

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207318Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207318

SUPPL #

HFD # 130

Trade Name Nuplazid

Generic Name pimavanserin

Applicant Name ACADIA Pharmaceuticals, Inc.

Approval Date, If Known April 29, 2016

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.

N/A

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:

N/A

c) Did the applicant request exclusivity?

YES NO

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

5 years

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?

N/A

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2

YES

NO

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

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

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

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

Investigation #1

IND #

YES

!
!

! NO

! Explain:

Investigation #2

IND #

YES

!
!

! NO

! Explain:

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

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

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

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

YES NO

If yes, explain:

=====

Name of person completing form: Brendan Muoio, PharmD, RAC
Title: Regulatory Project Manager, Division of Psychiatry Products
Date: 4/29/2016

Name of Office/Division Director signing form: Mitchell V. Mathis, MD
Title: Director, Division of Psychiatry Products

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

APPEARS THIS WAY ON ORIGINAL

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

/s/

BRENDAN MUOIO
05/02/2016

MITCHELL V Mathis
05/02/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207318 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: Nuplazid Established/Proper Name: pimavanserin Dosage Form: Immediate release, film-coated oral tablet		Applicant: ACADIA Pharmaceuticals Inc. Agent for Applicant (if applicable): Blake Burrell, MS, RAC
RPM: Brendan Muoio, PharmD, RAC		Division: Division of Psychiatry Products (DPP)
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><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) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> 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 <u>5/1/2016</u> 		<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 <u>N/A</u>		<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): Type 1
 (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 checked="" type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

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 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• 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)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ 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 (approvals only)	<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 (including approval letter with final labeling)	Action(s) and date(s): Approval, 4/29/2016
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<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 (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Proprietary Name Granted: 11/9/2015 Proprietary Name Review: 11/5/2015
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (indicate date(s)) Review(s) (indicate date(s)) 	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 3/18/2016 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 4/20/2016 CSS: <input type="checkbox"/> None 2/22/2016 Product Quality: <input type="checkbox"/> None 2/19/2016 Other: <input type="checkbox"/> None OPDP REMS Consult Review: 1/29/2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	10/8/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<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>12/2/2015</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	Granted: 8/13/2014
<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>	8/8/2014
❖ 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 OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	
❖ 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 checked="" 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 7/2/2014
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 9/29/2006
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 12/14/2015
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 3/15/2016
<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) 	3/29/2016
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/29/2016
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/29/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None See Division Director Summary Review
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 4 PMCs
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)		4/13/2016
• 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>)		4/13/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		<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 10/8/2015
❖ Risk Management		
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)		N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)		N/A
• 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 4/19/2016
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		<input type="checkbox"/> None requested 3/9/2016
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 type="checkbox"/> None
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 2/22/2016
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 2/8/2016, 4/27/2016
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		<input checked="" type="checkbox"/> None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

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 4/27/2016
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 2/22/2016, 4/13/2016
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/12/2016, 3/25/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/25/2016
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 12/10/2015
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 1/13/2016 Included in P/T review, page163-167
❖ 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 ⁶	
• 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 checked="" 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 2/19/2016, 4/14/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ 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>)	2/19/2016
<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

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • 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>)
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	<input checked="" 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 • 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 checked="" 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/

BRENDAN MUOIO
05/03/2016



NDA 207318

DEFICIENCIES PRECLUDE DISCUSSION

ACADIA Pharmaceuticals Inc.
Attention: Blake Burrell
Senior Director, Regulatory Affairs
3611 Valley Centre Drive, suite 300
San Diego, CA 92130

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) received September 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated oral tablets.

We also refer to our October 30, 2015, letter in which we notified you of our target date of February 19, 2016 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2013 Through 2017."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, contact me at (240) 402-4518 or brendan.muioio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Brendan Muoio, PharmD, RAC
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

BRENDAN MUOIO
02/19/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 4, 2016

Application Number: NDA 207318

Product Name: Nuplazid (pimavanserin)

Applicant Name: ACADIA Pharmaceuticals Inc.

Subject: Presentation of ACADIA's analysis of mortality in pimavanserin long term studies

FDA Participants

Mitch Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Lucas Kempf, MD	Clinical Team Leader, DPP
Paul Andreason, MD	Clinical Reviewer, DPP
Eiji Ishida, PhD	Biometrics reviewer, Office of Biostatistics
Brendan Muoio, PharmD, RAC	Regulatory Project Manager

Applicant Participants

Serge Stankovic, MD, MSPH	Executive Vice President, Research & Development
J. Randall Owen, MD	Senior Vice President, Clinical Development and Chief Medical Officer
George Demos, MD	Executive Director, Drug Safety & Pharmacovigilance
Mark Knowles, PhD	Executive Director, Biostatistics & SAS Programming
Blake Burrell, MS, RAC	Senior Director, Regulatory Affairs
Michael Monahan, MBA, RAC	Director, Regulatory Affairs
Marylynn Jones, RAC	Director, Regulatory Affairs
(b) (4)	Consultant, Interim Head of Regulatory Affairs
(b) (4)	Consultant

1.0 BACKGROUND:

ACADIA requested a teleconference with the Division of Psychiatry Products on January 29, 2016 to present a summary review of mortality in their long term studies for pimavanserin, titled "Important Characteristics of Patients Who Died During Pimavanserin Clinical Trials".

2.0 DISCUSSION:

See attached presentation slides.

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/s/

BRENDAN MUOIO
02/09/2016

Executive CAC

Date of Meeting: January 12, 2016

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Lois Freed, Ph.D., DNP, Alternate Member
Aisar Atrakchi, Ph.D., DPP, Pharm Tox Supervisor
Amy Avila, Ph.D., DPP, Presenting Reviewer

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

NDA # 207318

Drug Name: Pimavanserin (NUPLAZID)

Sponsor: Acadia Pharmaceuticals

NDA 207318 was submitted on September 1, 2015 to pursue marketing approval of pimavanserin for the treatment of psychosis associated with Parkinson's disease. 2-year mouse and rat carcinogenicity study results were submitted with the NDA.

Mouse Carcinogenicity Study

CD-1 mice (60/sex/group) were administered pimavanserin tartrate by oral gavage in a vehicle of deionized water for 104 consecutive weeks. Doses of 3, 7, and 15 mg/kg/day were used for males and 10, 25, and 50 mg/kg/day for females. Two identical control groups were administered the vehicle. Dosing was terminated during study week 101 for high dose males due to the number of surviving animals reaching 20. The sponsor received agreement from the division and the ECAC prior to the cessation of dosing for this group. There was a statistically significant decrease in survival rates for high dose males (15 mg/kg/day) compared to controls. There were no statistically significant drug-related neoplastic findings in either males or females.

Rat Carcinogenicity Study

Sprague Dawley rats (60/sex/group) were administered pimavanserin tartrate by oral gavage in a vehicle of deionized water for 104 consecutive weeks. Doses of 3, 10, and 30 mg/kg/day were used for males and 5, 15, and 50 mg/kg/day for females. Two identical control groups were administered the vehicle. Dosing was terminated during study week 96 for high dose males due to surviving animals reaching 20. Subsequently,

this group was euthanized during study week 101 due to the number of surviving animals reaching 15. Dosing was terminated during study week 103 for low dose males due to surviving animals reaching 20. The sponsor received agreement from the division and the ECAC prior to the cessation of dosing and/or premature sacrifice for these groups. There were no statistically significant drug-related neoplastic findings in either males or females.

Executive CAC Recommendations and Conclusions

Mouse

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Rat

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Karen Davis Bruno, Ph.D.

Chair, Executive CAC

cc:\

/Division File, DPP
/AAisar, DPP
/AAvila, DPP
/BMuoio, CSO/PM, DPP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
01/13/2016

KAREN L DAVIS BRUNO
01/13/2016

**PeRC Meeting Minutes
December 2, 2015**

PeRC Members Attending:

Lynne Yao

Linda Lewis

Lily Mulugeta

Thomas Smith

Dionna Green

Gerri Baer

Daiva Shetty

Meshaun Payne

Shrikant Pagay

Belinda Hayes

Michelle Roth-Cline

George Greeley

Hari Cheryl Sachs Non-Responsive

Dianne Murphy Non-Responsive

Non-Responsive

Wiley Chambers

Greg Reaman Non-Responsive

Non-Responsive

Agenda

9:00	Non-Responsive
9:30	
9:50	
10:10	
10:30	
10:50	
11:00	
11:20	
11:30	
11:40	
11:50	

	Non-Responsive				
	NDA 207318	Nuplazaid (pimavanserin) Full Waiver (with Agreed iPSP)	DPP	Brendan Muoio	Psychosis associated with Parkinson's Disease
	Non-Responsive				
	Non-Responsive				

Non-Responsive

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Non-Responsive

Nuplazaid (pimavanserin) Full Waiver (with Agreed iPSP)

- Proposed Indication: Psychosis associated with Parkinson's Disease
- *PeRC Recommendations:*
 - The PeRC concurred with the Division to grant a full waiver because the disease/condition does not exist in pediatric patients.

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/s/

GEORGE E GREELEY
12/15/2015



NDA 207318

MID-CYCLE COMMUNICATION

ACADIA Pharmaceuticals Inc.
Attention: Blake Burrell
Senior Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated tablets.

We also refer to the teleconference between representatives of your firm and the FDA on December 3, 2015. 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 Dr. Brendan Muoio, Regulatory Project Manager at (240) 402-4518 or brendan.muioio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
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 3, 2015 from 11 a.m. to 12 p.m. Eastern Standard Time

Application Number: NDA 207318
Product Name: Nuplazid (pimavanserin)
Indication: Treatment of psychosis associated with Parkinson's disease
Applicant Name: ACADIA Pharmaceuticals Inc.

Meeting Chair: Mitchell Mathis, MD
Director, Division of Psychiatry Products

Meeting Recorder: Brendan Muoio, PharmD
Regulatory Project Manager

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Marc Stone, PhD	Deputy Director for Safety, DPP
Lucas Kempf, MD	Clinical Team Leader, DPP
Paul Andreason, MD	Clinical Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
David Claffey, PhD	CMC Lead, Office of Product Quality (OPQ)
Eiji Ishida, PhD	Biometrics Reviewer, Office of Biostatistics (OB)
Michelle Campbell, PhD	Clinical Outcome Assessments Staff (COA)
Wen-Hung Chen, PhD	COA Staff
Ida-Lina Diak, PharmD	Team Leader, Division of Pharmacovigilance I (DPVI)
Vicky Chan	Safety Evaluator, DPVI
Kim Lehrfeld, PharmD, BCPS	Team Leader, Division of Risk Management (DRISK)
Somya Dunn, MD	Risk Management Reviewer, DRISK
Vasantha Ayalasomayajula, MBA	Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Marc Goldstein	Independent Assessor, Eastern Research Group (ERG)
Brendan Muoio, PharmD	Regulatory Project Manager, DPP

APPLICANT ATTENDEES

Blake Burrell	Senior Director, Regulatory Affairs
Michael Monahan	Director, Regulatory Affairs
Marylynn Jones	Director, Regulatory Affairs
Genevieve Shyffer	Director, Regulatory Affairs
Serge Stankovic, MD, MSPH	Executive VP, Head of Research & Development
George Demos, MD	Executive Director, Drug Safety and Pharmacovigilance
Mark Knowles, PhD	Executive Director, Biostatistics and SAS Programming
 (b) (4)	Toxicology Consultant

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

Thus far, in our initial review of the clinical material, we have the following concerns about risk and commensurate benefit:

1. There are five deaths in the three short-term randomized controlled trials (four drug, one placebo). The estimated odds ratio is 2.94 (95% CI 0.28 to 148, p=0.61).
2. In the review of serious adverse events (including deaths) the estimated odds ratio, stratified by study, for serious adverse events is
 - a. 1.99 (95% CI 0.87 to 4.53, p=0.10) for all drug vs. placebo
 - b. 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34 mg vs. placebo
 - c. 1.44 (95% CI 0.54 to 3.81, p=0.46) for less than 34 mg vs. placebo
3. The observed deaths and serious adverse events do not have an apparent unifying mechanism; this is consistent with what we observe with the use of conventional and new generation antipsychotics in the demented elderly population. FDA has not approved antipsychotic drugs with this safety signal for use in the agitated or psychotic demented elderly populations.
4. We are concerned about the relatively modest clinical improvement in the single positive trial as measured by the SAPS-PD in light of the previously failed trials using the unmodified BPRS and SAPS.

5. We currently do not believe that the pulmonary fibrosis findings in animals are connected to the observed disproportionate numbers of deaths and serious adverse events in the clinical trials population; however, we are concerned that pimavanserin may be used off-label in populations where the potential risk of pulmonary fibrosis is not outweighed by a commensurate clinical benefit. These populations would include patients with autism, schizophrenia and bipolar disorder.

3.0 INFORMATION REQUESTS

Office of Product Quality

1. We request that you tighten or justify the proposed drug substance particle size distribution (PSD) acceptance criterion (d (v, 90) of 20 µm to 100 µm). There is no concern from a dissolution perspective because the drug substance is highly soluble. However, from a drug product manufacturing perspective, (b) (4) (b) (4) the three registration batches had no blend uniformity or content uniformity issues, they were manufactured using drug substance (b) (4) of the proposed range. This is of particular concern for the commercial scale process where no data are available, especially as the drug product is manufactured (b) (4) (b) (4).
2. We request that you propose and justify a three-stage specification (b) (4) drug substance particle size distribution specification, or justify the proposed single-stage specification (e.g., demonstrate that it has and will continue (b) (4) (b) (4)).
3. The Agency acknowledges the equipment information provided for each process step during scale up to commercial batches. However, no information (b) (4) (b) (4) is provided for (b) (4) (b) (4). Comparison of use of capacity of equipment is important to consider during scale-up. Therefore provide such information for both the Phase 3 clinical scale (b) (4) and the commercial scale (b) (4) batches. If the use of capacity of certain process differs significantly from one scale to another, the adjustments in the process parameters need to be discussed and appropriate justification should be provided.
4. The Agency noted that one of the commercial-scale (b) (4) batches - (b) (4) (b) (4) failed the acceptable quality limit (AQL) (b) (4) (b) (4) tablets. (b) (4) (b) (4) No discussion was given on the reasons that this batch did not meet AQL. (b) (4) (b) (4). Therefore, provide the following:
 - a. Discussion on the failure of Batch (b) (4) to meet AQL and rational for ensuring future batches will meet the AQL;
 - b. (b) (4) (b) (4)
5. Explain why the commercial drug product tablets require (b) (4) (b) (4)

6. Provide all available batch analysis and stability study results for the drug product batches manufactured using the proposed commercial tablet formulation.
7. Provide updated long-term stability data for the drug product registration batches.
8. Provide the investigation report for the (b) (4) API screening in the production of batches (b) (4).

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We are concerned that the observed deaths and serious adverse events do not have an apparent unifying mechanism or premonitory signs. Therefore, we are not clear that one may mitigate the risk of increased mortality and serious morbidity with the use of pimavanserin in the proposed indicated population. This increased risk of mortality and serious morbidity is consistent with what we observe with the use of conventional and new generation antipsychotics in the demented elderly populations including psychosis associated with Parkinson's disease. FDA has not approved antipsychotic drugs with this safety signal for use in the agitated or psychotic demented elderly populations.

We are concerned that, if approved, pimavanserin may be used off-label in populations where the potential risk of pulmonary fibrosis is not outweighed by a commensurate clinical benefit. These populations would include patients with autism, schizophrenia and bipolar disorder.

5.0 ADVISORY COMMITTEE MEETING

The Psychopharmacologic Drugs Advisory Committee Meeting for pimavanserin will be held on March 29, 2016 from 8 a.m. to 5 p.m. at FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993-0002.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

1. We plan to communicate proposed labeling and if necessary, any postmarketing commitment requests by February 19, 2016, if major deficiencies are not identified during the review.
2. We are on track with completing GCP and GMP inspections by February 3, 2016.
3. We plan to take an action by the May 1, 2016 PDUFA date.

The Late-Cycle Meeting between you and the review team is currently scheduled for March 15, 2016. We intend to send the briefing package to you approximately 3 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/

MITCHELL V Mathis
12/14/2015



NDA 207318

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

ACADIA Pharmaceuticals Inc.
Attention: Blake Burrell
Senior Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) dated and received September 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated tablets.

We also refer to your submissions dated September 21, 2015, September 22, 2015, October 1, 2015, October 6, 2015, October 8, 2015, October 14, 2015, and November 11, 2015.

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

Biopharmaceutics

1. We acknowledge the receipt of the BCS classification report for pimavanserin tartrate contained in section 3.2.P.2. However, we note that the BCS classification is unlikely to hold up the evaluation of your Application as there is no BCS-based biowaiver request in the NDA. Therefore, we recommend that you submit an official request for BCS classification separately to the supporting IND Application.

Non-clinical

1. We acknowledge receipt of your justification for not conducting a combination (pimavanserin/carbidopa-levodopa) embryo-fetal development study in section 2.4.4.5 of the Nonclinical Overview. However, the adequacy of the justification and of all submitted embryo-fetal development data will be a review issue.
2. As noted in the pre-NDA meeting minutes, the division requested a 90-day toxicity study in one species to qualify two impurities (b) (4). The adequacy of the submitted 28-day toxicity studies with impurities (b) (4) will be a review issue.
3. The findings of pulmonary fibrosis in rats will be reviewed. We acknowledge receipt of your responses to our information requests regarding these and other nonclinical findings on October 14, 2015 and November 12, 2015.

Clinical

Thus far, in our initial review of the clinical material, we have the following concerns about risk and commensurate benefit:

1. There are 5 deaths in the three short-term randomized controlled trials (4 drug, one placebo). The estimated odds ratio is 2.94 (95% CI 0.28 to 148, p=0.61).
2. In the review of serious adverse events (including deaths) the estimated odds ratio, stratified by study, for serious adverse events is
 - a. 1.99 (95% CI 0.87 to 4.53, p=0.10) for all drug vs. placebo
 - b. 2.38 (95% CI 1.00 to 5.73, p=0.05) for 40mg vs. placebo
 - c. 1.44 (95% CI 0.54 to 3.81, p=0.46) for less than 40mg vs. placebo
3. The observed deaths and serious adverse events do not have an apparent unifying mechanism; this is consistent with what we observe with the use of conventional and new generation antipsychotics in the demented elderly population.
4. While we consider the above safety signals, we are concerned about the relatively modest clinical improvement in the single positive trial as measured by the SPS-PD in light of the previously failed trials using the unmodified BPRS and SPS.
5. We currently do not believe that the pulmonary fibrosis findings in animals are connected to the observed disproportionate numbers of deaths and adverse events in the clinical trials population; however, we are concerned that pimavanserin may be used off-label in populations where the potential risk of pulmonary fibrosis is not outweighed by a commensurate clinical benefit. These populations would include patients with autism, schizophrenia and bipolar disorder.

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

We request that you submit the following information:

1. Please provide evidence that the SAPS-PD is sufficiently comprehensive in measuring the concepts that are relevant and important to this patient population.
2. Please provide evidence that SAPS-PD does not exclude relevant and important concepts that are assessed by the full version SAPS.
3. We are not convinced that a 3-point change represents a clinically important change to patients. Please provide evidence that a 3-point change in the SAPS-PD is clinically meaningful (e.g., how the 3-point change can be translated into the change in how the patients feel and function that is clinically meaningful to them and to their caregivers). We typically rely on multiple sources of information to determine clinical meaningfulness including information from the literature, anchor-based methods from trial data and cumulative distribution function.

4. Please submit the scoring algorithm for the SAPS-PD (9 items) and the SAPS (20 items). Additionally, please provide the user manual and/or training materials on use of the SAPS by the independent, centrally-based clinician.
5. Please explain the method used to handle missing data from the SAPS-PD and SAPS.
6. Please provide the inter-rater reliability of the SAPS-PD and SAPS raters from the centralized rater service.
7. Please provide the item by item descriptive statistics of the 20 item SAPS, including but not limited to N, mean, standard deviation, minimum, maximum, frequency distribution, and percent missing. Additionally, please provide the inter-item correlations and item-total correlation (for both SAPS-PD and SAPS).

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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”** Please insert the manufacturer’s U.S. phone number in the Adverse Reactions section in Highlights.
2. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1). (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered. Please remove the period after sections and subsections (e.g., 12 CLINICAL PHARMACOLOGY and 12.1 Mechanism of Action).

3. Additional requested formatting and content changes are tracked and enclosed in the attached draft labeling. We request that you accept all tracked changes, and use this as the base document. Track all proposed edits and respond to our comments as “Accept” or provide an explanation for proposing new text/not accepting our request.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 27, 2015. 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 with 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). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Dr. Brendan Muoio, Regulatory Project Manager, at (240) 402-4518 or brendan.muio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

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

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/s/

MITCHELL V Mathis
11/13/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207318

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

ACADIA Pharmaceuticals Inc.
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

ATTENTION: Hilde Williams
Senior Vice President, Regulatory Affairs and Development

Dear Ms. Williams:

Please refer to your New Drug Application (NDA) dated and received September 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pimavanserin Tablets, 17 mg.

We also refer to your correspondence, dated and received September 1, 2015, requesting review of your proposed proprietary name, Nuplazid.

We have completed our review of the proposed proprietary name, Nuplazid and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 1, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Brendan Muoio, Regulatory Project Manager in the Office of New Drugs, at 240-402-4518.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
11/09/2015



NDA 207318

PRIORITY REVIEW DESIGNATION

ACADIA Pharmaceuticals Inc.
Attention: Hilde Williams
Senior Vice President, Regulatory Affairs and Development
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Ms. Williams:

Please refer to your New Drug Application (NDA) dated and received September 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated tablets.

We also refer to your submissions dated September 21, 2015, September 22, 2015, October 1, 2015, October 6, 2015, October 8, 2015, and October 14, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is May 1, 2016. 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>.

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 requirement/commitment requests by February 19, 2016. In addition, the planned date for our internal mid-cycle review meeting is November 23, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before November 14, 2015.

If you have any questions, contact Dr. Brendan Muoio, Regulatory Project Manager, at (240) 402-4518 or brendan.muioio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
10/30/2015



NDA 207318

NDA ACKNOWLEDGMENT

ACADIA Pharmaceuticals Inc.
Attention: Hilde Williams
Senior Vice President, Regulatory Affairs and Development
3611 Valley Centre Drive
San Diego, CA 92130

Dear Ms. Williams:

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: Nuplazid (pimavanserin) 17 mg immediate-release, film-coated tablets

Date of Application: August 31, 2015

Date of Receipt: September 1, 2015

Our Reference Number: NDA 207318

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 31, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

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

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, contact me at (240) 402-4518 or brendan.muio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Brendan Muoio, PharmD
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

BRENDAN MUOIO
09/15/2015



IND 68384

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Acadia Pharmaceuticals, Inc.
Attention: Hilde Williams
Vice President, Regulatory Affairs
11085 Torreyana Road, Suite 100
San Diego, CA 92121

Dear Ms. Williams:

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

We also refer to your June 19, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that pimavanserin for psychosis in patients with Parkinson's disease meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of pimavanserin for psychosis in patients with Parkinson's disease to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Attachment 1 lists potential topics for discussion at this initial breakthrough therapy meeting.

We note your recent Pre-New Drug Application meeting held on June 2, 2014. At this point in your drug development program, holding this initial breakthrough therapy meeting is not

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

necessary. However, please contact Simran Parihar, PharmD to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for pimavanserin for psychosis in patients with Parkinson's disease is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, please email Simran Parihar, PharmD, Regulatory Health Project Manager, at simran.parihar@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:
Meeting

Attachments:

Attachment 1: Possible Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting

ATTACHMENT 1: Possible Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting

The following are possible discussion topics for the initial comprehensive multidisciplinary breakthrough therapy Type B meeting depending on the therapeutic area, development phase, and specific development program issues.

General and/or Regulatory

- The planned target date for NDA/BLA submission, including plans for rolling review
- The specific indication that studies are intended to support
- Other indications in development
- Expanded access plans, including the intent to communicate these plans publicly
- Plans to seek accelerated approval
- Regulatory status with non-U.S. regulatory agencies
- Plans to defer or waive specific studies (e.g., pediatric studies), including those to be conducted as postmarketing requirements/postmarketing commitments
- Critical aspects of proposed studies, including enrichment designs, noninferiority designs, and historical controls, and any planned novel approaches
- Plans for submission of a proprietary name request
- If a drug/device combination product, the device development information and plan
- If the use of the drug will require a diagnostic test, the in vitro diagnostic development plan with the Center for Devices and Radiological Health (CDRH)
- The Gantt chart of the development timeline
- The proposed communication plan for managing interactions between CDER and the sponsor, including the timing and format of these interactions

Clinical and Statistical

- Existing and planned clinical sites and accrual data
- Efficacy:

- The status of all clinical trials and topline summary results
- The preliminary evidence of effectiveness
- The planned or completed clinical trials intended to support efficacy, including:
 - The overall trial design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials or any other adaptation, type I error control, and expected initiation and completion dates.
 - The justification for all dose selections, including number of doses and dose intervals and a discussion of all clinical trials that will provide dose-response information.
 - The validity of the outcomes and endpoints. If using patient-reported outcomes or surrogate endpoints, support for those endpoints or plans to support or validate them, as necessary.
- Safety:
 - Potential safety issues from nonclinical studies and early clinical trials
 - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, reproductive and developmental, and immunogenicity safety profiles
 - The clinical trial safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for postmarketing drug safety and surveillance (pharmacovigilance)
 - The proposed size of the safety population
 - The plan or the need for long-term safety studies or trials
 - Preapproval
 - Postapproval
 - The plans to mitigate or minimize risk, proposed risk evaluation and mitigation strategies, if needed
- Specific populations:
 - The dose, trial design, efficacy endpoints, size and composition of the population, and additional safety trials for populations such as:
 - Elderly patients
 - Pediatric patients
 - Hepatically and renally impaired patients

- The proposed pediatric development plan with outlines and synopses of additional studies

Clinical Pharmacology and Pharmacokinetics

- The clinical pharmacology, pharmacodynamic, and pharmacokinetic trials: completed, ongoing, planned, and requests for deferral
 - Immunogenicity assessments
 - Dosing information from pharmacodynamics studies
 - Single ascending dose
 - Multiple ascending dose
 - Dose response study
 - Food-effect
 - Drug-drug interactions (DDI)
 - Thorough QT/QTc
 - Pharmacokinetic studies in patients with renal or hepatic dysfunction
 - Pharmacogenomics
- The plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
- The plans for conducting population pharmacokinetics, exposure-response modeling and simulation analyses
- The plans to describe dose modifications in labeling based on DDI, age, organ impairment, among others

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

- The nonclinical studies completed, ongoing, and planned, including the number and sex of animals per dose, doses, route of administration, toxicities, duration of study, and study results. For planned studies, the timelines for initiation and submission of study reports. Examples of such studies include:
 - Subacute and chronic toxicology and associated toxicokinetics
 - Genetic toxicology
 - Reproductive and developmental toxicology
 - Carcinogenicity studies

- Animal models of disease and pharmacokinetic parameters associated with efficacy
- Evidence of mechanism of action
- Absorption, distribution, metabolism, and excretion
- Safety pharmacology, where appropriate

Chemistry, Manufacturing, and Controls

- Drug product:
 - The dosage form
 - The formulation description
 - Administration instructions, delivery systems (e.g., vials, prefilled syringes) proposed draft packaging, and disposal instructions
 - Critical quality attributes
 - The control and stability strategies
 - The proposed shelf life and required stability studies
- Drug substance:
 - Characterization
 - Critical quality attributes
 - The control and stability strategies
 - The proposed shelf life or retest period and required stability studies
- Proposed commercial processes:
 - The manufacturing process, in-process controls, scale-up plans
 - A comparison of the proposed commercial manufacturing process to the clinical manufacturing process
 - Comparability of lots used in clinical trials and commercial lots or a plan to establish analytical comparability
 - The current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
 - The current release and stability testing site(s) and proposed commercial testing site(s), if different

- The anticipated market demand at launch
- Proposed validation approaches:
 - The drug substance and drug product manufacturing process
 - Microbial control and sterility assurance
 - Viral clearance
 - The analytical methods

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/s/

MITCHELL V Mathis
08/13/2014



IND 68384

MEETING MINUTES

Acadia Pharmaceuticals, Inc.
Attention: Hilde Williams
Vice President, Regulatory Affairs
11085 Torreyana Road, Suite 100
San Diego, CA 92121

Dear Ms. Williams:

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

We also refer to the telecon between representatives of your firm and the FDA on June 2, 2014. The purpose of the meeting was to discuss overall organizational and review aspects of the NDA, as well as specific questions relating to the content and format of the clinical and nonclinical information.

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

If you have any questions, please email Simran Parihar, PharmD, Regulatory Health Project Manager, at simran.parihar@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:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre - NDA

Meeting Date and Time: Monday, June 2, 2014 1:00 PM – 2:30 PM (EST)
Meeting Location: White Oak Building 22, Conference Room #1315

Application Number: IND 68384
Product Name: Pimavanserin tartrate
Indication: Treatment of Parkinson's disease psychosis (PDP)
Sponsor/Applicant Name: Acadia Pharmaceuticals, Inc.

FDA ATTENDEES

Robert Temple, MD	Deputy Center Director for Clinical Science
Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Mark Ritter, PharmD, MD	Clinical Team Leader
Lucas Kempf, MD	Clinical Reviewer
Linda Fossom, PhD	Pharmacology/Toxicology Supervisor
Violetta Klimek, PhD	Pharmacology/Toxicology Reviewer
David Claffey, PhD	CMC Team Leader
Wendy Wilson, PhD	CMC Reviewer
Hao Zhu, PhD	Clinical Pharmacology Team Leader
Kofi Kumi, PhD	Clinical Pharmacology Reviewer
Eiji Ishida, PhD	Statistical Reviewer
Jovita Randall-Thompson, PhD	Controlled Substance Staff Reviewer
Gerald David Podskalny, DO, MPH	Clinical Team Leader, Division of Neurology Products (DNP)
Tracy Peters, PharmD	Senior Regulatory Project Manager, Division of Neurology Products
Simran Parihar, PharmD	Regulatory Health Project Manager, DPP

EASTERN RESEARCH GROUP ATTENDEES

Patrick J. Zhou Independent Assessor

SPONSOR ATTENDEES

Hilde Williams	Vice President, Regulatory Affairs and Development
Marylynn Jones, RAC	Director, Regulatory Affairs
Blake Burrell, MS, RAC	Director, Regulatory Affairs-CMC
Roger Mills, MD	Chief Medical Officer and Executive Vice President, Development

Kathy Chi-Burris, MS
Rajesh Agarwal, PhD

(b) (4)
(b) (4)
(b) (4)

Director, Biostatistics and Programming
Senior Director, Pharmaceutical Development
Toxicology Consultant
Statistical Consultant
Abuse Liability and Drug Scheduling Consultant

1.0 BACKGROUND

Pimavanserin is a selective and potent serotonin 5-HT_{2A} receptor antagonist (inverse agonist) that has been developed for the treatment of Parkinson's disease psychosis (PDP). This development program has been conducted under IND 68,384 since 2003. There are no drugs currently approved for the treatment of PDP, though an NINDS/NIMH Consensus Meeting held in 2005 identified PDP as a discreet indication in need of improved treatment options. Recent literature supports the designation of PDP as a serious unmet medical need (Friedman et al., 2013).

Psychotic symptoms develop in about 50% of Parkinson's disease (PD) patients and are associated with a marked decline in patient quality of life and profound increases in caregiver burden. In PD patients, psychotic symptoms have been linked to increased morbidity, incident dementia and mortality. Progression of these symptoms is the single greatest precipitant for nursing home placement among PD patients. Current antipsychotics which are used off-label to treat PDP have unproven efficacy, complicate PD management and/or are associated with increased parkinsonism, sedation, cognitive deterioration, stroke, hematologic disorder, cardiovascular events and other significant side effects.

In April 2013, ACADIA Pharmaceuticals Inc. (ACADIA) met with FDA and gained agreement that an NDA would be accepted for filing on the basis of data from a single, strongly positive study (ACP-103-020) with supportive data from earlier trials. Since then, ACADIA has been working to finalize the data package for the NDA (including completion of the clinical pharmacology program and the chemistry, manufacturing and controls [CMC] information necessary to support the commercial drug supply). In addition, during this period, the data from Study ACP-103-020 were published in the Lancet (Cummings et al., 2014); a copy of this article, and a co-issued editorial authored by Dr. Susan Fox are provided in Appendix 1 of the briefing package along with other key publications.

2. DISCUSSION

2.1. General

Question 1: The NDA for pimavanserin will be submitted electronically in eCTD format. A draft table of contents (TOC), consistent with CTD/eCTD guidance, is included in this briefing package. It provides an outline of Modules 1 and 2 as well as an outline of the CMC package and nonclinical and clinical reports intended to support the NDA in Modules 3 through 5.

Does FDA agree that the proposed overall organization of the pimavanserin NDA, with particular attention to the Module 1 Regional Information, would support NDA filing?

FDA Response to Question 1:

We find your proposal acceptable.

Discussion at meeting: There was no further discussion.

Question 2: During the Pre-IND meeting held in July 2003, the Division of Neuropharmacological Drug Products agreed to a waiver of pediatric studies because Parkinson's disease (and therefore PDP) is a condition that occurs predominately in people over 40 years of age. According to the current FDA Guidance entitled *How to comply with the Pediatric Research Equity Act*, "When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision generally will be provided to applicants for their records." Recognizing that the Pre-IND meeting was held over 10 years ago and prior to the re-organization of the Division, we request that this waiver of pediatric studies be confirmed as documented in these previous FDA minutes.

Does FDA agree that a waiver of pediatric studies is granted for pimavanserin as a treatment for PDP?

FDA Response to Question 2:

You are still required to submit a pediatric plan with justification for a waiver request in order to receive the waiver. It is likely, given the age distribution of patients with Parkinson's disease, that a waiver will be granted.

Discussion at meeting: There was no further discussion.

Question 3: The proposed indication statement (as included in the preliminary draft labeling) is that TRADENAME (pimavanserin tartrate) is indicated for the treatment of Parkinson's disease psychosis (PDP). In light of the unprecedented nature of the indication, ACADIA believes that this nomenclature differentiates PDP from other forms of psychosis more clearly than the previously proposed language (b) (4)

In this way, the new indication statement better defines PDP as a discreet condition. Likewise, it provides better consistency with the designation applied in recent literature (e.g., Friedman, 2013) and is similar to the acronym 'PDPsy' that was applied in the diagnostic criteria established in 2007 (Ravina et al., 2007).

Does FDA agree that this is an acceptable indication statement for pimavanserin?

FDA Response to Question 3:

This will be a matter for review. However we generally feel that the previous language is preferred as it conforms to all previous and current diagnostic literature which is used in all diagnostic classification systems and payer programs.

Discussion at meeting: There was no further discussion.

Question 4: Parkinson's disease psychosis (PDP) is a serious, unmet medical need without any safe and effective treatment options. Onset of psychosis is associated with marked

decline in patients' quality of life and profound increases in caregiver stress and burden. Psychotic symptoms are the single greatest precipitant of nursing home placement among patients with PD, and result in substantial morbidity and mortality. In light of the data showing pimavanserin to be safe and effective in the treatment of PDP, and given the fact that there are no medications approved for this indication and that all drugs used off-label are associated with significant and relevant safety concerns, ACADIA intends to request priority review for the pimavanserin NDA. The formal request will be made in the NDA application. *Does FDA agree that the NDA for pimavanserin meets the criteria for priority review?*

FDA Response to Question 4:

We agree.

Discussion at meeting: There was no further discussion.

Question 5: In June of 2013, following our April Type C meeting with the Division, the FDA issued draft Guidance for Industry entitled *Expedited Programs for Serious Conditions-Drugs and Biologics*. This guidance outlines the qualifying criteria for breakthrough therapy designation and the features and benefits of this new status. Pimavanserin appears to qualify on the basis that it is intended to treat a serious condition, and clinical evidence indicates that it may offer substantial improvement over existing therapies on more than one clinically significant endpoint.

Does FDA consider that the development program for pimavanserin in PDP is eligible for breakthrough therapy designation and, if so, and in the light of the late stage of development, does FDA consider that there would be value in having the opportunity for more intensive discussions with the Division as we complete the remaining program and prepare for the NDA?

FDA Response to Question 5:

In order to consider your program as breakthrough therapy, we recommend that you submit your request to the Agency promptly in order to determine whether or not your product would be designated as a breakthrough therapy.

Discussion at meeting: There was no further discussion.

Question 6:

(b) (4)



(b) (4)



Does FDA agree (b) (4)
?

FDA Response to Question 6:

On its face, we do not find that your rationale supports (b) (4)
(b) (4) however a final decision will be made on review of the NDA.
We request that you include this rationale in the NDA along with any additional safety issues
(b) (4) that you may be aware of.

Discussion at meeting: The sponsor agreed to comply with the USP Salt Policy and will label the drug product based on the active moiety, the free base pimavanserin.

Question 7: Pimavanserin is a highly potent 5-HT_{2A} inverse agonist with no other clinically significant pharmacological actions. Although CNS-active, it appears to have no potential for abuse or dependence as determined by its *in vitro* profile, its effects in safety pharmacology evaluations and animal behavior models, and by the observed profile of subjective responses and adverse events (AEs) in human studies conducted to date. Accordingly, formal studies of abuse potential in animals (to evaluate drug discrimination, drug self-administration, physical dependence) and in humans (i.e., laboratory evaluation in abusers) have not been considered necessary. ACADIA proposes that the current nonclinical and clinical datasets will be sufficient to assess abuse potential as specified in 21 CFR 314.50(d)(5)(vii) and as described in the draft FDA guidance “Assessment of Abuse Potential of Drugs.” This analysis is expected to support a recommendation for non-scheduled status for pimavanserin.

Do the Division and CSS agree with this plan?

FDA Response to Question 7:

We request that the abuse potential assessment you submit in the NDA includes comprehensive descriptions of all pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, clinical studies, drug formulation data. We are available to review abuse potential protocols prior to the commencement of the studies. More

information may be required at the time of your NDA submission, see (e.g., page 5) the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Discussion at meeting: The sponsor agreed.

Post-meeting comment: In addition, the Agency does not conclude that your drug has no abuse potential and a determination of abuse potential and the need for scheduling will be made following review of the NDA.

Question 8: Tabulation datasets in Study Data Tabulation Model format version 3.1.2 (each with a corresponding Define.xml) along with the original legacy-format raw datasets (each with a corresponding Define.pdf) will be provided in the NDA for all of the Phase I, Phase II and Phase III clinical studies conducted with pimavanserin. The only exceptions are for the Phase I studies, ACP-103-003 and -004, which were not conducted under ACADIA sponsorship or under an ACADIA IND (see Question 18 for additional information on these studies). The SDTM datasets are being used to derive listings for the Integrated Summary of Efficacy (ISE) and/or the Integrated Summary of Safety (ISS) while the legacy-format datasets were used to derive the listings reflected in the original clinical study reports (CSRs). Legacy analysis datasets (including the Define.pdf) and the SAS programs used to produce the corresponding tables and figures for each of the blinded and open-label Phase II and Phase III PDP study reports (ACP-103-006, -010, -012, -014, -015, and -020), as well as for the thorough QT study, ACP-103-018, will be submitted in the NDA. Analysis Data Model (ADaM) v1.2 datasets and SAS programs, as described in the ISS/ISE statistical analysis plans, and used to produce the tables and figures for the ISS and ISE will also be submitted in the NDA.

With regard to datasets for drug product stability, these will be provided in .pdf table format in Module 3.

In addition, SAS transport datasets for the 2-year carcinogenicity studies in rats and mice will be provided in Legacy format SAS v5.0.

Does the Division agree with the plan outlined above for the submission of datasets in the NDA?

FDA Response to Question 8:

Your data submission plan is generally acceptable. To facilitate our review, please include the following items in your future NDA submission:

1. Variable definitions: All variable derivations (specifically, legacy-raw to legacy-analysis, legacy-raw to SDTM, SDTM to ADaM) need to be well documented in detail. In addition, please integrate all the definitions and derivations in one document per study. We also request that SAS programs you used for the variable derivations be submitted in a ready-to-use format that can be immediately usable for validation in our review.

2. Unique subject identifier: Please ensure that the identifiers of all subjects are unique across the submitted studies under an identifier variable USUBJID of SDTM datasets.

Please provide a list of submission history (including IND number, serial numbers and submission dates) associated with the protocol/SAP of the submitted studies and their amendments, and the meeting records. The list should cover the past discussions on the important study elements.

Discussion at meeting: There was no further discussion.

2.2. Nonclinical Safety

Question 9: The nonclinical safety package for pimavanserin includes a standard battery of safety pharmacology studies and acute toxicology, repeat-dose toxicology (up to 6-month and 12-month studies in rats and monkeys, respectively), genotoxicity, 2-year carcinogenicity (in rats and mice), and reproductive and developmental toxicity studies (in rats and rabbits).

Does FDA agree that the nonclinical safety package is complete and is sufficient to support filing of an NDA for pimavanserin as a treatment for PDP?

FDA Response to Question 9:

On face, we agree. However, it is always possible that additional studies may be needed based on the results of your ongoing pre- and post-natal reproductive toxicity study and your planned studies to assess the genotoxic potential of Impurities (b) (4) (see Question 12).

Discussion at meeting: There was no further discussion.

Question 10: At the Pre-IND meeting held in July 2003, FDA requested that nonclinical drug interaction studies of pimavanserin with Sinemet® (carbidopa-levodopa) be performed. In the End-of-Phase II meeting held in September 2006, a plan for the conduct of these studies was agreed. Study 1574-001 was subsequently conducted to characterize the toxicity and toxicokinetic profile of the pimavanserin/carbidopa-levodopa combination when administered via oral gavage to male rats for 14 consecutive days. The results suggested no effect of combination therapy on the toxicity profile or PK of pimavanserin. Though no additional studies were performed to assess the safety of the combination therapy in monkeys, additional clinical data obtained since the End-of-Phase II meeting support the safety of pimavanserin when given in combination with carbidopa-levodopa. These studies include placebo-controlled safety and efficacy studies in ~700 PDP patients (>95% of whom were on concomitant carbidopa-levodopa therapy), long-term open-label safety studies in ~500 of these same PDP patients, and a formal drug-drug interaction (DDI) study in 20 healthy normal volunteers. Data from all of these clinical studies support the conclusion that pimavanserin has no effect on carbidopa-levodopa blood levels and can safely be used in combination with Sinemet® and other carbidopa-levodopa therapies.

The proposal to not pursue further combination toxicity studies is consistent with the ICH Guidance M3(R2) on *Nonclinical Safety Studies for the Conduct of Human Clinical Trials*

And Marketing Authorization For Pharmaceuticals, which was issued 11 June 2009 (after the End-of-Phase II meeting). It states that “[f]or most combinations which involve two late stage entities and for which there is adequate clinical experience with co-administration, combination toxicity studies would generally not be recommended to support clinical studies or marketing unless there is significant toxicological concern.” ACADIA believes that the clinical experience with pimavanserin provides sufficient body of evidence to conclude that co-administration with Sinemet® (carbidopa-levodopa) is safe.

Does FDA agree that no additional nonclinical toxicity evaluation of the combination of pimavanserin with Sinemet® (carbidopa-levodopa) is needed to support filing and approval of the NDA for pimavanserin?

FDA Response to Question 10:

Based on your clinical experience with pimavanserin given in combination with carbidopa-levodopa, we consider your 14-day general toxicology study of pimavanserin/carbidopa-levodopa combination in rat of adequate duration to assess general toxicity of the combination. However, you will also need to submit an embryo-fetal development study with this combination in a single species, to support use in women of child-bearing potential. Justification should be provided for the species selected.

Discussion at meeting: The Agency agreed that an embryo-fetal development study with this combination would likely not be required for this indication; however, the sponsor should submit their justification, including the prevalence of this indication in women of child-bearing potential.

DNP Comment: This statement is generally true, in study ACP-103-020 the mean age of participants was 71 years (range 53-90 years). Delusions may occur in younger PD patients with dysregulation syndrome, including female patients with child bearing potential. In addition, pimavanserin may be used (off label) in other populations including patients with Huntington’s disease where most female patients would be in their 30s to early 40s.

DNP Comment: There are several examples of PD medications that have synergistic adverse effects on fetal development when give in combination with levodopa that are worse than the effects seen with the drug alone or with levodopa alone. The information is readily available in the approved product labels (see below).

From the Requip label: ”The combined administration of ropinirole (10 mg/kg/day, 8 times the maximum recommended human dose on a mg/m² basis) and L-dopa (250 mg/kg/day) to pregnant rabbits during organogenesis produced a greater incidence and severity of fetal malformations (primarily digit defects) than were seen in the offspring of rabbits treated with L-dopa alone. No indication of an effect on development of the conceptus was observed in rabbits when a maternally toxic dose of ropinirole was administered alone (20 mg/kg/day, 16 times the maximum recommended human dose on a mg/m² basis)”.

From the Tasmar label: “Tolcapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The combination of tolcapone (100 mg/kg/day) with levodopa/carbidopa (80/20 mg/kg/day) produced an

increased incidence of fetal malformations (primarily external and skeletal digit defects) compared to levodopa/carbidopa alone when pregnant rabbits were treated throughout organogenesis”.

Question 11: The ICH S8 Guidance document entitled *Immunotoxicity Studies for Human Pharmaceuticals* identifies factors to consider in the evaluation of drugs for potential immunotoxicity. Based on its pharmacologic activity as well as its safety and tissue distribution profile in the toxicology program, there is no suggestion of immunotoxic potential for pimavanserin. In addition, ACADIA is not aware of any structurally similar compounds with immunotoxic effects. Importantly, the structure of pimavanserin is markedly different from clozapine, the only other antipsychotic to have shown efficacy in PDP, but which sees limited use in this population in part because of its potential to cause agranulocytosis.

While the PDP population is generally an elderly one, and may suffer deficits in immune function associated with age, examination of the AEs and hematologic data from controlled clinical trials further supports pimavanserin’s lack of immunotoxicity. On the basis of these collective data, ACADIA believes that further assessment of immunotoxicity is not warranted for pimavanserin.

Does FDA agree that no additional assessments of immunotoxicity are needed to support NDA filing?

FDA Response to Question 11:

Yes, we agree.

Discussion at meeting: There was no further discussion.

Question 12: There are two related-substance impurities (b) (4) of the pimavanserin tartrate drug substance that will be specified (identified and qualified). These are designated as Impurities (b) (4). This impurity has been found to be at a level of up to (b) (4) % on release of drug substance. In drug product, Impurity (b) (4) has been observed (b) (4) up to (b) (4) % under accelerated conditions (40°C/75% RH) at six months.

Impurity (b) (4) has recently been identified in laboratory studies as a potential impurity that could be present above the (b) (4) % ICH qualification threshold in pimavanserin tartrate drug substance.

ACADIA plans to assess the genotoxic potential of Impurities (b) (4) using the bacterial mutation assay (Ames) and to conduct separate 28-day repeat-dose studies in rats with the respective impurities spiked at (b) (4) %.

Does FDA agree that the strategy described is adequate to qualify the impurities associated with pimavanserin's manufacturing, and storage?

FDA Response to Question 12:

CMC response – The approach seems reasonable from a CMC perspective. However, the final determination of the adequacy of a proposed control strategy, including testing and limits, for related substances will be determined as part of the NDA review based on the justification, supported by data, provided in the submission.

Nonclinical response - Your proposed strategy for qualification of impurities/degradants is inadequate. To assess genotoxicity, you will need to provide a study for chromosomal aberrations, in addition to point mutations (Ames). Because Parkinson's Disease is a chronic indication, you will need to provide a 90-day, not 28-day, general toxicity study in one species. Additionally, you will need to submit an embryo-fetal development study in a single species, to support use in women of child-bearing potential.

Discussion at meeting: The Agency noted that a 90-day general toxicity study is generally required to qualify impurities/degradants for chronic indications; however, the adequacy of the 28-day study will be a matter of review. We also noted that an embryo-fetal study will likely not be needed for this indication, but the sponsor should provide a justification (see discussion for Question 10, above).

Question 13: Six possible impurities (b) (4) of pimavanserin tartrate drug substance were determined to be mutagenic based on literature, in silico testing and/or Ames testing.

Two compounds (b) (4) were determined to be of minimal risk and analytical testing for these compounds was deemed unnecessary, (b) (4)

Analytical test methods were developed to quantitate the levels of the remaining four compounds in the drug substance (b) (4)

Six pilot and commercial-scale drug substance batches manufactured to date and tested for these four impurities demonstrate that they are present at a level below the Threshold of Toxicological Concern (TTC).

Question 13a: Does the Division agree that further monitoring of potential impurities (b) (4) in the commercial drug substance is not required?

Question 13b: Does the Division agree that further monitoring of potential impurities (b) (4) in the commercial drug substance will not be required based on the amounts detected in production batches below the TTC?

FDA Response to Question 13:

Please see CMC response to Q12. Include as part of the justification results [REDACTED] (b) (4) [REDACTED] and information on any proposed testing for these impurities upstream of the final drug substance.

Discussion at meeting: There was no further discussion.

2.3. Clinical Pharmacology

Question 14: Pimavanserin is both highly soluble and permeable and has a very predictable and dose-linear pharmacokinetic (PK) profile. Its terminal elimination half-life is ~57 hours, consistent with its slow rate of metabolism. Pimavanserin is being evaluated in a full panel of *in vitro* studies to assess its potential to be the perpetrator or victim of PK drug interactions. These studies include an evaluation of cytochrome P450 (CYP) enzyme induction in primary cultures of human hepatocytes; CYP enzyme inhibition (both reversible and irreversible) in human liver microsomes; transporter inhibition in cell monolayers or cell suspensions; transporter substrate studies in cell monolayers; and metabolic studies in human liver microsomes and recombinant human CYP and flavin-containing monooxygenase enzyme (FMO) enzymes.

Mass balance studies in rats and humans established that pimavanserin is extensively (>98%) absorbed from the gastrointestinal tract and is eliminated as unchanged drug to a negligible extent (<2%). Metabolite ID studies established that pimavanserin is not directly conjugated and that all of its metabolites are formed by Phase 1 metabolism followed by Phase 2 metabolism. Reaction phenotyping studies conducted in accordance with the *FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012*) established that the Phase 1 metabolism of pimavanserin is catalyzed by CYP3A4 and CYP3A5 (major), CYP2J2 (minor but probably significant) and CYP2D6 and various other CYP and FMO enzymes (minor and probably insignificant). On the basis of these data, a clinical DDI study was conducted to characterize the effects of ketoconazole, a potent inhibitor of CYP3A4/5 and CYP2J2, on the PK of pimavanserin. As expected, ketoconazole caused an increase in plasma C_{max} and AUC of pimavanserin (1.5-fold and 3.3-fold, respectively).

Additionally, based on an *in vitro* evaluation of pimavanserin as a reversible and irreversible inhibitor of the major CYP enzymes involved in drug metabolism, pimavanserin is predicted to cause no clinically-significant inhibition of hepatic CYP enzymes; however, these studies suggest the potential for inhibition of intestinal CYP3A4/5. A drug-drug interaction study is therefore being conducted to evaluate the effect of pimavanserin on the plasma PK of oral midazolam, a sensitive *in vivo* probe substrate for CYP3A4/5. Data from this study will be presented in the NDA.

An additional clinical DDI study was performed (as previously described in Question 10) to assess the effect of pimavanserin on the pharmacokinetic profile of carbidopa-levodopa (Sinemet®). This study was conducted on clinical grounds (though there was no anticipated pharmacokinetic interaction based on *in vitro* drug-interaction studies or based on clinical experience.) As expected, the formal DDI study confirmed no effect of pimavanserin on the pharmacokinetic profile of Sinemet®.

On the basis of all available data, pimavanserin is not anticipated to have any other drug-drug interaction potential that would warrant further nonclinical or clinical studies.

An overview of the *in vitro* and *in vivo* studies which have contributed to an understanding of the clinical pharmacokinetic profile of pimavanserin (and its significant metabolites) is included in this briefing package.

Does FDA agree that the studies conducted to assess the pharmacokinetic profile of pimavanserin and its drug-drug interaction profile are adequate for NDA filing?

FDA Response to Question 14:

On face, yes, however, additional information may be requested after review of the NDA.

Discussion at meeting: There was no further discussion.

Question 15: Metabolite formation following pimavanserin dosing has been evaluated in humans and compared across other animal species, including rat, mouse, rabbit, and monkey. A combination of radiometric HPLC and LC/MS analysis identified 39 metabolites in human plasma and 3 more in urine or feces. The 42 metabolites comprised 9 primary metabolites, 14 secondary metabolites, 8 tertiary metabolites, 4 quaternary metabolites, 2 quinary metabolites and 5 unknowns (3 of which were detectable in plasma). Importantly, none of the metabolites were unique to humans. The plasma levels of pimavanserin and 37 metabolites have been assessed by LC/MS on Days 1 and 20 of dosing, and, without exception, formation of each involved well-established pathways of xenobiotic biotransformation. A mass balance study established that pimavanserin is, for all practical purposes, completely absorbed (>98%) from the intestine (<2% of parent drug is excreted in feces after 240 hours) and parent drug accounts for approximately 30% of circulating drug-derived material. At steady state (Day 20), the AUC of a metabolite identified as AC-279 (N-desmethyl-pimavanserin) is greater than 25% of parent AUC. Accordingly, AC-279 meets the FDA's criteria for a significant circulating metabolite from a drug interaction perspective (FDA, 2012). In addition, AC-279 accounts for >10% of circulating drug-derived material and therefore meets ICH criteria for a significant circulating metabolite from a Metabolites in Safety Testing (MIST) perspective. When human Day 1 and steady state plasma levels are compared with nonclinical Day 1 data, exposure multiples range from 16- to 53-fold and 5- to 16-fold, respectively. Exposure of nonclinical species is therefore considered to have been adequate for toxicologic evaluation of AC-279.

Like the parent molecule, AC-279 is also being evaluated in a panel of *in vitro* studies to assess its potential to be the perpetrator or victim of pharmacokinetic drug interactions. These studies include studies evaluating CYP enzyme induction in primary cultures of human hepatocytes; CYP enzyme inhibition (both reversible and irreversible) in human liver microsomes; transporter inhibition in cell monolayers or cell suspensions; transporter substrate studies in cell monolayers; and metabolic studies in human liver microsomes and recombinant human CYP and FMO enzymes. The results of the completed studies demonstrate that AC-279 has a low potential for drug-drug interactions and support the conclusion that further clinical drug-drug interaction studies are not warranted.

An overview of the *in vitro* and *in vivo* studies which have contributed to an understanding of the clinical pharmacokinetic profile of pimavanserin, AC-279 (and other metabolites) is provided in this Briefing package.

Does FDA agree that the studies conducted to characterize the major circulating metabolite, AC-279, and its drug-drug interaction profile are adequate for NDA filing?

FDA Response to Question 15:

On face, yes, however, additional information may be requested after review of the NDA.

Discussion at meeting: There was no further discussion.

Question 16: At the End-of-Phase 2 meeting, the possibility of conducting a formal safety study in the elderly as well as studies in renally and hepatically impaired subjects was discussed. Because of the age of the PD/PDP population that were enrolled in pimavanserin clinical studies (mean age \approx 70 years), a special safety study in the elderly was deemed unnecessary because of the >1100 subjects exposed to pimavanserin, over half have been elderly patients with PD/PDP. Further, total patient exposure in this elderly population exceeds 800 patient years and the longest single exposure is >8 years. Most importantly, the great majority of PDP subjects with long-term exposure received once-daily doses of 40 mg pimavanserin, the intended pharmacologic dose, with some patients (including those with the longest exposures) receiving once-daily doses of 60 mg. ACADIA therefore believes that safety in the elderly population has been adequately addressed and that a formal elderly study is not warranted for pimavanserin. In addition, no formal studies of pimavanserin in patients with renal or hepatic impairment have been conducted? ACADIA proposes that the label include language cautioning against use in such subjects until studies in these special populations are completed. This is supported again by the demonstrated safety of long term exposure in elderly subjects, whose renal and hepatic functions would be compromised.

Does FDA agree that this plan is acceptable for NDA filing and approval?

FDA Response to Question 16:

It will be a matter of review to determine if that is the case. You may submit the NDA prior to completion of the organ (hepatic and renal) impairment studies. But you should provide a time line when studies in renal and hepatic impaired patients would be completed and submitted to the Agency. These studies are needed to adequately provide information, including dosing, in the label for these populations. The language in the label regarding use in renal and hepatic impaired patients would be determined after review of the NDA.

Discussion at meeting: The sponsor agreed to provide a concrete timeline for submission of the studies for organ (renal and hepatic) dysfunction when the NDA is submitted. Determination of the language to be included in the label would be made after review of the NDA.

It was recommended that the sponsor explore using population pharmacokinetics methods with creatinine clearance as a covariate to make initial determination whether renal function

is correlated to pimavanserin exposure. Furthermore, the sponsor should compare safety or efficacy data in patients with or without renal impairment. .

The sponsor was reminded that the Clinical Pharmacology Aid template provided was not intended to replace the Clinical Pharmacology Summary required to be incorporated in Module 2 of the NDA. The sponsor agreed to submit both the response to the Clinical Pharmacology Summary Aid template and the Clinical Pharmacology Summary required for Module 2 of the NDA

Question 17: ACADIA plans to conduct a population pharmacokinetic analysis (mixed-effects methods using NONMEM) for the NDA submission. The analysis will include data from two small studies in healthy subjects with extensive sampling, one study in subjects with Parkinson's disease but no psychosis (also with extensive sampling), and at least three large studies in subjects with PDP (each with sparse trough samples). The number of subjects in the pharmacokinetic analysis should exceed 300 (most of whom are subjects with PDP) and the population will include a broad distribution of age, gender, and other relevant covariates.

Additional details regarding the analysis plan and the subjects to be included in the analysis (e.g., a table showing the distribution of covariates) are included in this briefing package.

Does FDA agree that the proposed analysis plan is adequate to characterize the population PK of pimavanserin for NDA filing and approval?

FDA Response to Question 17:

Yes, your proposed population PK analysis plan appears acceptable. The adequacy of the analysis to characterize the population pharmacokinetics of pimavanserin will be a review issue.

In your Population PK Analysis Plan you also note that an exposure-response analysis for efficacy is planned. We ask that you also explore the relationship between exposure and safety, including the following adverse events: QT prolongation, hallucinations, confusional state, edema and gait disturbance.

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

The following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1_ctl.txt, run1_lst.txt, plot1.R.txt) with a define pdf file to explain the role of each

file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

Additional Clinical Pharmacology Comments:

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

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

Please refer to the Attached Clinical Pharmacology Summary Aid for details of the generic questions to be answered and provided as a clinical pharmacology reviewer's guide.

Discussion at meeting: There was no further discussion.

2.4. Clinical

Question 18: The clinical program for pimavanserin has been underway since 2003. There are two early clinical studies of pimavanserin for which full clinical study reports are not available and therefore will not be included in Module 5. Neither of these studies was conducted under ACADIA sponsorship or under an ACADIA IND. These include the ACP-103-003 study which was conducted in Sweden at the Karolinska Institute. Safety, pharmacokinetic and positron emission tomography data from the four subjects enrolled in this study were reported in the *International Journal of Neuropsychopharmacology* (Nordstrom et al., 2007). A more detailed synopsis of the safety data from this study will be included in Module 2 of the NDA along with the published manuscript. Likewise, for study ACP-103-004 which was conducted by the NIH/NINDS under their own IND (IND (b) (4) sponsored by Thomas N. Chase, MD), a summary of the safety data available to ACADIA will be summarized in Module 2 of the NDA.

In addition, for a number of other clinical trials, study reports were finalized in 'legacy' format and will therefore be submitted as single PDFs. These include early safety and

tolerability studies (ACP-103-001, -002, -005 and -017), pharmacodynamic studies in healthy normal volunteers (ACP-103-009 and -011), studies in schizophrenia patients (ACP-103-007 and -008), and the mass balance study (ACP-103-016).

All studies in PDP patients, including the placebo-controlled studies ACP-103-006, -012, -014 and -020 as well as the long-term open-label studies ACP-103-010 and -015 will be submitted in granular format per the ICH E3 guidance. In addition, later stage Phase I studies, including the thorough QT study (ACP-103-018) and the drug-drug interaction studies (ACP-103-023, -024 and -027) will be presented in the NDA in granular format.

Does the Division agree to this presentation format for the pimavanserin clinical trial reports?

FDA Response to Question 18:

All safety data for every subject in the study needs to be submitted in granular format.

Discussion at meeting: We agree that this will be acceptable at this time; however, we may request granular reports at a later time, if needed.

Question 19: Narratives and case report forms for all subjects who died, discontinued study drug due to an adverse event, or had a serious adverse event in a pimavanserin study will be included in the NDA.

Additionally, narratives or patient profiles for subjects who experienced important adverse events of special interest, as defined by ACADIA, will be included in the ISS. These may include events associated with the use of atypical antipsychotics in the elderly (e.g., significant hematologic changes, cardiovascular events, cerebrovascular events, and neuroleptic malignant syndrome or related events). In addition, important events from placebo-controlled studies that may be suggestive of suicidality or abuse/dependence potential (see Questions 22 and 7, respectively) will also be summarized in individual narratives or patient profiles.

Does FDA agree to the plan for inclusion of the specified narratives and CRFs in the NDA?

FDA Response to Question 19:

Additionally, include clotting events; (PE, DVTs, MIs, and strokes), and syncope, pre-syncope, orthostatic disorders, QT prolongation and arrhythmia, appendicitis and diverticulitis. Due to the long half-life of the compound and its metabolite, an analysis of timing of SAEs and frequent side effects is recommended.

Discussion at meeting: We agree but however with further review of the data we may request further narratives.

Question 20: The ISE will provide a comprehensive analysis and summary of the effectiveness of pimavanserin in the treatment of PDP. The scope of the ISE includes comparisons of results from individual studies and integrated analyses of pooled data from two studies. Specific objectives to be addressed by the analyses include the following:

- To demonstrate the efficacy of 40 mg pimavanserin compared to placebo based on SAPS-PD score reduction and proportion of SAPS-PD responders in the PDP population.

- To summarize the efficacy of pimavanserin compared to placebo based on SAPS-H+D, SAPS-H, SAPS-D, CGI-Improvement (CGI-I) scores and on reductions of CGI-Severity (CGI-S), Caregiver Burden Scale (CBS), SCOPA-nighttime sleep (SCOPA-NS) and SCOPA-daytime sleep (SCOPA-DS) scores in the PDP population. Proportions of CGI-I responders will also be summarized.
- To evaluate the efficacy of pimavanserin compared to placebo in subgroups of the PDP population based on age category, gender, race, region, MMSE scores, pre-adjustment of Parkinson's disease medications, and prior antipsychotics usage within 21 days prior to study treatment.
- To summarize the longer-term (open-label) effectiveness of pimavanserin as measured by SAPS-PD, SAPS-H+D, SAPS-H, SAPS-D, CGI-S, CGI-I and CBS in the PDP population.

Pooling is only justified when there are homogeneous conditions for patient population, duration of treatment and relative effect versus a common comparator for the regimens tested. These conditions are only met for studies ACP-103-020 and ACP-103-012 (North America, 40 mg and placebo groups). The efficacy endpoints of interest for the pooled efficacy analysis will be SAPS-PD, SAPS-PD Responder, SAPS-H+D, SAPS-H, SAPS-D, CGI-S, CGI-I, CGI-I Responder, CBS, SCOPA-NS, and SCOPA-DS. Subgroup summaries for each age group (<65, 65-75 and >75 years), sex (male and female), race (white vs. non-white), MMSE total score (<25, ≥25), concomitant Parkinson's disease medications/antipsychotics usage (yes, no), prior use of antipsychotics, and any adjustments (within 6 months) to Parkinson's disease medications will be presented.

The draft statistical analysis plan for the ISE is provided in this briefing package.

Does FDA agree that the analysis plan is adequate to support NDA filing?

FDA Response to Question 20:

Yes. We welcome any sensible exploratory analysis in the submission, including your current plan for the ISE. Besides, additional exploratory analyses may be requested during our review process.

Discussion at meeting: There was no further discussion.

Question 21: The ISS will reflect safety data for all subjects who received at least one dose of study drug. Pooled analyses will be performed within the PD/PDP population and the healthy normal volunteer (HNV) population. (The only exclusions are for studies ACP-103-004 and ACP-103-003 for the reasons previously identified in Question 18.)

The pooled PD/PDP dataset will provide an overall assessment of the safety and tolerability of pimavanserin within the target population and across different trial designs, treatment regimens and treatment durations. Additional analyses will also be performed to assess the safety and tolerability of pimavanserin in a 6-week placebo-controlled setting versus the long-term open-label setting.

The pooled HNV dataset will provide an overall assessment of the safety and tolerability of pimavanserin across a broad dose range within healthy normal volunteers who participated in Phase I studies. Each of these Phase I studies utilized a unique design and therefore only

exposure-adjusted AEs will be analyzed in the pooled analysis. Other safety assessments will be presented and discussed on an individual-study basis.

In addition, there are two Phase II studies conducted in schizophrenia patients. The treatment durations, types and dose levels of the adjunct therapies in these two studies were all different and therefore no pooled analyses will be performed. The results will therefore be presented and discussed on an individual-study basis.

The draft statistical analysis plan for the ISS is provided in this briefing package.

Does FDA agree that the analysis plan for the ISS is adequate to support NDA filing?

FDA Response to Question 21:

All studies need to be included in the pooled data.

Discussion at meeting: We agree but it will be a matter of review if we will need further analysis.

Question 22: All safety and efficacy studies in the pimavanserin clinical program were initiated prior to the release of the draft FDA guidance entitled *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials* where specific scales were recommended to evaluate suicidality risk. In order to address concerns regarding the potential for suicidal ideation and behavior with pimavanserin, ACADIA intends to review the safety database for any occurrences of the following preferred terms included in the high level group term (HLGT) of Suicidal and self-injurious behaviours NEC (MedDRA Version 15.1):

- Intentional self-injury
- Self-injurious ideation
- Self-injurious behavior
- Suicidal behavior
- Suicidal ideation
- Suicide attempt

A summary of these data and narratives for any identified events will be included in the Integrated Summary of Safety (ISS). It is intended that this information will serve to characterize the risk for suicidality that may be associated with pimavanserin,

Does FDA agree that this approach is adequate for the pimavanserin NDA?

FDA Response to Question 22:

Please map you data to the CSSRS standard and include all narratives for accidental injuries and overdoses.

Discussion at meeting: Please map the suicidal behaviors and ideation to the CSSRS as per the draft guidance. In regards to accidental injuries we generally agree but it will be a matter of review if this information will be needed to complete the NDA review.

Generally we do require narratives for suicidality data; however, since you only have 4 cases, it may be acceptable. We may request this at a later time, if needed. We would, however, like to have narratives for “fall”.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 26, 2014, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

4.0 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.

- Major components of the application are expected to be submitted with the original 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 is scheduled for Thursday, June 5, 2014. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

5.0 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>.

6.0 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.

7.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

8.0 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.				

9.0 ATTACHMENTS AND HANDOUTS

- The Clinical Pharmacology Summary Aid attached (refer to FDA Response to Question 17 above).
- Acadia Responses to FDA Preliminary Pre-NDA Comments for Selected Questions (Sent on May 31, 2014).

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

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

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

2. Question Based Review

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

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

2.2 General Attributes of the Drug

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

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug

products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

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

2.2.3 What are the proposed dosages and routes of administration?

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

2.3 General Clinical Pharmacology

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

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

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

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

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

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

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

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

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex,

race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

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

2.4.3 Does this drug prolong QT/QTc Interval?

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

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

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

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

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max}, t_{max}, AUC, C_{max,ss}, C_{min,ss}, C_{max,ss}/C_{min,ss}, t_{max,ss}, AUC_{0-τ}, CL/F, V/F and t_{1/2} (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

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

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

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

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max}, C_{min}, CL/F and t_{1/2} of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

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

2.5.5 What are the characteristics of drug distribution?

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

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

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

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

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to

be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

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

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

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

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

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

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

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

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

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

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

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

2.6 Intrinsic Factors

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

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

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target

population and their variability, what dosage regimen adjustments are recommended for each group?

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

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

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

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on Cl_{cr} for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly

altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

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

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the

rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

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

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

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

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

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

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

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

2.7.2 Is the drug a substrate of CYP enzymes?

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

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

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each

relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/K_i ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

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

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

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

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

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

2.7.7 What are the drug-drug interactions?

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

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

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t_{1/2}, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

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

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

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

2.8 General Biopharmaceutics

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

IR Product

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

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

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

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and

efficacy data support the approval of the to-be-marketed product?

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

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

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

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

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

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

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

2.8.8 What is evidence that MR formulation displays less variability in C_{max}, AUC and C_{min} than IR formulation?

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

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

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

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

2.8.11 Are the MR and IR products marketed simultaneously?

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

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

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

2.9 Analytical Section

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

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

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

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

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

Identify all studies that used a particular assay method. For each assay report

indicate the corresponding assay validation report.

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

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

2.9.5.1 What are the lower and upper limits of quantitation?

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

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

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

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

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

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

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

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

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

Briefly describe the methods and summarize the assay performance.

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

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

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

RESPONSES TO FDA'S PRELIMINARY COMMENTS
For the Pimavanserin Pre-NDA Meeting Scheduled for 2 June 2014
IND 68,384

In response to the preliminary comments provided by FDA in preparation for the Pre-NDA Clinical/Nonclinical meeting scheduled for June 2, ACADIA would like to revise the agenda and hold a teleconference instead of a face-to-face meeting. The Agency's comments are very helpful and have fully addressed 13 of the 22 questions raised in the briefing package. In light of these agreements, we would like to focus our teleconference discussions on just the 9 questions where we need further clarification. In brief, we believe that no further discussion is needed for Questions 1, 2, 3, 4, 5, 8, 9, 11, 13, 14, 15, 17 and 20, as the Agency's preliminary comments were clear and we will proceed as advised. In the June 2 teleconference, we would like to discuss Questions 6, 7, 10, 12, 16, 18, 19, 21 and 22 in order to gain further clarity on FDA's preliminary comments for these items. As an aid to the discussions, we have provided the following written responses to FDA's preliminary comments on the pertinent questions. To make our responses easier to find, they are presented in blue font and follow the FDA's comment on each question.

We appreciate the provision of the Clinical Pharmacology Summary Aid and will utilize it as we develop the Clinical Pharmacology Summary for submission in the NDA.

With regard to the need for submission of a formal waiver request for pediatric studies, we will prepare that in the coming weeks and submit it to the IND for consideration.

Question 6:

(b) (4)

(b) (4)

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[REDACTED] (b) (4)

Does FDA agree [REDACTED] (b) (4)

FDA Response to Question 6:

On its face, we do not find that your rationale supports [REDACTED] (b) (4)
[REDACTED] however a final decision will be made on review of the NDA.

We request that you include this rationale in the NDA along with any additional safety issues
[REDACTED] (b) (4) that you may be aware of.

ACADIA Response to FDA Comments on Question 6:

[REDACTED] (b) (4)

Question 7: Pimavanserin is a highly potent 5-HT_{2A} inverse agonist with no other clinically significant pharmacological actions. Although CNS-active, it appears to have no potential for abuse or dependence as determined by its in vitro profile, its effects in safety pharmacology evaluations and animal behavior models, and by the observed profile of subjective responses and adverse events (AEs) in human studies conducted to date. Accordingly, formal studies of abuse potential in animals (to evaluate drug discrimination, drug self-administration, physical dependence) and in humans (i.e., laboratory evaluation in abusers) have not been considered necessary. ACADIA proposes that the current nonclinical and clinical datasets will be sufficient to assess abuse potential as specified in 21 CFR 314.50(d)(5)(vii) and as described in the draft FDA guidance “Assessment of Abuse Potential of Drugs.” This analysis is expected to support a recommendation for non-scheduled status for pimavanserin.

Do the Division and CSS agree with this plan?

FDA Response to Question 7:

We request that the abuse potential assessment you submit in the NDA includes comprehensive

descriptions of all pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, clinical studies, drug formulation data. We are available to review abuse potential protocols prior to the commencement of the studies. More information may be required at the time of your NDA submission, see (e.g., page 5) the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

ACADIA Response to FDA Comments on Question 7:

It is our understanding, based on the preliminary comments received for this question, that the Agency accepts our proposal and that the NDA can be filed on the basis of available data from our clinical, nonclinical and CMC program. We will follow the cited draft guidance on assessment of abuse potential and will include in the NDA an abuse potential section with the following information from our current database:

- A summary, interpretation, and discussion of abuse potential data provided in the NDA
- A proposal and rationale for placing (or not placing) a drug into a particular schedule of the Controlled Substances Act
- All primary data related to the abuse potential characterization of the drug, organized under the following subheadings:
 - a. Chemistry
 - b. Preclinical Pharmacology
 - c. Animal Behavioral and Dependence Pharmacology
 - d. Pharmacokinetics/Pharmacodynamics
 - e. Human Abuse Potential Laboratory Studies
 - f. Clinical Trial Data Relative to Abuse and Dependence Potential
 - g. Integrated Summaries of Safety and Efficacy
 - h. Foreign Experience with the Drug (Adverse Events, Abuse Potential, Marketing and Labeling)

If we have misinterpreted the Agency's preliminary comments on this question, we ask that the Agency clarify its position in the meeting.

Question 10: At the Pre-IND meeting held in July 2003, FDA requested that nonclinical drug interaction studies of pimavanserin with Sinemet® (carbidopa-levodopa) be performed. In the End-of-Phase II meeting held in September 2006, a plan for the conduct of these studies was agreed. Study 1574-001 was subsequently conducted to characterize the toxicity and toxicokinetic profile of the pimavanserin/carbidopa-levodopa combination when administered via oral gavage to male rats for 14 consecutive days. The results suggested no effect of combination therapy on the toxicity profile or PK of pimavanserin. Though no additional studies were performed to assess the safety of the combination therapy in monkeys, additional clinical data obtained since the End-of-Phase II meeting support the safety of pimavanserin when given in combination with carbidopa-levodopa. These studies include placebo-controlled safety and efficacy studies in ~700 PDP patients (>95% of whom were on concomitant carbidopa-levodopa therapy), long-term open-label safety studies in ~500 of these same PDP patients, and a formal drug-drug interaction (DDI) study in 20 healthy normal volunteers. Data from all of these clinical studies support the conclusion that pimavanserin has no effect on carbidopa-levodopa

blood levels and can safely be used in combination with Sinemet® and other carbidopa-levodopa therapies.

The proposal to not pursue further combination toxicity studies is consistent with the ICH Guidance M3(R2) on Nonclinical Safety Studies for the Conduct of Human Clinical Trials And Marketing Authorization For Pharmaceuticals, which was issued 11 June 2009 (after the End-of-Phase II meeting). It states that “[f]or most combinations which involve two late stage entities and for which there is adequate clinical experience with co-administration, combination toxicity studies would generally not be recommended to support clinical studies or marketing unless there is significant toxicological concern.” ACADIA believes that the clinical experience with pimavanserin provides sufficient body of evidence to conclude that co-administration with Sinemet® (carbidopa-levodopa) is safe.

Does FDA agree that no additional nonclinical toxicity evaluation of the combination of pimavanserin with Sinemet® (carbidopa-levodopa) is needed to support filing and approval of the NDA for pimavanserin?

FDA Response to Question 10:

Based on your clinical experience with pimavanserin given in combination with carbidopa-levodopa, we consider your 14-day general toxicology study of pimavanserin/carbidopa-levodopa combination in rat of adequate duration to assess general toxicity of the combination. However, you will also need to submit an embryo-fetal development study with this combination in a single species, to support use in women of child-bearing potential. Justification should be provided for the species selected.

ACADIA Response to FDA Comments on Question 10:

We do not believe that an embryo-fetal development study evaluating the combination of pimavanserin and Sinemet is warranted on several grounds:

- The risk for use of pimavanserin with Sinemet in women of childbearing potential is limited by the indication. Psychotic symptoms generally occur late in the course of PD progression. The mean duration of PD among the PDP subjects enrolled in pimavanserin trials was about 10 years and the mean age was >70 years. In these studies, only 3 of the female subjects enrolled were likely of childbearing potential (i.e., under the age of 50).
- A standard battery of reproductive toxicity studies (Seg I-III) was conducted with pimavanserin, and in the Seg II studies, in particular, pimavanserin was shown not to produce embryo-fetal toxicity.
- Though Sinemet carries a Category C label due to malformations observed in reproductive toxicity studies, pimavanserin has shown no such effects and would not be anticipated (based on the clinical drug-drug interaction study, ACP-103-024, nor on the 14-day combination toxicity study in rats) to augment the reproductive toxicity of Sinemet. Consistent with the ICH M3(R2) Guidance, Sinemet’s label should therefore stand on its own to appropriately limit use in women of childbearing potential.
- Though we were not able to do an exhaustive search of relevant SBAs, the only similar precedent that we could find for combination reproductive toxicity studies being conducted with Sinemet was for Azilect®, but in that case there was overlapping toxicity with Azilect and Sinemet.
- Pimavanserin is not required to be used in combination with Sinemet. Although a substantial majority of study patients were on Sinemet, they were also taking an average

Comment [GDP1]: DNP Comment: This statement is generally true, in study ACP-103-020 the mean age of participants was 71 years (range 53-90 years). Delusions may occur in younger PD patients with dysregulation syndrome, including female patients with child bearing potential. In addition, pimavanserin may be used (off label) in other populations including patients with Huntington’s disease where most female patients would be in their 30s to early 40s.

Comment [GDP2]: DNP Comment: There are several examples of PD medications that have a synergistic adverse effects on fetal development when give in combination with levodopa that are worse than the effects seen with the drug alone or with levodopa alone. The information is readily available in the approved product labels (see below).

From the Requip label: “The combined administration of ropinirole (10 mg/kg/day 8 times the maximum recommended human dose on a mg/m² basis) and L-dopa (250 mg/kg/day) to pregnant rabbits during organogenesis produced a greater incidence and severity of fetal malformations (primarily digit defects) than were seen in the offspring of rabbits treated with L-dopa alone. No indication of an effect on development of the conceptus was observed in rabbits when a maternally toxic dose of ropinirole was administered alone (20 mg/kg/day, 16 times the maximum recommended human dose on a mg/m² basis)”.

From the Tasmar label: “Tolcapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The combination of tolcapone (100 mg/kg/day) with levodopa/carbidopa (80/20 mg/kg/day) produced an increased incidence of fetal malformations (primarily external and skeletal digit defects) compared to levodopa/carbidopa alone when pregnant rabbits were treated throughout organogenesis”.

of >10 other concomitant medications for which the combination policy is not being applied. It is therefore unclear why the combination policy is being applied in this case. Moreover, based on the M3(R2) Guidance, an embryo-fetal study would not be required unless there is a specific cause for concern.

We therefore respectfully request reconsideration of the requirement for a combination reproductive toxicity study on the grounds outlined above.

Question 12: There are two related-substance impurities (b) (4) of the pimavanserin tartrate drug substance that will be specified (identified and qualified). These are designated as Impurities (b) (4). This impurity has been found to be at a level of up to (b) (4)% on release of drug substance. In drug product, Impurity (b) (4) has been observed (b) (4) up to (b) (4)% under accelerated conditions (40°C/75% RH) at six months.

Impurity (b) (4) has recently been identified in laboratory studies as a potential impurity that could be present above the (b) (4)% ICH qualification threshold in pimavanserin tartrate drug substance.

ACADIA plans to assess the genotoxic potential of Impurities (b) (4) using the bacterial mutation (b) (4) (Ames) and to conduct separate 28-day repeat-dose studies in rats with the respective impurities spiked at (b) (4)%.

Does FDA agree that the strategy described is adequate to qualify the impurities associated with pimavanserin's manufacturing, and storage?

FDA Response to Question 12:

CMC response – The approach seems reasonable from a CMC perspective. However, the final determination of the adequacy of a proposed control strategy, including testing and limits, for related substances will be determined as part of the NDA review based on the justification, supported by data, provided in the submission.

Nonclinical response - Your proposed strategy for qualification of impurities/degradants is inadequate. To assess genotoxicity, you will need to provide a study for chromosomal aberrations, in addition to point mutations (Ames). Because Parkinson's Disease is a chronic indication, you will need to provide a 90-day, not 28-day, general toxicity study in one species. Additionally, you will need to submit an embryo-fetal development study in a single species, to support use in women of child-bearing potential.

ACADIA Response to FDA Comments on Question 12:

We agree to the request to conduct chromosomal aberration studies with Impurity (b) (4) and Impurity (b) (4). Please note that the Ames studies for each of these impurities have been completed and both were negative, but we will now also conduct the chromosomal aberration studies to further confirm a lack of genotoxic potential with the compounds.

With regard to the need for an additional 90-day toxicity study to support the safety profile of the two impurities, we wish to note that 14- and 28-day studies are commonly performed to qualify

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impurities in drug substances/products intended for chronic use. Consideration was given to the duration of the conduct of the toxicity studies in rats, and 28 days was determined to be appropriate. The primary findings of weight loss and phospholipidosis were identified in the 28-day rat toxicity study of pimavanserin and were seen in the 3-month and 6-month rat studies. Studies of longer duration did not identify additional effects. Therefore, 28-day studies were considered appropriate for detecting any toxicities that may result from the related compounds (b) (4)

(b) (4)

In the 28-day toxicity study with Impurity (b) (4) once daily oral administration of pimavanserin or pimavanserin + Substance (b) (4) was well tolerated in rats at levels of 30 mg/kg/day, 10 mg/kg/day + (b) (4) mg/kg/day or 30 mg/kg/day + (b) (4) mg/kg/day, respectively. The results were similar between the formulations at 30 mg/kg/day; therefore, the presence of Substance (b) (4) had no impact on the overall effects of pimavanserin. The 28-day study with Impurity (b) (4) has completed the in-life phase and no apparent differences in toxicity were observed between the pimavanserin and pimavanserin + Substance (b) (4) groups (30 mg/kg/day, 10 mg/kg/day + (b) (4) mg/kg/day or 30 mg/kg/day + (b) (4) mg/kg/day, respectively).

(b) (4)

(b) (4) **Specified Impurities**

Compound	Structure	Molecular Formula and Weight
(b) (4)		

Embryo-fetal development studies have not historically been required for qualification of impurities. ICH guidance Q3A(R2) does not specifically mention embryo-fetal development studies in the types of studies to be considered for qualification. "Other specific toxicity

endpoints, as appropriate” is listed as a bullet point in Attachment 3. However, for pimavanserin, there are no specific causes for concern as it relates to embryo-fetal toxicity and there is no reason to believe the related products would have any impact on embryo-fetal development. ACADIA considers that genotoxicity studies (both Ames and chromosomal aberration) and a 28-day toxicity study in rats are adequate to characterize and thus qualify Impurities (b) (4)

On the basis of the points made above, we respectfully ask the Agency to reconsider the requirement for 90-day toxicity studies and embryo-fetal development studies as outlined in the preliminary comments.

Question 16: At the End-of-Phase 2 meeting, the possibility of conducting a formal safety study in the elderly as well as studies in renally and hepatically impaired subjects was discussed. Because of the age of the PD/PDP population that were enrolled in pimavanserin clinical studies (mean age \approx 70 years), a special safety study in the elderly was deemed unnecessary because of the >1100 subjects exposed to pimavanserin, over half have been elderly patients with PD/PDP. Further, total patient exposure in this elderly population exceeds 800 patient years and the longest single exposure is >8 years. Most importantly, the great majority of PDP subjects with long-term exposure received once-daily doses of 40 mg pimavanserin, the intended pharmacologic dose, with some patients (including those with the longest exposures) receiving once-daily doses of 60 mg. ACADIA therefore believes that safety in the elderly population has been adequately addressed and that a formal elderly study is not warranted for pimavanserin. In addition, no formal studies of pimavanserin in patients with renal or hepatic impairment have been conducted? ACADIA proposes that the label include language cautioning against use in such subjects until studies in these special populations are completed. This is supported again by the demonstrated safety of long term exposure in elderly subjects, whose renal and hepatic functions would be compromised.

Does FDA agree that this plan is acceptable for NDA filing and approval?

FDA Response to Question 16:

It will be a matter of review to determine if that is the case. You may submit the NDA prior to completion of the organ (hepatic and renal) impairment studies. But you should provide a time line when studies in renal and hepatic impaired patients would be completed and submitted to the Agency. These studies are needed to adequately provide information, including dosing, in the label for these populations. The language in the label regarding use in renal and hepatic impaired patients would be determined after review of the NDA.

ACADIA Response to FDA Comments on Question 16:

ACADIA is currently planning to conduct organ-impairment studies in parallel with NDA finalization and review. The protocols are planned for finalization this summer and we anticipate starting the studies in the fall. However, given the nature of these studies, we do not anticipate completing them and having final study reports until near or after NDA approval. We propose therefore that the label at initial approval include language cautioning against use of pimavanserin in patients with hepatic or renal impairment. Following submission of the organ-impairment study data, the label could be modified to provide more specific guidance about the appropriate use of pimavanserin in these populations.

Question 18: The clinical program for pimavanserin has been underway since 2003. There are two early clinical studies of pimavanserin for which full clinical study reports are not available and therefore will not be included in Module 5. Neither of these studies was conducted under ACADIA sponsorship or under an ACADIA IND. These include the ACP- 103-003 study which was conducted in Sweden at the Karolinska Institute. Safety, pharmacokinetic and positron emission tomography data from the four subjects enrolled in this study were reported in the International Journal of Neuropsychopharmacology (Nordstrom et al., 2007). A more detailed synopsis of the safety data from this study will be included in Module 2 of the NDA along with the published manuscript. Likewise, for study ACP-103-004 which was conducted by the NIH/NINDS under their own IND (IND (b) (4) sponsored by Thomas N. Chase, MD), a summary of the safety data available to ACADIA will be summarized in Module 2 of the NDA.

In addition, for a number of other clinical trials, study reports were finalized in 'legacy' format and will therefore be submitted as single PDFs. These include early safety and tolerability studies (ACP-103-001, -002, -005 and -017), pharmacodynamic studies in healthy normal volunteers (ACP-103-009 and -011), studies in schizophrenia patients (ACP- 103-007 and -008), and the mass balance study (ACP-103-016). All studies in PDP patients, including the placebo-controlled studies ACP-103-006, -012, - 014 and -020 as well as the long-term open-label studies ACP-103-010 and -015, will be submitted in granular format per the ICH E3 guidance. In addition, later stage Phase I studies, including the thorough QT study (ACP-103-018) and the drug-drug interaction studies (ACP-103-023, -024 and -027) will be presented in the NDA in granular format.

Does the Division agree to this presentation format for the pimavanserin clinical trial reports?

FDA Response to Question 18:

All safety data for every subject in the study needs to be submitted in granular format.

ACADIA Response to FDA Comments on Question 18:

ACADIA wishes to clarify that this question related only to the electronic publishing format for the clinical study reports (not individual subject data). The study reports that cannot be published in the eCTD in granular format were produced as single scanned PDFs prior to the established guidelines for eCTD granularity. As this is the format in which these legacy reports were finalized and approved, we propose submitting them in this manner. There is no difference in the ability to review and navigate legacy vs. granular reports.

Please note that within all study reports (including those in legacy format and the newer reports published in granular format), all subjects are appropriately represented. In addition, the datasets provided with each report (see Question 8) will include data for all subjects enrolled.

We ask for confirmation from the Division that the submission of early reports in legacy format (i.e., as single, scanned PDFs) is acceptable, with the understanding that these reports (as well as later granular study reports) contain all data for all subjects on study. Please note, however, that Study -003 and -004, for the reasons described in the original question, will only be presented as synopses in Module 2.

Question 19: Narratives and case report forms for all subjects who died, discontinued study drug due to an adverse event, or had a serious adverse event in a pimavanserin study will be included in the NDA.

Additionally, narratives or patient profiles for subjects who experienced important adverse events of special interest, as defined by ACADIA, will be included in the ISS. These may include events associated with the use of atypical antipsychotics in the elderly (e.g., significant hematologic changes, cardiovascular events, cerebrovascular events, and neuroleptic malignant syndrome or related events). In addition, important events from placebo-controlled studies that may be suggestive of suicidality or abuse/dependence potential (see Questions 22 and 7, respectively) will also be summarized in individual narratives or patient profiles.

Does FDA agree to the plan for inclusion of the specified narratives and CRFs in the NDA?

FDA Response to Question 19:

Additionally, include clotting events; (PE, DVTs, MIs, and strokes), and syncope, pre-syncope, orthostatic disorders, QT prolongation and arrhythmia, appendicitis and diverticulitis. Due to the long half-life of the compound and its metabolite, an analysis of timing of SAEs and frequent side effects is recommended.

ACADIA Response to FDA Comments on Question 19:

We agree to provide narratives for all subjects who experienced clotting events, syncope, pre-syncope, QT prolongation and arrhythmia, and diverticulitis. There were no events of appendicitis reported in any study of pimavanserin (including in healthy volunteers and schizophrenia patients).

With regard to orthostatic disorders, we would like to note that in the 6-week placebo-controlled PDP studies there were 13 such events in the placebo group vs. 7 in the pimavanserin 10 mg arm and 3 in the pimavanserin 40 mg arm. In the long-term PDP program, there was 1 event of orthostatic tremor, 36 events of orthostatic hypotension and 1 event of postural dizziness over the life of the studies. Given that postural hypotension commonly occurs in PD patients and that our database shows a consistent reduction in these events for pimavanserin 40 mg over placebo, we do not believe that narratives are warranted for orthostatic disorders. We would like to seek agreement in the meeting on this proposal.

Question 21: The ISS will reflect safety data for all subjects who received at least one dose of study drug. Pooled analyses will be performed within the PD/PDP population and the healthy normal volunteer (HNV) population. (The only exclusions are for studies ACP-103-004 and ACP-103-003 for the reasons previously identified in Question 18.) The pooled PD/PDP dataset will provide an overall assessment of the safety and tolerability of pimavanserin within the target population and across different trial designs, treatment regimens and treatment durations. Additional analyses will also be performed to assess the safety and tolerability of pimavanserin in a 6-week placebo-controlled setting versus the long-term open-label setting.

The pooled HNV dataset will provide an overall assessment of the safety and tolerability of pimavanserin across a broad dose range within healthy normal volunteers who participated in Phase I studies. Each of these Phase I studies utilized a unique design and therefore only exposure-adjusted AEs will be analyzed in the pooled analysis. Other safety assessments will be presented and discussed on an individual-study basis.

In addition, there are two Phase II studies conducted in schizophrenia patients. The treatment durations, types and dose levels of the adjunct therapies in these two studies were all different

and therefore no pooled analyses will be performed. The results will therefore be presented and discussed on an individual-study basis.

The draft statistical analysis plan for the ISS is provided in this briefing package.

Does FDA agree that the analysis plan for the ISS is adequate to support NDA filing?

FDA Response to Question 21:

All studies need to be included in the pooled data.

ACADIA Response to FDA Comments on Question 21:

All safety data from all pimavanserin studies will be presented in the ISS (except ACP-103-003 and -004, which were not conducted under an ACADIA IND). These studies were conducted in healthy normal volunteers (HNV), subjects with schizophrenia and subjects with PD/PDP. The age distribution, general health status, underlying disease condition and comorbidities in these three populations are vastly different and therefore pooling all these populations together may skew the risk profiles for any particular population. In addition, in PD/PDP studies, subjects received pimavanserin (PIM) or placebo (PBO) as a monotherapy, while in the schizophrenia studies (ACP-103-007 and -008), subjects received PIM or PBO only in combination with other antipsychotics (haloperidol or risperidone). Furthermore, in study -007, subjects were randomized to receive either 60 mg PIM or PBO with various dose levels of haloperidol (stable dose \leq 20 mg/day) for 5 days; while in study -008, subjects were randomized to receive one of the following combinations for 6 weeks: 20 mg PIM + 2 mg risperidone, 20 mg PIM + 2 mg haloperidol, PBO + 2 mg risperidone, PBO + 2 mg haloperidol or PBO + 6 mg risperidone. The underlying disease, treatment regimen/duration and study designs of studies -007 and -008 made these 2 studies unique in our program and pooling them with other studies may obscure meaningful results. In our ISS SAP, we propose to properly combine data from studies that are of similar dose, duration, choice of control and population in order to provide better precision for risk estimation.

We would like to confirm the Division's understanding of our pooling plan and acceptance of the proposed ISS SAP.

Question 22: All safety and efficacy studies in the pimavanserin clinical program were initiated prior to the release of the draft FDA guidance entitled Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials where specific scales were recommended to evaluate suicidality risk. In order to address concerns regarding the potential for suicidal ideation and behavior with pimavanserin, ACADIA intends to review the safety database for any occurrences of the following preferred terms included in the high level group term (HLGT) of Suicidal and self-injurious behaviours NEC (MedDRA Version 15.1):

- Intentional self-injury
- Self-injurious ideation
- Self-injurious behavior
- Suicidal behavior
- Suicidal ideation
- Suicide attempt

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A summary of these data and narratives for any identified events will be included in the Integrated Summary of Safety (ISS). It is intended that this information will serve to characterize the risk for suicidality that may be associated with pimavanserin,

Does FDA agree that this approach is adequate for the pimavanserin NDA?

FDA Response to Question 22:

Please map your data to the CSSRS standard and include all narratives for accidental injuries and overdoses.

ACADIA Response to FDA Comments on Question 22:

We believe it may be unnecessary to map the suicidality data for pimavanserin to the CSSRS standard as there have been just four events associated with suicidal ideation or behavior in the PDP population and none in the schizophrenia or healthy volunteer studies. These include one event of accidental overdose in the pimavanserin 40 mg group in the blinded 6-week PDP studies. The overdose is not well-described but occurred 16 days after the patient completed the study and after all clinical supplies of pimavanserin had been returned. In the open-label studies, there were two events of suicidal ideation. In addition, one event of suicide attempt occurred in a subject who had been on study for >2 years. We will provide narratives for all of the events described above in the NDA.

With regard to events of accidental injury, we ask for clarification on the types of events that the Agency would be most interested in seeing, as the PDP population is highly prone to falls and the SOC for injury, poisoning and procedural complications reflects a correspondingly high number of event terms that are more likely fall-related than self-injurious events. The table below presents the injury data from across the placebo-controlled PDP studies and shows a low overall incidence of potentially self-injurious events, and, in fact, the incidence is lower in the pimavanserin arms compared to placebo. We therefore do not believe that narratives for accidental injury are warranted in the NDA. Does the Division agree?

Treatment-Emergent AEs of Injury, Poisoning and Procedural Complications in the 6-Week Placebo-Controlled PDP Studies of Pimavanserin

System Organ Class Preferred Term	Placebo (N=231) n(%)	PIM 10 mg (N=140) n(%)	PIM 20 mg (N=41) n(%)	PIM 40 mg (N=202) n(%)	All PIM (N=383) n(%)
Injury, poisoning and procedural complications					
Accidental overdose	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Fall	21 (9.1)	7 (5.0)	3 (7.3)	13 (6.4)	23 (6.0)
Contusion	5 (2.2)	0 (0.0)	1 (2.4)	4 (2.0)	5 (1.3)
Laceration	4 (1.7)	0 (0.0)	1 (2.4)	2 (1.0)	3 (0.8)
Limb injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Muscle strain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Periorbital haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Radial nerve injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Skeletal injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Excoriation	4 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Joint dislocation	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle rupture	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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System Organ Class Preferred Term	Placebo (N=231) n(%)	PIM 10 mg (N=140) n(%)	PIM 20 mg (N=41) n(%)	PIM 40 mg (N=202) n(%)	All PIM (N=383) n(%)
Spinal fracture	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stress fracture	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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
07/02/2014



IND 68,384 Serial #039

Acadia Pharmaceuticals INC.
Attention: Hilde Williams, Director, Regulatory Affairs
3911 Sorrento Valley Blvd.
San Diego, CA 92121

Dear Ms. Williams:

Please refer to the teleconference between representatives of your firm and FDA on September 25, 2006. The purpose of this meeting was to provide guidance regarding proposed phase IIb/III clinical design and the adequacy of the phase III clinical and preclinical program for registration.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING

IND 68,384, ACP-103
Acadia Pharmaceuticals INC.
Type B meeting / EOPII
September 25, 2006

Participants –

FDA

Robert Temple, MD	Director, Office of Drug Evaluation 1
Thomas Laughren, MD	Director, Division of Psychiatry Products
Ni Aye Khin, MD	Medical Team Leader, Division of Psychiatry Products
Earl Hearst, MD	Medical Reviewer, Division of Psychiatry Products
Marc Walton, MD	Deputy Director, Division of Neurology Products
Russell Katz, MD	Director, Division of Neurology Products
John Feeney III, MD	Medical Team Leader, Division of Neurology Products
Leonard Kapcala, MD	Medical Reviewer, Division of Neurology Products
Peiling Yang, PhD	Statistics Team Leader
Yeh-Fong Chen, PhD	Biostatistics Reviewer
Barry Rosloff, PhD	Supervisory Pharmacologist
April Robison	Pharmacy Student Intern
Keith Kiedrow, PharmD	Regulatory Project Manager

Attendees Representing the Sponsor

Marylynn Cain	Manager, Regulatory Affairs
David Furlano, PhD	Vice President, Regulatory Affairs
Roger Mills, MD	Executive Vice President, Development
Dan van Kammen, MD, PhD	Vice President, Clinical Development
Kim Vanover, PhD	Director, Clinical Operations
Hilde Williams	Director, Regulatory Affairs
(b) (4)	Clinical Pharmacology and Medical Consultant
(b) (4)	(b) (4)
(b) (4)	(clinical consultant)
(b) (4)	(b) (4) (statistical consultant)

Background:

ACP-103 is an inverse agonist of 5HT_{2A} and 5HT_{2C} receptors that the sponsor is developing for the treatment of Parkinson's disease psychosis (PDP). We have had several meetings with the sponsor, including: (1) a 7-2-03 preIND meeting (under IND 63,931); (2) an 11-12-03 telcon under IND 68,384; and (3) a 6-29-06 meeting during which we reached agreement on a number of issues pertinent to the development of this product for this indication. [See minutes for each of these meetings for additional background for this meeting.]

The sponsor is planning a 6-week phase IIb/III study (ACP-103-012) that will compare 2 dose levels of ACP-103 (10 and 40 mg/day) vs placebo in patients with PDP. Dose justification is based on experience from study 006 and PET receptor occupancy studies. Patients must be on stable anti-Parkinson's therapy with no changes within 1 week prior to starting, and must have an MMSE of ≥ 21 . The entry criteria for PDP are expected to be in line with the anticipated diagnostic criteria for PDP coming out of the recent NINDS meeting. As indicated in the 6-29-06 telcon, the primary assessment will be the combined hallucinations and delusions domains of

the SAPS. The study will be powered to detect a difference on the SAPS as well as a 5 point margin of difference between drug and placebo on the key secondary endpoint, i.e., the UPDRS Parts II and III. However, the sponsor apparently does not plan to formally assess noninferiority on this endpoint, but rather, provide only “descriptive statistics.”

The sponsor expects to begin a second trial in phase 3, i.e., Study ACP-103-014. This study would include patients with Parkinson’s disease with or without psychosis. For this trial, the primary endpoint would be UPDRS Parts II and III, with a key secondary for assessing psychosis improvement (i.e., SAPS hallucinations and delusions). This would be a 6-month study comparing up to 2 ACP-103 dose arms vs placebo. The primary hypothesis would be a non-inferiority hypothesis, i.e., that ACP-103 is no worse than placebo by some margin. The sponsor is requesting accelerated approval of ACP-103 under 21CFR314.520 (Subpart H), based on the rationale that PDP is a serious illness for which there are no approved treatments. Thus, they would hope to gain approval based on Study 012 alone, with a commitment to complete Study 014 post-approval.

If permitted to develop ACP-103 under Subpart H, the sponsor would expect to have approximately 1000 exposed patients at the time of initial NDA submission, including approximately 100 for 6 months but no more than 25 for > 6 months.

Questions:

Clinical/Biopharmaceutical Questions

Endorsement of PDP as an indication for ACP-103

Question 1 background: supporting info found in briefing document Section 3; P. 21, Appendix 1; P. 94: As discussed in the Type C teleconference held with the Agency on 29 June 2006, the development of psychotic features in PD patients is likely a result of Parkinson’s disease progression and other PD-related factors, possibly in combination with anti-Parkinson’s treatment. The National Institute on Neurological Disorders and Stroke (NINDS) consensus meeting attended by the Division and industry representatives last November concluded that PDP was a discrete indication which could be clinically distinguished from other forms of psychosis (including drug induced psychosis). Publication of diagnostic criteria by an independent working group established out of the NINDS Workshop is forthcoming. (As discussed at the Type C teleconference, ACADIA intends to use the NINDS draft criteria to determine study eligibility for psychotic symptoms in its Phase IIb/III study.)

1. In light of this developing framework, does the Division agree that treatment of PDP is an indication for which ACADIA can seek registration/labeling?

Preliminary Comments: Yes, we are in agreement that PDP is a legitimate clinical target for drug development. However, as noted in our 6-29-06 telcon, it will be important to have specific and widely-accepted diagnostic criteria for selecting patients for any future studies.

Discussion at Meeting: There was no further discussion at the meeting.

Question 2 background: supporting info found in briefing document Section 3; P. 21, Section 5.1.1.1; P. 58: ACADIA intends to seek approval for ACP-103 in the first-line treatment of PDP. In the absence of any approved treatments in the United States (U.S.), first-line management of PDP sometimes involves dose-adjustment or even cessation of anti-Parkinsonian therapy. However, this approach typically worsens Parkinsonism and does not improve the

patient's psychiatric condition. Although off-label use of currently available antipsychotics have been employed in the treatment of PDP, most have not consistently demonstrated efficacy or an acceptable safety profile (e.g., 'black box' in this and other patient populations). Within this framework, there continues to be a need for proven safe and effective antipsychotic therapy that does not require pre-adjustment of anti-Parkinsonian treatment. Hence, for the proposed Phase IIb/III program, entry of PDP patients into ACP-103 trials will not be limited to those with previous adjustments of their dopaminergic therapy. Patients with and without prior reductions in L-dopa will be allowed to enroll, assuming they meet all other entry criteria.

2. If ACP-103 is demonstrated to be effective in improving psychotic symptoms while preserving motor function in patients with PDP, would the Division agree that a first-line label claim for ACP-103 may be endorsed without recommendations for prior adjustment of anti-Parkinsonian treatment?

Preliminary Comments: *As indicated in our 6-29-06 telcon, we would not require patients having had prior adjustment of anti-Parkinsonian treatment, providing that ACP-103 can be shown not to worsen Parkinsonian symptoms. However, we will ask that patients be carefully characterized with regard to adjustments in anti-Parkinson's drug treatments in the period preceding entry into your trials, so that treatment response can be explored in the 2 subgroups, i.e., those with and those without adjustment of their anti-Parkinson's drug treatments.*

Discussion at Meeting: *The sponsor agreed to collect information regarding adjustments in anti-Parkinson's drug treatments in the period preceding entry into their trials, so that treatment response can be explored post hoc in the 2 subgroups, i.e., those with and those without adjustment of their anti-Parkinson's drug treatments. They indicated their expectation was that a majority of patients would have had prior dosage adjustments. They then requested confirmation that this approach would suffice for gaining an indication without constraints on prior dose adjustments. We agreed in principle that their proposed approach should suffice, however, we cautioned that it would be a review issue and, in addition, any future NDA would very likely be presented to the PDAC. In addition, we asked that they provide preliminary data on the proportion of the first 50 patients who fell into each of these 2 subgroups. They agreed to provide this information.*

The adequacy of the Phase IIb/III study design for NDA filing and registration of ACP-103 for treatment of PDP

Questions 3, 4, and 5 supporting info found in briefing document Section 5.1.1.1; P. 58

3. Is the population, as proposed in the Phase IIb/III protocol synopsis, appropriate for NDA filing/registration to support the intended indication?

Preliminary Comments: *The population described generally appears to be appropriate, however, we would like clarification that a clearly defined set of diagnostic criteria will be in place at the time the trial is started and that patients will be expected to satisfy these criteria. In general, we want better characterization of the patients you intend to recruit for your trials. It is our expectation that most patients will have advanced Parkinson's disease, and we would like confirmation on this point. In addition, we recommend that the minimum MMSE score be set at 24, rather than 21.*

Discussion at Meeting: *The sponsor indicated that they do intend to use the NINDS Workshop criteria for PDP, and they agreed to submit to us within the next month a draft publication discussing these criteria. They did ask for confirmation that we would not require a particular threshold of severity of Parkinson's disease for entry into their trials, and we agreed. They did confirm, nevertheless, that they expect a majority of patients in these trials will have advanced Parkinson's disease. Finally, they argued that requiring an MMSE score of ≥ 24 rather than ≥ 21 would be too restrictive, and we agreed to accept 21 as a threshold score.*

4. Based on the proposed study design as outlined in the protocol synopsis, is the proposed Phase IIb/III trial of sufficient duration to support the intended indication?

Preliminary Comments: *Six weeks should be of sufficient duration to establish short-term antipsychotic efficacy.*

Discussion at Meeting: *The sponsor wanted confirmation that 2 positive studies of 6 weeks duration would be sufficient to support an antipsychotic claim that is not restricted regarding duration. We clarified that 2 such studies would support a general antipsychotic claim in PDP, however, labeling would also note that longer-term efficacy (i.e., beyond 6 weeks) had not yet been established.*

5. The proposed Phase IIb/III study will be powered to demonstrate superiority against placebo on the primary endpoint (mean combined Scale for the Assessment of Positive Symptoms [SAPS] hallucinations and delusions scores). The size of the proposed study (N = 280, with 2 active and 1 placebo arms), and specifically the number of patients per arm (n = ~80), was calculated (assuming a 10% drop out rate) to be able to detect a difference of 4.75 points on this endpoint at $\alpha = 0.05$ using a 2-sided test with 90% power.

This proposed sample size is also sufficient to ensure non-inferiority with 90% power on the key secondary endpoint, Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III scores, based on a 5-point non-inferiority margin with a 90% 2-sided CI on the treatment difference. Effects on this secondary endpoint will be reported using descriptive statistics.

- a) Does the Division agree that for the primary endpoint, a difference of 4.75 points in mean combined SAPS scores between placebo and ACP-103 is an appropriate margin for use in the Phase IIb/III program?

Preliminary Comments: *Yes.*

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

- b) Does the Division agree that the study will be sufficiently powered to support approval for the intended indication?

Preliminary Comments: *The power calculations seem reasonable, however, since the true effect size is not known, there is no guarantee the study will be sufficiently powered. We also notice that there are two doses of ACP-103 included in study 012 in comparison with placebo, but your sample size calculation did not take the multiple comparisons into consideration.*

Discussion at Meeting: *The sponsor proposed that the multiplicity issues would be handled using a Bonferroni adjustment or a stepdown approach, and we agreed that their proposed approaches were acceptable, but the explicit approach needs to be pre-specified in the protocol or SAP.*

- c) Does the Division agree with the proposal to use descriptive statistics to evaluate the key secondary endpoint, UPDRS Parts II and III scores?

Preliminary Comments: *Given the very wide margin for non-inferiority, we would expect that the non-inferiority hypothesis would be satisfied. If not, there would be concern that ACP-103 may not be an acceptable treatment because of a significant worsening of the Parkinsonian symptoms. Thus, we consider this critical information in our evaluation of any future NDA that must be evaluated along with the efficacy data before reaching a judgment about risk and benefit. Furthermore, this should be a 2-sided test using a 95% CI on the difference, because it is our understanding that you intend to consider both inferiority and superiority of ACP-103 to placebo on this outcome. Please send the statistical analysis plan to the FDA for review as early as possible prior to data unblinding to allow a sufficient time to finalize it.*

Discussion at Meeting: *The sponsor agreed to a 2-sided test using a 95% CI on the difference between drug and placebo. They asked if submitting a final SAP as late as a month before unblinding would be acceptable. We expressed reservations about such a late SAP. We asked that the protocols for their studies include sufficient detail about the planned analyses that it would not be necessary to make major changes late in the study.*

The adequacy of the overall clinical plan for ACP-103 to support a marketing application for the proposed indication of PDP

6. Is the clinical program, as proposed in the briefing package, for ACP-103 in PDP adequate for filing/registration? Specifically,
- a. Will the Phase IIb/III study, as outlined, provide adequate and well-controlled evidence of safety and efficacy in the PDP population? (background info Section 5.1.1.1; p.58)

Preliminary Comments: *We have several comments:*

-For Study 012, we strongly recommend that you include an active control group, e.g., quetiapine, even though there are no drugs approved for this indication. Having quetiapine as a control would help in the interpretation of both the efficacy benefit as well as any effect on motor function.

-Study 012 by itself will not be sufficient as a source of efficacy and safety data, even if it is positive on the efficacy outcome and meets the noninferiority hypothesis. We do not accept your argument for a Subpart H filing, thus, you must have evidence from 2 trials.

Discussion at Meeting: *The sponsor argued strongly against having an active control arm, and we agreed that this would not be a requirement, but rather, was a suggestion to help in interpretation of the findings from their studies. We explained our basis for rejecting a Subpart H filing, and also the alternative of 1 positive study plus confirmatory evidence. The sponsor asked if two placebo-controlled 6-week studies*

would suffice, and we indicated our agreement. We strongly encouraged them to utilize fixed dose designs in both studies.

- b. Given that PDP is a serious and life-shortening (if not life-threatening) condition without adequate treatment options, would the Division endorse accelerated approval under 21 CFR 314.520 (Subpart H), based on this single Phase IIb/III study, if the results are sufficiently robust? (background info Section 5.3.1; p.64)

Preliminary Comments: *As noted for question a, we do not agree with a Subpart H filing.*

Discussion at Meeting: *See 6a.*

- c. A second adequate and well-controlled study is proposed in patients with Parkinson's disease patients with or without psychosis. The primary endpoint is UPDRS Parts II and III (i.e., motor function) with a key secondary endpoint for assessing psychosis (i.e., SAPS Hallucinations and Delusions Total Score). (background info Section 5.1.2; p.62)

Assuming that this second study is initiated prior to NDA submission, would FDA accept study completion and submission of the data as a post-marketing commitment based on accelerated approval per 21 CFR 314.520 (Subpart H) with a single pivotal trial? (background info Section 5.3.1; p.64)

Preliminary Comments: *As noted for question a, we do not agree with a Subpart H filing.*

Discussion at Meeting: *See 6a.*

- d. Is the proposal for conducting drug-drug interaction studies, as outlined in Section 5.2.3, adequate for NDA filing/approval? (background info Section 5.2.3; p.64)

Preliminary Comments: *More information is needed about the range of likely co-administered drugs in this population before we can reach a judgment on this issue. We ask that you provide such information.*

Discussion at Meeting: *The sponsor provided a list of drugs expected to be coadministered with ACP-103, and indicated that they will study the interaction of ACP-103 and L-DOPA. In addition, they indicated that, based on the results of in vitro metabolism studies, they will likely study other interactions in vivo as well.*

- e. Will a QT study, conducted as per ICH E14 Guidance to Industry, provide adequate assessment of the risk for QT prolongation for ACP-103? Is the study adequate for NDA filing/approval? (background info Section 5.2.2; p.64)

Preliminary Comments: *A thorough QT study meeting ICH E14 standards should be capable of adequately addressing this question.*

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

- f. Is the plan for conducting studies in other special populations, as outlined in Section 5.2.2, adequate for NDA filing/approval? (background info Section 5.2.2; p.64)

Preliminary Comments: *Your plans to conduct special safety studies in the elderly, in hepatically impaired patients, in renally impaired patients, and a thorough QT study may be adequate, however, a final judgment on this issue must await review of emerging data from your development program.*

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

- g. Are the adsorption, distribution, metabolism, and excretion (ADME) studies, as proposed in Section 5.2.1, adequate for NDA filing/approval? (background info Section 5.2.1; p.64)

Preliminary Comments: *On face, the planned clinical pharmacology program appears to be adequate, however, a final judgment on what specific studies are needed will have to depend on emerging data from your development program.*

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

- h. Are there any other special or supportive clinical safety studies that the Division will require at time of NDA filing? (background info Section 5.2; p.64)

Preliminary Comments: *We have no specific advice to offer on this question at this early stage of development, however, a final judgment on what specific additional studies may be needed will have to depend on emerging data from your development program.*

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

7. As currently planned, at NDA submission more than 1000 subjects will have been exposed to various doses of ACP-103 (from 1 to 60 mg) and for periods up to 12 months (with most exposed for periods of 2-6 weeks). Because ACP-103 is being developed for multiple indications, the safety database will include patients with PDP as well healthy volunteers and patients with other diseases (e.g., schizophrenia). The safety database can be updated with additional exposures at the time of the 120-day update and further safety experience may be garnered in postmarketing studies. Given that patients with PDP are underserved by currently available treatment options and the population is inherently small (U.S. estimates range from <200,000 [Noyes, 2006] to 600,000 [Marsh, 2005]), ACADIA requests comment from the Division as to the adequacy of the projected safety database for NDA filing and approval.

Preliminary Comments: *ACP-103, if approved, would be a chronically used drug, and the NDA should meet ICH exposure criteria for such drugs.*

Discussion at Meeting: *The sponsor argued that PDP is a serious condition with substantial morbidity and is also hard to study because it is difficult to recruit patients. Even with 2 studies, they indicated that it will be very difficult to recruit ICH numbers for this program. We indicated that it would be acceptable to include safety data for other indications they plan to study, in particular, schizophrenia, and we suggested they consider a Treatment IND if their initial study is positive. Finally, we suggested that one factor in deciding how much exposure data might be acceptable would be the size of the treatment effect demonstrated by their studies. A very substantial benefit might well be an argument in favor of compromising somewhat on the total safety database.*

Nonclinical

The adequacy of the nonclinical plan for ACP-103 to support a marketing application for the proposed indication of PDP

1. Is the proposed nonclinical program to NDA adequate for filing/registration? (background info Section 6.2; p.88)

Preliminary Comments: *The nonclinical program is adequate in form but we, of course, will need to review the data. There is always the possibility that additional studies may be needed based on the results of the ongoing animal and human studies. In addition, you will need to characterize the in vivo metabolism of ACP-103 in rats and monkeys as well as in humans. Human metabolites which are not well covered in the animal toxicity studies may need further evaluation.*

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

2. Question background; supporting info found in briefing document Section 6.1.5.3; P. 86: Dose and duration-dependent phospholipidosis (PL) has been observed in toxicity studies of ACP-103 at doses of 90 mg in the rat (subchronic 3-month study) and ≥ 25 mg in the monkey (subchronic 3-month study). Drug-induced PL is considered an adaptive response to compounds like ACP-103 with a cationic amphiphilic structure (CADs), and its clinical significance is unknown. The PL observed in rat and monkey subchronic toxicity studies has demonstrated partial or complete reversibility following 4-week recovery periods. To date, the absence of PL has been used to define no-observed-effect levels (NOELs) in the subchronic toxicity studies.
 - a. Does the Division agree that doses of ACP-103 which result in PL (but demonstrate reversibility and occur in the absence of any persistent histopathological correlates) may be considered no-observed-adverse-effect levels (NOAELs) in these studies and that a reversible profile of PL is not of great clinical concern?

Preliminary Comments: *The Division cannot comment on this issue prior to our evaluation of the data in the 3, 6, and 12 month toxicity studies. If we concur that the PL is reversible and occurs in the absence of any persistent histopathological correlates, we would likely agree.*

Discussion at Meeting: There was no further discussion at the meeting.

- b. The 6- and 12-month chronic toxicity studies with ACP-103 in rats and monkeys are currently ongoing. The designs of these studies include an extended treatment period for the monkey study and extended post-treatment recovery phase (3 and 4 months for rats and monkeys, respectively) for all treatment groups in both the rat and monkey studies. These additions to the standard chronic design were incorporated to provide a clearer occurrence and reversibility profile of PL in these studies. Does the Division agree with this approach to chronic toxicity assessments, and that no additional studies would be necessary to further characterize PL?

Preliminary Comments: The Division cannot concur prior to our evaluation of the results of these studies. There is one concern with regard to the dose selection for the 6 month rat study. You state that an extended post-treatment recovery phase of up to 3 months in rats was “incorporated to provide a clearer occurrence and reversibility profile of PL.”. However, the high dose in this study is 30 mg/kg which is the NOEL for phospholipidosis based on the results of the three month rat study; thus the proposed study may not be adequate to evaluate reversibility.

Discussion at Meeting: The sponsor argued that duration of exposure was an important factor as well as dose in the development of PL, and that based on effects in shorter term rat studies PL is likely to become evident by 6 months of treatment at the 30 mg/kg dose. We agreed with this reasoning, but noted that this would still be a review issue.

3. ACADIA intends to conduct 2-year bioassays in rats and mice to assess the carcinogenic potential of ACP-103. Given the age of the population, the seriousness of the disease and the lack of other approved treatment options, would FDA accept ongoing carcinogenicity studies at time of accelerated approval and submission of the study reports as a post-approval commitment? (background info Section 6.2.3; p.89)

Preliminary Comments: The Division believes that submission of the 2-year carcinogenicity study in rats and mice after submission of the NDA is not warranted.

Discussion at Meeting: There was no further discussion at the meeting.

Question 4 background: supporting info found in briefing document Section 6.2.4; p.89: In light of the general use of dopaminergic therapy in Parkinson’s patients, FDA noted the need to conduct nonclinical ACP-103/Sinemet interaction studies during the Pre-IND meeting. ACADIA is currently planning to perform an evaluation of tolerability, pharmacokinetics, and toxicity of ACP-103 in combination with a fixed dose of L-dopa:carbidopa. This evaluation will be performed in two stages: (1) Initial studies in both rat and monkey will be designed to evaluate pharmacokinetics and determine the maximum tolerated dose of ACP-103 in combination with L-dopa:carbidopa; (2) A definitive 13-week study will then be conducted in rats, the most sensitive toxicology species to ACP-103.

4. Acadia's proposal to pursue a single subchronic bridging study to support adjunctive use of ACP-103 in Parkinson's patients is consistent with the Agency's recent Guidance for Industry entitled Nonclinical Safety Evaluation of Drug or Biologic Combinations (issued in March 2006). Is this proposal for non-clinical evaluation of potential ACP-103/Sinemet interactions acceptable to FDA?

Preliminary Comments: *The proposal for non-clinical evaluation of potential ACP-103/Sinemet interactions is acceptable.*

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

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Acadia Pharmaceuticals Inc. is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Keith Kiedrow, Pharm.D.
Regulatory Project Manager

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

/s/

Thomas Laughren
9/29/2006 02:30:11 PM

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 207318

LATE-CYCLE MEETING MINUTES

ACADIA Pharmaceuticals Inc.
Attention: Blake Burrell, MS, RAC
Senior Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) dated September 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 15, 2016.

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 Dr. Brendan Muoio, Regulatory Project Manager at (240) 402-4518 or brendan.muio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: March 15, 2016 from 1 to 2 p.m. EDT
Application Number: NDA 207318
Product Name: pimavanserin
Applicant Name: ACADIA Pharmaceuticals Inc.

Meeting Chair: Mitch Mathis, MD
Director, Division of Psychiatry Products (DPP)

Meeting Recorder: Brendan Muoio, PharmD, RAC
Regulatory Project Manager, DPP

FDA ATTENDEES

Robert Temple, MD	Deputy Director, Office of Drug Evaluation I and Deputy Center Director for Clinical Science
Mitch Mathis, MD	Director, DPP
Tiffany Farchione, MD	Deputy Director, DPP
Paul Andreason, MD	Clinical Team Leader (acting), DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biometrics (OB)
Eiji Ishida, MS	Biometrics Reviewer, OB
Cara Alfaro, PharmD	Reviewer, Office of Scientific Investigations
Somya Dunn, MD	Risk Management Reviewer, Division of Risk Management
Brendan Muoio, PharmD, RAC	Regulatory Project Manager, DPP

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein	Independent Assessor
----------------	----------------------

APPLICANT ATTENDEES

Serge Stankovic, MD, MSPH	Executive Vice President, Research & Development
J. Randall Owen, MD	Senior Vice President, Clinical Development and Chief Medical Officer
George Demos, MD	Executive Director, Drug Safety & Pharmacovigilance
Mark Knowles, PhD	Executive Director, Biostatistics & SAS Programming
Kathy Chi-Burris, MPH	Senior Director, Biostatistics
France LaPierre-Holme	Senior Director, Project Management
Blake Burrell, MS, RAC	Senior Director, Regulatory Affairs
Michael Monahan, MBA, RAC	Director, Regulatory Affairs

Marylynn Jones, RAC
(b) (4)

Director, Regulatory Affairs
Consultant, Interim Head of Regulatory Affairs

1.0 BACKGROUND

NDA 207318 was submitted on September 1, 2015 for Nuplazid (pimavanserin).

Proposed indication: Treatment of psychosis associated with Parkinson's disease.

PDUFA goal date: May 1, 2016

FDA issued a Background Package in preparation for this meeting on March 11, 2016.

2.0 DISCUSSION

1. Introductory Comments

Discussion: *The Division explained the purpose of the Late-Cycle Meeting and provided an overview of topics for discussion. The Division also informed ACADIA that the application had not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the final regulatory decision for the application would not be addressed at the meeting.*

2. Discussion of Substantive Review Issues

- Morbidity and mortality in short-term randomized controlled trials.
- No unifying mechanism for observed deaths and serious adverse events.
- Modest clinical improvement shown by the SAPS-PD results from study ACP-130-020 (study 020) must be weighed against the observed safety profile for pimavanserin.
- Concern for off-label use.

Discussion: *The Division stated that the disproportionate number of deaths and serious adverse events in the controlled trial population remained a concern. In NDA 207318, the review of serious adverse events (including deaths) revealed an estimated odds ratio, stratified by study, for serious adverse events of 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34 mg vs. placebo in the 6-week, controlled trial population (PDP6). The Division agreed that pimavanserin appeared to demonstrate efficacy in study 020; however, it was not certain that this benefit would outweigh the above risk. The Division reviewed the types of analyses that would be presented to the Advisory Committee and encouraged ACADIA to provide information to the Advisory Committee that would address this concern. FDA discussed that it would use Number Needed to Treat (NNT) as a calculation to provide context to the benefits and risks that were observed in the controlled clinical trial population.*

FDA noted that the deaths that occurred in the open-label phase of pimavanserin treatment could not be attributed to the drug due to the high background rate of death and serious medical illness in the Parkinson's disease psychosis (PDP) population; therefore ACADIA was not required to address these events in detail at the Advisory Committee.

3. Information Requests

Nonclinical

We remind you of the pending nonclinical information request to submit the finalized amendment to the (b) (4)-616007 study report. You previously mentioned that you anticipate submitting this amendment to the NDA shortly after March 18, 2016.

Discussion: ACADIA stated that the report is near completion and they are on schedule for submitting it shortly after March 18, 2016. ACADIA stated that the changed data was included in the submitted Pathology Working Group (PWG) report. The Division acknowledged receiving the PWG report and told them it was helpful; however reminded them that the finalized, quality assurance audited, amended study report is still necessary to finalize our review.

Clinical Pharmacology

We acknowledge and remind you of your February 3, 2016 email (b) (4)

Discussion: The Division inquired whether studies (b) (4) were on track to meet the completion dates stated in the February 3, 2016 email. ACADIA indicated that, yes they were on track to meet the deadlines stated in the email. ACADIA also clarified that the final reports for these studies will be submitted to the Agency within two weeks of the stated completion dates.

4. Discussion of Upcoming Advisory Committee Meeting

Discussion: The Division stated that the major goal of the Advisory Committee meeting is to gain expert advice on the risk-benefit profile for pimavanserin and that the general nature of the questions for the committee, as described in the Late-Cycle Background Package, will be in line with this goal.

ACADIA sought clarification on which population data the Division intended to use for the purpose of efficacy analysis and presentation at the Advisory Committee meeting. The Division stated that they preferred the modified Intent to Treat (mITT) population. Both parties agreed to use this data for presentation at the Advisory Committee meeting.

The Division also noted that the focus of their discussion on safety at the upcoming Advisory Committee meeting would be on the deaths and serious adverse events in the controlled trial population as opposed to the open-label treatment population.

5. Postmarketing Requirements/Postmarketing Commitments

Clinical

If pimavanserin is approved for the treatment of PDP, we anticipate that a randomized withdrawal study will be required.

Discussion: ACADIA indicated that they would be amenable to a randomized withdrawal study if requested.

Nonclinical

If pimavanserin is approved for the indication of PDP, we are considering a nonclinical postmarketing requirement to further evaluate the effects of phospholipidosis in animals. Additional required data may include microscopic re-evaluation of lung tissue samples using special stains to detect collagen from rats treated with pimavanserin at lower doses to obtain a more accurate No-Observed-Effect Level (NOEL) for phospholipidosis-induced inflammation. Microscopic re-evaluation of lung tissue samples using special stains to detect collagen may also be required from the 12-month monkey study in order to determine if inflammation can be detected in the lungs of monkeys using more detailed microscopic techniques.

Discussion: ACADIA asked if the Division had reviewed the nonclinical Pathology Working Group (PWG) report and if we had any questions. The Division informed them that we are still reviewing the report. ACADIA acknowledged the proposed nonclinical postmarketing requirement (PMR) if pimavanserin is approved and stated that it appears reasonable. ACADIA asked if they could have future discussions with the Division regarding the design and conduct of the PMR. The Division agreed and would welcome communication regarding the design and conduct of any nonclinical PMRs, if applicable.

6. Review Plans

Discussion: The Division indicated that internal labeling discussions are ongoing and further labeling negotiations would await Advisory Committee input. It was also noted that the Division was on schedule to conclude their review and take action by the May 1, 2016 PDUFA goal date.

7. Wrap-up and Action Items

Discussion: The Division thanked ACADIA for their participation and the meeting was adjourned.

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/s/

MITCHELL V Mathis
03/30/2016



NDA 207318

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

ACADIA Pharmaceuticals Inc.
Attention: Blake Burrell
Sr. Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Mr. Burrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nuplazid (pimavanserin) 17 mg immediate-release, film-coated tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for March 15, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, contact Dr. Brendan Muoio, Regulatory Project Manager, at (240) 402-4518 or brendan.muioio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
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: March 15, 2016 from 1 to 2 p.m. EST
Application Number: NDA 207318
Product Name: pimavanserin
Indication: Treatment of psychosis associated with Parkinson's disease
Applicant Name: ACADIA Pharmaceuticals Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, 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, 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 issues have been identified to date:

Clinical

1. There are 5 deaths in the three short-term randomized controlled trials (4 drug, one placebo). The estimated odds ratio is 2.94 (95% CI 0.28 to 148, p=0.61).
2. In the review of serious adverse events (including deaths) the estimated odds ratio, stratified by study, for serious adverse events is
 - a. 1.99 (95% CI 0.87 to 4.53, p=0.10) for all drug vs. placebo
 - b. 2.38 (95% CI 1.00 to 5.73, p=0.05) for 40 mg vs. placebo

- c. 1.44 (95% CI 0.54 to 3.81, p=0.46) for less than 40mg vs. placebo
3. The observed deaths and serious adverse events do not have an apparent unifying mechanism; this is consistent with what we observe with the use of conventional and new generation antipsychotics in the demented elderly population.
 4. In considering the above safety signals, we note the relatively modest mean clinical improvement in the single positive trial as measured by the Scale for the Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) in light of the previously failed trials using the unmodified Brief Psychiatric Rating Scale (BPRS) and SAPS.
 5. We are concerned about the potential risk of phospholipidosis that may, over time, lead to chronic inflammation and possible secondary fibrosis in the lungs. This may be an acceptable risk in the Parkinson's Disease Psychosis (PDP) population; however, for patients with a longer anticipated duration of treatment, the potential benefits of pimavanserin are unlikely to outweigh this risk. We are considering ways to communicate these concerns in labeling to discourage off-label use.

ADVISORY COMMITTEE MEETING

Date of AC meeting: March 29, 2016

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: March 9, 2016

Potential questions and discussion topics for AC Meeting are as follows:

Questions

1. Has the applicant provided substantial evidence of effectiveness for pimavanserin for the treatment of psychosis associated with Parkinson's disease?
2. Has the applicant adequately characterized the safety profile of pimavanserin?
3. Do the benefits of pimavanserin for the treatment of psychosis associated with Parkinson's disease outweigh the risks of treatment?

Discussion Topics

Substantive review issues 1-4 will be discussed in greater detail at the upcoming Advisory Committee Meeting.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

Though an increased risk for serious adverse events including death appears to be present, we do not believe that a REMS would mitigate this risk. It will be important to label the drug with the identified risks so that prescribers can make informed risk/benefit decisions for their patients.

LCM AGENDA

1. Introductory Comments – 5 minutes

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.

Clinical

- Morbidity and mortality in short-term randomized controlled trials.
- No unifying mechanism for observed deaths and serious adverse events.
- Modest clinical improvement shown by the SAPS-PD results from study ACP-130-020 must be weighed against observed safety profile for pimavanserin.
- Concern for off-label use.

3. Information Requests – 5 minutes

Nonclinical

We remind you of the pending nonclinical information request to submit the finalized amendment to the (b) (4)-616007 study report. You previously mentioned that you anticipate submitting this amendment to the NDA shortly after March 18, 2016.

Clinical Pharmacology

We acknowledge and remind you of your February 3, 2016 email (b) (4)

4. Discussion of Upcoming Advisory Committee Meeting – 10 minutes

5. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical

If pimavanserin is approved for the treatment of PDP, we anticipate that a randomized withdrawal study will be required.

Nonclinical

If pimavanserin is approved for the indication of PDP, we are considering a nonclinical postmarketing requirement to further evaluate the effects of phospholipidosis in animals.

Additional required data may include microscopic re-evaluation of lung tissue samples using special stains to detect collagen from rats treated with pimavanserin at lower doses to obtain a more accurate No-Observed-Effect Level (NOEL) for phospholipidosis-induced inflammation. Microscopic re-evaluation of lung tissue samples using special stains to detect collagen may also be required from the 12-month monkey study in order to determine if inflammation can be detected in the lungs of monkeys using more detailed microscopic techniques.

6. Review Plans – 5 minutes

- Internal labeling discussions are ongoing. Further labeling negotiations are pending Advisory Committee input.
- We plan to complete our review and take action by the May 1, 2016 PDUFA goal date.

7. Wrap-up and Action Items – 5 minutes

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/s/

MITCHELL V Mathis
03/11/2016