA – CMC

Meeting Date and Time: September 25, 2013
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: INDs 101,871 and 103,958
Product Name: Brexpiprazole
Indication: Schizophrenia (IND 101,871) and Major Depressive Disorder (IND 103,958)
Sponsor/Applicant Name: Otsuka Pharmaceutical Company, Ltd.

FDA ATTENDEES (tentative)

Office of New Drug Quality Assessment

Ramesh Sood, Ph.D., Branch Chief
Chhagan Tele, Ph.D., CMC Lead
Shastri Bhamidipati, Ph.D., Review Chemist
Okpo Eradiri, Ph.D., Biopharmaceutics Reviewer
Teshara G. Bouie, Regulatory Health Project Manager

Office of Compliance

Juandria Williams, Ph.D., Chemist

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 25, 2013 between Otsuka Pharmaceutical Company, Ltd. and the Office of New Drug Quality Assessment. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional

questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

IND 101, 871 was submitted March 21, 2008, for the treatment of schizophrenia. IND 103,958 was submitted on December 15, 2008, for the treatment of Major Depressive Disorder (MDD). An End-of-Phase 2 CMC meeting was held April 2, 2013. On July 12, 2013, the sponsor requested a Pre-NDA CMC meeting to discuss their submission plans for brexpiprazole immediate release (IR) (b) (4) oral tablets. Background packages were received on August 22, 2013.

2. QUESTIONS

DRUG SUBSTANCE

Question 1 - Stability Update of Brexpiprazole Drug Substance During NDA Review Period

The NDA will include at least 24-month long-term and 6-month accelerated results from three lots of pilot-scale drug substance manufactured at Second Tokushima Factory. Also, according to the agency's recommendation in the EOP2 meeting preliminary response, three months of accelerated and long-term stability data from three pilot-scale batches made at Saga Factory will also be provided in the initial NDA. Otsuka plans to update the drug substance stability data with results at the 36-month time point during the first half of PDUFA V NDA review clock to extend the re-test period.

Does the agency agree with the update plan?

FDA Response: We recommend that you submit any additional stability data within 30 days from original NDA submission as per PDUFA V requirements.

DRUG PRODUCT

Question 2 - Specification of Brexpiprazole (b) (4) Tablets

(b) (4)
(b) (4) Otsuka
is proposing the specification for brexpiprazole (b) (4) tablets as presented in the briefing package.

Does the agency agree with the proposed provisional specification for brexpiprazole (b) (4) tablets?

FDA Response: Based on the information provided in the briefing package, we agree that the proposed testing parameters for (b) (4) brexpiprazole tablets are appropriate. However, the acceptance criteria are subject to review of the data submitted in the NDA. Please be advised that the limits for impurities/ degradants in the drug product specification should be same for all strengths based on maximum daily dose.

Question 3 - Stability Update of Brexpiprazole Tablets During NDA Review Period

The NDA will include at least 18-month long term and 6-month accelerated stability data from three primary stability batches of each of brexpiprazole 0.25- through 4-mg tablets. The NDA will also include at least 12-month long-term and 6-month accelerated data for (b) (4) tablets. Otsuka plans to submit stability update (24-month data for 0.25 mg through 4 mg tablets, (b) (4) (b) (4)) during the first half of the PDUFA V NDA review clock to extend the tablet shelf life.

Does the agency agree with the update plan?

FDA Response: We recommend that you submit any additional stability data within 30 days from original NDA submission as per PDUFA V requirements.

Question 4 - Batch Size

Brexpiprazole tablets are manufactured by (b) (4). To provide a flexible manufacturing to meet market demands, one batch (b) (4) may compose one lot of tablets, or two batches (b) (4) may be one lot. The manufacturing process and equipment used are the same for both approaches.

Does the agency agree with this flexible batch size plan?

FDA Response: We recommend that you incorporate the control strategy in to batch records for (b) (4) in-process quality attributes.

Question 5 - Process Validation Scheme for Brexpiprazole Tablets

(b) (4)
All strengths of proposed commercial tablets are of the same shape (round), and same (b) (4) total weight of 93 mg. The strengths are differentiated by (b) (4) color and debossing. Additionally, the manufacturing process and the equipment used is the same for all strengths of tablets. Otsuka is proposing (b) (4)

(b) (4) for the manufacturing process validation of brexpiprazole tablets of all strengths.

Does the agency agree with the process validation plan?

FDA response: At this time we cannot provide meaningful feedback as we would need to understand, for example, how your process controls address variability. FDA is concerned with the lower strengths as variability may have a larger impact on quality attributes as compared to higher strengths. We suspect that you will have to power your process qualification study(ies) such that variability in quality attributes are adequately detected for all strengths. This may impact your sample size, testing frequency and location. Your process qualification study(ies) must result in a demonstration of process control across all strengths, and your decisions should be statistically justified.

Please note the FDA does not approve process validation approaches or protocols; these will be evaluated during an on-site inspection of the relevant facilities. It is, however, the company's responsibility to conduct all studies necessary to ensure that the commercial manufacturing process is capable of consistently delivering quality product. FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not stipulate how the study is to be performed. Prior to marketed product distribution it is necessary for firms to demonstrate that the intended manufacturing process will reliably reproduce the intended product for each individual site. Process performance qualification studies are evaluated during on-site inspections.

Please find more information in the Guidance for Industry, Process Validation: General Principles and Practices (January 2011):

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

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/s/

RAMESH K SOOD
09/23/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205422/Original-1
NDA 205422/Original-2

LATE-CYCLE MEETING MINUTES

Otsuka Pharmaceutical Company, Ltd.
Attention: Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
C/o Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Guinn:

Please refer to your New Drug Application (NDA) dated July 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on April 2, 2015.

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, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Late Cycle Meeting Minutes (with Sponsor's Slides attached)



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: April 2, 2015
Meeting Location: FDA White Oak Campus, Bldg. 22, Room #1419
10903 New Hampshire Ave, Silver Spring MD 20993

Application Number: NDA 205422/Original-1 and NDA 205422/Original-2
Product Name: Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg
Applicant Name: Otsuka Pharmaceutical Company, Ltd.

Meeting Chair: Mitchell Mathis, M.D., CAPT USPHS

FDA ATTENDEES

Ellis Unger, M.D.	Director, Office of Drug Evaluation-I (ODE-I)
Robert Temple, M.D.	Deputy Director, ODE-I
Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Tiffany R. Farchione, M.D.	Deputy Director, DPP
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Violetta Klimek, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology, Team Leader, OCP
Peiling Yang, Ph.D.	Biometrics Team Leader, DBI/OB
George Kordzakhia, Ph.D.	Biometrics Reviewer, DBI/OB
Xiang Ling, Ph.D.	Biometrics Reviewer, DBI/OB
Danny S. Gonzalez, Pharm.D., MS	Risk Management Analyst, Office of Surveillance and Epidemiology/Division of Risk Management

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou	Eastern Research Group
Christopher Sese	Eastern Research Group

APPLICANT ATTENDEES

Otsuka Pharmaceuticals Company, Ltd.:

David Goldberger, R.Ph., RAC	Vice President, Global Regulatory Affairs
Nick (Nobuyuki) Kurahashi	Global Project Leader, Vice President, CNS Business
Robert McQuade Ph.D.	Executive Vice President, Global Medical Affairs
Raymond Sanchez, M.D.	Senior Vice President, Global Clinical Development

Henrietta Ukwu, M.D.	Senior Vice President, Global Regulatory Affairs
Mary Hobart, Ph.D.	Senior Director, Global Clinical Development
Robert Berman	Consultant, Global Clinical Development
Aleksandar Skuban M.D.	Director, Global Clinical Development
Timothy Goggin, Ph.D.	Vice President, Clinical Pharmacology & Pharmacometrics
Patrick Guinn	Director, Global Regulatory Affairs
June Li	Vice President, Biostatistics

H. Lundbeck A/S

Attendance in Person:

Helle Birgitte Mengel	Senior Vice President, Global Clinical Research
Karim Benslimane	Regulatory Strategy Leader, Development Strategy and Policy

Attendance by Phone:

Iman Barilero, Ph.D.	Vice President, Regulatory Development Strategy and Policy
Allan Wehnert	Group Senior VP R&D Project Strategy & Portfolio Management
Raimund Buller	Vice President, International Clinical Research Psychiatry
Jacob Strøyer Christophersen	Chief Project Director
Hans Eriksson, M.D.	Chief Medical Specialist, International Clinical Research Psychiatry
Mette Krog Josiassen	Senior Specialist, Biostatistics
Frank Larson	Chief Specialist, Clinical & Quantitative Pharmacology

1.0 BACKGROUND

NDA 205422/Original-1 and NDA 205422/Original-2 was submitted on July 11, 2014 for Brexpiprazole Tablet 0.25, 0.5, 1, 2, 3, and 4 mg.

Proposed indication(s): Adjunctive Treatment of Major Depressive Disorder & Treatment of Schizophrenia

PDUFA Goal Date: July 11, 2015

FDA issued a Background Package in preparation for this meeting on March 23, 2015 (with an addendum issued on March 29, 2015).

2.0 DISCUSSION

1. Introductory Comments

After brief welcoming comments, introductions were exchanged, and then the ground rules and objectives of the meeting were laid out.

2. Substantive Review Issues – As noted in the mid-cycle communication, it is our view that you have only submitted one positive study for the adjunctive treatment of MDD.

Discussion: *The bulk of discussion was centered on this issue. The Sponsor presented the attached slides, and outlined the case for approval while acknowledging failure on the primary outcome. The Sponsor also acknowledged that, despite informing FDA contemporaneously of the change in inclusion criteria with Amendment 3, no request was made to modify the primary analysis in the statistical analysis plan.*

Dr. Unger, the signatory authority, was present at the meeting.

3. Major Labeling Issues

Discussion: *The sponsor acknowledged receipt of the Agency's initial round of labeling comments sent to them on March 27, 2015, and noted that they will provide their response in a separate communication.*

4. Review Plans -- We plan to complete our review and take action by July 10, 2015 or the PDUFA goal date.

Discussion: *No further discussion.*

5. Wrap-up and Action Items – *The Division acknowledged the sponsor's presentation (copy attached) and noted that we would take the information the sponsor provided into consideration as we make our decision.*

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.

Attachment: Sponsor's Slide Presentation

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/s/

MITCHELL V Mathis
05/01/2015