

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207318Orig1s000

OTHER REVIEW(S)

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Randomized withdrawal trial comparing pimavanserin 34 mg/day to placebo.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Pimavanserin was approved based on the results of one study and a controlled trial safety database of 202 patients taking pimavanserin 34 mg daily versus 231 placebo. There were a disproportionate number of deaths and serious adverse events between pimavanserin and placebo. It is unclear if the disproportionate numbers of deaths and serious adverse events observed with pimavanserin are due to chance, and if not, how these risks compare to the currently accepted off-label clinical standard of care. (b) (4)

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- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Randomized placebo-controlled trial or trials with predominantly frail and elderly subjects that would involve exposure of at least 500 subjects to pimavanserin 34 mg daily for a minimum of 8 weeks.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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(signature line for BLAs)

Per the Drug Interaction Studies guidance (February 2012), the effect of inducers on the metabolism of new drugs need to be evaluated. The administration of CYP3A4 inducers with pimavanserin could lead to a decrease in exposure to pimavanserin that may lead to reduction in efficacy. The goal of the study is to determine the degree of change in vivo when strong CYP3A4 inducers are co-administered with pimavanserin. The result of the study will inform the recommendation of maximum dose if dose increase is needed.

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

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- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

In vivo drug-drug interaction study

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

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

-
- Other
In vivo drug-drug interaction study
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- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
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- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
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(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # NDA 207318
Product Name: Nuplazid (pimavanserin)

PMR/PMC Description: PMC: [REDACTED] (b) (4)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	12/2017
	Other: Final data submission	12/2017

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

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

Late in the review cycle, the applicant submitted new nonclinical data in the form of a pathology working group (PWG) report and an amended study report for a 6-month chronic repeat-dose toxicity study in rats (study (b) (4)-616007). As part of the PWG report, all lung sections from all animals in study (b) (4)-616007 were recut and stained with a special stain to detect collagen (Masson's Trichrome (MTC)). As a result, new diagnoses of inflammation were found in lung tissue samples that were not previously detected in the originally submitted study report. These new findings of inflammation in the lungs of rats did not change the nonclinical recommendation for approval of pimavanserin for the indication of Parkinson's disease psychosis (PDP). However, these new data resulted in a lower, estimated, safety margin for chronic inflammation in the lungs of rats and changed the recommended language for section 13.2 (Animal Toxicology and/or Pharmacology) of the label. The re-evaluation of lung tissue samples using a stain to detect collagen was only conducted for one particular rat study and inflammation was detected at both dose levels that were used in that study.

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

The use of more sensitive microscopic techniques (including the use of a special stain to detect collagen) identified inflammation in the lungs of rats treated with pimavanserin that was not previously identified with H&E staining (subacute and/or chronic inflammation in males and females at both dose levels tested, 60 and 90 mg/kg/day). These more sensitive microscopic techniques were only used in this particular 6-month rat study and not in any other chronic toxicity studies including the 6-month rat toxicity study where the highest dose tested was 30 mg/kg/day, which is the current “estimated” No Observed Effect Level (NOEL) for inflammation in the lungs of rats. It is important to know if inflammation and/or inflammatory lung fibrosis are present in other chronic toxicity studies. One way to answer this question is to use the same sensitive microscopic techniques and staining to re-evaluate lung tissues from other chronic repeat-dose studies in rats (the first 6-month rat study and the 2-year carcinogenicity study) or from monkeys in the chronic 12-month repeat-dose toxicity study. Without this re-assessment, the currently identified NOEL is only an estimate for lung inflammation. Therefore, the goal of the PMC is to identify an accurate NOEL for inflammation and/or inflammatory fibrosis in lungs of animals treated chronically with pimavanserin. The new information could then be used to more accurately reflect the safety margin to the clinical dose (a margin that could be smaller than the current value), and this information will be used to update section 13.2 of the label, if necessary.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The PMC is to conduct microscopic re-evaluation of lung tissue samples using special stains to detect collagen from high dose (30 mg/kg/day male and female groups) of the 6-month rat study ((b) (4).146.02), the high dose groups (30 mg/kg/day male and 50 mg/kg/day female) from the 2-year rat carcinogenicity study ((b) (4)-6160004), and also the high dose groups (25/60 mg/kg/day) from the 12-month monkey study ((b) (4).146.01). If drug-related inflammation is detected in the lungs of any of the re-evaluated high dose groups from a particular study, then re-evaluation of lung tissue samples from the low and mid dose groups of that study should be conducted in order to identify a No Observed Effect Level (NOEL) for inflammation in the lungs of animals.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

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

- Other
Additional data for previously submitted nonclinical studies.

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

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

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

BRENDAN MUOIO
04/29/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 20, 2016

To: Brendan Muoio, PharmD, RAC
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 207318**
NUPLAZID™ (pimavanserin) tablets, for oral use

OPDP has reviewed the draft product labeling (PI) and carton/container labeling for NUPLAZID™ (pimavanserin) tablets, for oral use (Nuplazid) as requested in the consult from DPP dated September 16, 2015.

OPDP's comments on the draft PI for Nuplazid are based on the version in Sharepoint dated April 19, 2016 (File: [Nuplazid Draft PI](#)).

OPDP has reviewed the proposed carton/container labeling, obtained from the EDR ([Application 207318 - Sequence 0025 - 0025 \(26\) 04/08/2016 ORIG-1 /Labeling/Container-Carton Draft](#)) on April 18, 2016, and has no comments at this time.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

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

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/s/

SUSANNAH O'DONNELL
04/20/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 18, 2016
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 207318
Product Name and Strength: Nuplazid (pimavanserin) Tablets
17 mg
Submission Date: December 29, 2015
Applicant/Sponsor Name: ACADIA Pharmaceuticals, Inc.
OSE RCM #: 2015-2078-1
DMEPA Primary Reviewer: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the updated container labels and carton labeling for Nuplazid (pimavanserin) Tablets (see Appendix A) to determine if they are acceptable from a medication error perspective. We previously reviewed the container labels and carton labeling in OSE Review 2015-2078.¹

2 CONCLUSION

The updated container labels and carton labeling are unacceptable from a medication error perspective. We noted areas where necessary information is not present or is not in an optimal location. We provide recommendations in Section 3, below.

~~3~~ RECOMMENDATIONS FOR ACADIA PHARMACEUTICALS

¹ Myers D. Label and Labeling Review for Nuplazid (NDA 207318). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Nov 06. 6 p. OSE RCM No.: 2015-2078.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label (Trade)

1. Relocate the net quantity statement (b) (4) such as farther to the bottom left or right of the principal display panel. Alternatively, consider switching the (b) (4) positions. (b) (4)

2. Add a barcode to the label [see 21 CFR 201.25(c)(2)].

B. Container Label (Professional Sample)

1. See comment A.1, above.
2. The statement "SAMPLE: NOT FOR SALE" is in a (b) (4) font (b) (4). Consider using a darker color or some other color that provides sufficient contrast in order to improve the readability of the statement.

C. Carton Labeling (Professional Sample)

1. See comment A.1, above.
2. The statement of strength lacks sufficient prominence. Increase the size of the statement of strength.
3. The statement (b) (4) is not required. Please delete this statement since it adds clutter and diverts attention away from other statements.
4. The statement (b) (4) is on the carton labeling. However, it is not clear what (b) (4) you are referring to. Please clarify.

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

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/s/

LORETTA HOLMES
03/18/2016

DANIELLE M HARRIS
03/18/2016

Clinical Inspection Summary

Date	3/9/2016
From	Cara Alfaro, Pharm.D.
To	Brendan Muoio Pharm.D., Regulatory Project Manager DPP Paul Andreason M.D., Medical Officer DPP Jing Zhang M.D., Team Leader DPP
NDA/BLA #	NDA 207318
Applicant	ACADIA Pharmaceuticals Inc.
Drug	pimavanserin
NME	Yes
Therapeutic Classification	Priority Review
Proposed Indication	Psychosis associated with Parkinson's Disease
Consultation Request Date	9/29/2015
Summary Goal Date	3/15/2016
Action Goal Date	4/29/2016
PDUFA Date	5/1/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 207318, three clinical investigator sites, the sponsor (Acadia Pharmaceuticals) and the contract research organization (CRO) (b)(4) responsible for clinical site monitoring were inspected. The clinical investigator inspections did not reveal significant regulatory violations and no Form FDA 483s were issued. These inspections are preliminarily classified as No Action Indicated (NAI). Establishment Inspection Reports (EIRs) have been received and reviewed. Classification will be finalized when the inspection correspondence is sent to the inspected entity. Based on results of the clinical investigator inspections, it appears that the data submitted by the sponsor in support of the pending application at these sites are acceptable and the studies appear to have been conducted adequately.

Observations during inspections of both the sponsor and CRO indicated that there was inadequate monitoring/oversight to ensure compliance with the investigational plan. The major issue in regards to monitoring was that a draft version of the study-specific monitoring plan was not complete and did not provide monitors with adequate instructions in how to clarify and correct errors in data recording and study conduct in real time. Specifically, protocol violations related to enrollment of subjects who did not meet eligibility criteria were not always promptly noted and corrected, allowing subjects who did not meet eligibility criteria to participate in the study. Also, waivers documenting that the sponsor's medical monitor approved randomization and treatment of subjects were not available at the time of inspection. It is not clear how the enrollment of subjects not meeting eligibility criteria in this randomized, double blind study would impact efficacy analysis and we recommend the review division examine the eligibility criteria violations and perform sensitivity analyses based upon their interpretation of importance of the specified eligibility criteria. Based upon inspections at

three clinical sites, the data as reported in the NDA appears to be reliable and reflects source documentation at those sites.

Form FDA 483s were issued to both the sponsor and CRO, these inspections are preliminarily classified as Official Action Indicated (OAI) and Voluntary Action Indicated (VAI), respectively. Observations noted for the sponsor and CRO inspections are based on communications with the field investigators and the Form FDA 483s. EIRs have not been received from the field and are pending final review. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

II. BACKGROUND

Pimavanserin is a 5-HT_{2A} receptor inverse agonist being evaluated for the treatment of psychosis associated with Parkinson's disease. No medications are currently approved for this indication. This NDA submission included four placebo-controlled clinical efficacy/safety studies, Protocol ACP-103-020 is considered pivotal to demonstrate efficacy for this application. ACP-103-012 was a Phase 3 trial with the largest sample size which contributed safety data in support of this application. The following overview of the two studies (ACP-103-020 and ACP-103-012) is intended as background context for interpreting the inspectional findings.

ACP-103-020: A multi-center, placebo-controlled, double-blind trial to examine the safety and efficacy of pimavanserin in the treatment of psychosis in Parkinson's disease

Treatment Groups: pimavanserin 40 mg/day, placebo

Subjects: 199 subjects in the United States (52 sites) and Canada (2 sites)

Study Initiation/Completion: August 11, 2010 – October 10, 2012

The primary efficacy endpoint was the mean change from baseline comparing pimavanserin 40 mg/day to placebo in the 9-item Scale for the Assessment of Positive Symptoms-Parkinson's Disease (SAPS-PD). The key secondary endpoint was the mean change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II + III. The sponsor's primary efficacy analysis showed that subjects treated with pimavanserin had a statistically significant decrease in the SAPS-PD score compared to subjects treated with placebo ($p = 0.001$). No statistically significant differences between pimavanserin and placebo were noted for the UPDRS (e.g. pimavanserin did not worsen or improve motor symptoms compared to placebo).

ACP-103-012: A multi-center, placebo-controlled, double-blind trial to examine the safety and efficacy of ACP-103 [pimavanserin] in the treatment of psychosis in Parkinson's disease

Treatment Groups: pimavanserin 10 mg/day, pimavanserin 40 mg/day, placebo

Subjects: 298 subjects in the United States (34 sites), Eastern Europe (16 sites), Western Europe (10 sites) and India (13 sites)

Study Initiation/Completion: June 6, 2007 – July 13, 2009

The primary efficacy endpoint was the mean change from baseline in the 20-item Scale for the Assessment of Positive Symptoms- Hallucinations and Delusions subscales (SAPS-H+D). The key secondary endpoint was the mean change from baseline in the UPDRS Parts II + III. (b) (4)

Inspections of clinical sites, the sponsor and CRO were considered essential to verify the quality of conduct of the studies for this NME application. Clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site and/or site-specific efficacy effect size. Each of the clinical sites enrolled subjects in both protocols. The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events and verification of the key secondary efficacy endpoint. Primary efficacy data (SAPS-PD and SAPS-H+D) could not be verified at the sites since these ratings were obtained via remote ratings by MedAvante who sent the data directly to the sponsor.

The sponsor inspection was performed in conjunction with a For-Cause sponsor inspection (Complaint #5450). The complaint outlined several potential GMP and GCP noncompliance issues, the latter including lack of an effective monitoring program for the CRO and vendors; operating without Quality Assurance staff, compliance controls or Standard Operating Procedures; protocol violations; unsigned consent forms and enrolling subjects not meeting eligibility criteria. The focus of both the sponsor and CRO inspections was adequacy of monitoring and ensuring that the study was conducted in accordance with the investigational plan.

III. RESULTS (by site)

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects Enrolled	Inspection Date	Final Classification
Stuart Isaacson, M.D. Site #10 Parkinson's Disease and Movement Disorder Center 951 NW 13 th Street, Building 5E Boca Raton, FL	ACP-103-020: 14 subjects ACP-103-012: 14 subjects	12/16/2015 – 1/6/2016	Pending Interim classification = NAI

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects Enrolled	Inspection Date	Final Classification
Edward Drasby, D.O. Site #19 Port City Neurology 7 Portland Farms Road Scarborough, ME	ACP-103-020: 7 subjects ACP-103-012: 7 subjects	11/2/2015 - 11/6/2015	NAI
(b) (4) Site #21 St. Joseph's Hospital and Medical Center Barrow Neurology Clinics 240 West Thomas Road Phoenix, AZ	ACP-103-020: 7 subjects ACP-103-012: 4 subjects	12/29/2015 – 1/5/2016	Pending Interim classification = NAI
(b) (4)	ACP-103-020	1/26/2016 – 2/16/2016	Pending Interim classification = VAI
ACADIA Pharmaceuticals Inc. 3611 Valley Centre Drive Suite 300 San Diego, CA 92130	ACP-103-020 ACP-103-012	1/19/2016 – 2/17/2016	Pending Interim classification = OAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations, data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. **Clinical Investigator:** Stuart Isaacson, MD; Boca Raton FL; Site #10

- a. **What was inspected:** For Protocol ACP-103-012, 24 subjects were consented and screened, 14 were enrolled and 13 completed the study. For Protocol ACP-103-020, 22 subjects were consented and screened, 14 were enrolled and 12 completed the study. Signed informed consent forms were present for all subjects who were screened to participate in the studies prior to participation. An audit of the study records for 11 subjects for each study (total of 22 subjects) was conducted. Records reviewed included source documents, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, protocol deviations, and key secondary efficacy data. Primary efficacy data (SAPS-PD and SAPS-H+D) could not be verified since these ratings were performed via remote ratings by MedAvante who sent the data directly to the sponsor.
- b. **General observations/commentary:** Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection.

- c. **Assessment of data integrity:** The studies appear to have been conducted adequately at this site and the data submitted by this site appear acceptable in support of the pending application.

2. **Clinical Investigator:** Edward Drasby DO; Scarborough ME; Site #19

- a. **What was inspected:** For Protocol ACP-103-012, seven subjects were consented, screened, enrolled and completed the study. For Protocol ACP-103-020, eight subjects were screened, seven were enrolled and five completed the study. An audit of the study records for all subjects who were screened for both studies was conducted. Signed informed consent forms were present for all subjects who were screened to participate in the study prior to participation. Other records reviewed included source documents, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, protocol deviations, and key secondary efficacy data. Primary efficacy data (SAPS-PD and SAPS-H+D) could not be verified since these ratings were performed via remote ratings by MedAvante who sent the data directly to the sponsor.
- b. **General observations/commentary:** Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately and the data submitted by this site appear acceptable in support of the pending application.

3. **Clinical Investigator:** (b) (4) Phoenix AZ; Site #21

(b) (4) is no longer at this clinical site. Abraham Lieberman, M.D. was present during the inspection. Dr. Lieberman was a subinvestigator when studies were initiated and listed as the investigator on FDA 1572s for study ACP-103-020 dated 3/24/2011 and 6/13/2011. (b) (4) is listed as subinvestigator on these 1572s (dated 2011) as he was transitioning to leave the site.

- a. **What was inspected:** For Protocol ACP-103-012, six subjects were screened and four were enrolled and completed the study. For Protocol ACP-103-020, 15 subjects were screened, seven were enrolled and six completed the study. An audit of the study records was conducted for only 10 subjects, four subjects for ACP-103-012 and six subjects for ACP-103-020. Records reviewed included source documents, informed consent documents, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, protocol deviations, and key secondary efficacy data. Primary efficacy data (SAPS-PD and SAPS-H+D) could not be verified since these ratings were performed via remote ratings by MedAvante

who sent the data directly to the sponsor.

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

4. **Contract Research Organization:** [REDACTED] (b) (4)

This CRO was contracted by Acadia Pharmaceuticals to provide clinical and medical monitoring for Study ACP-103-020.

- a. **What was inspected:** This inspection covered monitoring practices related to Protocol ACP-103-020. Regulatory documents for six clinical sites (010, 013, 056, 063, 303 and 310) were reviewed. Documentation was reviewed during this inspection for organization and personnel including review of written agreements with the sponsor; qualifications, experience and training of monitors; monitoring procedures; safety, adverse event reporting and protocol deviations; data collection and handling including SOPs; 1572s; and test article accountability.
- b. **General observations/commentary:**
The sponsor initially contracted with [REDACTED] (b) (4) as the CRO responsible for clinical site and medical monitoring for Study ACP-103-020. [REDACTED] (b) (4) [REDACTED] (b) (4) acquired [REDACTED] (b) (4) and assumed subsequent responsibility for these functions.

Monitoring deficiencies were observed during the inspection and the firm was issued a Form FDA 483, List of Inspection Observations related to inadequate monitoring of the study and lack of documentation of training in study-specific procedures for clinical and medical monitors. Regulatory violations listed included:

1. Failure to ensure proper monitoring of the study.

The CRO used a draft version of a study-specific monitoring plan over a period of approximately six months covering a period during which site initiation visits were conducted at most clinical sites, ongoing enrollment of subjects was occurring at 12 of these sites, and at four of six sites reviewed, multiple interim monitoring visits were conducted. The draft version of this monitoring plan failed to provide complete and adequate guidance for the monitors to appropriately monitor the study.

For example, instruction in use of the data clarification form, correction of data during monitoring visits, and provision of an actual maximum dose threshold over protocol dose specifications for reporting to the Lead Clinical Research Associate or Project Manager and subsequently initiating discussion with the clinical investigator to be cautious about potential adverse events due to possible overdose were not provided.

At one of the six sites reviewed, the monitors failed to identify enrollment of subjects not meeting eligibility criteria until 58 to 731 days after enrollment, did not include an explanation for why deviations occurred, what actions were taken by the monitor to bring the site into compliance and that the site put in corrective actions to prevent these errors from recurring.

2. Monitors not qualified by experience and training were selected to monitor the progress of a clinical investigation.

Many (10/15) of the clinical research monitors and some (3/5) of the medical monitors were not trained on study-related procedures prior to study initiation. Documentation was lacking to indicate that 2 of 15 clinical research monitors were qualified by experience to monitor the study.

OSI reviewer's comment: Although monitoring deficiencies were identified, some of which resulted in delayed reporting of protocol deviations, the deviations were ultimately recognized by the monitors and reported to the sponsor. Delayed reporting of violations of inclusion/exclusion criteria allowed some subjects who may have been ineligible because of concomitant medication use or altered sensorium at the time of randomization to be enrolled in the study. The deviations were evaluated in a blinded fashion by the sponsor and subsequently those deviations thought by the sponsor to potentially bias efficacy results were included in the NDA. However, the sponsor upon request, did subsequently provide a list of all protocol deviations to the NDA.

- c. **Assessment of data integrity:** Inspection of the CRO responsible for monitoring revealed inadequacies in study conduct and monitoring that resulted in numerous protocol violations including randomization of subjects who did not meet eligibility criteria for a variety of reasons, including use of prohibited medication (potential confounder of efficacy assessment or potential safety risk, e.g. prolonged QT) or mental status at baseline not satisfactory to participate. Some of these protocol deviations were not identified by study monitors until after the subject(s) had been randomized, treated, and possibly completed study treatment. It is unclear whether delayed detection of eligibility criteria violations by the monitors had a significant impact on analysis of safety and efficacy (see further discussion under inspection findings/assessment of data integrity for the sponsor (Acadia) inspection). Inspections conducted at three

clinical sites indicated that monitoring was adequate at those sites and provided evidence that data reported by the sites were verified with source documents and subsequently reported correctly by the sponsor to the NDA.

5. **Sponsor:** ACADIA Pharmaceuticals Inc., 3611 Valley Centre Drive, Suite 300, San Diego CA, 92130

a. **What was inspected:** This inspection covered sponsor practices related to Protocol ACP-103-020 and, to a lesser extent, Protocols ACP-103-012 and ACP-103-015 (open-label extension study). Regulatory documents for three clinical sites (010, 013 and 303) participating in Study ACP-103-020 were reviewed. Documentation was reviewed during this inspection for organization and personnel including review of written agreements with vendors and CROs; registration of studies on ClinicalTrials.gov; selection and monitoring of clinical investigators including agreements, non-compliance, and training; monitoring procedures; Quality Assurance (QA) including audit plan and QA audits; safety, adverse event reporting and protocol deviations; data collection and handling including SOPs; financial disclosure; 1572s; electronic records including transmission of data and system security and test article accountability.

b. **General observations/commentary:**

Significant monitoring deficiencies were observed during the inspection of the sponsor. A Form FDA 483 was issued for regulatory violations related to study monitoring. Specifically:

1. Failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan.

The sponsor failed to provide a complete, finalized version of the monitoring plan to the CRO until after site initiation visits, subject enrollment, and interim monitoring visits had occurred at some sites. The study protocol included a statement that waivers could be sought from the study medical monitor for subjects not meeting eligibility criteria, but a formal written plan was not developed to document the procedure for granting waivers and there was no documentation indicating that 49 of the 199 subjects enrolled in violation of some eligibility criteria were granted waivers by the sponsor's Chief Medical Officer.

2. Failure to monitor the progress of an investigation conducted under your IND.

The sponsor failed to recognize that the CRO monitors were not

detecting protocol deviations related to enrollment of subjects not meeting eligibility criteria, nor were they providing documentation in the monitoring reports regarding the reason for the deviation, attempts to re-educate the site to prevent the error from recurring and to obtain a corrective action plan from the clinical site.

OSI reviewer's comment: Finalization of the monitoring plan prior to study initiation may have prevented some of the observations related to inadequate monitoring including enrollment of 49/199 (24%) subjects not meeting eligibility criteria. A review of these eligibility protocol deviations indicated that approximately 70% were for concomitant use of prohibited medications as listed in Appendix 1 (Prohibited and Restricted Concomitant Medications) of the study protocol and occurred with similar frequency in the placebo and pimavanserin groups. However, although listed as protocol deviation(s) in the NDA (Listing 16.2.1.6), some of these concomitant medications were not listed in Appendix 1 of the protocol (e.g. modafinil). As noted in a comment in Listing 16.2.1.6, "patient on Provigil (modafinil) which is unaddressed in protocol but was decided by medical monitor that it should be treated as a prohibited medication"; however, there is no documentation that the determination of modafinil as a prohibited medication was communicated to clinical sites.

Similarly, although listed as protocol deviation(s) in the NDA (Listing 16.2.1.6), some of these concomitant medications were not prohibited or restricted (e.g. tolterodine). Appendix 1 states that centrally-acting anticholinergic medications are prohibited, however, "anticholinergic agents that act predominantly on the peripheral nervous system, such as tolteradine [sic] or oxybutynin, are allowed".

c. Assessment of data integrity:

The inspectional observations indicated failure to ensure adequate monitoring of the study. It is unclear whether more rigorous monitoring and identification of protocol violations, clinical site education and re-training on the protocol, and escalation of repeated protocol violations to monitoring CRO or sponsor administrators could have decreased the number of protocol violations over the course of the study. The sponsor did not have a well-defined process for documenting waivers granted by the Chief Medical Officer to allow subjects not meeting protocol-defined inclusion/exclusion criteria to be enrolled in the study. With approximately 25% of the study population having protocol violations related to eligibility criteria, the review division may wish to review the specific protocol deviations considered "important" by the sponsor against the list of all protocol deviations reported to the NDA to see if they agree with the sponsor's assessment and considering conducting sensitivity analyses based on their determination of the population with critical eligibility violations that could impact efficacy or safety.

Based upon inspection, monitoring problems did not appear to be pervasive and data reported to the NDA by the sponsor appear to be consistent with source

documentation at the site.

{ See appended electronic signature page }

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/s/

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MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 22, 2016

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Controlled Substance Staff

Jovita Randall-Thompson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Pimavanserin Immediate Release (IR) Tablets - NDA 207318
Generic Name (Trade Name): pimavanserin (Nuplazid)
Dosages: 34 mg (equivalent to 40 mg pimavanserin tartrate) 1x/day
Formulations: 17 mg IR tablets (equivalent to 20 mg pimavanserin tartrate)
Route: oral
NDA/IND Number(s): IND 68384 (b) (4)
Indication(s): Treatment of drug-induced psychosis in patients with Parkinson's disease (PD)
Sponsor: Acadia Pharmaceuticals Inc.
PDUFA Goal Date: May 1, 2016

Materials Reviewed:

- NDA 207318, Module 2.5 Clinical Overview
- NDA 207318, Module 1.14.1.3 Medication Guide
- NDA 207318, Module 1.14.1.3 Labeling
- NDA 207381, Abuse Potential Assessment and Scheduling Recommendation for Pimavanserin Tartrate (ACP-103), Abuse Liability White Paper

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I. Summary

1. Background

This memorandum responds to a consult dated September 14, 2015, from the Division of Psychiatry Products (DPP). The consult pertains to the new drug application (NDA) (b) (4) for the pimavanserin immediate release (IR) tablets, proprietary trade name Nuplazid (accepted by the Agency on 11/09/2015). Pimavanserin is a new molecular entity (NME) that is indicated for the treatment of drug-induced psychosis in patients with Parkinson’s disease. Pimavanserin has never been marketed in the United States or internationally.

The NDA is designated as a priority review based on the product’s Breakthrough Therapy (BT) designation granted on 08/13/2014 under the investigational new drug application (IND) 68384. The psychosis of Parkinson’s disease, occurring in about 50% of PD patients, is manifested primarily in the form of visual hallucinations and delusions which over time become disabling. There are no approved therapies for this indication. Off-label, D₂ (dopamine) antagonists antipsychotics (i.e. clozapine) are used for these symptoms, however their use poses an increased risk of stroke in elderly patients (DARRTS FRM-MINUTES-01(Internal Meeting Minutes), 08/08/2014).

The prescribing information for pimavanserin IR tablets indicates that it is taken as two 17 mg strength tablets once daily. Dosing should be initiated at 34 mg without prior titration. It can be taken with or without food.

In the current application, 23 clinical studies (21 sponsored by ACADIA) were completed to support pimavanserin’s approval for treatment of Parkinson’s disease psychosis (PDP). These include: 12 clinical studies conducted in healthy subjects (4 Phase 1 pharmacokinetic (PK) tolerability studies, 4 Phase 1 PK extrinsic factors studies and 4 Phase 1 pharmacodynamic /PK studies), 5 clinical studies conducted in Parkinson’s disease psychosis (PDP) patients (a Phase 2 efficacy and safety study, 2 Phase 2-3 studies and a Phase 3 uncontrolled clinical study conducted in and a Phase 2 efficacy and safety study with PD patients), and 2 clinical studies conducted in Parkinson’s disease (PD) patients (a Phase 1-2 pharmacokinetic (PK) tolerability study conducted in PD patients, a Phase 2 PD/PK study with PD dyskinesia patients). Along with the studies examining the safety and efficacy of the PDP indication,

the Sponsor submitted studies conducted in other subject populations, a Phase 2 pharmacodynamic/PK efficacy and safety study in schizophrenia patients and one in Alzheimer's disease patients with psychosis.

The Sponsor also submitted pre-clinical findings on the pharmacodynamics, safety pharmacology, PK, and toxicology of pimavanserin. Among the PK and safety pharmacology information, the Sponsor included pre-clinical abuse evaluations. These include a functional assay testing abuse-related receptor sites and neurotransmitter activity to the exposure of pimavanserin, a drug discrimination study that evaluated whether interoceptive cues of pimavanserin generalized to the interoceptive cues of a drug with abuse potential and a conditioned place preference study which examined pimavanserin rewarding effects.

DPP requested that CSS review the current efficacy supplement from a controlled substance/abuse potential perspective. The primary basis of our conclusions and recommendations are based on an assessment of the safety data collected during clinical trial testing, with exception of Study ACP-103-003, ACP-103-004 and ACP-103-018. The first was a single-dose positron emission tomography study in healthy volunteers; the second was a single-dose crossover evaluation in PD patients with dyskinesia and the last was a QT/QTc evaluation. Abuse pre-clinical findings were reviewed and were found to have significant methodology inadequacies. These findings therefore were inconclusive.

2. Conclusions

1. An assessment of the safety data from the pimavanserin clinical studies revealed no evidence of drug abuse potential or drug dependence liability. The most common AEs potentially related to abuse were dizziness and somnolence, mostly reported by subjects treated with high doses of pimavanserin (particularly at doses of 100 mg or greater).
2. There were no other abuse-related AEs found to meaningfully differ from placebo or were not reported in healthy volunteers, even at doses of 100 mg or greater; findings therefore indicate that there is a low risk of abuse associated with the use of pimavanserin.
3. The findings from the pre-clinical abuse assessments are inconclusive due to significant methodology inadequacies.

3. Recommendations

Based on our findings, as captured in the Conclusions section, we recommend the following:

1. Scheduling pimavanserin under the Control Substance Act is not recommended at this time.
2. Section 9.0, Abuse and Dependence is not recommended for labeling.

II. Discussion

Pimavanserin tartrate (pimavanserin, also known as ACP-103), is a selective 5-HT_{2A} (serotonin) antagonist. It is a novel small-molecule therapeutic agent designed to selectively attenuate serotonergic neurotransmission mediated by the human 5-HT_{2A} receptor subtype. The precise mechanism(s) by which pimavanserin exerts its antipsychotic effect is unknown.

ACADIA proposes pimavanserin should not be scheduled. According to the Sponsor no signal from the published literature or publicly available sentinel databases suggests that use of medications with prominent 5-HT_{2A} antagonist activity results in abuse or dependence liability.

The Sponsor submits Modified Irwin Screen data which they claim shows no psychoactivity by pimavanserin (Abuse Potential Assessment, page 15), however hypoactivity is shown in rats at 10 mg/kg and at increasing doses (up to 100 mg/kg (Report 2002-07)). The Sponsor also states that orally administered pimavanserin did not decrease locomotor behavior in mice up to a dose of 3 mg/kg, and there was no evidence that pimavanserin produced hyperlocomotion in any experiment at any dose (Abuse Potential Assessment, page 15). However, these findings show a decrease in locomotor behavior when injected subcutaneous (SC) and intraperitoneal (IP) in rats at doses of 0.1, 0.3 and 1 mg/kg.

To further characterize the abuse potential of pimavanserin the Sponsor submitted a conditioned place preference (see below) and a review of the clinical adverse event profile of pimavanserin as it pertains to the potential for abuse and dependence.

1. Chemistry

Pimavanserin is produced as a tartrate salt with the chemical name (United States Adopted Name [USAN]) urea, N-[(4-fluorophenyl)methyl]-N-(1-methyl-4-piperidiny)-N'-[[4-(2-methylpropoxy)phenyl]methyl]-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (molecular formula (C₂₅H₃₄FN₃O₂)₂·C₄H₆O₆ and its molecular weight is 1005.2 (tartrate salt)). Pimavanserin is not an analogue or precursor to any controlled substance.

1.1 Substance information

Pimavanserin is formulated as an immediate-release tablet for oral administration at a single nominal strength of 17 mg (equivalent to 20 mg of pimavanserin tartrate). The tablet consists of pimavanserin tartrate, Starch (b) (4), magnesium stearate, and microcrystalline cellulose (b) (4) with (b) (4) white film coat. The dose advanced in the NDA for approval is 34 mg/day administered once daily as two 17 mg tablets (equivalent to 40 mg pimavanserin tartrate).

2 Pharmacokinetics (Clinical Pharmacology)

Pharmacokinetic parameters for pimavanserin were determined in healthy volunteers at single doses 20, 25, 40, 50, 100, 120, 150, 160, 200 up to 300 mg. According to the label, pimavanserin demonstrates dose proportional pharmacokinetics that are similar in PD patients and healthy volunteers. According to the Sponsor, the median T_{max} value is approximately 6 hours and the mean plasma t_{1/2} for pimavanserin is approximately 57 hours while the elimination half-life of pimavanserin ranged from 48 to 77 hours, and was independent of dose over the range of 20 mg to 300 mg (Abuse Potential Assessment, page 19)

3. Absorption, Distribution, Metabolism, Elimination (ADME)

According to the label, the absorption of pimavanserin occurs with a median T_{max} of 6 hours (range 4-24) and was generally unaffected by dose. It is estimated that 98% of an administered dose is absorbed in the intestine. High-fat meal had no effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure. There were 3 metabolites (M1, M36 and AC-279) that accounted for more than 10% of circulating drug-derived material.

4. Pharmacodynamics (receptor binding and functional assays)

Pimavanserin was evaluated in radioligand binding assays (at 10 μM) for activity at serotonin 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Pimavanserin showed a K_i of 0.087 ± 0.011 nM for 5-HT_{2A} receptors, a K_i of 0.33 ± 0.10 μM for 5-HT_{2B} receptors, and a K_i of 0.44 ± 0.029 nM for 5-HT_{2C} (Study report 2013 – 03). Functional assay findings show that pimavanserin displays potent functional inverse agonist activity in vitro at 5-HT_{2A} sites and to a much reduced extent at 5-HT_{2C} sites, with IC₅₀ values of 1.9 nM and 91 nM (Vanover et al., 2006¹).

The Sponsor conducted receptor binding experiments on a broad panel of 65 radioligand binding assays (Report 2004-01) using abuse-related targets of interest identified in the FDA draft guidance on abuse potential assessment (b) (4) of pimavanserin (b) (4). Each assay evaluated (b) (4) at 10 μM , a concentration estimated to be more than 50-fold greater than the estimated pimavanserin C_{max} in plasma (total) and >600-fold greater than the free pimavanserin C_{max} after oral administration of 40 mg/day to healthy volunteers (values adjusted based on steady-state results at 50 mg/day in Study ACP-103-002). Findings were considered noteworthy if >50% inhibition of ligand binding was observed, other than the serotonergic receptors (above), dopamine transporter, norepinephrine transporter, and dopamine D₃, muscarinic M₁, muscarinic M₂, muscarinic M₃, adrenergic α 1B, adrenergic α 1D, sigma 1, and sigma 2 receptors all other targets that were assessed demonstrated less than 50% inhibition.

Using the marketed formulation of pimavanserin (tartrate salt, (b) (4)), functional studies were conducted as well, using a proprietary cell-based functional assay the Sponsor demonstrated that pimavanserin lacks agonist or competitive antagonist activity at muscarinic subtypes or D₃ receptors (Report 2013-04). Also, using the marketed formulation of pimavanserin, a follow-up radioligand binding study (Report 2014-02, included full concentration curves for those targets at which >50% inhibition of ligand binding was observed) was conducted to repeat the assessments of the muscarinic receptor subtypes, the D₃ receptor subtype, the norepinephrine and dopamine transporters, and the sigma receptor subtypes. Four additional sites not examined in the original study, the cannabinoid CB₁ and CB₂ receptors (only at 10 μM), as well as muscarinic sites M₄ and M₅, were also evaluated. The binding affinity of pimavanserin ranged from 120 nM to 4200 nM at the various targets tested and thus lacked affinity and functional activity at D₃ receptors, and other human monoaminergic receptors.

5. Clinical Efficacy, Safety and Physical Dependence Studies

Abuse-Related AEs during All Clinical Studies

Except for the 3 Phase 1 studies detailed below, the Sponsor evaluated all clinical trials in this NDA, Phases 1 through 3, for adverse events (AEs) which might signal a potential for abuse and dependence.

¹ Vanover KE, Weiner DM, Makhay M, Veinbergs I, Gardell LR, Lameh J, Del Tredici AL, Piu F, Schiffer HH, Ott TR, Burstein ES, Uldam AK, Thygesen MB, Schlienger N, Andersson CM, Son TY, Harvey SC, Powell SB, Geyer MA, Tolf BR, Brann MR, Davis RE. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy phenylmethyl) carbamide (2R, 3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine (2A) receptor inverse agonist. *J Pharmacol Exp Ther*. 2006 May;317(2):910-8

Treatment-emergent adverse events (TEAEs) were evaluated for events potentially related to abuse or dependence potential. The integrated databases were searched for Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and text strings which included 1) euphoria-related terms; 2) terms related to impaired attention, psychomotor events, cognition and mood; and 3) dissociative and psychotic terms. An additional list of preferred terms (PT) potentially reflective of drug dependence or overt drug seeking behavior e.g., drug dependence, intentional drug misuse, substance use was also included. These analyses were performed on seven datasets.

There were three studies not included in the assessment of abuse potential.

One was a single-dose positron emission tomography evaluation (N=4) conducted in healthy volunteers; another was a single dose crossover evaluation of 20 and 60 mg pimavanserin in PD patients with dyskinesia (N=23), and the third was a thorough QT/QTc evaluation of 20 or 80 mg pimavanserin administered once daily for 20 days (N=252) to healthy volunteers.

All of the remaining studies were grouped in seven datasets because of their similarities:

1. *Healthy Volunteers Single-Dose Dataset*: Three single-dose studies in human volunteers.
2. *Healthy Volunteers Multiple-Dose Dataset*: Five multiple-dose studies in healthy volunteers.
3. *ACP-103-009 Dataset*: One study of healthy volunteers who were administered pimavanserin in combination with haloperidol.
4. *PD/PDP 4 Weeks Dataset*: Two safety and efficacy studies, ≤ 4 weeks, evaluating PD patients.
5. *Schizophrenia Studies Dataset*: Two studies in schizophrenia patients.
6. *PDP Randomized Double-Blind Placebo-Controlled Studies Dataset*: Four studies with exposure for the first 6 weeks of treatment in long-term safety and efficacy trials, including the safety populations from all fixed-dose, double-blind studies as well as patients in the open-label extension trial who had previously received placebo and subsequently enrolled to receive once-daily 40 mg pimavanserin in the open-label setting.
7. *PD/PDP Open-label Long-term Follow-up Studies Dataset*: Two open-label safety extension studies.

1. *Healthy Volunteer Single-Dose Dataset*

The only significant AE from this cohort of healthy volunteers, suggestive of abuse, was the elevated incidence of somnolence, mostly in those receiving high doses of pimavanserin, particularly at doses of 100 mg or greater. All of these AEs were reported in male subjects. These findings are shown in Table 1.

Table 1 Possible Abuse-Related Adverse Events in Single-Dose Healthy Volunteers

Possible Abuse-Related PT	Pimavanserin Dose	N (%)	Placebo N (%)
Dizzy	≥ 100 mg	1 (5%)	0 (0%)
Somnolence	≥ 100 mg	4 (20%)	0 (0%)
Feeling Drunk	≥ 100 mg	1 (5%)	0 (0%)
Hangover Feeling	≥ 300 mg	1 (5%)	0 (0%)

2. Healthy Volunteers Multiple-Dose Dataset

As in Cohort #1, there was an elevated incidence of somnolence, mostly in those receiving high doses of pimavanserin? Additionally there was also a greater incidence of dizziness, compared to placebo, again mostly in those receiving high doses of primavanserin. There was no apparent relationship between these events to the sex of the subject. These finding are shown in Table 2.

Table 2 Possible Abuse-Related Adverse Events in Healthy Volunteers Multiple-Dose Dataset

Possible Abuse-Related PT	Pimavanserin Dose	N (%)	Placebo N (%)
Dizzy	≤ 20 mg	2 (2.1%)	4 (4.9%)
	50-80 mg	14 (17.9%)	
	≥ 100mg	12 (42.9%)	
Somnolence	50-80 mg	2 (2.6%)	3 (3.7%)
	≥ 100 mg	8 (28.6%)	
Disturbance in Attention	≤ 20 mg	3 (3.1%)	1 (1.2%)
Agitation and Thought Blocking	≥ 100 mg	1 (3.6%)	0 (0%)

3. *ACP-103-009 Dataset*

There were no abuse-related AEs in which the incidence rates exceeded the placebo rates.

4. *PD/PDP 4 Weeks Dataset*

For ACP-103-005, one report of somnolence occurred at 100 mg pimavanserin in 1 subject (25%) versus no reports for placebo. For ACP-103-006, somnolence occurred in 3 subjects (10.3%) at 20 - 60 mg pimavanserin versus 1 subject (3.2%) in the placebo group. There were no other events of interest occurring at a greater rate in pimavanserin treated subjects than in placebo-treated subjects.

5. *Schizophrenia Studies Dataset*

The two studies contributing to this dataset (ACP-103-007 and ACP-103-008) were not pooled. For each study, results are presented for the entire safety dataset. For Study ACP 103-007 there were 5 reports of somnolence in the pimavanserin 60 mg group (31.3%) versus 2 reports (11.1%) in the placebo group. There was 1 report (6.3%) of dizziness in the pimavanserin 60 mg group versus none in the placebo group. There were no other TEAEs of interest occurring at a greater rate in pimavanserin-treated subjects than in placebo-treated subjects.

For the haloperidol + pimavanserin group, there was one AE of euphoric mood and one of thinking abnormal, both in the same subject (1.2%) versus none in the haloperidol-alone group. Somnolence occurred in 8 subjects (9.8%) in the haloperidol + pimavanserin group versus 6 subjects (7.2%) in the haloperidol-alone group.

For the risperidone + pimavanserin group, there was somnolence, which occurred in 9 subjects (11.4%) in the risperidone + pimavanserin group versus 3 subjects (3.6%) in the risperidone-alone group. Emotional disorder and emotional distress, both of which occurred in 1 subject (1.3%) in the risperidone + pimavanserin group versus none in the risperidone-alone group.

6. *PDP Randomized Double-Blind Placebo-Controlled Studies Dataset*

This was the largest pimavanserin study. There were six individual TEAE PTs which were considered relevant if they occurred with a higher incidence rate on pimavanserin treatment than on placebo treatment and there was $\geq 1\%$ difference between the two. These findings are shown in Table 3. One additional TEAE, not meeting the criterion, was nevertheless identified for further review: one instance of Accidental overdose (0.5%) occurring in the 40 mg group, versus none in any other group.

Table 3 Possible Abuse-Related Adverse Events in PDP Randomized Double-Blind Placebo-Controlled Studies Dataset

Possible Abuse-Related PT	Pimavanserin Dose N (%)			Placebo N (%)	
Hallucinations	10 mg	3	(2.1%)	7	(3.0%)
	20 mg	2	(4.9%)		
	40 mg (DB)	10	(5.0%)		
	40 mg (OL)	9	(4.9%)		
Confusional State	10 mg	6	(4.3%)	6	(2.6%)
	20 mg	2	(4.9%)		
	40 mg (DB)	12	(5.9%)		
	OL	3	(1.6%)		
Agitation	10 mg	2	(1.4%)	1	(0.4%)
	40 mg (DB)	1	(0.5%)		
	OL	1	(0.5%)		
Somnolence	10 mg	5	(3.6%)	6	(2.6%)
	20 mg	1	(2.4%)		
	40 mg	5	(2.5%)		
	OL	4	(2.2%)		
Delusion	10 mg	1	(0.7%)	0	(0%)
	20 mg	2	(4.9%)		
	40 mg	1	(0.5%)		
	OL	4	(2.2%)		
Cognitive Disorder	OL	3	(1.6%)	1	(0.4%)

DB=double blind, OL=open label

7. PD/PDP Open-label Long-term Follow-up Studies Dataset

The most common TEAEs reported over the entire treatment period were: hallucination (14.3%), confusional state (10.4%), dizziness (8.0%), agitation (5.8%) and somnolence (5.2%). Two individual events of interest were identified: drug dependence, which occurred in 1 subject (0.2%), and substance-induced psychotic disorder, which occurred in 2 subjects (0.4%). There was no consistent relationship

between event incidence and onset time period, although hallucination appeared to occur with a higher incidence rate after 1 year of treatment. There was no consistent relationship between event incidence and age group, although confusional state and agitation appeared to be more frequent with advancing age in males. Overall, the frequency of the most common TEAEs of interest was similar for males and females, with the exception of agitation, which was more common in males.

Conclusions: Abuse-Related AEs during All Clinical Studies

The most common finding was an elevated incidence of somnolence and dizziness, mostly in subjects treated with high doses of pimavanserin (particularly at doses of 100 mg or greater). There was no evidence that these were associated with elevated mood or drug-seeking behavior.

Three additional events of interest occurred in the exploratory datasets, one report of feeling drunk, one report of euphoric mood, and one report of hangover. The report of euphoric mood occurred in a schizophrenic patient concurrently treated with 2 mg haloperidol and 20 mg pimavanserin in Study ACP-103-008.

In the PDP Randomized Double-Blind Placebo-Controlled Studies, interesting TEAEs were those related to Hallucination and Confusional state. As the inclusion criteria for the studies of PDP included active psychosis, TEAEs of hallucinations, delusions or psychosis appeared to result from worsening of the AE rather than their first appearance. Neither hallucinations nor confusion was observed in healthy volunteers receiving pimavanserin, even at high doses. Another contributing factor to the observation of psychosis-related TEAEs is the discontinuation of antipsychotic medications shortly before randomization; in many of the reviewed cases, the appearance of worsened psychotic symptoms corresponded with the discontinuation of these medications

The event of Drug Dependence occurred in one subject receiving 40 mg pimavanserin in Study ACP-103-015. The onset of the event coincided with discontinuation of treatment with acetaminophen/hydrocodone for pain and was attributed to opioid dependency.

The two reports of Substance-induced psychotic disorder were both associated with ongoing dementia and psychosis, and were not attributable to acute subjective effects of study drug.

In summary, the review of safety data from the pimavanserin clinical studies revealed no evidence of drug abuse or drug dependence. There was no evidence of drug induced subjective effects indicative of mood elevation, stimulation, or alterations in perception or cognition. Review of drug accountability records in patients experiencing abuse related TEAEs did not reveal any evidence of drug diversion. There was no evidence of drug-induced subjective effects reflective of drug-induced mood elevation or psychomotor stimulation

6. Conditioned Place Preference (CPP)

Pimavanserin was evaluated in the CPP procedure (Report 2013-02). Sprague-Dawley rats received pairings of pimavanserin (3 mg/kg, SC), morphine (5 mg/kg, SC, CII) or clozapine (10 mg/kg, SC, not scheduled) with a novel environment in 30-minute sessions. Plastic chambers (42 cm x 42 cm x 30 cm) with black vertical bars on the front half and white horizontal bars on the rear half served as the novel environment for these experiments. Prior to each behavioral session, a small amount of corn bedding was sprinkled on the white side of the chamber, and a kimwipe with balsamic vinaigrette was rubbed along the black side of the chambers. Each rat's activity was monitored during the session with photocell beams equipped in each chamber. A pre-test session was conducted during which rats were given access to explore each side of the chamber to test each rat's side preference. Rats were then assigned to treatment conditions that counterbalanced whether drug treatment sessions occurred in the rat's preferred or non-preferred side and whether this was the black or white chamber. In total there were seven pairing sessions, 4 in which rats received test compound restricted to one side of the chamber, and 3 sessions in which rats received vehicle and were restricted to the other. Following session pairing, rats were allowed full access to the both side of the chamber and assessed for a tendency to prefer or avoid one side over the other in a drug-free state during 15-min test sessions.

Based on the Sponsor's analysis of the data, pairings conducted with morphine functioning as the positive control produced a statistically significant place preference ($p < 0.05$) for the novel environment, demonstrating rewarding effects. Pairing conducted with clozapine, a control with known aversive properties, produced a statistically significant ($p < 0.05$) place aversion, demonstrating no reward. In contrast, pairings of pimavanserin at the same dose did not produce either a preference or aversion for the novel environment. According to the Sponsor, these data suggest that pimavanserin is unlikely to have reinforcing properties in rats and that pimavanserin might lack both the abuse liability of compounds that tend to elicit a place preference and the negative hedonic state of compounds that elicit a place aversion.

Significant inadequacies were found with this study.

1. The Sponsor assessed only one dose of pimavanserin. Several doses should be assessed; a low, moderate and high dose to obtain a full dose response of the drug's effects.
2. In addition, the dose assessed (3 mg/kg) produces a C_{max} level (1.91 ng/ml, Study (b) (4) 142.02, page 81) that is not comparable to the C_{max} levels reported in humans at therapeutic doses, approximately 65 ng/ml (predicted steady-state 1606.6 ng·hr/mL) based on a 40 mg/kg dose (pimavanserin tartrate, ISS page 67 and 70). The no observable adverse effect level (NOAEL) in rats reported by the Sponsor was 10 mg/kg/day (C_{max} 48 ng/ml, ISS, page 70); still higher doses could have been tested.
3. It appears that rats are more sensitive to the effects of pimavanserin due to bioavailability differences which seem dependent on the drug formulation ((b) (4) versus tartrate salt form). In rats, the bioavailability of (b) (4) ((b) (4) form) was dependent upon the dose administered; at 3.0 mg/kg, the bioavailability was 2.84%, while after 10 mg/kg, the bioavailability was 42.6%. These issues could have impacted results, it is not clear if the tartrate form was assessed in the CPP study.
4. Drug plasma levels were not assessed.

5. The Sponsor provides no justification for not assessing pimavanserin's metabolite N-desmethyl-pimavanserin (AC-279). AC-279 was identified as an active and significant circulating metabolite in humans. AC-279 has similar receptor activity to pimavanserin; it is a potent 5-HT_{2A} antagonist, with moderate potency as a 5-HT_{2C} antagonist and no significant activity as an agonist or antagonist of 5-HT_{2B} receptors (Study 2014-01).
6. The Sponsor does not justify the use of a CPP procedure over a self-administration procedure. Typically a CPP procedure is conducted as a preliminary assessment and not as a substitute for a self-administration study unless justified.

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/s/

MARTIN S RUSINOWITZ
02/22/2016

JOVITA F RANDALL-THOMPSON
02/22/2016

MICHAEL KLEIN
02/22/2016

Internal Consult

*** Pre-decisional Agency Information ***

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan E. Blair, Health Communications Analyst, DRISK

From: Susannah O'Donnell, Regulatory Review Officer, OPDP

CC: Mathilda Fienkeng, Team Leader, OPDP
Louis Flowers, RPM, OSE
Kim Lehrfeld, Team Leader, DRISK
Cathy Miller, Risk Management Analyst, DRISK
Kate Heinrich Oswell, Health Communications Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: January 29, 2016

Re: **NDA 207318**
Nuplazid (pimavanserin) tablets
Draft Risk Evaluation and Mitigation Strategies (REMS) Material

Reference is made to the Division of Risk Management's (DRISK) consult request dated October 15, 2015 for review of REMS materials for Nuplazid (pimavanserin) tablets.

DRISK confirmed in an e-mail on January 19, 2016 that a review of the REMS materials was no longer needed.

OPDP requests that DRISK submit a new consult request if a review of REMS materials is needed during a subsequent review cycle.

Thank you for your consult.

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/s/

SUSANNAH O'DONNELL
01/29/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 6, 2015
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 207318
Product Name and Strength: Nuplazid (pimavanserin) Tablets, 17 mg
Product Type: Single-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Acadia Pharmaceuticals, Inc.
Submission Date: September 1, 2015
OSE RCM #: 2015-2078
DMEPA Primary Reviewer: Deborah Myers, RPh, MBA
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review is written in response to a request from the Division of Psychiatry Products (DPP) to review the proposed labels and labeling for Nuplazid (pimavanserin) tablets [NDA 207318] for vulnerabilities to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling identified areas that can be improved to increase clarity, improve readability, and add important information to minimize the risk of medication errors and promote the safe use of Nuplazid.

We note that the intended route of administration is not included in the Highlights of Prescribing Information, *Dose and Administration* and Full Prescribing Information, Section 2 *Dose and Administration*, which could increase the potential for wrong route medication errors.

Our review notes that the National Drug Code (NDC) numbers, both on the container label and in Section 16, *How Supplied/Storage and Handling* of the Full Prescribing Information, are currently denoted by placeholders. We will request that the Sponsor submit the NDC number for this product for our review with the next label revision.

We note on the container label [REDACTED] (b) (4)

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling that can be revised to increase clarity, improve readability, and add important information to mitigate medication errors and promote the safe use of Nuplazid. We provide recommendations in Sections 4.1 and 4.2 below and advise they are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Highlights of Prescribing Information, *Dosage and Administration*
 - 1. Consider adding the word “orally” so that this statement reads “(b) (4) recommended dose (b) (4) is 34 mg, taken orally as two 17 mg tablets once daily without titration” to provide clarity regarding the route of administration.
- B. Full Prescribing Information, Section 2 *Dose and Administration*
 - 1. Consider adding “orally” in the dosing statement so that it reads, “The recommended dose of Nuplazid is 34 mg taken orally as two 17 mg strength tablets once daily without titration.”
- C. Full Prescribing Information, Section 16, *How Supplied/Storage and Handling*
 - 1. As currently presented, the NDC is denoted by a placeholder (63090-YYY-ZZ). Since the NDC number on the container labels submitted is also denoted by a placeholder (XXXX-XXXX-XX), we will request that the Sponsor submit the NDC number for this product for our review with the next container label revision.

4.2 RECOMMENDATIONS FOR ACADIA PHARMACEUTICAL, INC.

We recommend the following be implemented prior to approval of this NDA 207318:

Container Labels

- 1. As currently presented, the NDC is denoted by a placeholder (XXXX-XXXX-XX). Please add the intended NDC number to the container labels and submit for our review.
- 2. Relocate the net quantity statement (b) (4) such as farther to the bottom left or right of the principal display panel. (b) (4)

(b) (4)

(b) (4)

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nuplazid that Acadia Pharmaceuticals, Inc. submitted on September 1, 2015.

Table 2. Relevant Product Information for Nuplazid	
Initial Approval Date	N/A
Active Ingredient	Pimavanserin
Indication	For the treatment of psychosis associated with Parkinson's disease.
Route of Administration	Oral
Dosage Form	Tablet
Strength	17 mg
Dose and Frequency	Two 17 mg tablets (34 mg) once daily
How Supplied	60-count bottles intended for commercial use 14-count bottles intended for physician samples
Storage	Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 6, 2015, we searched the L:drive and AIMS using the term, pimavanserin, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews^{1,2}, and we confirmed that our previous reviews contained no outstanding recommendations.

¹ Holmes, L. Proprietary Name Review for Nuplazid IND 068384. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APR 29. RCM No.: 2013-16613.

² Myers, D. Proprietary Name Review for Nuplazid NDA 207318. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 05. RCM No.: 2015-5619460.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Nuplazid labels and labeling submitted by Acadia Pharmaceuticals, Inc. on September 1, 2015.

- Prescribing Information (no image)
- Container Label



- Professional Sample Container Label



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DEBORAH E MYERS
11/06/2015

DANIELLE M HARRIS
11/06/2015

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

IND or NDA	207318
Brand Name	NUPLAZID™
Generic Name	Pimavanserin
Sponsor	Acadia Pharmaceuticals Inc.
Indication	Treatment of psychosis associated with Parkinson's disease
Dosage Form	Tablets
Drug Class	Selective serotonin inverse agonist
Therapeutic Dosing Regimen	34 mg pimavanserin PO QD (equivalent to 40 mg pimavanserin tartrate PO QD)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single-dose MTD is >300 mg PO Multiple-dose MTD is 100 mg QD PO
Submission Number and Date	001 / 9/1/2015
Review Division	DPP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Using QTcI correction, a marginal QTc prolongation effect of pimavanserin at the 80 mg doses once daily after 20 consecutive days of dosing is detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between pimavanserin 80 mg and placebo is 16.6 ms at 6 hours postdose on Day 20. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

This is a double-blinded, placebo- and positive-controlled, 4-arm, multiple-dose parallel design study, 252 subjects receive pimavanserin 20 mg, pimavanserin 80 mg, placebo and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Pimavanserin (20 mg and 80 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Pimavanserin 20 mg	1	4.4	(1.6, 7.2)
Pimavanserin 80 mg	6	13.5	(10.3, 16.6)
Moxifloxacin 400 mg*	4	11.2	(8.2, 14.2)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.1 ms.

The therapeutic dose of 40 mg once daily for pimavanserin is not directly studied in this TQT trial. Based on the linear PK of pimavanserin, the 80 mg dose studied in this study is expected to provided a 2-fold margin over the therapeutic exposure. CYP3A4/5 inhibitor ketoconazole increases pimavanserin Cmax 50% and triples AUC in the single dose study. The effect of hepatic impairment and renal impairment on pimavanserin PK are unknown. Based on the concentration-QTc relationship, a marginal QTc prolongation is expected at the therapeutic concentration.

2 PROPOSED LABEL

The following is the sponsor’s proposed labeling language related to QT.



QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

5.1 QT Prolongation

(b) (4)

NUPLAZID prolongs the QT interval.

(b) (4)

The use of NUPLAZID should be avoided in combination with other drugs known to prolong QT_d including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias (b) (4) other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death (b) (4) including bradycardia; hypokalemia, or hypomagnesemia; and presence of congenital prolongation of the QT interval.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of NUPLAZID on the QTc interval was evaluated in a (b) (4) randomized placebo and positive controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (b) (4) upper bound of the two-sided 90% CI) was 13.5 (16.6) ms at the dose twice the therapeutic dose. A pharmacokinetic/pharmacodynamic analysis with NUPLAZID suggested a concentration-dependent QTc prolongation (b) (4) the therapeutic range.

In 6-week, placebo-controlled (b) (4) studies, mean increases in QTc interval of ~5-8 msec (b) (4) observed in patients receiving once-daily doses of NUPLAZID 34 mg. These

patient data are consistent with the profile observed in a thorough QT study in healthy volunteers. Sporadic QTcF values ≥ 500 ms and change from baseline values ≥ 60 msec were observed in (b) (4) treated with NUPLAZID 34 mg; (b) (4) incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of NUPLAZID, including those (b) (4) patients.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Pimavanserin is a selective serotonin inverse agonist indicated for the treatment of psychosis associated with Parkinson's disease.

3.2 MARKET APPROVAL STATUS

Pimavanserin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

In vitro: A GLP hERG study showed that pimavanserin inhibited hERG (human ether a-go-go-related Gene) potassium currents by $10.6 \pm 2.3\%$, $25.1 \pm 2.4\%$, $54.0 \pm 4.3\%$, $80.3 \pm 0.6\%$, and $99.3 \pm 0.3\%$ (mean \pm standard error of the mean) at 0.03, 0.075, 0.24, 0.83, and 9.35 nM, respectively (Study 061019.DPW). The concentration eliciting 50% inhibition (IC₅₀) for the effect of pimavanserin on hERG current was 210 nM.

In vivo: Oral administration of pimavanserin at 1, 10, and 100 mg/kg in a GLP study in telemetered cynomolgus monkeys had no marked effect on arterial blood pressure (systolic, diastolic, and mean) or heart rate, or on electrocardiogram (ECG) parameters (RR interval, PR interval, QT interval, QTcF interval [QTc calculated using Fridericia's formula], or QRS interval) when compared with time-matched vehicle controls (Study DHTI1004). Vomiting was noted in two of four monkeys following administration of 100 mg/kg pimavanserin. Statistically significant QTc interval prolongation was observed at two time points (2 and 6 hours) in the high dose group; however, the magnitude of the effect was considered small and not time-related, thus the relationship to pimavanserin treatment is uncertain.

Supportive data: In an exploratory study of cardiovascular response, pimavanserin administered intravenously (iv) to anesthetized Beagles had no notable effects except for an increase in heart rate at the highest dose (1.8 mg/kg) (Study 2002-19).

In the 1-, 3-, or 12-month GLP toxicity studies in monkeys at doses up to 51 mg/kg/day (Studies HTI1003, (b) (4).177.01, and (b) (4).146.01) there were no changes in ECG parameters. Mean C_{max} values in these studies ranged from 669-916 ng/mL.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of pimavanserin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study under NDA 207318. The sponsor submitted the study report ACP-103-018 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Parallel, Double-Blind, Placebo-Controlled, Multiple-Dose, Thorough QT/QTc Study of Pimavanserin in Healthy Adults

4.2.2 Protocol Number

ACP-103-018

4.2.3 Study Dates

First subject enrolled: 25 July 2008

Last assessment: 04 December 2008

4.2.4 Objectives

The primary objective is to determine the potential for electrocardiogram (ECG) effects with focus on the individualized corrected QT intervals (QTcI) of multiple dosing over 20 days of once-daily dosing with pimavanserin (20 mg and 80 mg once daily) in healthy adult volunteers.

4.2.5 Study Description

4.2.5.1 Design

This was a double-blind, placebo-controlled, 4-arm, multiple-dose parallel design evaluation of QT/QTc interval effects of pimavanserin 20 mg and 80 mg doses once daily in healthy adults after 20 consecutive days of dosing. Study drug was administered for up to 20 days.

The study included a screening period of up to 30 days that included two days of baseline assessments (Days -2 and -1), a 20-day double-blind treatment period, a final study visit (Day 21) or early termination, PK sample visits on Days 21 through 24, and a follow-up phone visit on Day 35 (± 2 days).

On Day 1, subjects were randomized to receive pimavanserin 20 mg, pimavanserin 80 mg, placebo/moxifloxacin, or placebo daily for 20 days. Subjects randomized to the placebo/moxifloxacin group received placebo for Days 1 through 20 plus moxifloxacin 400 mg on Day 20 only.

4.2.5.2 Controls

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

4.2.5.3 Blinding

This study was a double-blind study in which all subjects, study staff, investigators, and the sponsor remained blinded to treatment throughout the duration of the study. With the exception of moxifloxacin (Day 20), all pimavanserin and placebo doses appeared identical in appearance to ensure blinding.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

This study includes four treatment groups listed as below:

- pimavanserin 20 mg: one 20 mg tablet of pimavanserin and three placebo tablets administered once daily for 20 days
- pimavanserin 80 mg: four 20 mg tablets of pimavanserin administered once daily for 20 days
- placebo group: four placebo tablets matched to the pimavanserin 20 mg tablet once daily for 20 days
- placebo/moxifloxacin group: four placebo tablets matched to the pimavanserin 20 mg tablet once daily for 20 days plus one 400 mg tablet moxifloxacin on Day 20

4.2.6.2 Sponsor's Justification for Doses

This was a double-blind, placebo-controlled, 4-arm, multiple-dose parallel design evaluation of QT/QTc interval effects of pimavanserin 20 mg and 80 mg doses once daily in healthy adults after 20 consecutive days of dosing. The four treatment groups included pimavanserin 20 mg (clinical dose), pimavanserin 80 mg (supratherapeutic dose), placebo plus moxifloxacin 400 mg (moxifloxacin on Day 20 only), and placebo.

The worst case scenario is illustrated by CYP3A4/5 inhibition with ketoconazole where exposure to pimavanserin increased 1.5-fold for C_{max} (from 17.1 to 25.1 ng/mL) and 3-fold for AUC₀₋₂₄ (from 1224 to 3415 ng·h/mL; Study ACP-103-023). These increases are well-covered by available safety and associated exposure data in humans where single doses of up to 300 mg and multiple doses of up to 150 mg for 14 days have resulted in C_{max} values of up to 152 ng/mL (300 mg single dose) and 248 ng/mL (150 mg for 14 days) and corresponding AUCs of up to 10,798 and 4680 ng·h/mL. At doses ≥100 mg, adverse events of dizziness, somnolence, lethargy, nausea, vomiting, dyspepsia, epistaxis, back pain and fatigue have been reported with pimavanserin at rates at least twice those for placebo.

The supratherapeutic dose of 80 mg pimavanserin tested in the thorough QT study also encompasses the exposures seen when pimavanserin 40 mg was coadministered with ketoconazole. In the tQT study, the 80 mg dose was associated with C_{max} values of 49.43 and 205.92 ng/mL and AUC values of 860.3 and 3817.1 ng·h/mL at Day 1 and Day 20, respectively. The tQT study also tested pimavanserin 20 mg, moxifloxacin, and placebo and across the four dose groups, the most common TEAE across treatment groups was headache (13.3%, pimavanserin 20 mg; 22.2%, pimavanserin 80 mg; 22.0%, placebo/moxifloxacin; 19.7%, placebo). Events that occurred in >5% of subjects included headache in the pimavanserin 20 mg, headache, dizziness (15.3%), nausea (12.5%), and

rash (5.6%) in the pimavanserin 80 mg group, headache, pharyngolaryngeal pain and diarrhea (5.1%) in the placebo/moxifloxacin group, and nausea (6.6%) in the placebo group. Events that occurred in $\geq 10.0\%$ of pimavanserin 80 mg-treated subjects and twice the incidence of pimavanserin 20 mg-treated subjects included nausea (12.5% vs. 1.7%) and dizziness (15.3% vs. 3.3%).

Reviewer's Comment: The studied doses are acceptable. The study result is positive. Although the therapeutical dose (40 mg q.d.) was not directly studied in this TQT study, the studied exposure range covered the clinically relevant exposure.

4.2.6.3 Instructions with Regard to Meals

Drug was administered under fasting condition on Day 1 and non-fasting condition thereafter.

Reviewer's Comment: Acceptable. It appears no food effect on pimavanserin exposure. Study drug could be administered orally once daily regardless of food intake.

4.2.6.4 ECG and PK Assessments

On Day 1, subjects were randomized to study drug (pimavanserin 20 mg, 80 mg, placebo/moxifloxacin, or placebo), which was administered daily for 20 days. Continuous 24-hour Holter ECG recordings were obtained on Days -1 (baseline) and Day 20 for all subjects who met the dosing requirement. Triplicate ECG recordings were obtained at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 23.5 hours postdose on Day -1 and Day 20. To minimize the effect of intrinsic variability, ECGs were recorded in triplicate, approximately 1 minute apart. All ECGs were read at a central laboratory by a central cardiologist blinded to study treatment.

Serial pharmacokinetic (PK) samples to measure plasma concentrations of study drug were obtained on Day 1, predose and up to 24 hours postdose and on Day 20, predose and up to 96 hours postdose. Subjects returned to the study center on Days 21 through 24 for the PK sample collection. Only pimavanserin 20 mg and 80 mg groups were analyzed.

Reviewer's Comment: The proposed ECG and PK sampling times are appropriate to capture the peak ($T_{max} = 9$ hours).

4.2.6.5 Baseline

The sponsor used time-match pre-dose on Day -1 as baseline.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 252 subjects were randomized to receive pimavanserin 20 mg (n=60), pimavanserin 80 mg (n=72), placebo/moxifloxacin (n=59), or placebo (n=61). An equal number of males (n=126) and females (n=126) were randomized.

Subjects eligible to participate in the study were males and females aged 18 to 45 years in good general health.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was a time-matched mean differences between pimavanserin (20 mg and 80 mg) and placebo in Δ QTcI. The sponsor used analysis of covariance (ANCOVA) and the results presented in Table 2 and Figure 1. The model included treatment, time, treatment-by-time interaction as fixed effect terms, baseline as a covariate, and subject as a random effect.

Sponsor concluded that the time-matched analysis for the QTcI interval change for the 20 mg clinical dose of pimavanserin showed at all time points that the point estimates were less than 5.0 ms and that the upper bound of the 2-sided 90% CI did not exceed 10.0 ms (maximum of 6.8 ms at 10 hours postdose). A similar comparison was performed for the suprathreshold dose of pimavanserin 80 mg that showed point estimates of approximately 11 to 14 ms at many time points with the maximum upper bound of the 2-sided 90% CI exceeding 10.0 ms at all time points (15.9 ms at 6 hours postdose on Day 20).

Table 2: Sponsor's Results of $\Delta\Delta\text{QTcI}$ for Pimavanserin 20 mg, Pimavanserin 80 mg and Moxifloxacin 400 mg

Table 14.2.3-16
 Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
 QTc Individual (msec)
 ECG Population

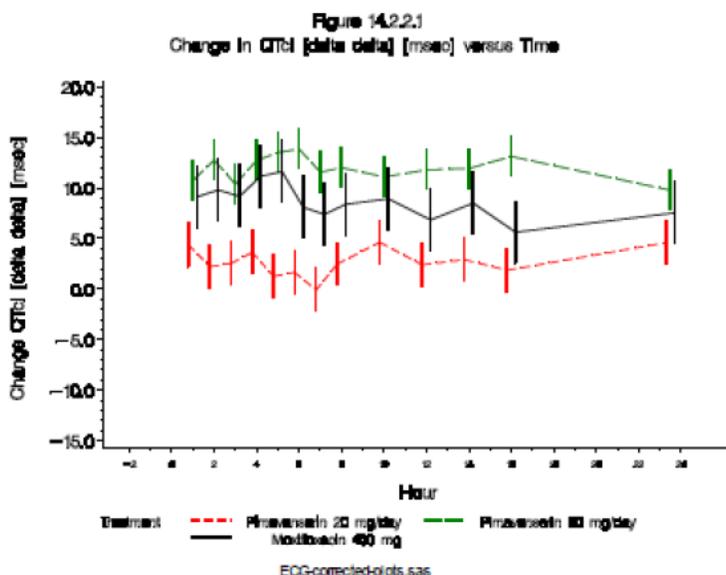
Time (hr)	Pimavanserin 20 mg/day (n=57)			Pimavanserin 80 mg/day (n=67)			Moxifloxacin 400 mg (n=55)		
	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
1 hr	4.4	2.3	6.6	10.8	8.8	12.8	9.2	6.2	12.3
2 hr	2.3	0.2	4.5	12.9	10.9	14.9	9.8	6.8	12.9
3 hr	2.6	0.5	4.7	10.5	8.5	12.4	9.2	6.2	12.3
4 hr	3.7	1.6	5.9	12.8	10.9	14.8	11.2	8.1	14.3
5 hr	1.4	-0.7	3.5	13.5	11.6	15.5	11.7	8.6	14.7
6 hr	1.8	-0.3	3.9	13.9	11.9	15.9	8.1	5.1	11.2
7 hr	0.0	-2.1	2.1	11.6	9.6	13.6	7.5	4.4	10.6
8 hr	2.5	0.4	4.6	12.1	10.1	14.0	8.5	5.4	11.5
10 hr	4.7	2.5	6.8	11.1	9.1	13.1	9.0	6.0	12.1
12 hr	2.5	0.4	4.6	11.8	9.9	13.8	6.9	3.9	10.0
14 hr	3.0	0.9	5.2	12.0	10.1	14.0	8.6	5.5	11.7
16 hr	1.9	-0.2	4.0	13.2	11.2	15.1	5.7	2.6	8.8
23.5 hr	4.5	2.4	6.7	9.8	7.9	11.8	7.7	4.6	10.7
Time Ave	3.0	1.7	4.3	12.3	11.1	13.5	9.0	7.2	10.9

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for: treatment, gender, time, and interactions: treatment by time, treatment by gender and treatment by time by gender. Subject is included as random effects term.

[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.
 p-values for gender effects: Gender is 0.3635, and treatment by gender is 0.0202.

Source: Clinical Study Report, Table 14.2.3-16, page 48/314

Figure 1: Sponsor's Results of $\Delta\Delta\text{QTcI}$ for Pimavanserin and Moxifloxacin



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Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to the sponsor's results of $\Delta\Delta\text{QTcI}$.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcI effect for moxifloxacin. The analysis results were presented in Table 2 and Figure 1. The largest unadjusted lower bound was 8.6 ms. Thus, assay sensitivity in this thorough QTcI study was established.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.3 Categorical Analysis

Pimavanserin demonstrated no effects on heart rate, PR, and QRS interval duration or cardiac morphology and no subject had a QTcI or QTcF interval >480 ms or increase >60 ms.

4.2.8.3 Safety Analysis

No deaths or other serious treatment-emergent adverse events (TEAEs) were reported during the study. One (1.7%) subject in the pimavanserin 20 mg group and three (4.2%) in the 80 mg group vs. no subject in the placebo/moxifloxacin group or placebo group discontinued the study due to a TEAE. In the pimavanserin 80 mg group, two of the three subjects discontinued due to dizziness, which was the most common event causing discontinuation.

A higher percentage of subjects in the pimavanserin 80 mg group (58.3%) vs. the pimavanserin 20 mg (38.3%), placebo/moxifloxacin (37.3%) or placebo (39.3%) groups experienced any TEAE. Events within the Nervous System Disorders and

Gastrointestinal Disorders system organ classes were the most frequently reported. The most frequently occurring TEAE across all treatment groups was headache (13.3%, pimavanserin 20 mg; 22.2%, pimavanserin 80 mg, 22.0%, placebo/moxifloxacin; 19.7% placebo). Events that occurred in $\geq 10.0\%$ of pimavanserin 80 mg-treated subjects and twice the incidence of pimavanserin 20 mg-treated subjects were nausea (12.5% vs. 1.7%) and dizziness (15.3% vs. 3.3%); these events are possibly dose-related.

With the exception of syncope in two (2.8%) subjects in the pimavanserin 80 mg group and one (1.7%) subject in the placebo/moxifloxacin group, there were no additional TEAEs reported in any treatment group suggestive of proarrhythmic potential (defined in ICH E14 guidance) or any clinically significant cardiovascular-related TEAEs. No apparent trends or clinically meaningful changes were observed from baseline in clinical laboratory test results, vital sign measurements, or ECG recording (overall clinical impressions).

A summary of overall TEAEs experienced during treatment is summarized below:

- TEAEs were more frequently reported among subjects in the pimavanserin 80 mg group (58.3%) than the pimavanserin 20 mg (38.3%), placebo/moxifloxacin (37.3%) or placebo (39.3%) groups.
- No deaths or other serious TEAEs were reported.
- TEAEs considered treatment-related (possible, probably, or highly probable) by the Investigator were more common among subjects in the pimavanserin 80 mg group (44.4%) than the 20 mg (16.7%), placebo/moxifloxacin (20.3%) or placebo (32.8%) groups.
- One (1.7%) subject in the pimavanserin 20 mg group and three (4.2%) in the 80 mg group discontinued due to a TEAE vs. no subject in the placebo/moxifloxacin or placebo

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Pimavanserin pharmacokinetic profiles of 20 mg and 80 mg on Day 1 (Single-Dose) and Day 20 are demonstrated in the following tables and figures.

PK Parameter	Statistics	Pimavanserin 20 mg (n=35)	Pimavanserin 80 mg (n=38)
Day 1			
C_{max} (ng/mL)	Mean (%CV)	12.11 (42.9)	49.43 (22.8)
	Median	10.40	48.25
	Min, Max	6.3, 35.9	25.6, 72.3
$AUC_{(0-24hr)}$ (hr*ng/mL)	Mean (%CV)	200.98 (29.2)	860.30 (22.4)
	Median	185.20	870.65
	Min, Max	118.8, 330.8	480.8, 1271.0
t_{max} (hr)	Mean (%CV)	9.37 (27.4)	9.08 (33.6)
	Median	9.00	9.00
	Min, Max	6.0, 16.0	6.0, 16.0
Day 20			
C_{max} (ng/mL)	Mean (%CV)	46.11 (32.7)	205.92 (34.4)
	Median	42.80	198.50
	Min, Max	21.5, 93.2	93.1, 440.0
$AUC_{(0-24hr)}$ (hr*ng/mL)	Mean (%CV)	849.28 (33.4)	3817.1 (38.4)
	Median	802.11	3502.28
	Min, Max	398.4, 1801.8	1862.5, 9169.5
$AUC_{(0-14hr)}$ (hr*ng/mL)	Mean (%CV)	2245.68 (42.7)	10482.60 (55.3)
	Median	2053.90	9190.15
	Min, Max	909.5, 5891.0	4440.7, 34817.6
$AUC_{(0-inf)}$ (hr*ng/mL)	Mean (%CV)	3118.28 (63.1)	16418.53 (90.3)
	Median	2627.10	13341.50
	Min, Max	1056.3, 11741.0	5398.7, 84988.0
t_{max} (hr)	Mean (%CV)	6.91 (18.7)	7.16 (14.0)
	Median	7.00	7.00
	Min, Max	5.0, 12.0	5.0, 10.0
$t_{1/2}$ (hr)	Mean (%CV)	46.50 (31.0)	54.33 (42.7)
	Median	43.04	47.84
	Min, Max	31.3, 94.7	30.6, 116.7
RAC	Mean (%CV)	4.30 (23.9)	4.46 (30.2)
	Median	4.22	4.10
	Min, Max	2.28, 7.45	2.56, 9.32
% Fluctuation	Mean (%CV)	51.46 (23.7)	53.53 (22.5)
	Median	48.56	51.89
	Min, Max	31.4, 89.7	28.5, 78.5

Source: sponsor's QT study Table 11-4

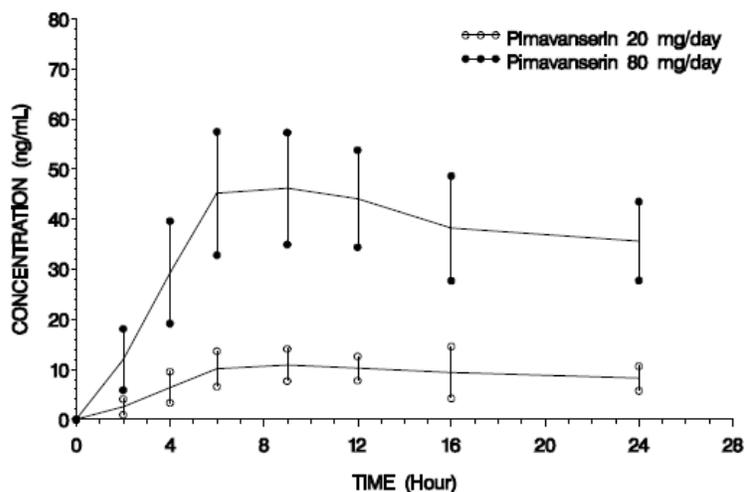


Figure 1.1: Mean Plasma Pimavanserin Concentration on Day 1 (Linear Scale)
Protocol ACP-103-018

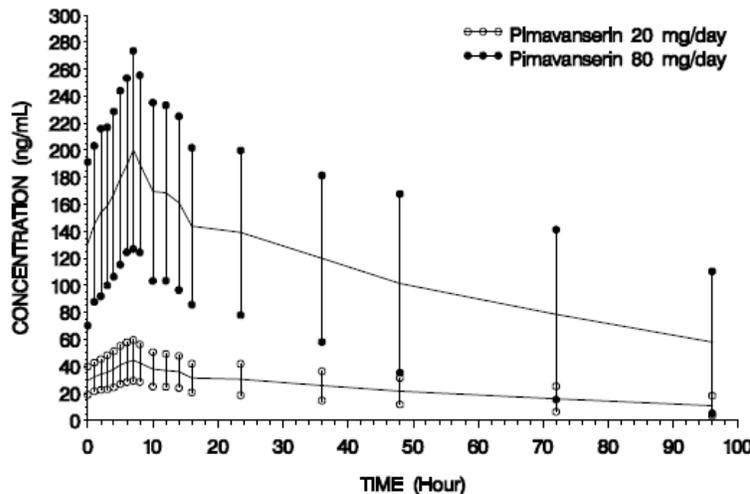
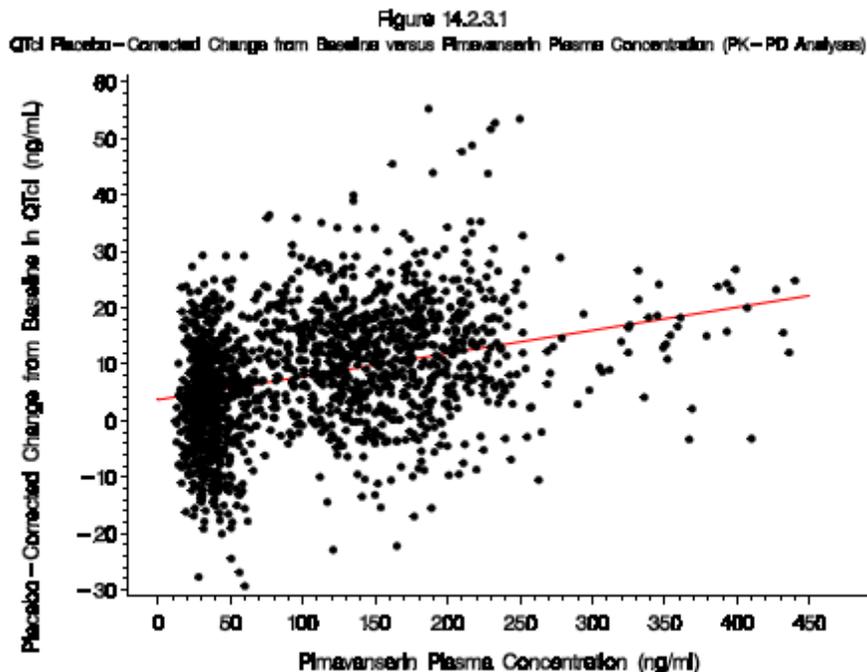


Figure 1.2: Mean Plasma Pimavanserin Concentration on Day 20 (Linear Scale)

Source: sponsor's QT study Figure 11-1

4.2.8.4.2 Exposure-Response Analysis

A pharmacokinetic/pharmacodynamic relationship (PK/PD) analysis was conducted on Day 20 to explore the relationship between plasma pimavanserin concentration and the placebo-corrected change from baseline in QTc intervals. The predicted QTcI for pimavanserin 80 mg at average C_{max} (200 ng/ml) was 12 ms (upper limit of the one-sided 95% CI was 13.39), exceeding 10 ms.



Reviewer's Analysis: The PK/PD analysis combined the data of pimavanserin 20 mg and 80 mg. There is a trend of increase QT placebo-corrected change from baseline with higher pimavanserin plasma concentration. >50% observed data exceed 10.0 ms. Reviewer's exposure-response analysis plot of $\Delta\Delta QTc$ vs. drug concentrations is presented in Figure 4.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

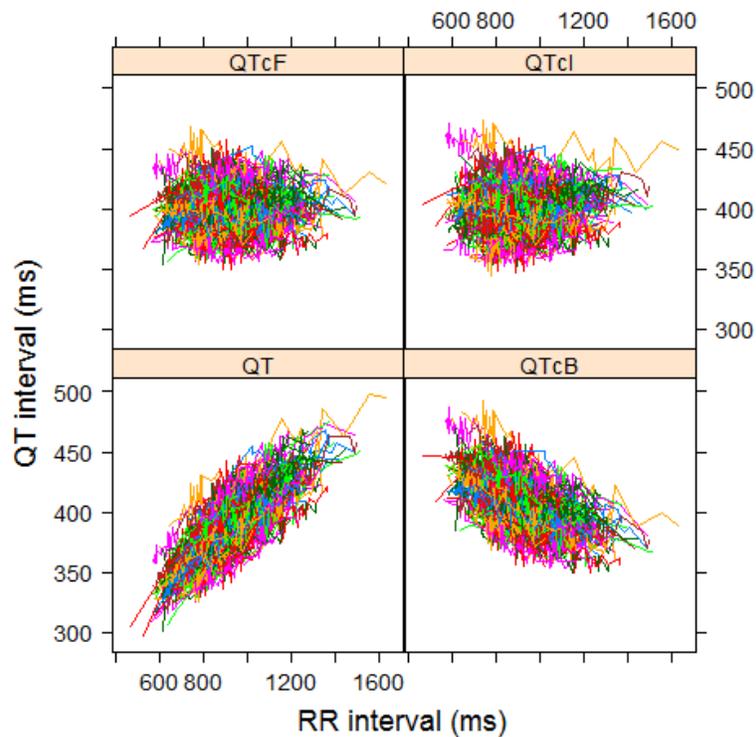
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 3, it appears that QTcI is better than QTcF. This reviewer used QTcI as primary statistical analysis.

Table 3: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcI		QTcB		QTcF	
	N	MSSS	N	MSSS	N	MSSS
Moxifloxacin 400 mg	58	0.0007	58	0.0040	58	0.0016
Pimavanserin 20 mg/day	60	0.0006	60	0.0049	60	0.0016
Pimavanserin 80 mg/day	72	0.0007	72	0.0043	72	0.0015
Placebo	61	0.0007	61	0.0041	61	0.0018
All	251	0.0007	251	0.0044	251	0.0016

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Pimavanserin

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 4. The largest upper bounds of the 2-sided 90% CI for the mean differences between Pimavanserin 20 mg and placebo, and between Pimavanserin 80 mg and placebo are 7.7 ms and 16.6 ms, respectively.

Table 4: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Pimavanserin 20 mg and Pimavanserin 80 mg

	Treatment Group								
	Placebo	Pimavanserin 20 mg/day				Pimavanserin 80 mg/day			
	Δ QTcI	Δ QTcI		$\Delta\Delta$ QTcI		Δ QTcI		$\Delta\Delta$ QTcI	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-6.6	56	-2.2	4.4	(1.6, 7.2)	67	3.9	10.5	(7.8, 13.2)
2	-4.0	57	-1.4	2.6	(-0.3, 5.5)	66	8.7	12.7	(9.9, 15.5)
3	-1.4	57	1.6	3.1	(0.4, 5.8)	67	9.0	10.5	(7.8, 13.1)
4	-3.1	57	0.9	4.1	(1.1, 7.0)	67	9.5	12.7	(9.8, 15.5)
5	-1.5	57	0.1	1.7	(-1.3, 4.6)	67	11.4	12.9	(10.1, 15.7)
6	-1.6	57	0.5	2.1	(-1.1, 5.4)	67	11.9	13.5	(10.3, 16.6)
7	0.1	56	0.5	0.4	(-2.5, 3.3)	67	11.4	11.3	(8.5, 14.1)
8	-2.6	57	0.3	2.9	(0.2, 5.6)	67	9.2	11.7	(9.1, 14.4)
10	-0.1	57	4.8	4.9	(2.2, 7.7)	67	10.8	10.9	(8.3, 13.6)
12	-1.0	57	1.8	2.8	(0.0, 5.5)	67	10.4	11.4	(8.7, 14.0)
14	-0.9	57	2.4	3.3	(0.4, 6.1)	67	10.8	11.7	(9.0, 14.4)
16	-2.2	57	0.3	2.5	(-0.3, 5.4)	68	10.6	12.8	(10.1, 15.6)
23.5	-1.2	57	3.2	4.3	(1.6, 7.1)	65	8.5	9.6	(7.0, 12.3)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 5. The largest unadjusted 90% lower confidence interval is 8.2 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.1 ms, which indicates that an at least 5 ms QTcI

effect due to moxifloxacin can be detected from the study.

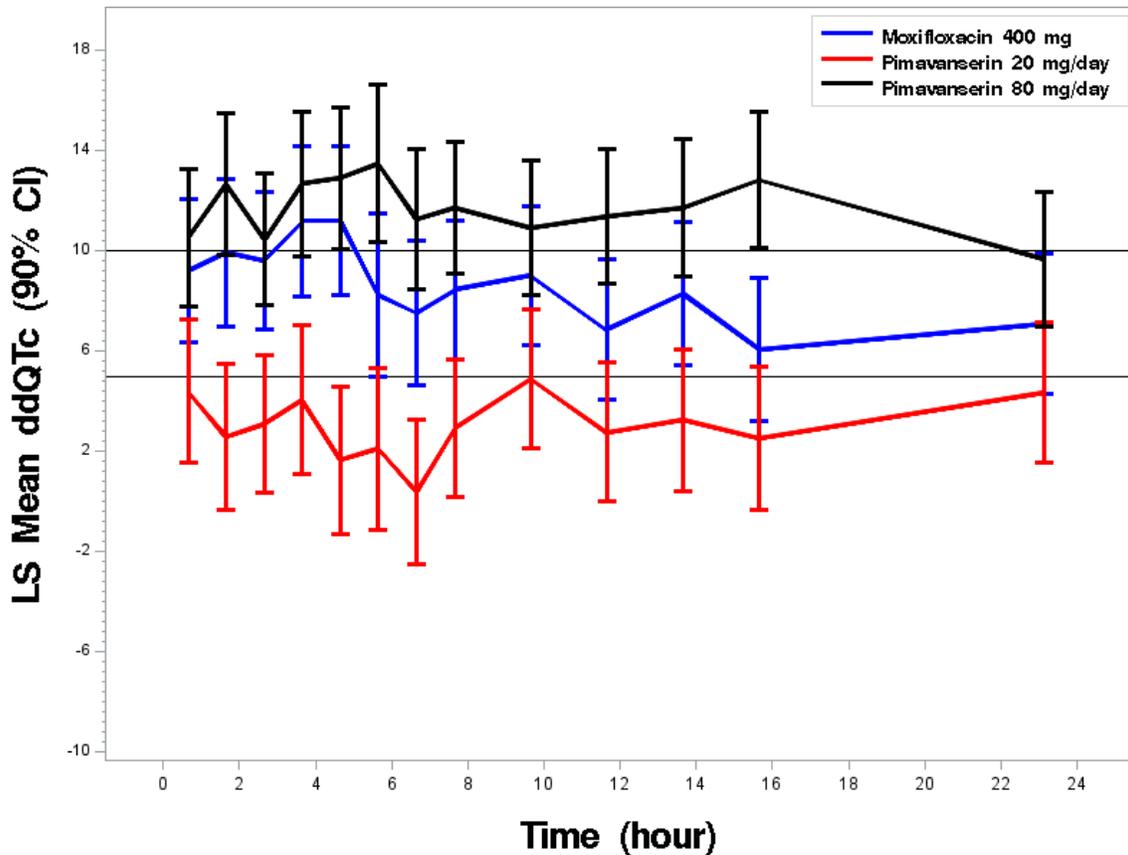
Table 5: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin

	Placebo	Moxifloxacin 400 mg				
	Δ QTcI	Δ QTcI		$\Delta\Delta$ QTcI		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
1	-6.6	55	2.6	9.2	(6.4, 12.1)	(5.3, 13.1)
2	-4.0	55	6.0	9.9	(7.0, 12.9)	(5.9, 14.0)
3	-1.4	55	8.2	9.6	(6.9, 12.4)	(5.8, 13.4)
4	-3.1	55	8.1	11.2	(8.2, 14.2)	(7.1, 15.3)
5	-1.5	55	9.7	11.2	(8.2, 14.2)	(7.1, 15.3)
6	-1.6	55	6.6	8.2	(5.0, 11.5)	(3.8, 12.7)
7	0.1	55	7.6	7.5	(4.6, 10.4)	(3.6, 11.5)
8	-2.6	55	5.9	8.4	(5.7, 11.2)	(4.7, 12.2)
10	-0.1	55	8.9	9.0	(6.2, 11.8)	(5.2, 12.8)
12	-1.0	55	5.8	6.8	(4.1, 9.6)	(3.0, 10.7)
14	-0.9	55	7.4	8.3	(5.5, 11.2)	(4.4, 12.2)
16	-2.2	55	3.9	6.1	(3.2, 8.9)	(2.2, 10.0)
23.5	-1.2	55	5.9	7.1	(4.3, 9.9)	(3.3, 10.9)

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

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

Figure 3: Mean and 90% CI Δ QTcI Time Course



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500, and >500 ms. No subject's QTcF is above 480 ms.

Table 6: Categorical Analysis for QTcI

	Total N	Value ≤ 450 ms	450 $ms < Value \leq 480$ ms	480 $ms < Value \leq 500$ ms	Value > 500
Treatment Group					
Moxifloxacin 400 mg	55	53 (96.4%)	2 (3.6%)	0 (0.0%)	0 (0.0%)
Pimavanserin 20 mg/day	57	57 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pimavanserin 80 mg/day	67	64 (95.5%)	3 (4.5%)	0 (0.0%)	0 (0.0%)
Placebo	55	55 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 7 lists the categorical analysis results for Δ QTcI. No subject's change from baseline was above 60 ms.

Table 7: Categorical Analysis of Δ QTcI

	Total N	Value\leq30 ms	30 ms\leqValue\leq60 ms	60 ms\leqValue\leq90 ms	Value$>$90 ms
Treatment Group					
Moxifloxacin 400 mg	55	52 (94.5%)	3 (5.5%)	0 (0.0%)	0 (0.0%)
Pimavanserin 20 mg/day	57	57 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pimavanserin 80 mg/day	67	53 (79.1%)	14 (20.9%)	0 (0.0%)	0 (0.0%)
Placebo	55	55 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between pimavanserin 20 mg and placebo, and between pimavanserin 80 mg and placebo are 6.1 bpm and 8.3 bpm, respectively. Table 9 presents the categorical analysis of HR. Five subjects who experienced HR interval greater than 100 bpm are in pimavanserin 20-mg and 80-mg groups.

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR for Pimavanserin 20 mg and Pimavanserin 80 mg

		Treatment Group													
		Placebo		Moxifloxacin 400 mg				Pimavanserin 20 mg/day				Pimavanserin 80 mg/day			
		Δ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI		
1	-0.8	55	5.3	6.1	(4.2, 8.1)	56	2.6	3.4	(1.4, 5.4)	67	4.9	5.7	(3.8, 7.6)		
2	-0.9	55	2.9	3.9	(1.7, 6.0)	57	3.0	3.9	(1.7, 6.1)	66	5.3	6.3	(4.2, 8.3)		
3	0.3	55	3.5	3.2	(1.0, 5.4)	57	2.8	2.4	(0.2, 4.7)	67	5.6	5.3	(3.1, 7.4)		
4	-1.1	55	2.0	3.0	(1.0, 5.1)	57	2.3	3.3	(1.3, 5.3)	67	5.3	6.4	(4.5, 8.3)		
5	0.6	55	0.9	0.3	(-2.2, 2.8)	57	0.8	0.2	(-2.3, 2.6)	67	3.9	3.3	(0.9, 5.6)		
6	0.5	55	1.4	0.9	(-1.7, 3.5)	57	-0.3	-0.9	(-3.5, 1.7)	67	4.7	4.2	(1.6, 6.7)		
7	1.7	55	2.8	1.1	(-1.3, 3.5)	56	4.2	2.5	(0.1, 4.9)	67	6.4	4.7	(2.4, 7.0)		
8	-0.1	55	3.6	3.7	(1.3, 6.1)	57	3.0	3.1	(0.7, 5.4)	67	5.8	5.9	(3.6, 8.2)		
10	1.5	55	3.2	1.8	(-0.4, 4.0)	57	5.4	3.9	(1.7, 6.1)	67	5.5	4.1	(2.0, 6.2)		
12	1.4	55	2.8	1.4	(-0.8, 3.7)	57	2.2	0.9	(-1.4, 3.2)	67	6.0	4.7	(2.5, 6.9)		
14	-1.7	55	0.7	2.4	(0.2, 4.6)	57	1.0	2.7	(0.5, 4.9)	67	2.8	4.5	(2.4, 6.6)		
16	4.0	55	4.4	0.4	(-1.9, 2.6)	57	3.1	-0.9	(-3.2, 1.3)	68	6.9	2.9	(0.7, 5.0)		
23.5	0.9	55	0.6	-0.2	(-3.0, 2.5)	57	3.1	2.3	(-0.4, 5.0)	65	5.7	4.9	(2.3, 7.5)		

Table 9: Categorical Analysis of HR

	Total N	HR \leq 100 ms	HR $>$ 100 ms
Treatment Group			
Moxifloxacin 400 mg	55	55 (100%)	0 (0.0%)
Pimavanserin 20 mg/day	57	56 (98.2%)	1 (1.8%)
Pimavanserin 80 mg/day	67	63 (94.0%)	4 (6.0%)
Placebo	55	54 (98.2%)	1 (1.8%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between pimavanserin 20 mg and placebo, and between pimavanserin 80 mg

and placebo are 5.1 ms and 7.5 ms, respectively. Table 11 presents the categorical analysis of HR. Six subjects who experienced PR interval greater than 200 ms are in pimavanserin 20-mg and 80-mg groups.

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for Pimavanserin 20 mg and Pimavanserin 80 mg

		Treatment Group											
		Moxifloxacin 400 mg				Pimavanserin 20 mg/day				Pimavanserin 80 mg/day			
		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	0.3	55	-0.2	-0.6	(-3.3, 2.2)	56	2.0	1.7	(-1.0, 4.4)	67	0.0	-0.3	(-2.9, 2.3)
2	-1.0	55	-1.1	-0.0	(-2.9, 2.9)	57	1.2	2.3	(-0.6, 5.1)	66	2.1	3.1	(0.3, 5.9)
3	1.4	55	-2.2	-3.6	(-6.3, -1.0)	57	0.1	-1.3	(-3.9, 1.3)	67	3.3	1.9	(-0.7, 4.4)
4	1.3	55	0.2	-1.1	(-3.7, 1.5)	57	1.9	0.6	(-2.0, 3.2)	67	2.8	1.5	(-1.0, 4.0)
5	1.3	55	-0.2	-1.5	(-4.0, 1.0)	57	0.8	-0.5	(-3.0, 2.0)	67	2.9	1.6	(-0.8, 4.0)
6	2.0	55	-0.1	-2.0	(-5.2, 1.1)	57	2.1	0.2	(-2.9, 3.3)	67	4.9	3.0	(-0.1, 6.0)
7	-0.9	55	-0.5	0.4	(-2.1, 2.9)	56	1.4	2.2	(-0.3, 4.7)	67	4.2	5.1	(2.7, 7.5)
8	-0.4	55	0.1	0.4	(-2.0, 2.9)	57	1.6	2.0	(-0.4, 4.4)	67	3.0	3.3	(1.0, 5.6)
10	0.3	55	-0.1	-0.3	(-2.7, 2.0)	57	-1.6	-1.9	(-4.3, 0.4)	67	0.5	0.3	(-2.0, 2.5)
12	-0.8	55	-2.5	-1.7	(-4.3, 0.8)	57	-0.1	0.6	(-1.9, 3.2)	67	2.8	3.6	(1.1, 6.0)
14	-0.5	55	-0.2	0.3	(-2.5, 3.1)	57	0.3	0.8	(-1.9, 3.6)	67	2.8	3.4	(0.7, 6.0)
16	-0.1	55	0.5	0.6	(-2.2, 3.4)	57	1.3	1.4	(-1.3, 4.2)	68	3.3	3.5	(0.8, 6.1)
23.5	-0.5	55	1.2	1.7	(-1.3, 4.8)	57	0.2	0.7	(-2.3, 3.8)	65	2.1	2.6	(-0.3, 5.6)

Table 11: Categorical Analysis for PR

	Total N	PR \leq 200 ms	PR $>$ 200 ms
Treatment Group			
Moxifloxacin 400 mg	55	53 (96.4%)	2 (3.6%)
Pimavanserin 20 mg/day	57	53 (93.0%)	4 (7.0%)
Pimavanserin 80 mg/day	67	65 (97.0%)	2 (3.0%)
Placebo	55	53 (96.4%)	2 (3.6%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between pimavanserin 20 mg and placebo, and between pimavanserin 80 mg and placebo are 1.1 ms and 1.4 ms, respectively. Table 13 presents the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms are in pimavanserin 80-mg group.

Table 12: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Pimavanserin 20 mg and Pimavanserin 80 mg

		Treatment Group											
Placebo		Moxifloxacin 400 mg				Pimavanserin 20 mg/day				Pimavanserin 80 mg/day			
Δ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		Δ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	0.8	55	0.2	-0.6	(-1.9, 0.7)	56	-0.6	-1.4	(-2.7, -0.1)	67	-0.1	-0.9	(-2.2, 0.3)
2	0.4	55	0.6	0.1	(-1.0, 1.3)	57	-0.5	-0.9	(-2.0, 0.2)	66	0.7	0.3	(-0.8, 1.4)
3	1.1	55	-0.4	-1.5	(-2.7, -0.3)	57	-0.5	-1.7	(-2.9, -0.5)	67	-0.2	-1.3	(-2.5, -0.2)
4	0.8	55	0.5	-0.3	(-1.5, 0.8)	57	-0.8	-1.6	(-2.8, -0.5)	67	0.5	-0.3	(-1.4, 0.8)
5	1.6	55	0.7	-0.9	(-2.2, 0.3)	57	-0.1	-1.8	(-3.0, -0.5)	67	0.4	-1.3	(-2.4, -0.1)
6	1.2	55	0.4	-0.7	(-1.9, 0.4)	57	-0.3	-1.5	(-2.7, -0.3)	67	0.7	-0.5	(-1.6, 0.7)
7	1.6	55	0.2	-1.3	(-2.5, -0.1)	56	-0.3	-1.8	(-3.0, -0.6)	67	0.4	-1.1	(-2.3, 0.0)
8	0.7	55	-0.4	-1.0	(-2.3, 0.2)	57	-0.5	-1.2	(-2.4, 0.1)	67	0.3	-0.3	(-1.6, 0.9)
10	0.4	55	-0.2	-0.6	(-1.8, 0.5)	57	-0.2	-0.6	(-1.8, 0.5)	67	0.0	-0.4	(-1.5, 0.7)
12	-0.0	55	0.3	0.3	(-0.9, 1.4)	57	-1.6	-1.6	(-2.8, -0.5)	67	-0.1	-0.1	(-1.2, 1.0)
14	-0.0	55	-0.4	-0.3	(-1.6, 0.9)	57	-0.7	-0.7	(-1.9, 0.5)	67	-0.6	-0.5	(-1.7, 0.6)
16	0.1	55	0.8	0.7	(-0.5, 1.9)	57	-0.1	-0.1	(-1.3, 1.1)	68	-0.0	-0.1	(-1.2, 1.0)
23.5	0.3	55	0.4	0.1	(-1.1, 1.2)	57	-0.7	-1.0	(-2.2, 0.2)	65	0.5	0.2	(-0.9, 1.3)

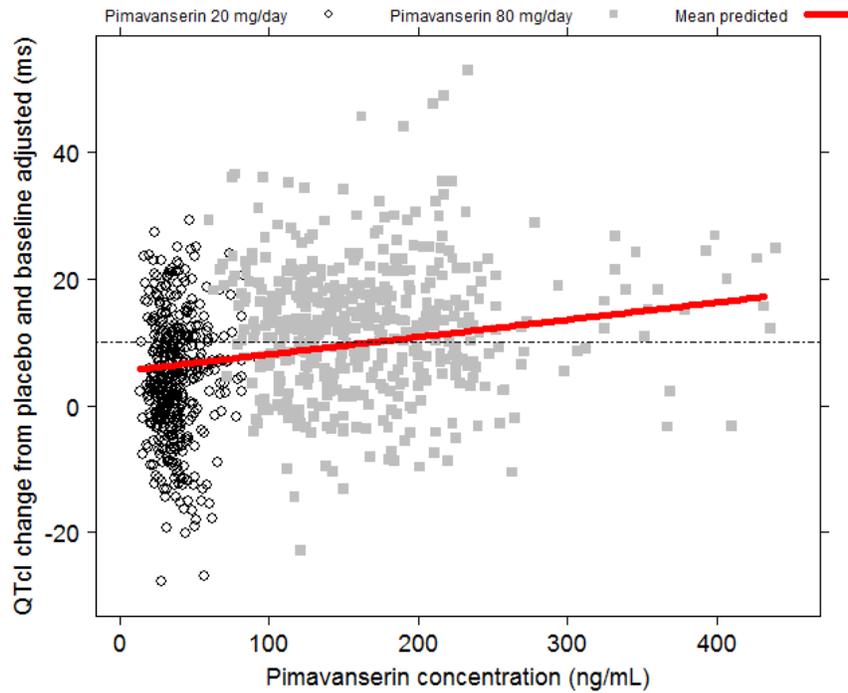
Table 13: Categorical Analysis for QRS

	Total N	QRS ≤ 110 ms	QRS > 110 ms
Treatment Group			
Moxifloxacin 400 mg	55	55 (100%)	0 (0.0%)
Pimavanserin 20 mg/day	57	57 (100%)	0 (0.0%)
Pimavanserin 80 mg/day	67	65 (97.0%)	2 (3.0%)
Placebo	55	53 (96.4%)	2 (3.6%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta\text{QTcI}$ and pimavanserin concentrations is visualized in Figure 4. Based on graphical evaluation and linear mixed effects modeling, a linear mixed effects model with random intercept and random slope was selected. A significantly positive relationship between pimavanserin plasma concentrations and $\Delta\Delta\text{QTcI}$ was detected (with a slope of 0.0272 ms per ng/mL and 95% CI: 0.0104-0.044). AC-279 is the major metabolite of pimavanserin with terminal half-life of 200 hours. However, the plasma concentrations of AC-279 were not included in the sponsor's report and were provided for formal analysis. This may limit the reliability of our concentration-QTc analysis.

Figure 4: $\Delta\Delta$ QTcI vs. Pimavanserin Concentration



The relationship between $\Delta\Delta$ QTcI and pimavanserin concentrations was investigated by linear mixed effects modeling. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

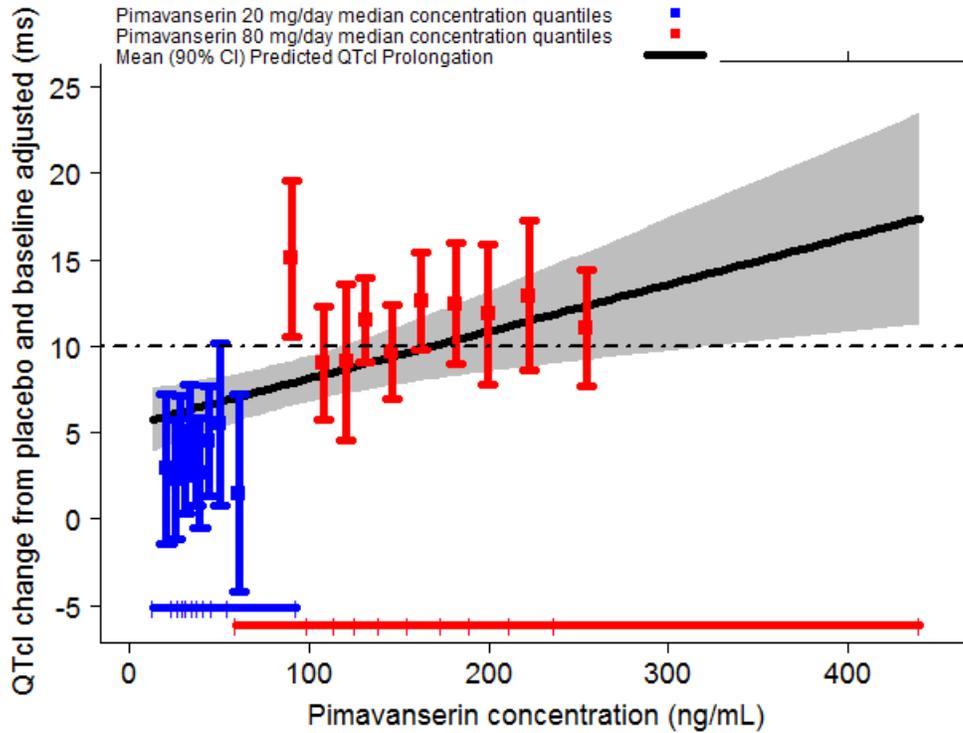
Table 14 summarizes the results of the pimavanserin concentration- $\Delta\Delta$ QTcI analyses.

Model 1 was used for further analysis since the model with an intercept was found to fit the data best based on model selection criteria (log likelihood and AIC).

Table 14: Exposure-response Analysis of pimavanserin Associated $\Delta\Delta$ QTcI Prolongation

Parameter	Estimate	p-value	Interindividual Variability (CV%)
Model 1: $ddQTcI = \text{Intercept} + \text{slope} * \text{Pimavanserin Concentration}$			
Intercept (ms)	5.4 (3.43; 7.37)	<.0001	5.83
Slope (ms per ng/mL)	0.0272 (0.0104; 0.044)	0.0095	0.02
Residual Variability (ms)	8.07		
Model 2: $ddQTcI = \text{Intercept} + \text{slope} * \text{Pimavanserin Concentration (Fixed Intercept)}$			
Intercept (ms)	0		5.86
Slope (ms per ng/mL)	0.061 (0.0491; 0.0728)	<.0001	0.02
Residual Variability (ms)	8.15		
Model 3: $ddQTcI = \text{slope} * \text{Pimavanserin Concentration (No Intercept)}$			
Slope (ms per ng/mL)	0.0882 (0.0682; 0.108)	<.0001	0.09
Residual Variability (ms)	8.32		

Figure 5: Observed Median-Quantile Pimavanserin Concentrations and Associated Mean (90% CI) $\Delta\Delta$ QTcI (color dots) Together with the Mean (90% CI) Predicted $\Delta\Delta$ QTcI (black line with shaded grey area)

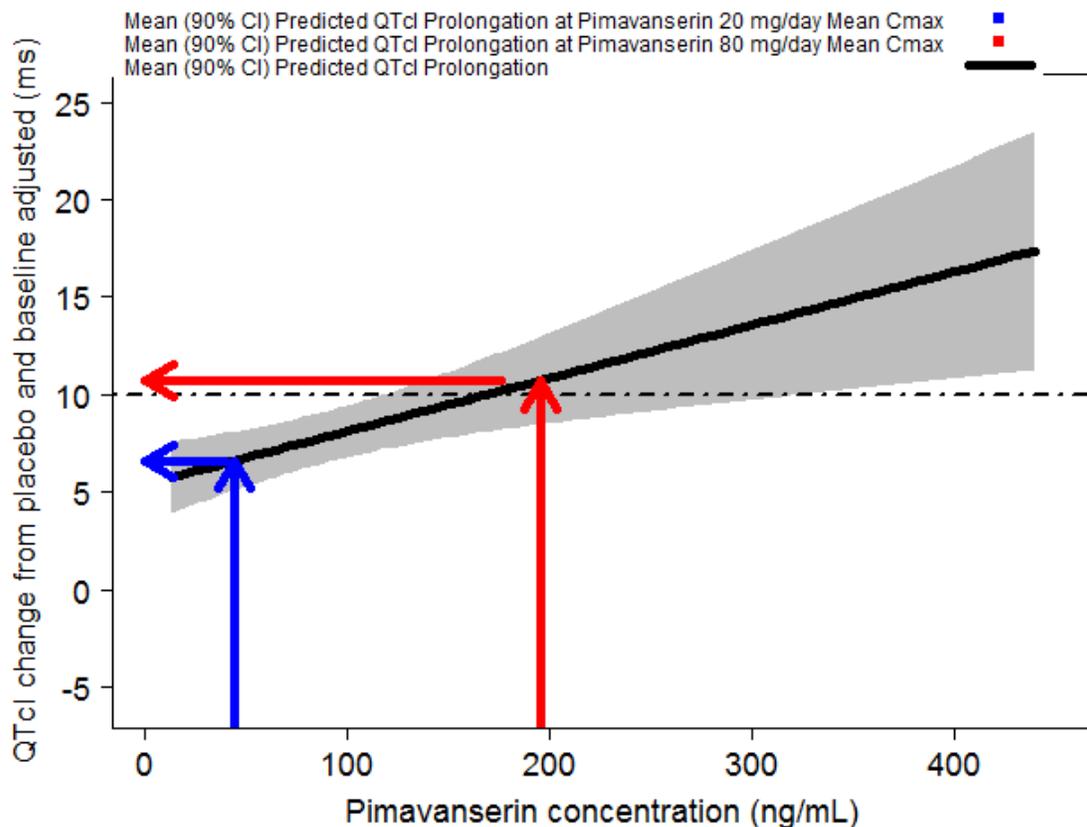


The predicted $\Delta\Delta$ QTcI at the mean C_{max} pimavanserin concentrations can be found in Table 15 and Figure 6.

Table 15: Predicted $\Delta\Delta$ QTcI Interval at Mean C_{max} pimavanserin Concentration Using Model 1

Treatment	Conc	Pred (ms)	90% CI
Pimavanserin 20 mg/day	43.9 ng/mL	6.6	(5.09; 8.11)
Pimavanserin 80 mg/day	196 ng/mL	10.7	(8.47; 13)
Pimavanserin 40 mg/day	@ 100 ng/mL	8.1	(6.5, 9.7)

Figure 6: $\Delta\Delta$ QTcI vs. Pimavanserin Peak Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Two subjects syncopized on the high dose, but both had no evidence of arrhythmia on ECG. There were no other identified clinical events of potential concern.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically relevant effect on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

		Source
Therapeutic dose	<p>Include maximum proposed clinical dosing regimen</p> <p>34 mg pimavanserin PO QD (equivalent to 40 mg pimavanserin tartrate PO QD); tartrate salt equivalents are used throughout the remainder of Table 1 in order to be consistent with original protocols and clinical study reports.</p>	<p>ACP-103-006 ACP-103-012 ACP-103-014 ACP-103-020</p>
Maximum tolerated dose	<p>Include if studied or NOAEL dose</p> <p>Single-dose MTD is >300 mg PO Multiple-dose MTD is 100 mg QD PO</p>	<p>ACP-103-001 ACP-103-002 ACP-103-017</p>
Principal adverse events	<p>Include most common adverse events; dose-limiting adverse events</p> <p>In multi-dose healthy volunteer studies at pimavanserin tartrate doses of ≤40 mg, TEAEs were generally lower in incidence compared to those for placebo. The only exceptions were small increases in back pain (3.1% PIM ≤20 mg vs. 2.4% placebo) and disturbance in attention (3.1% pimavanserin ≤20 mg vs. 1.2% placebo).</p> <p>At higher doses (≥50 mg PIM), the following TEAEs occurred at twice the rate of placebo: dizziness (including postural dizziness), somnolence, lethargy, nausea, vomiting, dyspepsia, epistaxis, back pain, fatigue, rash, and disturbance in attention. Above 100 mg, dose-limiting side effects were nausea and vomiting.</p> <p>For subjects in the Parkinson's disease psychosis (PDP) population (the proposed indication), the most frequent TEAEs (≥5%) experienced by subjects in the All PIM group compared with the placebo group were fall (6.0% PIM vs. 9.1% PBO), urinary tract infection (5.5% PIM vs. 6.9% PBO), confusional state (5.2% PIM vs. 2.6% PBO), and nausea (5.2% PIM vs. 4.3% PBO).</p>	<p>ISS Section 9.2.1.4.2</p>
Maximum dose tested	<p>Single Dose</p> <p>Specify dose</p> <p>300 mg PO</p>	ACP-103-001
	<p>Multiple Dose</p> <p>Specify dosing interval and duration</p> <p>160 mg PO QD × 7 days; 150 mg PO QD × 14 days</p>	<p>ACP-103-017 ACP-103-002</p>

		Source																																																																																		
Exposures Achieved at Maximum Tested Dose	<p>Single Dose (300 mg dose PO)</p> <p>Mean (%CV) C_{max} and AUC</p> <p>C_{max}: 152 ng/mL (28.9) AUC_{0-∞}: 10798 ng·h/mL (38.4)</p>	<p>ACP-103-001, Table 5</p>																																																																																		
	<p>Multiple Dose (150 mg dose PO, QD for 14 days)</p> <p>Mean (%CV) C_{max} and AUC</p> <p>C_{max,ss}: 248 ng/mL (14.2) AUC_{0-24,ss}: 4680 ng·h/mL (11.7)</p>	<p>ACP-103-002, Table 5.2</p>																																																																																		
Range of linear PK	<p>Specify dosing regimen</p> <ul style="list-style-type: none"> - Single Ascending Dose groups: PBO, 20 mg, 50 mg, 100 mg, 200 mg, 300 mg PIM PO (N = 1 for PBO; N = 4/PIM group) - 14-Day Multiple Ascending Dose groups: PBO, 50 mg, 100 mg, 150 mg PIM QD PO (N = 6/group) - Healthy males were dosed according to dose group <ul style="list-style-type: none"> o Range of linear PK based on linear regression analyses: <ul style="list-style-type: none"> o SAD: 20 mg to 300 mg o MAD: 50 mg to 150 mg o Dose-proportional PK following both single and multiple dosing 	<p>ACP-103-001, Table 6 ACP-103-002, Table 7</p>																																																																																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="7">Single Ascending Dose</th> </tr> <tr> <th rowspan="2">Parameter</th> <th colspan="3">Intercept</th> <th colspan="3">Slope</th> </tr> <tr> <th>Estimate</th> <th>SE</th> <th>95% CI</th> <th>Estimate</th> <th>SE</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-∞} (ng·h/mL)</td> <td>3.2766</td> <td>0.2975</td> <td>(2.6515, 3.9016)</td> <td>1.0495</td> <td>0.0646</td> <td>(0.9138, 1.1852)</td> </tr> <tr> <td>C_{max} (ng/mL)</td> <td>-1.0539</td> <td>0.2337</td> <td>(-1.5449, -0.5629)</td> <td>1.0680</td> <td>0.0507</td> <td>(0.9614, 1.1746)</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="7">Multiple Ascending Dose</th> </tr> <tr> <th rowspan="2">Parameter</th> <th colspan="3">Intercept</th> <th colspan="3">Slope</th> </tr> <tr> <th>Estimate</th> <th>SE</th> <th>95% CI</th> <th>Estimate</th> <th>SE</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>AUC₀₋₂₄ (ng·h/mL)</td> <td>1.6305</td> <td>0.3576</td> <td>(0.8724, 2.3886)</td> <td>1.0955</td> <td>0.0789</td> <td>(0.9282, 1.2627)</td> </tr> <tr> <td>AUC_{0-24,ss} (ng·h/mL)</td> <td>3.8669</td> <td>0.5929</td> <td>(2.5860, 5.1477)</td> <td>0.9283</td> <td>0.1330</td> <td>(0.6411, 1.2156)</td> </tr> <tr> <td>C_{max} (ng/mL)</td> <td>-1.2084</td> <td>0.3535</td> <td>(-1.9578, -0.4590)</td> <td>1.0841</td> <td>0.0780</td> <td>(0.9187, 1.2495)</td> </tr> <tr> <td>C_{max,ss} (ng/mL)</td> <td>0.7785</td> <td>0.5513</td> <td>(-0.4125, 1.9696)</td> <td>0.9554</td> <td>0.1236</td> <td>(0.6883, 1.2225)</td> </tr> </tbody> </table>			Single Ascending Dose							Parameter	Intercept			Slope			Estimate	SE	95% CI	Estimate	SE	95% CI	AUC _{0-∞} (ng·h/mL)	3.2766	0.2975	(2.6515, 3.9016)	1.0495	0.0646	(0.9138, 1.1852)	C _{max} (ng/mL)	-1.0539	0.2337	(-1.5449, -0.5629)	1.0680	0.0507	(0.9614, 1.1746)	Multiple Ascending Dose							Parameter	Intercept			Slope			Estimate	SE	95% CI	Estimate	SE	95% CI	AUC ₀₋₂₄ (ng·h/mL)	1.6305	0.3576	(0.8724, 2.3886)	1.0955	0.0789	(0.9282, 1.2627)	AUC _{0-24,ss} (ng·h/mL)	3.8669	0.5929	(2.5860, 5.1477)	0.9283	0.1330	(0.6411, 1.2156)	C _{max} (ng/mL)	-1.2084	0.3535	(-1.9578, -0.4590)	1.0841	0.0780	(0.9187, 1.2495)	C _{max,ss} (ng/mL)	0.7785	0.5513	(-0.4125, 1.9696)	0.9554	0.1236	(0.6883, 1.2225)
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C _{max} (ng/mL)	-1.2084	0.3535	(-1.9578, -0.4590)	1.0841	0.0780	(0.9187, 1.2495)																																																																														
C _{max,ss} (ng/mL)	0.7785	0.5513	(-0.4125, 1.9696)	0.9554	0.1236	(0.6883, 1.2225)																																																																														

		Source																																																										
Accumulation at steady state	<p>Mean (%CV); specify dosing regimen</p> <ul style="list-style-type: none"> - Dose groups: PBO, 50 mg, 100 mg, 150 mg QD PO - Healthy males were dosed 14 consecutive days, according to dose group (N = 6/group) <table border="1"> <thead> <tr> <th>Dose Group</th> <th>Parameter</th> <th>Study Day</th> <th>Geometric LS Mean</th> <th>Ratio (%)</th> <th>90% CI</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td rowspan="4">50 mg</td> <td rowspan="2">AUC₀₋₂₄ (ng·h/mL)</td> <td>1</td> <td>372.1</td> <td rowspan="2">471.7</td> <td rowspan="2">(357.1-623.0)</td> <td rowspan="2"><0.0001</td> </tr> <tr> <td>14</td> <td>1755.1</td> </tr> <tr> <td rowspan="2">C_{max} (ng/mL)</td> <td>1</td> <td>20.94</td> <td rowspan="2">426.5</td> <td rowspan="2">(325.9-558.3)</td> <td rowspan="2"><0.0001</td> </tr> <tr> <td>14</td> <td>89.31</td> </tr> <tr> <td rowspan="4">100 mg</td> <td rowspan="2">AUC₀₋₂₄ (ng·h/mL)</td> <td>1</td> <td>785.8</td> <td rowspan="2">479.3</td> <td rowspan="2">(406.6-565.1)</td> <td rowspan="2"><0.0001</td> </tr> <tr> <td>14</td> <td>3766.7</td> </tr> <tr> <td rowspan="2">C_{max} (ng/mL)</td> <td>1</td> <td>42.94</td> <td rowspan="2">446.8</td> <td rowspan="2">(385.6-517.7)</td> <td rowspan="2"><0.0001</td> </tr> <tr> <td>14</td> <td>191.83</td> </tr> <tr> <td rowspan="4">150 mg</td> <td rowspan="2">AUC₀₋₂₄ (ng·h/mL)</td> <td>1</td> <td>1242.5</td> <td rowspan="2">374.7</td> <td rowspan="2">(325.5-431.4)</td> <td rowspan="2"><0.0001</td> </tr> <tr> <td>14</td> <td>4656.1</td> </tr> <tr> <td rowspan="2">C_{max} (ng/mL)</td> <td>1</td> <td>69.34</td> <td rowspan="2">354.4</td> <td rowspan="2">(309.1-406.3)</td> <td rowspan="2"><0.0001</td> </tr> <tr> <td>14</td> <td>245.69</td> </tr> </tbody> </table>	Dose Group	Parameter	Study Day	Geometric LS Mean	Ratio (%)	90% CI	p-value	50 mg	AUC ₀₋₂₄ (ng·h/mL)	1	372.1	471.7	(357.1-623.0)	<0.0001	14	1755.1	C _{max} (ng/mL)	1	20.94	426.5	(325.9-558.3)	<0.0001	14	89.31	100 mg	AUC ₀₋₂₄ (ng·h/mL)	1	785.8	479.3	(406.6-565.1)	<0.0001	14	3766.7	C _{max} (ng/mL)	1	42.94	446.8	(385.6-517.7)	<0.0001	14	191.83	150 mg	AUC ₀₋₂₄ (ng·h/mL)	1	1242.5	374.7	(325.5-431.4)	<0.0001	14	4656.1	C _{max} (ng/mL)	1	69.34	354.4	(309.1-406.3)	<0.0001	14	245.69	ACP-103-002, Table 6
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Metabolites	<p>Include listing of all metabolites and activity</p> <p>A combination of radiometric and mass spectrophotometric analyses identified 42 metabolites in plasma, urine, and/or feces in human. This large number of metabolites is a predictable consequence of the high lipophilicity of pimavanserin, which must undergo multiple, sequential metabolic steps to produce metabolites that are sufficiently hydrophilic to be efficiently excreted in urine and feces. The 42 metabolites comprised 10 primary metabolites, 14 secondary metabolites, 8 tertiary metabolites, 4 quaternary metabolites, 2 quinary metabolites and 4 unknowns (2 of which were detectable in plasma). Without exception, the formation of each of the 38 known metabolites involved well-established pathways of xenobiotic biotransformation, primarily via CYP enzymes (b) (4)-13-019). Please refer to Appendix 1 for the full list of the 42 metabolites.</p> <p>Two of the 42 metabolites were identified as major circulating metabolites in humans: M1 and AC-279. Based on extensive investigation, M1 has been putatively identified as CO₂. Given the large number of minor metabolites, only the activity of AC-279 is discussed here.</p> <p>The functional activity of AC-279 was tested at human 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} serotonin receptors and was shown to have similar antagonist activity to pimavanserin (2014-01, potent antagonist at 5-HT_{2A} receptors, moderate antagonists at 5-HT_{2C} receptors and no antagonist activity at 5-HT_{2B} receptors).</p>	(b)-13-019 2014-01 XT135136 XT143022 ACP-103-029 XT148017 ACP-103-023, Tables 5 and 7 ACP-103-029, Tables 14.3.9.10 and 14.3.9.11																																																										

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<p>AC-279 is predicted to cause no clinically-significant inhibition of the seven major human hepatic CYP enzymes involved in drug metabolism (XT135136). Based on induction studies in human hepatocytes, AC-279 may cause weak induction of hepatic CYP3A4 (Study XT143022); however, results from Study ACP-103-029 showed that AC-279 was not an inducer of CYP3A4/5 in humans.</p> <p>AC-279 is not an inhibitor of any of the seven drug transporters or a substrate for BCRP (Study XT148017).</p> <p>Pharmacokinetic parameters of pimavanserin (N =19) and AC-279 (N =19) following single administration of pimavanserin 40 mg (Study ACP-103-023)</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Pimavanserin*</th> <th>AC-279*</th> </tr> </thead> <tbody> <tr> <td>AUC₀₋₄ (ng·h/mL)</td> <td>1224 ± 433</td> <td>746.9 ± 160</td> </tr> <tr> <td>AUC_{0-∞} (ng·h/mL)</td> <td>1257 ± 464</td> <td>1108 ± 257</td> </tr> <tr> <td>C_{max} (ng/mL)</td> <td>17.1 ± 3.8</td> <td>3.960 ± 0.996</td> </tr> <tr> <td>T_{max} (h)</td> <td>9.00</td> <td>36.00</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>58.2 ± 13.2</td> <td>199.6 ± 64.7</td> </tr> <tr> <td>CL/F (L/h)</td> <td>36.2 ± 15.3</td> <td>-</td> </tr> <tr> <td>V_d/F (L)</td> <td>2836 ± 650</td> <td>-</td> </tr> </tbody> </table> <p>* Mean (±SD), except for T_{max} which is shown as median</p> <p>Pharmacokinetic parameters of pimavanserin (N =18) and AC-279 (N =18) following steady state administration of pimavanserin 40 mg (Study ACP-103-029)</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Pimavanserin</th> <th>AC-279</th> </tr> </thead> <tbody> <tr> <td>AUC₀₋₄ (ng·h/mL)</td> <td>992.6 ± 442</td> <td>701.0 ± 314</td> </tr> <tr> <td>C_{max} (ng/mL)</td> <td>51.42 ± 23.3</td> <td>34.64 ± 15.7</td> </tr> <tr> <td>T_{max} (h)</td> <td>7.35 ± 1.0</td> <td>7.23 ± 1.7</td> </tr> <tr> <td>t_{1/2} (h)</td> <td>38.0 ± 9.3</td> <td>65.0 ± 25.5</td> </tr> </tbody> </table> <p>Note: t_{1/2} N = 6 for PIM; N = 8 for AC-279</p>	Parameter	Pimavanserin*	AC-279*	AUC ₀₋₄ (ng·h/mL)	1224 ± 433	746.9 ± 160	AUC _{0-∞} (ng·h/mL)	1257 ± 464	1108 ± 257	C _{max} (ng/mL)	17.1 ± 3.8	3.960 ± 0.996	T _{max} (h)	9.00	36.00	t _{1/2} (h)	58.2 ± 13.2	199.6 ± 64.7	CL/F (L/h)	36.2 ± 15.3	-	V _d /F (L)	2836 ± 650	-	Parameter	Pimavanserin	AC-279	AUC ₀₋₄ (ng·h/mL)	992.6 ± 442	701.0 ± 314	C _{max} (ng/mL)	51.42 ± 23.3	34.64 ± 15.7	T _{max} (h)	7.35 ± 1.0	7.23 ± 1.7	t _{1/2} (h)	38.0 ± 9.3	65.0 ± 25.5	
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Absorption	Absolute/Relative Bioavailability	<p>Mean (%CV)</p> <p>The relative bioavailability of pimavanserin tablets relative to solution in fasted subjects was 99.7% (90% CI: 90.9 – 109.4).</p>	ACP-103-001, Table 7
	T _{max}	<p>• Median (range) for parent</p> <p>The median T_{max} value for pimavanserin was 9.00 hours (9.00-16.0) in Study ACP-103-016.</p> <p>• Median (range) for metabolites</p> <p>The median T_{max} value for AC-279 was 36.00 hours (6.0-71.5) in Study ACP-103-023.</p>	ACP-103-016, Table 14.2.2-1a ACP-103-023, Table 14.3.8.4
Distribution	V _d /F or V _d	<p>Mean (%CV)</p> <p>V_d/F: 2173 L (SD: 307) in human plasma</p>	ACP-103-016, Table 14.2.2-1a
	% bound	<p>Mean (%CV)</p> <p>The protein binding of pimavanserin from human plasma samples ranged from 91.23% to 96.80%.</p>	BA030066, Section 13.4

			Source
Elimination	Route	<p>• Primary route; percent dose eliminated</p> <p>The primary route of elimination for pimavanserin is hepatic metabolism. Based on the radiolabeled study, the mean recovery of pimavanserin total radioactivity was 45.5% in feces.</p> <p>• Other routes</p> <p>Pimavanserin is also cleared by the kidneys; the mean recovery of pimavanserin total radioactivity was 23.1% in urine. Respiration is also an elimination route of pimavanserin. Metabolite M1, putatively identified as CO₂, is eliminated in expired breath and its estimated contribution to the overall disposition of pimavanserin may be above 12%.</p>	ACP-103-016 ACP-103-016, (b)-13-019
	Terminal t _{1/2}	<p>• Mean (%CV) for parent</p> <p>In the PK study of radiolabeled pimavanserin (ACP-103-016), the elimination of parent drug from human plasma conformed to a monophasic elimination process with a half-life of 51.4 hours (SD: 6.69). The elimination of total radioactivity from plasma conformed to a biphasic process with t_{1/2} of 17.0 hours and t_{1/2β} of 63.6 hours, suggesting that some metabolites were eliminated faster and some slower than parent drug. The half-life of pimavanserin was also measured in other clinical studies and the average was ~57 hours.</p> <p>• Mean (%CV) for metabolites</p> <p>The terminal half-life for AC-279 was 199.59 hours (%CV: 32.42) in Study ACP-103-023.</p>	ACP-103-016, 14.2.2-1a ACP-103-001, ACP-103-002, ACP-103-005, ACP-103-018 ACP-103-023, Table 14.3.8.4
	CL/F or CL	<p>Mean (%CV)</p> <p>The CL/F for pimavanserin was 29.7 L/hour (SD: 6.04) in human plasma.</p>	ACP-103-016, Table 14.2.2-1a

			Source
Intrinsic Factors	Age	<p>Specify mean changes in C_{max} and AUC</p> <p>No formal analysis was conducted, but based on population PK analysis on the effect of clearance for age as a covariate (Pharmacokinetic Modeling of Pimavanserin in Healthy Subjects, Subjects with Parkinson's Disease, and Subjects with Parkinson's Disease Psychosis, Dennis Fisher, M.D.), the effects of age on systemic exposure are relatively small.</p>	Pharmacokinetic Modeling of Pimavanserin in Healthy Subjects, Subjects with Parkinson's Disease, and Subjects with Parkinson's Disease Psychosis, Section 5.3.3.5
	Sex	<p>Specify mean changes in C_{max} and AUC</p> <p>No formal analysis was conducted.</p>	
	Race	<p>Specify mean changes in C_{max} and AUC</p> <p>No formal analysis was conducted.</p>	
	Hepatic & Renal Impairment	<p>Specify mean changes in C_{max} and AUC</p> <p>Studies to evaluate safety and pharmacokinetics in subjects with organ impairment are scheduled to initiate in a few weeks.</p>	

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Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in C_{max} and AUC</p> <ul style="list-style-type: none"> - ACP-103-023: Ketoconazole 400 mg QD Days 15-28; PIM 40 mg QD Days 1, 19 <ul style="list-style-type: none"> - Objective: Evaluate effect of ketoconazole on the PK of PIM - Conclusions: Coadministration of PIM with ketoconazole resulted in an approximately 3-fold increase in PIM AUC and a 1.5-fold increase in PIM C_{max}; i.e., strong inhibition of CYP3A can increase PIM exposure up to ~3-fold - ACP-103-024: Carbidopa/levodopa 25/100 IR TID Days 1-3 and 15-17; PIM 40 mg QD Days 4-17 <ul style="list-style-type: none"> - Objective: Evaluate the potential effect of multiple doses of PIM on the PK of levodopa - Conclusions: Coadministration of PIM with carbidopa/levodopa has no effect on levodopa exposure - ACP-103-029: Midazolam 2 mg QD Days 1, 3, 20 and 40; PIM 40 mg QD Days 3-40 <ul style="list-style-type: none"> - Objective: Evaluate the effect of PIM and AC-279 on the PK of midazolam and its metabolites - Conclusions: Coadministration of PIM and AC-279 to steady state had no significant effect on midazolam exposure; i.e., PIM is neither an inhibitor or an inducer of CYP3A4/5 	Section 2.7.2, Table 2.7.2.23 ACP-103-023 ACP-103-024 ACP-103-029																																		
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	Food Effects	<p>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat)</p> <ul style="list-style-type: none"> - Dose groups: PBO, 100 mg PO (crossover, N = 8/group) - Healthy males were dosed according to dose group - Complete crossover design with fasting/high-fat meal - Conclusion: A high-fat meal had no effect on PIM systemic exposure <table border="1" data-bbox="581 369 1195 459"> <thead> <tr> <th>Dose</th> <th>AUC_{0-∞} (ng·h/mL)</th> <th>C_{max} (ng/mL)</th> </tr> </thead> <tbody> <tr> <td>100 mg Fasted</td> <td>3871</td> <td>57.01</td> </tr> <tr> <td>100 mg Fed</td> <td>4269</td> <td>52.15</td> </tr> </tbody> </table>	Dose	AUC _{0-∞} (ng·h/mL)	C _{max} (ng/mL)	100 mg Fasted	3871	57.01	100 mg Fed	4269	52.15	ACP-103-001, Table 5
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Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>The worst case scenario is illustrated by CYP3A4/5 inhibition with ketoconazole where exposure to pimavanserin increased 1.5-fold for C_{max} (from 17.1 to 25.1 ng/mL) and 3-fold for AUC₀₋₂₄ (from 1224 to 3415 ng·h/mL; Study ACP-103-023). These increases are well-covered by available safety and associated exposure data in humans where single doses of up to 300 mg and multiple doses of up to 150 mg for 14 days have resulted in C_{max} values of up to 152 ng/mL (300 mg single dose) and 248 ng/mL (150 mg for 14 days) and corresponding AUCs of up to 10,798 and 4680 ng·h/mL. At doses ≥100 mg, adverse events of dizziness, somnolence, lethargy, nausea, vomiting, dyspepsia, epistaxis, back pain and fatigue have been reported with pimavanserin at rates at least twice those for placebo.</p> <p>The supratherapeutic dose of 80 mg pimavanserin tested in the thorough QT study also encompasses the exposures seen when pimavanserin 40 mg was coadministered with ketoconazole. In the tQT study, the 80 mg dose was associated with C_{max} values of 49.43 and 205.92 ng/mL and AUC values of 860.3 and 3817.1 ng·h/mL at Day 1 and Day 20, respectively. The tQT study also tested pimavanserin 20 mg, moxifloxacin, and placebo and across the four dose groups, the most common TEAE across treatment groups was headache (13.3%, pimavanserin 20 mg; 22.2%, pimavanserin 80 mg; 22.0%, placebo/moxifloxacin; 19.7%, placebo). Events that occurred in >5% of subjects included headache in the pimavanserin 20 mg, headache, dizziness (15.3%), nausea (12.5%), and rash (5.6%) in the pimavanserin 80 mg group, headache, pharyngolaryngeal pain and diarrhea (5.1%) in the placebo/moxifloxacin group, and nausea (6.6%) in the placebo group. Events that occurred in ≥10.0% of pimavanserin 80 mg-treated subjects and twice the incidence of pimavanserin 20 mg-treated subjects included nausea (12.5% vs. 1.7%) and dizziness (15.3% vs. 3.3%).</p>		ACP-103-023 ACP-103-001 ACP-103-002 ACP-103-018 ISS Section 9.2.1.4.2									
Preclinical Cardiac Safety	<p>Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.</p> <p><i>In vitro</i>: A GLP hERG study showed that pimavanserin inhibited hERG (human ether a-go-go-related Gene) potassium currents by 10.6 ± 2.3%, 25.1 ± 2.4%, 54.0 ± 4.3%, 80.3 ± 0.6%, and 99.3 ± 0.3% (mean ± standard error of the mean) at 0.03, 0.075, 0.24, 0.83, and 9.35 μM, respectively (Study 061019.DPW). The concentration eliciting 50% inhibition (IC₅₀) for the effect of pimavanserin on hERG current was 210 nM.</p> <p><i>In vivo</i>: Oral administration of pimavanserin at 1, 10, and 100 mg/kg in a GLP study in telemetered cynomolgus monkeys had no marked effect on arterial blood pressure (systolic, diastolic, and mean) or heart rate, or on electrocardiogram (ECG) parameters (RR interval, PR interval, QT interval, QTcF interval [QTc calculated using Fridericia's formula], or QRS interval) when compared with time-matched vehicle controls (Study DHTI1004). Vomiting was noted in two of four monkeys following administration of 100 mg/kg pimavanserin. Statistically significant QTc interval prolongation was observed at two time points (2 and 6 hours) in the high dose group; however, the magnitude of the effect was considered small and not time-related, thus the relationship to pimavanserin treatment is uncertain.</p> <p>Supportive data: In an exploratory study of cardiovascular response, pimavanserin administered intravenously (iv) to anesthetized Beagles had no notable effects except for an increase in heart rate at the highest dose (1.8 mg/kg) (Study 2002-19).</p> <p>In the 1-, 3-, or 12-month GLP toxicity studies in monkeys at doses up to 51 mg/kg/day (Studies HTI1003, (b) (4), 177.01, and (b) (4), 146.01) there were no changes in ECG parameters. Mean C_{max} values in these studies ranged from 669-916 ng/mL.</p>		061019.DPW DHTI1004 2002-19 HTI1003 (b) (4), 177.01 (b) (4), 146.01									

Clinical Cardiac Safety	<p>Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).</p> <p>The clinical safety and efficacy of pimavanserin has been evaluated across a series of 23 Phase 1 through Phase 3 clinical studies, enrolling a total of 1592 subjects (1096 exposed to pimavanserin), and evaluating doses ranging from 10 to 300 mg of pimavanserin. Of the 1096 subjects exposed to pimavanserin, over half (N=616) were patients with Parkinson's disease psychosis (PDP, the proposed indication; mean age 72 years) who received doses of 10, 20, 40, and/or 60 mg pimavanserin. An ongoing open-label study (ACP-103-015) enrolled 459 PDP subjects where the median duration of treatment is 15 months and the longest exposure reported in the NDA is >8 years. Total subject exposure in PDP currently exceeds 800 subject-years (the large majority at the pharmacologic dose of 40 mg).</p> <p>The table below summarizes the ICH E14 cardiac events reported at the various dose levels and in an open label extension study. Please also note that independent reviews and assessments of the cardiovascular profile, including QTc prolongation and deaths, have been provided in the NDA submission and include the following reports: Expert Cardiology Review of the Electrocardiographic Effects of Pimavanserin and the CV Adverse Events During the Phase 3 Pimavanserin Development Program by Dr. Philip Sager, FDA Cardiovascular and Renal Drugs Advisory Committee and Chair of the Scientific Oversight Committee for the FDA-sponsored Cardiac Safety Research Consortium; Exposure-Response Analysis for QTcF for Pimavanserin in Phase 3 Studies and a Limited Re-Analysis of QTcI Data from the Thorough QT Study, by Dennis Fisher, MD and Philip Sager, MD, FACC, FAHA, FHRS; Cardiac Safety Report by Robert B. Kleiman, MD; and Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: Adverse Events, by Dennis Fisher, MD.</p> <p>ICH E14 Cardiac Events Double-blind Placebo-controlled Studies</p> <table border="1"> <thead> <tr> <th></th> <th>Pbo (N=231)</th> <th>Pim 10mg (n=140)</th> <th>Pim 20mg (n=41)</th> <th>Pim 40mg (n=202)</th> <th>All Pim (n=383)</th> </tr> </thead> <tbody> <tr><td>Arrhythmia</td><td>1 (0.4)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Cardiac Arrest</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Cardio-respiratory Arrest</td><td>1 (0.4)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Electrocardiogram QT prolonged</td><td>0</td><td>0</td><td>0</td><td>2 (1.0)</td><td>2 (0.5)</td></tr> <tr><td>Sudden death</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Syncope</td><td>0</td><td>1 (0.7)</td><td>0</td><td>1 (0.5)</td><td>2 (0.5)</td></tr> <tr><td>Seizure*</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Torsades de pointes</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Ventricular arrhythmia</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Ventricular fibrillation</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Ventricular tachycardia</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Ventricular flutter</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> </tbody> </table> <p>*Includes all terms from Convulsion SMQ ** Long-term open-label study with subjects followed for >8 years</p>		Pbo (N=231)	Pim 10mg (n=140)	Pim 20mg (n=41)	Pim 40mg (n=202)	All Pim (n=383)	Arrhythmia	1 (0.4)	0	0	0	0	Cardiac Arrest	0	0	0	0	0	Cardio-respiratory Arrest	1 (0.4)	0	0	0	0	Electrocardiogram QT prolonged	0	0	0	2 (1.0)	2 (0.5)	Sudden death	0	0	0	0	0	Syncope	0	1 (0.7)	0	1 (0.5)	2 (0.5)	Seizure*	0	0	0	0	0	Torsades de pointes	0	0	0	0	0	Ventricular arrhythmia	0	0	0	0	0	Ventricular fibrillation	0	0	0	0	0	Ventricular tachycardia	0	0	0	0	0	Ventricular flutter	0	0	0	0	0	ACP-103-015 Expert Cardiology Review of the Electrocardiographic Effects of Pimavanserin and the CV Adverse Events During the Phase 3 Pimavanserin Development Program: Exposure-Response Analysis for QTcF for Pimavanserin in Phase 3 Studies and a Limited Re-Analysis of QTcI Data from the Thorough QT Study: Cardiac Safety Report: and Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: Adverse Events, Section 5.3.5.3
	Pbo (N=231)	Pim 10mg (n=140)	Pim 20mg (n=41)	Pim 40mg (n=202)	All Pim (n=383)																																																																											
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	ICH E14 Cardiac Events Open-label Extension Study (ACP-103-015)								
	First 4 weeks (N[1]=459)	1 - 3 months (N[1]=459)	>3 - 6 months (N[1]=384)	>6 - 12 months (N[1]=334)	>1 - 2 years (N[1]=267)	>2 - 3 years (N[1]=134)	>3 - 4 years (N[1]=78)	>4 years (N[1]=57)	Overall (N=459)
Arrhythmia	0	0	0	0	0	0	0	0	0
Cardiac Arrest	0	1 (0.2)	0	1 (0.3)	0	0	0	0	2 (0.4)
Cardio-respiratory Arrest	0	0	1 (0.3)	0	0	0	0	1 (1.8)	2 (0.4)
Electrocardiogram QT prolonged	1 (0.2)	2 (0.4)	0	0	1 (0.4)	1 (0.7)	0	0	5 (1.1)
Sudden death	0	0	0	0	0	0	0	0	0
Syncope	2 (0.4)	1 (0.2)	1 (0.3)	5 (1.5)	1 (0.4)	1 (0.7)	2 (2.6)	0	11 (2.4)
Seizure*	0	0	0	0	0	1 (0.7)	0	1 (1.8)	2 (0.4)
Torsades de pointes	0	0	0	0	0	0	0	0	0
Ventricular arrhythmia	0	0	0	0	0	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0	0	0	0
Ventricular flutter	0	0	0	0	0	0	0	0	0

[1] The denominator for a time period is the number of subjects on treatment (including a 30-day follow-up) during that particular time period.
A subject may have more than one TEAE per system organ class (or preferred term); in such case, the subject is counted only once per system organ class (or preferred term) per time period.
*Includes all terms from Convulsion SMQ

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

/s/

LI ZHANG
10/27/2015

JIANG LIU
10/27/2015

MOH JEE NG
10/27/2015

QIANYU DANG
10/27/2015

MICHAEL Y LI
10/27/2015

NORMAN L STOCKBRIDGE
10/27/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 207318 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Nuplazid Established/Proper Name: pimavanserin Dosage Form: film-coated tablet Strengths: 17 mg		
Applicant: ACADIA Pharmaceuticals Inc. Agent for Applicant (if applicable): Hilde Williams		
Date of Application: 9/1/2015 Date of Receipt: 9/1/2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 5/1/2016		Action Goal Date (if different): 4/29/2016
Filing Date: 10/31/2015		Date of Filing Meeting: 9/29/2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of psychosis associated with Parkinson's disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 068384

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If affected by AIP, has OC been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested: 5					
Note: An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Electronic submission
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> 9/14/2015 <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Request for full waiver included in the submission and part of the agreed iPSP (9/12/2014).

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

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<i>(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9/12/2014
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i> QT-IRT 9/10/2015, Biometrics 9/17/2015, CSS 9/14/2015, OSE 9/16/2015, DPMH 10/1/2015				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 4/9/2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 6/2/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-NDA
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): 9/11/2007, 11/1/2007	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Both for Carcinogenicity Studies
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/8/2015

BACKGROUND: NDA 207318 for Nuplazid (pimavanserin) was received on September 1, 2015. Pimavanserin is a new molecular entity (in the Program), characterized as a serotonin-selective, inverse agonist that preferentially targets the 5-HT_{2A} receptor subtype. It was developed for the treatment of psychosis associated with Parkinson’s disease under IND 68384 and currently holds breakthrough therapy designation. A request for priority review was submitted with the NDA and was granted at the filing meeting.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brendan Muoio, PharmD	Y
	CPMS/TL:	Steve Hardeman, RPh	N
Cross-Discipline Team Leader (CDTL)	Lucas Kempf, MD (CDTL), Jing Zhang, MD attended filing meeting		Y
Division Director/Deputy	Mitch Mathis, MD/Tiffany Farchione, MD		Y
Office Director/Deputy	Ellis Unger, MD/Robert Temple, MD		N
Clinical	Reviewer:	Paul Andreason, MD	Y
	TL:	Lucas Kempf, MD	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Kofi Kumi, PhD	Y
	TL:	Hao Zhu, PhD	Y
• Genomics	Reviewer:		

• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Eiji Ishida, PhD	Y
	TL:	Peiling Yang, PhD	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Avila, PhD	Y
	TL:	Aisar Atrakchi, PhD	Y
Statistics (carcinogenicity)	Reviewer:	Hepei Chen, PhD	Y
	TL:	Karl Lin, PhD	N
Product Quality (CMC) Review Team:	ATL:	David Claffey, PhD	Y
	RBPM:	Dahlia Woody	Y
• Drug Substance	Reviewer:	Gaetan Ladouceur, PhD	N
• Drug Product	Reviewer:	Rao Kambhampati, PhD	Y
• Process	Reviewer:	Ziyang Su, PhD	N
• Microbiology	Reviewer:	Ziyang Su, PhD	N
• Facility	Reviewer:	Steven Hertz, PhD	N
• Biopharmaceutics	Reviewer:	Jing Li, PhD, Okpo Eradiri, PhD	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Branch Chief:	Wendy Wilson-Lee, PhD	N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Susannah O'donnell, PharmD	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Deborah Myers	Y
	TL:	Danielle Harris	Y
OSE/DRISK (REMS)	Reviewer:	Somya Dunn	Y
	TL:	Kim Lehrfeld	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cara Alfaro, PharmD	Y
	TL:	Janice Pohlman, MD, MPH	N
Controlled Substance Staff (CSS)	Reviewer:	Jovita Randall-Thompson	Y
	TL:	Michael Klein	Y
Other reviewers/disciplines			
<ul style="list-style-type: none"> • Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: March 29, 2015 (tentatively) <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Advise submission of request for BCS classification to IND 68384</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Robert Temple, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 11/23/2015 (tentatively)

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Filing Meeting	9/29/2015
Mid-Cycle Meeting	11/23/2015
Post Mid-Cycle Communication Meeting	12/3/2015
Pre-Meeting for Late-Cycle Meeting	3/8/2016
Late-Cycle Meeting	3/15/2016
Wrap-up Meeting	2/10/2016

Comments: Meeting dates subject to change

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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
10/08/2015

CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 207318

Applicant: Acadia
Pharmaceuticals Inc.

Filing Date: October 31, 2015

Drug Name: Nuplazid
(Pimavanserin, 17 mg IR tablets)

IND Number: 68384

Checklist	Yes	No	NA	Comment
What is the regulatory history of this application?				Under IND 68384, CSS comments were conveyed in a Type B Pre-NDA Meeting Minutes to the Sponsor, found in DARRTS dated 07/02/2014.
Abuse potential assessment is required if any of the following are true for a drug^{1,2}:				
It affects the CNS	X			
It is chemically or pharmacologically similar to other drugs with known abuse potential		X		
It produces psychoactive effects such as sedation, euphoria, and mood changes	X			Sponsor reports dizziness and somnolence (Abuse Potential Assessment of Pimavanserin (ACP-103), page 22).
Is the drug a new molecular entity?	X			<p>Pimavanserin tartrate is an inverse agonist at the 5-HT_{2a} (K_i = 0.087 nM) receptor and has affinity for the 5-HT_{2b} (K_i = 0.33) and 5H-T_{2c} (K_i = 0.44) receptors (Study 2013-03).</p> <p>The pimavanserin metabolites AC-279, AC-423, AC-527 and AC-627 had functional antagonist activity with potencies ranging from 2 to 20 nM at 5-HT_{2a} (compared to 2 nM for pimavanserin) and 50 to 250 nM potency at 5-HT_{2c} receptors (compared to 25 nM for pimavanserin) (Study 2014-01). No antagonist or agonist activity of the pimavanserin metabolites was found at 5-HT_{2B} receptors.</p>
Is this a new or novel drug formulation?		X		Pimavanserin tartrate is formulated as immediate release (IR) tablets.
Content of NDA abuse potential section:				
<i>Module 1: Administrative Information and Prescribing Information</i> 1.11.4 Multiple Module Information Amendment contains:		X		Module 1.11.4 is not listed in this NDA
<ul style="list-style-type: none"> A summary, interpretation, and discussion of abuse potential data provided in the NDA. 	X			See Abuse Liability White Paper, Module 3.3.5.3 (Abuse Potential

1 21 CFR 314.50(d)(5)(vii): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdose is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21USC811(f) Abuse potential: If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

CSS Filing Checklist for NDA/BLA or Supplement

Checklist	Yes	No	NA	Comment
				Assessment of Pimavanserin (ACP-103)).
<ul style="list-style-type: none"> A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential. 	X			See Abuse Liability White Paper, Module 3.3.5.3 (Abuse Potential Assessment of Pimavanserin (ACP-103)).
<ul style="list-style-type: none"> A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA 	X			See Abuse Liability White Paper, Module 3.3.5.3 (Abuse Potential Assessment of Pimavanserin (ACP-103)).
Module 2: Summaries				
2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.			X	Brief summaries of nonclinical studies (receptor binding, functional binding, animal behavioral studies) conducted by the Sponsor (Nonclinical Overview, Section 2.4.2 Pharmacology, page 7).
Module 3: Quality				
3.2.P.1 Description and Composition of the Drug Product - describes any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).			X	
Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?			X	
3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.			X	
Is this an extended release or abuse-resistant formulation?		X		
Module 4: Nonclinical Study Reports				
4.2.1 Pharmacology	X			See Abuse Liability White Paper, Module 3.3.5.3 (Abuse Potential Assessment of Pimavanserin (ACP-103)), pages 11, 19 - 20.
4.2.1.1 Primary Pharmacodynamics - contains study reports (<i>in vitro</i> and <i>in vivo</i>) describing the binding profile of the parent drug and all active metabolites.	X			
Are <i>in vitro</i> receptor binding studies included?	X			See filing checklist section above (4.2.1 Pharmacology)
Are functional assays included?	X			See filing checklist section above (4.2.1 Pharmacology)
4.2.3.7.4 Dependence – section includes:				
<ul style="list-style-type: none"> A complete discussion of the nonclinical data related to abuse potential. Complete study reports of all nonclinical abuse potential studies. 	X			
Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA				
Was a self administration study conducted?			X	
Was a conditioned place preference study conducted?	X			Title: Pimavanserin treatment produces neither a conditioned place preference nor a conditioned place aversion (Study Report 2013-02, Module 4.2.1.1): The design of the study is

CSS Filing Checklist for NDA/BLA or Supplement

Checklist	Yes	No	NA	Comment
				deficient. The positive control used in this study was morphine, a drug with a pharmacological mechanism of action dissimilar to that of pimavanserin. Taken into account mechanistic and potency differences, higher scores are predicted for morphine when compared to pimavanserin. The study report does not include a rationale for dose selection, and an assessment of drug plasma levels.
Was a drug discrimination study conducted?		X		
Was a physical dependence study conducted?		X		
<i>Module 5: Clinical Study Reports</i>				
5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.				
Human abuse potential study:				
Was a human abuse potential study conducted?		X		
Are all the primary data included in the NDA?	X			
Is a Statistics consult necessary?		X		
Other Clinical trials:				
Is there evidence of drug accountability issues or overt evidence of misuse, abuse, or diversions?	X			See Abuse Liability White Paper, Module 3.3.53 (Abuse Potential Assessment of Pimavanserin (ACP-103)).
Are all abuse/misuse Case Report Forms submitted [addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study]?	X			See Abuse Liability White Paper, Module 3.3.53 (Abuse Potential Assessment of Pimavanserin (ACP-103)).
Does Compliance need to be consulted re: site inspection for data integrity or other issues?		X		
5.3.6.1 Reports of Postmarketing Experience - includes information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product				
Did you review the scientific literature?	X			
Did you conducted a search of databases and other information related to misuse, abuse, and addiction?	X			
Is there evidence for any of the following:				
Accidental overdose in the patient population and vulnerable populations	X			
Overdose associated with misuse and abuse		X		
Unintended pediatric exposures to product		X		
Labeling issues				
Drug disposal issues?		X		
Postmarketing activities [PMRs, PMCs, REMS]	X			A PMR may be requested (i.e. ^{(b) (4)} study).

CSS Filing Checklist for NDA/BLA or Supplement

	Checklist	Yes	No	NA	Comment
	Scheduling activities		X		

Is NDA FILEABLE from a CSS perspective? _____ YES _____

If the Application is not fileable, state the reasons and provide comments to be sent to the Applicant.

CSS Pharmacology Reviewer: Jovita Randall-Thompson, Ph.D.

Date: October 8, 2015

CSS Medical Reviewer: Martin Rusinowitz, M.D.

Date: October 8, 2015

Director: Michael Klein, Ph.D.

Date: October 8, 2015

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

/s/

JOVITA F RANDALL-THOMPSON
10/08/2015
CSS Filing Checklist

MARTIN S RUSINOWITZ
10/08/2015

MICHAEL KLEIN
10/08/2015

**CDER Medical Policy Council Brief
Breakthrough Therapy Designation
[Division of Psychiatric Products]
[8-8-2014 MPC Meeting]**

Summary Box

1. IND Number **68384**
2. Company name **Acadia**
3. Drug name **Pimavanserin Tartrate**
4. Indication **Psychosis in Parkinson's Disease**
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? **Yes**
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? **N/A**
There are currently no drug products approved for this indication. D2 antagonist antipsychotics are used off-label for these symptoms. Atypical and typical antipsychotics worsen motor symptoms in patients with Parkinson's Disease, and the FDA has a boxed warning for their use in the elderly population due to increased risk of stroke. Pimavanserin tartrate does not demonstrate a risk for worsening the motor symptoms. Clozapine is the only other drug with positive study, but it is not indicated for this condition; it carries the risk of agranulocytosis and requires weekly CBCs for monitoring.

Division: **Psychiatric Products**

Medical officer: **Lucas Kempf, MD**

Clinical Team Leader: **Mark Ritter, MD**

1. Brief description of the drug

Pimavanserin is the active moiety of the tartrate salt with the chemical name, Urea, N-[(4-fluorophenyl)methyl]-N-(1-methyl-4-piperidiny)-N'-[[4-(2-methylpropoxy)phenyl]methyl]-, (2R,3R)-2,3-dihydroxybutanedioate (2:1). It is a novel small molecule designed to selectively block signaling from the 5-HT_{2A} serotonin receptor subtype. Its only other measurable activity is a weaker antagonism at 5-HT_{2C} receptors. In addition to blocking 5-HT_{2A} receptors, atypical antipsychotics also primarily block dopamine 2 receptors.

2. Brief description of the disease and intended population

Parkinson's disease (PD) is a common progressive neurodegenerative disorder; its clinical diagnosis is based on the presence of a core set of neurological symptoms including rest tremor, bradykinesia, rigidity, and disturbances of balance and posture. Although PD has been defined

by the motor symptoms, patients with PD also experience a number of non-motor symptoms that are equally important to address. Among these, perhaps the most significant with respect to morbidity, quality of life, and difficulty of treatment is psychosis.

The psychosis of Parkinson's disease manifests in the form of hallucinations (predominantly visual) and delusions. Although at onset, psychotic symptoms in PD may be considered "benign" and patients typically retain insight, this belies the progressive and chronic nature of the condition which, over time, becomes more threatening and disabling. Psychotic symptoms occur in about 50% of PD patients and are more prevalent in advanced PD. Onset of psychosis is associated with a marked decline in patient 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. Published longitudinal outcome assessments of subjects with comorbid psychosis have reported life span to be only 4.4 years after development of psychosis and 2 years after nursing home placement.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

Study ACP-103-020 was a 6-week Phase III study evaluating the efficacy, tolerability and safety of pimavanserin in patients with psychosis of Parkinson's disease. Pimavanserin met the **primary endpoint** in the trial by demonstrating highly significant antipsychotic efficacy as measured using the 9-item SAPS-PD scale (**p=0.001, effect size 0.50**). The SAPS-PD scale is an optimized scale for the specific psychotic symptoms seen in Parkinson's disease. Consistent with previous studies, pimavanserin also met the **key secondary endpoint** for motoric tolerability as measured using Parts II and III of the UPDRS. These scales are used commonly as outcome measures in Parkinson's motor symptom trials on the recommendation of the Division of Neurology Products (DNP). These results were further supported by a highly significant improvement in the secondary efficacy measure, the Clinical Global Impression Improvement, or CGI-I, scale (**p=0.001**), as well as on the CGI-S (Clinical Global Impression Severity) scale (**p<0.001**). In addition, clinical benefits were observed in all exploratory efficacy measures with significant improvements in nighttime sleep, daytime wakefulness and caregiver burden.

4. Brief description of available therapies (if any)

There are no approved therapies for this indication.

The main off-label pharmacological options are antipsychotic medications, but the adverse effect profile, including the exacerbation of extra-pyramidal symptoms (EPS), poses major tolerability issues. Typical antipsychotics are not a treatment option due to the greater risk of EPS. Open trials of risperidone and randomized controlled trials (RCTs) of olanzapine have indicated that they are not well-enough tolerated to consider them as routine treatment options in clinical practice (1). Initial open trials of quetiapine suggested good tolerability (1), but

the evidence from 4 RCTs in people with PD psychosis (2-5) and 1 RCT treating psychosis in PD Dementia and Lewy Body Dementia (6) indicates that quetiapine does not confer significant benefit and is not an effective treatment option.

Four small RCTs have been conducted with atypical antipsychotic clozapine, each with less than 100 patients and with short treatment durations of less than 6 weeks (7-10). Three of the studies did indicate significant benefit in psychosis without worsening of motor symptoms (7-9), but an increased number of deaths was reported in one of these studies (9). The other study used high doses of clozapine, with resultant poor tolerability (10). Clozapine carries boxed warnings for increased mortality, agranulocytosis, seizures, myocarditis, and other cardiovascular and respiratory effects. In addition, the risk of agranulocytosis requires stringent blood monitoring.

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

None.

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6. Description of preliminary clinical evidence

Summary table of development programs phase 2 and 3 trials digitally copied below.

Table 4. Overview of Pimavanserin Placebo-Controlled Studies in PDP

Study Suffix (ACP-103-XXX)	Phase	N	Region	Dosing Duration (wks)	Dose	Design	Key Efficacy Results*
-006 (Meltzer et al., 2010; Appendix 1)	II	60	US	4	20-60 mg (escalating) 1:1 vs. PBO	Visits at D1, 8, 15, 28 Once-daily oral dosing Dose escalation: 20-40-60 mg at 1-week intervals. 1 st endpoint: Motor tolerability (UPDRS) 2 nd endpoints for efficacy: SAPS H+D, CGI-S, and PPRS Site raters	Although not powered for efficacy, PDI arm showed consistent improvements in all psychosis measures (effect sizes 0.4-0.6) SAPS-H+D D28 LSMΔ = -4.6 (p=0.09, effect size=0.66)
-012	III	298	US Europe India	6	10, 40 mg (fixed) 1:1:1 vs. PBO	Visits at D1, 8, 15, 28, 43 Once daily oral fixed dosing 1 st endpoint: 20-item SAPS H+D 2 nd efficacy endpoints: CGI-I, CGI-S Other exploratory measures: SCOPA-sleep, CBS, NMSS, RUD-Lite Central raters (1 st endpoint and US only)	(b) (4)
-014	III	123	US Europe	6	10, 20 mg (fixed) 1:1:1 vs. PBO	Identical to -012 (with exception of dose levels)	Terminated early following receipt of -012 data (and because lower doses and same study design used) (b) (4)
-020 (Cummings et al., 2013; Appendix 1)	III	199	US Canada	6	40 mg (fixed) 1:1 vs. PBO	Enhanced criteria for symptom freq and severity 2-week screening with non-pharmacologic BPST Visits at D1, 15, 28, 43 Once daily oral fixed dosing 1 st endpoint: 9-item SAPS PD 2 nd efficacy endpoints: CGI-I, CGI-S Other exploratory measures: SCOPA-sleep, CBS Central raters (1 st endpoint only)	Highly significant separation on SAPS-PD (1 st) as well as on secondary psychosis measures CGI-I, CGI-S and on a number of sensitivity measures including SAPS H+D and Global SAPS H+D Significant separation on SCOPA-sleep (including improvements in nighttime sleep without sedation) and caregiver burden SAPS-H+D D43 LSMΔ = -3.4 (p=0.001, effect size=0.50) SAPS-PD D43 LSMΔ = -3.1 (p=0.001, effect size=0.50)

*For each study efficacy data using the primary analysis method are shown. (For -006, -012 and -014 ANCOVA LOCF; For -020 MMRM (OC))

7. Division's recommendation and rationale

- Recommendation: Approve breakthrough status.

- Rationale: The disease is a serious condition without current treatments and preliminary clinical evidence indicates a substantial improvement over available off label therapies.

8. Division's next steps and sponsor's plan for future development

- The division is already in pre-NDA discussions with the Sponsor and has supplied a first round of responses to a pre-NDA meeting.

9. References (if any)

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