CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210793Orig1s000
207318Orig1s003

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA and sNDA
Application Number(s)	NDA 210793 NDA 207318/s-003
Priority or Standard	Standard
Submit Date(s)	August 31, 2017 (NDA 210793) October 27, 2017 (NDA 207318/s-003)
Received Date(s)	August 31, 2017 (NDA 210793) October 27, 2017 (NDA 207318/s-003)
PDUFA Goal Date	June 30, 2018 (ACTION on: June 29, 2018)
Division/Office	Division of Psychiatry Products/ODE I
Review Completion Date	May 23, 2018
Established Name	Pimavanserin
(Proposed) Trade Name	Nuplazid
Pharmacologic Class	Atypical antipsychotic
Code name	NA
Applicant	Acadia Pharmaceuticals, Inc.
Formulation(s)	(capsule) NDA 210793 (tablet) NDA 207318/s-003
Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of hallucinations and delusions associated with Parkinson's disease psychosis (already approved under NDA 207318 on April 29, 2016)
Recommendation on Regulatory Action	Approval for both NDA 210793 and NDA 207318/S-003
Recommended Indication(s)/Population(s) (if applicable)	NA

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act

GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

Pimavanserin was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP) on 29 April 2016. The recommended dose was 34 mg, taken orally as two 17-mg tablets once daily, without titration.

On 31 August 2017, Acadia submitted NDA 210793 for the 34-mg capsule to replace the two 17-mg tablets for once daily dosing. On 27 October 2017, Acadia submitted NDA 207318 Supplement S-003 to support the approval of 10-mg pimavanserin tablets for use in patients with concomitant strong CYP3A4 inhibitors. This 10-mg tablet would replace the 17-mg tablet.

Overall, the review team recommends approval for both NDA 210793 and NDA 207318 Supplement S-003. No additional post-marketing studies are recommended by the review team. Given the indication, no pediatric development program is expected. This document includes the primary reviews from both Division of Psychiatry Products (DPP) and Office of Clinical Pharmacology (OCP). The primary reviews from other disciplines were recorded separately (Table 1).

Table 1: Other Primary Reviews for NDA 210793 and NDA207318/S-003

Submission	Review Disciplines	Finalized Date
NDA210793 & NDA207318/S-003	OPDP review	5/9/2018
	DMEPA review	4/20/2018
NDA 210793	OPQ review	5/21/2018
	Pharm/Tox review	4/11/2018
NDA207318/S-003	OPQ review	6/13/2018
	Pharm/Tox review	4/11/2018

The executive summary summarizes the findings from all review disciplines. No significant issue has been identified. The basis for the recommended action is listed below:

1. The approval basis for NDA 210793:
   - Per OCP, the average exposure of pimavanserin was shown to be similar (within the bioequivalence limits for Cmax, AUC0-inf, AUC0-t) between the 34-mg capsule and the two 17-mg tablets in the relative bioavailability study (The data is considered acceptable by the OSIS). Hence, the efficacy and safety profiles of the 34-mg capsule in general population are expected to be similar to those for the two17-mg tablets. In addition, the new 34-mg capsule can be taken with or without food.
   - Per DPP, the safety data submitted with this review is consistent with the existing pimavanserin label. The benefit-risk assessment for pimavanserin is unchanged.
   - Per OPQ, the drug substance, drug product, and manufacture process are acceptable. The drug product specifications, including specifications for dissolution, are acceptable. A shelf life of 24-month when the 34-mg capsule is stored at appropriate condition is supported by the stability data.

- Per Pharmacology/toxicology review, no new excipient was used and no new impurity/degradation was identified. Therefore, there is no additional safety concern for the capsule formulation.

2. The approval basis for NDA 207318/S-003:
   - Per OCP, the 10-mg dose is considered appropriate in patients receiving a strong CYP3A4 inhibitor concomitantly.
   - Per OPQ, the 10-mg tablet is developed based on the composition of the pimavanserin 17 mg tablet (b) (4). Appropriate rationales and data were provided to support the proposed composition change for the 10 mg pimavanserin tablets. The manufacture process and facility are considered appropriate.
   - Per Pharmcology/toxicology review, no new excipients were used and no new impurity/degradation was identified. Therefore, there is no additional safety concern for the 10-mg tablet formulation.

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Cross-Disciplinary Team Leader

2. Clinical Pharmacology

2.1 Executive Summary

NUPLAZID (pimavanserin) 17-mg tablet (NDA 207318) was developed by Acadia Pharmaceuticals and was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP) on 29 April 2016. The recommended dose was 34 mg, taken orally as two 17-mg tablets once daily, without titration.

On 31 August 2017, Acadia submitted NDA 210793 for the 34-mg capsule to replace the two 17-mg tablets for once daily dosing. In this submission, one pivotal relative bioavailability study (Study ACP-103-043) was conducted in healthy adult volunteers.

On 27 October 2017, Acadia submitted NDA 207318 Supplement S-003 to support the approval of 10-mg pimavanserin tablets for use in patients with concomitant strong CYP3A4 inhibitors. This 10-mg tablet would replace the 17-mg tablet. In this submission, the Applicant submitted new modeling and simulation (M&S) data to demonstrate that the 10-mg tablet provides better dosage adjustment than the 17-mg tablet in patients who are concomitantly administered with a strong CYP3A4 inhibitor.

2.1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has determined that there is sufficient clinical pharmacology information provided in the NDAs to support recommendations of (1) approval of 34-mg capsule and 10-mg tablet, and (2) dosage adjustment to 10 mg, rather than 17 mg, in patients receiving a strong CYP3A4 inhibitor concomitantly. The acceptability of specific drug information is provided below

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	1. The 34-mg capsule produced similar average exposure to two 17-mg tablets, which is the approved dosing regimen with the marketed product and was shown to be safe and efficacious in clinical trials. 2. The biowaiver for 10-mg tablet has been granted by the biopharmaceutical team at OPQ.
General dosing instructions	34 mg once daily (using the 34-mg capsule), without titration.

Dosing in patient subgroups (strong CYP3A4 inhibitors)	Reduce dose to10 mg once daily (using the 10-mg tablet) when coadministered with strong CYP3A4 inhibitors.
Labeling	Pending satisfactory agreement with the Applicant.
Bridge between the to-be-marketed and clinical trial formulations	N/A
Other (specify)	N/A

Per the recommendation (Appendix 22.4.4) from the Office of Study Integrity and Surveillance (OSIS), the data from the pivotal relative bioavailability study is considered acceptable. No inspection of the clinical or analytical site for the pivotal study ACP-103-043 was deemed necessary, because those sites were recently inspected and no issues were identified.

2.1.2 Post-Marketing Requirements and Commitments

No PMR or PMC study is necessary for these submissions.

2.2 Summary of Clinical Pharmacology Assessment

- The average exposure of pimavanserin was shown to be similar (within the bioequivalence limits for Cmax, AUC0-inf, AUC0-t) between the 34-mg capsule and the two 17-mg tablets in the relative bioavailability study. Hence, the efficacy and safety profiles of the 34-mg capsule in general population are expected to be similar to those for the two 17-mg tablets.

- The 10-mg tablet given to patients receiving a CYP3A4 strong inhibitor concomitantly is anticipated to produce similar average exposure as compared to patients receiving a 34-mg capsule.

- No clinically relevant food effect is expected for the 34-mg pimavanserin capsule.

2.3 Comprehensive Clinical Pharmacology Review

2.3.1 General Pharmacology and Pharmacokinetic Characteristics

N/A

2.3.2 Clinical Pharmacology Questions

2.3.2.1 Are similar efficacy and safety profiles expected for two 17-mg pimavanserin tablets and one 34-mg pimavanserin capsule?

Yes, similar efficacy and safety profiles are expected between two 17-mg pimavanserin tablets and one 34-mg pimavanserin capsule.

Two 17-mg pimavanserin tablets given once daily has been shown to be safe and effective for the treatment of the hallucinations and delusions of Parkinson's disease. The 34-mg capsule demonstrated similar exposure (i.e., Cmax, AUC0-t, and AUC0-inf) to two 17-mg tablets in a relative bioavailability study (Table 1 and Figure 1). Therefore, the 34-mg capsule is expected to produce similar efficacy and safety profiles following the treatment of two 17-mg tablet (See Appendix 22.4.1 for detail).

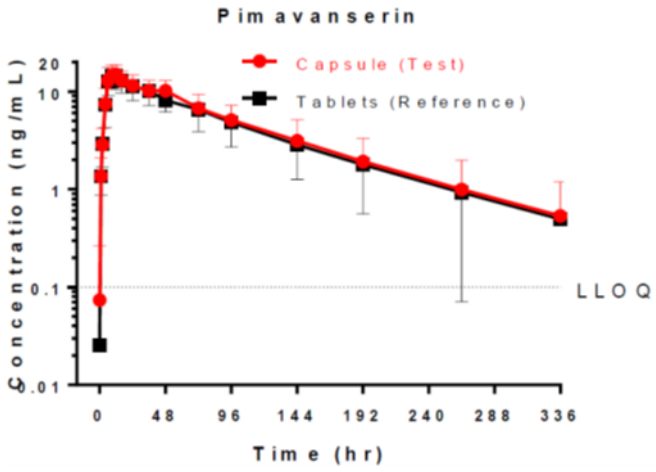
Table 1 Mean (SD) Pharmacokinetic Parameters for Pimavanserin in Subjects Receiving Two 17 mg Tablets or One 34 mg Capsule of Pimavanserin - Pharmacokinetic Analysis Set

Parameter	Reference Formulation (Two 17 mg Tablets) (N=40)	Test Formulation (One 34 mg Capsule) (N=39)
C_{max} (ng/mL)	15.7 (3.85)	16.1 (4.35)
AUC_{0-t} (h•ng/mL)	1250 (475)	1330 (517)
$AUC_{0-\infty}$ (h•ng/mL)	1320 (550)	1400 (616)
T_{max} (h)	10.5 (6.00, 16.0)	12.0 (6.00, 24.00)
$t_{1/2}$ (h)	66.8 (23.7)	67.0 (22.4)
λ_z (/h)	0.0113 (0.00303)	0.0112 (0.00289)
V_z/F (L)	2640 (823)	2580 (1060)
CL/F (L/h)	29.3 (9.76)	29.2 (15.5)

Table 2 Primary Bioequivalence Analysis of Cmax and AUC of Pimavanserin Between Test Capsule Formulation and Reference Tablet Formulation - Pharmacokinetic Analysis Set

Parameter	N[a]	%Geometric Mean Ratio (Capsule/Tablet)	90% CI (Lower)	90% CI (Upper)
$AUC_{0-\infty}$	Capsule (38) vs Tablet (38)	102.39%	95.35%	109.95%
AUC_{0-t}	Capsule (38) vs Tablet (38)	102.69%	95.59%	110.32%
C_{max}	Capsule (38) vs Tablet (38)	99.44%	92.55%	106.85%

Figure 1 Mean (±SD) Plasma Concentration by Time Profiles of Pimavanserin in Subjects Following a Single 34 mg Oral Dose of Pimavanserin With a Test Capsule Formulation (+SD) or Reference Tablet Formulation (-SD) a Semi-Log Scale – Pharmacokinetic Analysis Set



2.3.2.2 Is the proposed dosing regimen of 10 mg once daily appropriate for patients coadministered with strong CYP3A4 inhibitors?

Yes, the proposed dosing regimen of 10 mg once daily is appropriate for patients coadministered with strong CYP3A4 inhibitors.

The current recommended dose for patients coadministered with strong CYP3A4 inhibitors is 17 mg once daily, taken as a single tablet. This dosing regimen is based on a dedicated drug interaction study with ketoconazole, a strong CYP3A4 inhibitor. The study indicated that ketoconazole increased pimavanserin AUC(0-∞) by about 3-fold. A reduction to 1/3 of the original exposure/dose seems to be appropriate. However, the label recommended 50% reduction in dose when pimavanserin is used in combination with a strong CYP3A4 inhibitor, because only 17-mg tablet was available when pimavanserin was approved.

The Applicant developed a 10-mg tablet, which ensures a better dosage adjustment than the 17-mg tablet when pimavanserin is used in combination with a strong CYP3A4 inhibitor. The 10-mg tablet is expected to generate 1/3 of the exposures compared with 34 mg dose. As demonstrated by population PK modeling and simulation, at steady state, a 10-mg dose coadministered with a strong CYP3A4 inhibitor will produce pimavanserin systemic exposure similar to that following pimavanserin 34 mg once daily in patients not receiving a strong CYP3A4 inhibitor (Table 3). Given the 10-mg strength is available, it seems to be appropriate to adjust the pimavanserin dose to 10 mg rather than 17 mg when it is used in combination with a strong CYP3A4 inhibitor.

Table 3 Summary of Geometric Least Squares Means of Exposure Parameters for Observed and Simulated Trials

Parameter	Study ACP-103-023 Observed Single Dose Geometric Means (SD)[a]		Simulated Trials Steady-State Results (Mean of Geometric Least Squares Means [SD])[b]			Simulated Trials Dose Reduction at Steady-State Results (Mean of Geometric Least Squares Means [SD])[c,d,e]		
	34 mg Alone (N = 19)	34 mg With Ketoconazole (N = 19)	34 mg Alone	10 mg With Ketoconazole	17 mg With Ketoconazole	34 mg Alone	10 mg With Ketoconazole	17 mg With Ketoconazole
AUC (h × ng/mL)[f]	1182.5 (464)	3656.1 (912)	1159.57 (32.08)	1157.18 (31.63)	1961.34 (53.60)	1153.31 (108.71)	1074.44 (107.88)	1166.96 (109.15)
C_{max} (ng/mL)[g]	16.74 (3.80)	24.53 (5.47)	60.77 (1.63)	59.25 (1.63)	100.37 (2.77)	60.44 (5.54)	55.01 (5.57)	59.57 (5.63)

Abbreviations: AUC, area under the concentration-time curve; AUC_{inf}, area under the concentration-time curve from the time of drug administration (time 0) extrapolated to infinity; AUC_{tau}, area under the concentration-time curve from the time of drug administration (time 0) to the end of the dosing interval, τ; C_{max}, maximum observed drug concentration; $C_{max,ss}$, maximum observed drug concentration at steady state; SD, standard deviation.

[a] From Clinical Study Report; Table 14.3.8.2.

[b] Reference treatment is steady-state 34 mg pimavanserin; Test treatment is steady-state 10 mg or 17 mg pimavanserin + ketoconazole; Number of trials = 500; Number of subjects per trial = 150.

[c] Reference treatment is 34 mg pimavanserin alone dosed to presumed steady state; Test treatment is first dose 10 or 17 mg pimavanserin + ketoconazole after switching from 34 mg pimavanserin at presumed steady state; Number of trials = 500; Number of subjects per trial = 12.

[d] AUC_{tau} for Reference treatment and AUC_{0-24} for Test treatment.

[e] $C_{max,ss}$ for Reference treatment and C_{max} for Test treatment.

[f] For Study ACP-103-023, AUC is AUC_{inf} and for the simulated trials, AUC is AUC_{tau}.

[g] For Study ACP-103-023, C_{max} is Day 1 C_{max} and for the simulated trials, C_{max} is $C_{max,ss}$.

2.3.2.3 What is the effect of food on the bioavailability of the drug when administered as 34-mg pimavanserin capsule?

No clinically relevant food effect is expected for the 34-mg pimavanserin capsule.

Pimavanserin tartrate is a highly soluble and highly permeable compound, which behaves like a BCS Class 1 drug, and dissolves rapidly from tablet or capsule formulation. Pimavanserin 34 mg capsules contain essentially a subset of the excipients in pimavanserin 17 mg tablets, which are commonly used in immediate release formulations. In addition, the rate and extent of absorption following tablet or capsule administration are both similar. No clinically meaningful food effect has been identified from the tablet formulation. Hence, we expect the food effect for the immediate release capsule to be similar to the tablet formulation.

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Primary Reviewer Team Leader

3. Efficacy and Safety

Efficacy Overview

NDA 207318, s-003 used computer simulations and no human data was submitted. Therefore, this section is not applicable to this supplement.

The review that follows is for study ACP-103-043, which was completed in support of NDA 210793. Because the Applicant successfully demonstrated bioequivalence between the two 17mg tablets and the single 34mg capsules, this application relies on the Agency's previous efficacy findings for pimavanserin.

Clinical Study

ACP-103-043: A Phase 1, Randomized, Open-label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 17-mg Tablets and One 34-mg Capsule of Pimavanserin in Healthy Subjects.

ACP-103-043

A Phase 1, Randomized, Open-label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 17-mg Tablets and One 34-mg Capsule of Pimavanserin in Healthy Subjects.

Study Design

Objectives

Study Endpoints

Primary Endpoints: The bioequivalence of treatment A (two 17-mg pimavanserin tablets, reference) and treatment B (one 34-mg pimavanserin capsule, test) were assessed by comparing the following primary PK parameters for pimavanserin: AUC0-∞, AUC0-t, and Cmax.

Secondary Endpoints: These endpoints were: time to maximum observed plasma drug concentration (t_{max}) by inspection, elimination half-life ($t_{1/2}$), apparent terminal elimination rate constant (λ_z), percentage extrapolation ($100x[AUC_{0-\infty}-AUC_{0-t}]/AUC_{0-\infty}$); and, when possible all noted PK parameters were to be calculated as appropriate for the pimavanserin metabolite (AC-279). Safety endpoints for pimavanserin in this study were: physical examinations, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiograms (ECG), and adverse event reporting.

Trial Design

This was a randomized, open-label, 2-period crossover, single center study to assess the bioequivalence of two 17-mg tablets and one 34-mg capsule of pimavanserin in healthy subjects. Subjects were randomized to one of two treatment sequences: AB or BA, for which A was two 17-mg pimavanserin tablets and B was one 34-mg pimavanserin capsule.

The study consisted of a screening period (Days -28 to -2), a baseline evaluation (Day -1); followed by a 36-day treatment period, an End of Study (EOS) procedures on Day 36, and a follow-up visit 1 week (±2 days) following the EOS.

Study Results

Financial Disclosure

No investigator reported financial interests or arrangements that existed with ACADIA; therefore, ACADIA did not include Form FDA 3455.

Patient Disposition[1]

	2×17 mg Tablets then 1×34 mg Capsule	1×34 mg Capsule then 2×17 mg Tablets	All Subjects
	n (%)	n (%)	n (%)
Screen failures			31[a]
Randomized subjects	21	19	40
Safety analysis set	21	19	40
PK analysis set	21 (100.0)	19 (100.0)	40 (100.0)
Completed both pimavanserin formulations	20 (95.2)	19 (100.0)	39 (97.5)
Completed 2×17 mg pimavanserin tablets	21 (100.0)	19 (100.0)	40 (100.0)
Completed 1×34 mg pimavanserin capsule	20 (95.2)	19 (100.0)	39 (97.5)
Completed study	20 (95.2)	18 (94.7)	38 (95.0)
Early termination	1 (4.8)	1 (5.3)	2 (5.0)
Reason for early termination			
Withdrawal by subject	1 (4.8)	1 (5.3)	2 (5.0)

Abbreviations: AUC=area under the plasma concentration-time curve; AUC - = area under the plasma concentration-time curve from 0 to infinity; AUC_{0-t}= area under the plasma drug concentration by time curve from time 0 to the time of the last plasma concentration measurement; C_{max}=maximum observed plasma drug concentration; n=sample size; PK=pharmacokinetics

Notes: Percentages are based on the number of subjects in the Safety Analysis Set. The Safety Analysis Set is defined as all subjects who received at least 1 dose of pimavanserin in either the tablet or capsule formulation. The PK Analysis Set is defined as all subjects who received at least 1 dose of pimavanserin in either the tablet or capsule formulation, had no major PK-related protocol deviations, and had sufficient data to calculate the $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for pimavanserin for either administration period.

[a] An additional 11 subjects were considered to have failed screening because enrollment was full.

[1] Study ACP-103-043 Clinical Study Report, Table 10-1, pgs. 43/618; August 18, 2017

Protocol Deviations[2]

Significant time deviations for PK blood draws were noted as follows: Subject (b) (6) (Period 2 at 336 hours post-dose), Subject (b) (6) (Period 1 at 264 hours post-dose), and Subject (b) (6) (Period 2 at 36 hours post-dose). The protocol deviations did not affect the results of the analyses.

Table of Demographic Characteristics-Safety Analysis Set[3]

		All Subjects (N=40)
Gender	n	40
Male	n (%)	30 (75.0)
Female	n (%)	10 (25.0)
Race	n	40
White	n (%)	17 (42.5)
Black or African American	n (%)	23 (57.5)
Asian	n (%)	0
American Indian or Alaska Native	n (%)	0
Native Hawaiian or Other Pacific Islander	n (%)	0
Other: Specify	n (%)	0
Ethnic group	n	40
Hispanic or Latino	n (%)	3 (7.5)
Not Hispanic or Latino	n (%)	37 (92.5)
Not reported	n (%)	0
Unknown	n (%)	0

[2] Study ACP-103-043 Clinical Study Report, Sec. 20.2 Protocol Deviations, pg. 43/618; August 18, 2017
[3] Study ACP-103-043 Clinical Study Report, Table 11-1, pgs. 44-45/618; August 18, 2017

		All Subjects (N=40)
Age (years) at Screening	n	40
	Mean	36.7
	SD	10.28
	SE	1.62
	Min	21
	Median	34
	Max	54
Height (cm) at Screening	n	40
	Mean	171.60
	SD	8.529
	SE	1.349
	Min	154.5
	Median	172.00
	Max	188
Weight (kg) at Screening	n	40
	Mean	77.96
	SD	10.521
	SE	1.664
	Min	59.1
	Median	78.05
	Max	104.9
BMI (kg/m^2) at Screening	n	40
	Mean	26.46
	SD	2.771
	SE	0.438
	Min	19.8
	Median	27.35
	Max	31.3

Treatment Compliance, Concomitant Medications Use

Treatment Compliance

All subjects received single doses of two 17 mg strength tablets of pimavanserin and one 34 mg capsule as specified in the protocol.

Concomitant Medications

A summary of concomitant medications for the Safety Analysis Set is provided in ACADIA's Table[4], copied and pasted below. Overall, eight (20.0%) subjects used concomitant medications. The most commonly used concomitant medication was paracetamol for headache (6 subjects [15.0%]).

ATC Classification/ Medication Preferred Term	2 x 17 mg Tablets (N=40) n (%)	1 x 34 mg Capsule (N=39) n (%)	Both Periods (N=40) n (%)
Any Concomitant Medications	7 (17.5)	4 (10.3)	8 (20.0)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	1 (2.5)	1 (2.6)	1 (2.5)
Ibuprofen	1 (2.5)	1 (2.6)	1 (2.5)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	1 (2.5)	0	1 (2.5)
Diphenhydramine hydrochloride	1 (2.5)	0	1 (2.5)
OTHER ANALGESICS AND ANTIPYRETICS	5 (12.5)	3 (7.7)	6 (15.0)
Cotylenol	1 (2.5)	0	1 (2.5)
Paracetamol	5 (12.5)	3 (7.7)	6 (15.0)

Efficacy Results – Primary Endpoint

There were no clinical efficacy endpoints in this study.

Data Quality and Integrity

No data quality issues were identified.

[4]Study ACP-103-043 Clinical Study Report, 14.1.4.1 Summary of Concomitant Medications - Safety Analysis Set, pg. 78/618; August 18, 2017

Integrated Review of Effectiveness

Assessment of Efficacy Across Trials

This was a single pharmacokinetic study. No comparisons were made across trials.

Statistical Issues

No statistical review was performed.

Safety Overview

NDA 207318, s-003 used computer simulations and no human data was submitted. Therefore, this section is not applicable to this supplement.

The review that follows is for study ACP-103-043, which was completed in support of NDA 210793. Because the Applicant successfully demonstrated bioequivalence between the two 17mg tablets and the single 34mg capsules, this application relies on the Agency's previous safety findings for pimavanserin. Furthermore, patients only received single doses of two 17mg tablets and 34mg pimavanserin capsules in order to establish bioequivalency. No placebo was used during study ACP-103-043. Because of these limitations, no new meaningful conclusions on the safety profile of pimavanserin can be drawn. Only high-level safety data (deaths, SAEs, AEs leading to discontinuation) will be discussed here.

There were no deaths, SAEs, or TEAEs leading to early termination.

Overall, the safety profile of pimavanserin submitted with these applications is consistent with the existing label of the drug.

Safety Review Approach

Because of the trial design, only high level safety findings will be addressed in this review for NDA 210793 (i.e., deaths, SAEs, AEs leading to discontinuation). No human data were submitted with Supplement 3 of NDA 207318.

Review of the Safety Database

Overall Exposure

This is a study single-dose study of pimavanserin on Days 1 and 22.

Relevant characteristics of the safety population:

The study included 30 male and 10 female subjects, who were either Black or African American (57.5%) or White (42.5%). The mean (SD) age at screening was 36.7 (10.28) years and ranged between 21 and 54 years.

Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues related to data integrity or problems with the quality of the submission were identified.

Categorization of Adverse Events

AE's were defined "as any untoward medical occurrence associated with the use of a drug during the study, whether considered drug related[5]", and were coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA,), Version 19.0. They were classified by the Investigator as being related or not related to the study drug. Coding was done in accordance with the procedures established in the Study Protocol[6].

Safety Results

Deaths

No deaths occurred during the Study.

Serious Adverse Events

There were no Serious Adverse Events or other Significant Adverse Events including Adverse Events Leading to Early Termination from the Study.

Dropouts and/or Discontinuations Due to Adverse Effects

Two (5 %) of the 40, randomized subjects terminated the study early (withdrew consent), one from each treatment group, reportedly not the result of an Adverse Event. One subject who withdrew consent and terminated the study early (AB sequence group) had abnormal ECG results of nonspecific intraventricular conduction delay at screening and early termination. It was not thought to be clinically significant.

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[5] ACP-103-043-Protocol-and-Amend; Sec. 7. Assessment of Safety; Sec. 7.1.1. Definition of Adverse Event, pgs. 50-51/65.pdf

[6] Protocol No. ACP-103-043, entitled: A Phase 1, Randomized, Open-label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 17-mg Tablets and One 34-mg Capsule of Pimavanserin in Healthy Subjects; acp-103-043-protocol-and-amend.pdf; pgs. 50-51/65.

Significant Adverse Events

No significant adverse events occurred during the Study.

Analysis of Submission-Specific Safety Issues

No specific safety issues were identified in Study ACP-103-043.

Safety Issue

None were identified in this single study.

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The following safety endpoints were assessed in the study.

- physical examinations
- clinical laboratory tests including hematology, serum chemistry, and urinalysis
- vital sign measurements
- 12-Lead ECG
- adverse event (AE) reporting
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Subjects experiencing treatment related adverse advents were compared among study groups.

Safety Analyses by Demographic Subgroups

Forty (40) subjects (30 males and 10 females), between 21-55 years of age (mean age: 36.7 [10.28[years), who were either Black or African American (57.5 %) or White (42.5 %) were randomized and treated. Given the small number of common reported adverse events (headache, n =9) and nasal congestion (n=3) and small number of subjects, no sub-group analysis was conducted.

Specific Safety Studies/Clinical Trials

This was a bioequivalence study and the assessment of specific safety issues was not the evaluated in this trial.

Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Since Pimavanserin's approval on April 29, 2016, there have been post-marketing reports of deaths, without a clearly defined pattern.
A FAERS data mining analysis by the Division of Applied Regulatory Science suggested that pimavanserin may exacerbate/potentiate certain Parkinson's disease co-morbidities (autonomic dysfunction, falls and insomnia). Interval Periodic Adverse Event Reports indicate reports of deaths from multiple causes. A report (November 1, 2017) by the Institute for Safe Medication Practices highlighted serious or fatal postmarketing reports with pimavanserin, and noted that many reports involved combination with other antipsychotics.

FDA created a Tracked Safety Issue (TSI) for pimavanserin on April 06, 2018, posing four Tracked Safety Issue Queries. ACADIA submitted a response[7] to an FDA Information Request of April 13, 2018. This is currently being evaluated by the Division of Pharmacovigilance (DPV) and Division of Epidemiology (DEPI).

Expectations on Safety in the Postmarket Setting

The Benefit/Risk Assessment of this product will remain unchanged by the approval of these two submissions.

[7] NDA 207,318 (Seq 71(, dated May 10, 2018.

SUMMARY AND CONCLUSIONS

No significant safety signal was identified in Study ACP-103-043. The safety findings of this submission are generally consistent with the pimavanserin label.

Conclusions and Recommendations

There are no findings from Study ACP-103-043 which precludes approval. Treatment Formulation B (one 34 mg pimavanserin capsule, test) was bioequivalent to Treatment Formulation A (two 17 mg pimavanserin tablets, reference), and no significant safety signal was present.

Post-marketing reports of deaths are being evaluated under FDA's Tracked Safety Issue (TSI No. 1890), which we concur with. FDA's Office of Surveillance and Epidemiology is evaluating data resources to address this TSI, pursuant to the Division of Psychiatry Products (DPP) consultative request.

X _____

Primary Clinical Reviewer (NDA 207318/s-003)

X _____ X _____

Primary Clinical Reviewer (NDA 210793) Clinical Team Leader

Pediatrics

Not applicable for this review.

Postmarketing Requirements and Commitment

No PMR or PMC study is necessary for these submissions. The Applicant has ongoing PMCs from pimavanserin's initial approval:

- 3069-1: Conduct a randomized withdrawal trial comparing pimavanserin 34 mg/day to placebo.
- 3069-2: Conduct a 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.
- 3069-3: Conduct an in vivo drug-drug interaction study to measure the effect of strong CYP3A4 inducers (e.g., rifampin) on the exposure to pimavanserin. Depending on the results of the study, a maximum dose could be recommended when CYP3A4 inducers are co-administered with pimavanserin.
- 3069-4: Perform microscopic re-evaluation of lung tissue samples using special stains to detect collagen from high dose (30 mg/kg/day male and female group) 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.

Division Director (DPP)

I concur with the findings of this review and will approve the application with the negotiated labeling on or before the PDUFA Date.

X

4. Appendices

OCP Appendices (Technical documents supporting OCP recommendations)

22.4.1 Bioequivalence Study Report for Study ACP-103-043

Report # ACP-103-043 **Study Period**: 10/26/2016-12/29/2016
Title: A Phase 1, Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 17 mg Tablets and One 34 mg Capsule of Pimavanserin in Healthy Subjects

- **Objective:**

Primary

- To assess the bioequivalence of two 17 mg pimavanserin tablets and one 34 mg pimavanserin capsule, as assessed by the area under the plasma drug concentration-time curve (AUC) from time 0 to infinity (AUC0-∞), AUC from time 0 to time of last plasma concentration measurement at time t (AUC0-t), and the maximum observed plasma drug concentration (Cmax) of pimavanserin

Secondary

- To evaluate the safety and tolerability profile of a single oral dose of 34 mg pimavanserin administered as two 17 mg tablets or one 34 mg capsule in healthy adults
- To assess the secondary pharmacokinetic (PK) parameters for pimavanserin and the metabolite N-desmethyl-pimavanserin (AC-279)

- **Study Design:**

This was a Phase 1, randomized, open-label, 2-period crossover study to evaluate the PK of pimavanserin and the significant circulating metabolite, AC-279, following administration of two 17 mg pimavanserin tablets (Treatment Formulation A) or one 34 mg pimavanserin capsule (Treatment Formulation B) in healthy subjects to assess the bioequivalence of the study treatments.
Potential subjects were screened for study eligibility; the Screening phase was 2 to 28 days in duration. Subjects were randomized to either treatment sequence AB or BA, and on Day -1 (Baseline), the subjects entered a 36-day treatment period during which they remained in a Clinical Pharmacology Unit (CPU). On Day 1, subjects received a single dose of Treatment Formulation A or Treatment Formulation B, depending on the randomized treatment sequence, following an overnight fast of approximately 10 hours. PK samples for measurement of plasma concentrations of pimavanserin and AC-279 were collected prior to pimavanserin dosing and at scheduled timepoints for 14 days. Following the final PK sample collection on Day 15, subjects were not administered study treatment, and PK samples were not collected. On Day 22, subjects received a single dose of Treatment Formulation B or Treatment Formulation A, depending on the randomized treatment sequence. Samples for pimavanserin and AC-279 PK

analysis were collected prior to pimavanserin dosing and at scheduled timepoints for an additional 14 days.
Following the final PK sample on Day 36, other end-of-study assessments were performed, and subjects were discharged from the CPU. Subjects were to return to the CPU 7 (±2) days after the end of study (EOS)/early termination (ET) for a follow-up visit. Safety was assessed throughout the study.
Number of Subjects: Forty subjects were planned. A total of 40 subjects were enrolled in the following groups

Group	Number of Subjects
AB	21
BA	19
Note: Group AB=Treatment Formulation A on Day 1 and Treatment Formulation B on Day 22; Group BA=Treatment Formulation B on Day 1 and Treatment Formulation A on Day 22; Treatment Formulation A=two 17 mg pimavanserin tablets; Treatment Formulation B=one 34 mg pimavanserin capsule.	

Diagnosis and Main Criteria for Admission: Subjects enrolled into the study were male or female subjects between the ages of 18 and 55 years, inclusive, with a body mass index between 18 and 32 kg/m2, inclusive. Concomitant medications during the study and 30 days or 5 half-lives prior to the treatment period, except for acetaminophen and ibuprofen, were prohibited. Healthy subjects could not be smokers, drug users, or heavy alcohol drinkers and could not have clinically significant laboratory test values based on Screening medical history, physical examination, laboratory test profile, vital signs, or electrocardiogram (ECG), as judged by the Investigator or Medical Monitor.

Duration of Treatment: The duration of an individual subject's participation in the study was approximately 10 weeks, consisting of a screening period (up to 4 weeks), a 5-week treatment period, and a follow-up period (approximately 1 week).

Test and Reference product:
Test: Pimavanserin 34 mg IR capsules, each capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base
Reference: Pimavanserin 17 mg IR tablets, each tablet contains 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of pimavanserin free base

- **Criteria for Evaluation:**

  Pharmacokinetics (Primary): PK blood samples for pimavanserin and its primary metabolite, AC-279, were collected predose and 1, 2, 4, 6, 9, 12, 16, 24, 36, 48, 72, 96, 144, 192, 264, and 336 hours after pimavanserin administration.
  Primary PK endpoints: AUC0-∞, AUC0-t, Cmax.
  Secondary PK endpoints: Tmax, t1/2, λz, percentage extrapolation (100×[AUC0-∞-AUC0-t]/AUC0-∞). When possible, all noted PK parameters were calculated as appropriate for the pimavanserin metabolite, AC-279.
  Safety and Tolerability (Secondary): physical examinations; clinical laboratory tests including hematology, serum chemistry, and urinalysis; vital sign measurements; 12-Lead ECG; adverse event (AE) reporting; Columbia-Suicide Severity Rating Scale (C-SSRS)

- **Analytical Method:**

Analyte		ACP-103	AC-260279
Method		LC/MS/MS	LC/MS/MS
Matrix		Plasma	Plasma
Calibration	Range	0.100 – 100 ng/mL	0.500 – 500 ng/mL
	#Conc	8	8
	%CV	2.2 – 3.7	2.4 – 7.5
	%Bias	-4.0 – 4.0	-5.0 – 4.4
	R2	0.9970 – 0.9991	0.9972 – 0.9979
Quality Control	Range	0.100 – 80 ng/mL	0.500 – 400 ng/mL
	#Conc	5	5
	%CV	0.0 – 2.3	0.0 – 3.2
	%Bias	3.9 – 7.0	1.0 – 4.7
Performance		Acceptable	Acceptable

- **Results:**

Study Population

Table 4 Summary of Subject Disposition – All Subjects

	2×17 mg Tablets then 1×34 mg Capsule	1×34 mg Capsule then 2×17 mg Tablets	All Subjects
	n (%)	n (%)	n (%)
Screen failures			31[a]
Randomized subjects	21	19	40
Safety analysis set	21	19	40
PK analysis set	21 (100.0)	19 (100.0)	40 (100.0)
Completed both pimavanserin formulations	20 (95.2)	19 (100.0)	39 (97.5)
Completed 2×17 mg pimavanserin tablets	21 (100.0)	19 (100.0)	40 (100.0)
Completed 1×34 mg pimavanserin capsule	20 (95.2)	19 (100.0)	39 (97.5)
Completed study	20 (95.2)	18 (94.7)	38 (95.0)
Early termination	1 (4.8)	1 (5.3)	2 (5.0)
Reason for early termination			
Withdrawal by subject	1 (4.8)	1 (5.3)	2 (5.0)

Table 5 Summary of Demographics – Safety Analysis Set

		All Subjects (N=40)
Gender	n	40
Male	n (%)	30 (75.0)
Female	n (%)	10 (25.0)
Race	n	40
White	n (%)	17 (42.5)
Black or African American	n (%)	23 (57.5)
Asian	n (%)	0
American Indian or Alaska Native	n (%)	0
Native Hawaiian or Other Pacific Islander	n (%)	0
Other: Specify	n (%)	0
Ethnic group	n	40
Hispanic or Latino	n (%)	3 (7.5)
Not Hispanic or Latino	n (%)	37 (92.5)
Not reported	n (%)	0
Unknown	n (%)	0
Age (years) at Screening	n	40
	Mean	36.7
	SD	10.28
	SE	1.62
	Min	21
	Median	34
	Max	54
Height (cm) at Screening	n	40
	Mean	171.60
	SD	8.529
	SE	1.349
	Min	154.5
	Median	172.00
	Max	188
Weight (kg) at Screening	n	40
	Mean	77.96
	SD	10.521
	SE	1.664
	Min	59.1
	Median	78.05
	Max	104.9
BMI (kg/m^2) at Screening	n	40
	Mean	26.46
	SD	2.771
	SE	0.438
	Min	19.8
	Median	27.35
	Max	31.3

Pharmacokinetics

Table 6 Mean (SD) Pharmacokinetic Parameters for Pimavanserin in Subjects Receiving Two 17 mg Tablets or One 34 mg Capsule of Pimavanserin - Pharmacokinetic Analysis Set

Parameter	Reference Formulation (Two 17 mg Tablets) (N=40)	Test Formulation (One 34 mg Capsule) (N=39)
C_{max} (ng/mL)	15.7 (3.85)	16.1 (4.35)
AUC_{0-t} (h•ng/mL)	1250 (475)	1330 (517)
$AUC_{0-\infty}$ (h•ng/mL)	1320 (550)	1400 (616)
T_{max} (h)	10.5 (6.00, 16.0)	12.0 (6.00, 24.00)
$t_{1/2}$ (h)	66.8 (23.7)	67.0 (22.4)
λ_z (/h)	0.0113 (0.00303)	0.0112 (0.00289)
V_z/F (L)	2640 (823)	2580 (1060)
CL/F (L/h)	29.3 (9.76)	29.2 (15.5)

Note: Tmax=median (min, max). Subjects 001-030 and 001-074 were included in the descriptive statistics of the PK Analysis Set.

Table 7 Primary Bioequivalence Analysis of Cmax and AUC of Pimavanserin Between Test Capsule Formulation and Reference Tablet Formulation - Pharmacokinetic Analysis Set

Parameter	N[a]	%Geometric Mean Ratio (Capsule/Tablet)	90% CI (Lower)	90% CI (Upper)
$AUC_{0-\infty}$	Capsule (38) vs Tablet (38)	102.39%	95.35%	109.95%
AUC_{0-t}	Capsule (38) vs Tablet (38)	102.69%	95.59%	110.32%
C_{max}	Capsule (38) vs Tablet (38)	99.44%	92.55%	106.85%

Note: Geometric Mean, Geometric Mean Ratios, and 90% CIs for log-transformed AUC0-∞, AUC0-t, and Cmax were calculated from a mixed effects model that included treatment formulation, sequence, and period as the fixed effects and subject as a random effect.
a Subjects 001-030 and 001-074 were excluded in the primary bioequivalence analysis.

Figure 2 Mean (±SD) Plasma Concentration by Time Profiles of Pimavanserin in Subjects Following a Single 34 mg Oral Dose of Pimavanserin With a Test Capsule Formulation (+SD) or Reference Tablet Formulation (-SD) a Semi-Log Scale – Pharmacokinetic Analysis Set

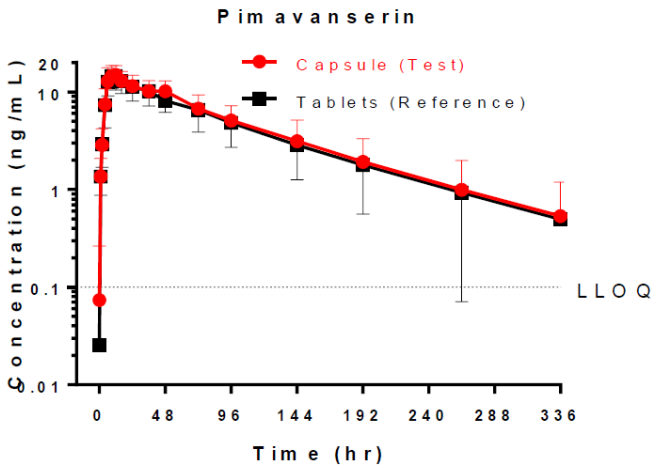
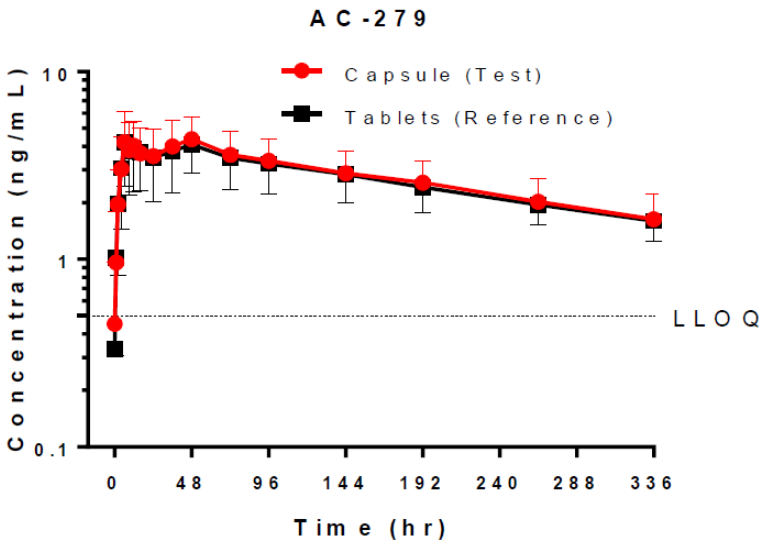


Table 8 Mean (SD) Pharmacokinetic Parameters for AC-279 in Subjects Receiving Two 17 mg Tablets or One 34 mg Capsule of Pimavanserin - Pharmacokinetic Analysis Set

Parameter	Reference Formulation (Two 17 mg Tablets) (N=40)	Test Formulation (One 34 mg Capsule) (N=39)
AUC_{0-t} (hr•ng/mL)	872 (246)	926 (273)
C_{max} (ng/mL)	4.46 (1.72)	4.58 (1.61)
T_{max} (h)[a]	12.0 (4.00, 144)	12.0 (4.00, 192)

Note: Subjects 001-030 and 001-074 were included in the descriptive statistics of the PK Analysis Set.

Figure 3 Mean (±SD) Plasma Concentration by Time Profiles of AC-279 in Subjects Following a Single 34 mg Oral Dose of Pimavanserin With Test Capsule Formulation (+SD) or Reference Tablet Formulation (-SD) in a Semi-Log Scale – Pharmacokinetic Analysis Set



- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

A total of 16 (40.0%) subjects had TEAEs, and 8 (20.0%) of these subjects experienced treatment-related TEAEs. Subjects treated with two 17 mg tablets had a higher incidence of treatment-related TEAEs than subjects treated with one 34 mg capsules (7 subjects [17.5%] versus 3 subjects [7.7%], respectively). All TEAEs were mild or moderate in severity. There were no deaths, SAEs, or TEAEs leading to early termination.

- **Conclusion:**

  - The test capsule formulation is bioequivalent to the reference tablet formulation of pimavanserin; these formulations may be used interchangeably at the same dose.
  - Pimavanserin 34 mg tablet and capsule formulations were shown to be generally safe and

well tolerated.

Reviewer's comments

1. *Study Design: This is a randomized, open-label, 2-period crossover study to evaluate the PK of pimavanserin and the significant circulating metabolite, AC-279, following administration of two 17 mg pimavanserin tablets (Treatment Formulation A) or one 34 mg pimavanserin capsule (Treatment Formulation B) after an overnight fast of approximately 10 hours in healthy subjects to assess the bioequivalence of the study treatments. T1/2 for pimavanserin and the active metabolite (AC-279) are approximately 57 hours and 200 hours, respectively. A 7-day washout period appeared long enough since there was a 14-day PK sampling and safety assessments following the first dose of pimavanserin prior to the 7-day washout period. The PK samples are sufficient to characterize the Cmax and AUC for all the active moieties. The overall design and study conduct were acceptable.*

2. *No major protocol deviations were reported for this study. Time deviation for PK blood draws were noted in 37 out of the 40 subjects in the PK analysis set. The deviation range from -0.2 to 2 hours. However, the majority (>90%) of the deviation occurs at 48 hours post-dose. Considering that the median Tmax of pimavanserin and AC-279 is about 6 (range 4-24) hours, this deviation is not expected to compromise PK evaluations. In addition, among the 37 subjects, 5 subjects missed one actual time point over the course of PK blood draws, respectively. Planned (nominal) sampling times were used as a*

   replacement for these missing time points. Therefore, missing data is not expected to affect overall PK evaluations.
3. *Data Analysis: A total of 40 subjects were randomized and treated. All randomized subjects completed treatment with two 17 mg pimavanserin tablets, and 39 subjects completed treatment with both pimavanserin formulations. A total of 38 (95.0%) subjects completed the study, and 2 (5.0%) subjects terminated the study early; of these 2 subjects, 1 from each treatment sequence group withdrew consent. PK analysis for the 17 mg tablet formulation was based on the available PK data from all 40 subjects while PK analysis for the 34 mg capsule formulation was based on the available PK data from 39 subjects. The overall PK results were not expected to be compromised by the discontinued subjects since the missing data only accounted for <5% of the overall PK dataset.*

4. *Based on the results, the 90% CIs for the geometric mean ratios for AUC0-tlast, AUC0-∞, and Cmax of the parent compound (pimavanserin) for the approved 2 × 17 mg tablets compared with the 1 × 34 mg capsule were all within the bioequivalence*

range of 80% to 125%. The Applicant's bioequivalence analysis excluded 2 subjects due to the reasons in table 6 below. However, when adding subject (b) (6) *back to the dataset, bioequivalence could still be established. Therefore, the exclusion of subject* (b) (6) *does not have significant impact on the bioequivalence conclusion.*

Table 9 Subjects Excluded from Primary Analysis of Bioequivalence for Pimavanserin

Subject	Period	PK Parameter	Reason for Exclusion
(b) (6)	1	C_{max}	Early withdrawal before end of Period 1
	1	AUC_{0-t}	Early withdrawal before end of Period 1
	1	$AUC_{0-\infty}$	Early withdrawal before end of Period 1
	1	C_{max}	Predose plasma concentration >5% of the Cmax in period 2 and %AUCext >20% in both periods
	1	AUC_{0-t}	Predose plasma concentration >5% of the Cmax in period 2 and %AUCext >20% in both periods
	1	$AUC_{0-\infty}$	Predose plasma concentration >5% of the Cmax in period 2 and %AUCext >20% in both periods
	2	C_{max}	Predose plasma concentration >5% of the Cmax in period 2 and %AUCext >20% in both periods
	2	AUC_{0-t}	Predose plasma concentration >5% of the Cmax in period 2 and %AUCext >20% in both periods
	2	$AUC_{0-\infty}$	Predose plasma concentration >5% of the Cmax in period 2 and %AUCext >20% in both periods

22.4.2 Population PK and/or PD Analyses

Objectives

- Refine a previous Pop PK model developed in healthy subjects for pimavanserin.
- Evaluate the DDI effect of ketoconazole on the pharmacokinetics of pimavanserin.
- Use clinical trial simulations to predict the probability that the exposures of 10 or 17 mg pimavanserin given with ketoconazole will be bioequivalent to the exposure of 34 mg pimavanserin given alone.

Model development

A previous base structural Pop PK model for Phase 1 data was used as the starting point for model development for Study ACP-103-023. This was a 1-compartment model with first-order absorption and linear apparent clearance. This model was refined to include evaluation of additional absorption models and various covariate relationships.

A 1-compartment model with sigmoid absorption, linear apparent clearance (CL/F), and an effect of ketoconazole on pimavanserin CL/F and relative bioavailability (F) adequately described the data. Clearance decreased by approximately 60% and F increased by approximately 35% with ketoconazole. The final parameter estimates and standard errors associated with the final Pop PK model are shown in Table 1. The model diagnostic plots are shown in Figure 1 and prediction-corrected visual predictive check (pc-VPC) by treatment are shown in Figure 2.

Using the final PopPK model, predicted exposures following a 34-mg single dose of pimavanserin with and without ketoconazole were calculated for each subject and compared against the results obtained from the NCA of the observed data from the clinical trial. The comparison is summarized in Table 2.

Clinical trial simulation

The final Pop PK model was used to generate 500 individual clinical trials to determine the probability of success of attaining BE between administration of 34 mg of pimavanserin alone compared with either 10 or 17 mg administered with ketoconazole. Day 1 and steady-state comparisons were made for trials simulated with a 3-treatment parallel design with the following dosing regimens:

Treatment A: Pimavanserin 34 mg (40-mg tartrate salt) dosed once a day for 60 days (n = 150)
Treatment B: Pimavanserin 10 mg (11.8-mg tartrate salt) dosed in combination with ketoconazole once a day for 60 days with both drugs dosed at the same time (n = 150)
Treatment C: Pimavanserin 17 mg (20-mg tartrate salt) dosed in combination with ketoconazole once a day for 60 days with both drugs dosed at the same time (n = 150)

Additional clinical trial simulations allowed for comparisons of exposure after steady-state dosing with 34 mg pimavanserin alone followed by dose reduction to 10 or 17 mg pimavanserin with concomitant administration of ketoconazole:
Treatment D: Pimavanserin 34 mg dosed once a day up to presumed steady state followed by dose reduction to 10 or 17 mg pimavanserin with concomitant administration of ketoconazole (n = 12).

Table 3 shows the mean GLSMs after steady state in each of these dosing scenarios for the simulated trials compared to the observed single-dose geometric means from Study ACP-103-023.

Bioequivalence assessment

Using simulated clinical trials, BE was assessed for dosing to steady state with 10 or 17 mg pimavanserin with ketoconazole (Test) when compared to 34 mg administered alone (Reference). Log-transformed Day 1 and steady-state exposures were analyzed to estimate geometric mean ratios of Test/Reference with 90% confidence intervals for each scenario. Results for the 500 simulated trials were summarized to assess the probability of concluding equivalence at steady state using the maximum observed drug concentration at steady state (Cmax,ss) and AUCtau for each of the scenarios of reduced pimavanserin dose administered with ketoconazole compared to 34 mg pimavanserin alone. Bioequivalence assessment was also made for the scenario where 34 mg pimavanserin was dosed to steady state and then the pimavanserin dose was reduced to 10 or 17 mg with ketoconazole. The results are summarized in Figure 3 and Table 4.

According to the Applicant, the simulated trials predict that on Day 1 the mean point estimates of geometric mean ratios for both Cmax and AUC0-24 are approximately 0.44 and 0.73 for the 10- and 17-mg pimavanserin dose regimen with ketoconazole (Treatment B and C), respectively, compared to 34 mg pimavanserin alone (Treatment A). For 10 mg pimavanserin plus ketoconazole, the simulated trials predict that, at steady state, mean point estimates of geometric mean ratios for both Cmax,ss and AUCtau are close to 1. In contrast, for 17 mg pimavanserin with ketoconazole, the mean ratios are close to 1.7. In the simulation of dose reduction after

steady-state dosing at 34 mg, the mean point estimates of geometric mean ratios for Cmax and AUC0-24 are approximately 0.91 and 0.93, respectively, for the 10-mg pimavanserin dose with ketoconazole and 0.99 and 1.01, respectively, for the 17-mg pimavanserin dose with ketoconazole.

The Applicant indicated that for both the 10- and 17-mg dose regimens (Treatment B and C, respectively) on Day 1 of dosing with ketoconazole, confidence intervals for both AUC0-24 and Cmax are predicted to fall entirely below the 0.8 to 1.25 boundaries. At steady state, the confidence intervals for both AUCtau and Cmax,ss for 10-mg pimavanserin dosing with ketoconazole fall entirely within the 0.8 to 1.25 boundaries, and for 17-mg pimavanserin dosing with ketoconazole, the confidence intervals for both parameters fall entirely above the 0.8 to 1.25 boundaries.

Reviewer's comments

During the NDA stage, several Pop PK models for pimavanserin were developed by the Applicant. This overall model development was a 3-stage process where Stage 1 focused on the PK in healthy subjects, Stage 2 focused on patients with Parkinson's who had an intensive sampling strategy, and Stage 3 focused on patients with Parkinson's and accompanying psychosis with a sparse sample design. Each previous stage (1 - 3) was built independently. Per the pharmacometrics review (DARRTS Date: 02/08/2016), data from 3 stages of the Applicant's analysis were merged together and analyzed by the Agency, and a side by side comparison of FDA PK model and Applicant's 3 stage PK model parameters were shown in Table 5. There are no major differences in model parameters other than covariates. The Applicant's model was deemed to provide a reasonable fit to the data.

In this report, the base Pop PK model for Phase 1 data (Stage 1) was used as the starting point, studies in this stage include single and multiple ascending dose studies with multiple samples per subject in healthy young subjects over a range of doses, with three formulations (solution, tablet, capsule), and with a food-effect crossover arm. The model in this report was refined using the data from healthy subjects in Study ACP-103-023 alone. The final 1-compartment model with sigmoid absorption, linear apparent clearance (CL/F), and an effect of ketoconazole on pimavanserin CL/F and relative bioavailability (F) appears adequately fit the data.

The final model was utilized to simulate 500 individual clinical trials to assess the probability of attaining BE using various dosing regimens. The simulation results were validated and consistent with the Applicant's analysis. The steady-state exposures (Cmax,ss and AUCtau) for 10 mg pimavanserin with ketoconazole are expected to be bioequivalent to exposures for 34 mg pimavanserin alone.

Table 10 Parameter Estimates and Standard Errors from the Pimavanserin Population Pharmacokinetic Final Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
CL/F: Apparent Central Clearance (L/hour)[a]	29.3	8.48	32.5 %CV	49.1
CL/F: Proportional Shift for Ketoconazole on CL/F (-)[a]	-0.602	3.38		
V_c/F: Apparent Central Volume of Distribution (L)	2050	4.99	20.3 %CV	29.5
KA: Absorption Rate Constant (1/hour)	1.63	30.4	NE	NA
D1: Duration of Zero-Order Absorption Process (hour)	6.29	5.40	NE	NA
F: Bioavailability (-)[a]	1.00	FIXED	NE	NA
F: Proportional Shift for Ketoconazole on F (-)[a]	0.349	10.6		
Residual Variability Proportional	0.0226	26.8	601 - 15.2 %CV[b] F [0.1 - 30]	NA
Residual Variability Additive	0.361	54.0		
Minimum value of the objective function = 1256.264				

Abbreviations: %CV, coefficient of variation expressed as a percentage; NA, not applicable; NE, not estimated; %SEM, standard error of the mean expressed as a percentage.

[a] Equations for the typical value of CL/F are as follows:

$$CL/F_i = 29.3 \times (1 - 0.602 \times KETO)$$

$$F_i = 1 \times 0.851 \times (1 + 0.349 \times KETO)$$

CL/F_i is the typical value of apparent clearance (L/hour) in the *i*th subject

F_i is the typical value of relative bioavailability in the *i*th subject and 0.851 is the bioavailability factor for the free base of pimavanserin

$KETO_i$ is an indicator variable for the concomitant administration of ketoconazole in the *i*th subject (1 = present, 0 = absent)

[b] The residual variability (%CV) was calculated using the following equation:
(SQRT(power(F,2)*0.0226+0.361)/F)*100

Source: d1pk\tables\doc\final-model-sigmoid_r166247.docx.

Table 11 Comparison of Observed and Predicted (Model-Based) Pimavanserin Exposure Measures for Study ACP-103-023: Single Dose

Exposure Measure	Statistic	34 mg Pimavanserin Alone		34 mg Pimavanserin + Ketoconazole	
		Observed n = 19	Model-based n = 19	Observed n = 19	Model-based n = 19
AUC_{inf} (ng × h/mL)	Mean[a] (SD)	1260 (443)	1200 (348)	3490 (782)	3530 (923)
	Median	1160	1180	3390	3460
	Minimum, Maximum	453, 2510	439, 2070	1460, 4680	1460, 5710
	N	19	19	19	19
AUC_{last} (ng × h/mL)	Mean[a] (SD)	1220 (433)	1200 (345)	3410 (768)	3390 (865)
	Median	1140	1170	3300	3250
	Minimum, Maximum	438, 2440	435, 2050	1450, 4580	1450, 5410
	N	19	19	19	19
C_{max} (ng/mL)	Mean[a] (SD)	17.1 (3.80)	15.7 (3.18)	25.1 (5.47)	22.3 (4.47)
	Median	16.2	14.8	24.0	20.6
	Minimum, Maximum	12.1, 25.8	11.1, 22.3	15.3, 40.0	16.0, 31.5
	N	19	19	19	19

Abbreviations: AUC_{inf}, area under the concentration-time curve from the time of drug administration (time 0) extrapolated to infinity; AUC_{last}, area under the concentration-time curve from the time of drug administration (time 0) to the time of the last non-zero concentration; C_{max}, maximum observed drug concentration; N, number of patients; SD, standard deviation.

[a] Arithmetic mean.

Subject (b) (6) was excluded from the summary statistics since the subject withdrew early and only had the first treatment in the sequence (34 mg pimavanserin, alone).

Table 12 Summary of Geometric Least Squares Means of Exposure Parameters for Observed and Simulated Trials

Parameter	Study ACP-103-023 Observed Single Dose Geometric Means (SD)[a]		Simulated Trials Steady-State Results (Mean of Geometric Least Squares Means [SD])[b]			Simulated Trials Dose Reduction at Steady-State Results (Mean of Geometric Least Squares Means [SD])[c,d,e]		
	34 mg Alone (N = 19)	34 mg With Ketoconazole (N = 19)	34 mg Alone	10 mg With Ketoconazole	17 mg With Ketoconazole	34 mg Alone	10 mg With Ketoconazole	17 mg With Ketoconazole
AUC (h × ng/mL)[f]	1182.5 (464)	3656.1 (912)	1159.57 (32.08)	1157.18 (31.63)	1961.34 (53.60)	1153.31 (108.71)	1074.44 (107.88)	1166.96 (109.15)
C_{max} (ng/mL)[g]	16.74 (3.80)	24.53 (5.47)	60.77 (1.63)	59.25 (1.63)	100.37 (2.77)	60.44 (5.54)	55.01 (5.57)	59.57 (5.63)

Abbreviations: AUC, area under the concentration-time curve; AUC_{inf}, area under the concentration-time curve from the time of drug administration (time 0) extrapolated to infinity; AUC_{tau}, area under the concentration-time curve from the time of drug administration (time 0) to the end of the dosing interval, τ; C_{max}, maximum observed drug concentration; $C_{max,ss}$, maximum observed drug concentration at steady state; SD, standard deviation.

[a] From Clinical Study Report; Table 14.3.8.2.

[b] Reference treatment is steady-state 34 mg pimavanserin; Test treatment is steady-state 10 mg or 17 mg pimavanserin + ketoconazole; Number of trials = 500; Number of subjects per trial = 150.

[c] Reference treatment is 34 mg pimavanserin alone dosed to presumed steady state; Test treatment is first dose 10 or 17 mg pimavanserin + ketoconazole after switching from 34 mg pimavanserin at presumed steady state; Number of trials = 500; Number of subjects per trial = 12.

[d] AUC_{tau} for Reference treatment and AUC_{0-24} for Test treatment.

[e] $C_{max,ss}$ for Reference treatment and C_{max} for Test treatment.

[f] For Study ACP-103-023, AUC is AUC_{inf} and for the simulated trials, AUC is AUC_{tau}.

[g] For Study ACP-103-023, C_{max} is Day 1 C_{max} and for the simulated trials, C_{max} is $C_{max,ss}$.

Table 13 Summary of Bioequivalence Confidence Intervals from Simulated Trials

Exposure Measure		Point Estimate			Lower 90% Confidence Limit			Upper 90% Confidence Limit		
		Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean (SD)	Min	Max
Day 1[a]	AUC_{0-24} 10 mg	0.437 (0.00162)	0.432	0.441	0.42 (0.00186)	0.416	0.427	0.454 (0.00189)	0.448	0.458
	AUC_{0-24} 17 mg	0.739 (0.00221)	0.733	0.746	0.711 (0.00265)	0.704	0.72	0.768 (0.00282)	0.758	0.776
	C_{max} 10 mg	0.438 (0.00212)	0.432	0.444	0.42 (0.00224)	0.414	0.429	0.455 (0.00246)	0.447	0.462
	C_{max} 17 mg	0.729 (0.00265)	0.721	0.737	0.701 (0.00294)	0.692	0.711	0.759 (0.00332)	0.748	0.768
Steady State[b]	AUC_{tau} 10 mg	0.998 (0.000675)	0.995	1	0.938 (0.00369)	0.922	0.947	1.06 (0.00361)	1.05	1.08
	AUC_{tau} 17 mg	1.69 (0.00119)	1.69	1.69	1.59 (0.00626)	1.56	1.61	1.8 (0.00612)	1.78	1.83
	$C_{max,ss}$ 10 mg	0.975 (0.00355)	0.964	0.985	0.917 (0.00514)	0.899	0.93	1.04 (0.00463)	1.02	1.05
	$C_{max,ss}$ 17 mg	1.65 (0.00604)	1.63	1.67	1.55 (0.00874)	1.52	1.58	1.76 (0.00782)	1.73	1.78
Dose Reduc -tion at Steady State[c]	AUC[d] 10 mg	0.931 (0.0238)	0.841	0.998	0.891 (0.0246)	0.809	0.958	0.973 (0.0266)	0.875	1.05
	AUC[d] 17 mg	1.01 (0.0247)	0.927	1.08	0.97 (0.0252)	0.891	1.05	1.06 (0.0278)	0.962	1.14
	C_{max}[e] 10 mg	0.91 (0.0318)	0.827	1	0.856 (0.0336)	0.765	0.968	0.968 (0.0348)	0.875	1.06
	C_{max}[e] 17 mg	0.986 (0.0333)	0.899	1.08	0.93 (0.0344)	0.842	1.04	1.05 (0.0369)	0.943	1.14

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; AUC_{tau}, area under the concentration-time curve from the time of drug administration (time 0) to the end of the dosing interval, τ; C_{max}, maximum observed drug concentration; $C_{max,ss}$, maximum observed drug concentration at steady state; Max, maximum; Min, minimum; SD, standard deviation.

[a] Reference treatment is single dose 34 mg pimavanserin; Test treatment is single dose 10 mg or 17 mg pimavanserin + ketoconazole; Number of trials = 500; Number of subjects per trial = 150.

[b] Reference treatment is steady-state 34 mg pimavanserin; Test treatment is steady-state 10 mg or 17 mg pimavanserin + ketoconazole; Number of trials = 500; Number of subjects per trial = 150.

[c] Reference treatment is 34 mg pimavanserin alone dosed to presumed steady state; Test treatment is first dose 10 or 17 mg pimavanserin + ketoconazole after switching from 34 mg pimavanserin at presumed steady state; Number of trials = 500; Number of subjects per trial = 12.

[d] AUC_{tau} for Reference treatment and AUC_{0-24} for Test treatment.

[e] $C_{max,ss}$ for Reference treatment and C_{max} for Test treatment.

Table 14 Comparison of FDA developed Pop-PK Model with Applicant's Model

		FDA Model	Sponsor's Model			
Theta	Description	Estimate	STAGE1	STAGE2	STAGE3.1	STAGE 3.2
1	CL/F	588	590 * $(WT/76)^{0.75}$	550* $(WT/75)^{0.75}$	587	588
2	V/F	2090	1850* $(WT/76)^{0.75}$	1897* (WT/75)	2021	2007
5	Absorption Rate	10.9	11.38	7.43	7.43 (FIX)	7.43 (FIX)
6	Absorption Lag	0.0268	0.0138	0.07	0.07 (FIX)	0.07 (FIX)
	Covariates	WT ~V LBM ~CL CrCl ~CL			Height ~CL Age ~CL	Height ~ CL CrCL~CL
Omega						
1,1	IIV of CL/F	0.149	0.052	0.112	0.153	0.149
2,2	IIV of V1/F	0.036	0.01	0.0193	0.282	0.29
3,3	IIV of KA	0.33	0.237	0.296	---	---
4,4	IIV of ALAG	0.0309	0.132	0.115	---	---
Sigma						
1,1	Proportional component of error	0.0175	0.0298	0.0142	0.0186	0.0186
2,2	Additive component of error	16	0.126	0.491	30.72	30.689

Source: FDA's Pharmacometrics Review, Table 10, Page 27

Figure 4 Goodness-of-Fit Plots for Final Population Pharmacokinetic Model for Pimavanserin

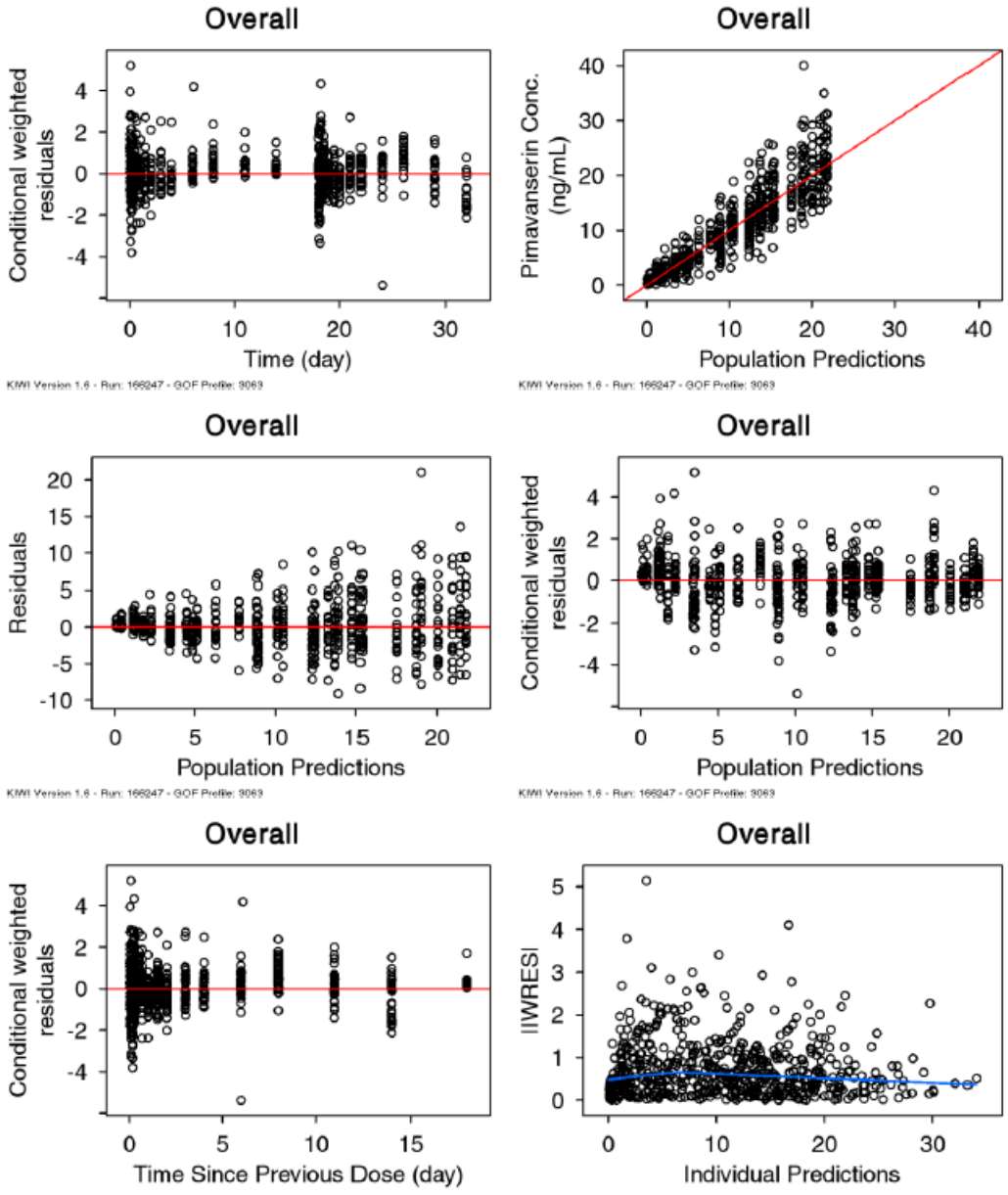


Figure 5 Prediction-Corrected Visual Predictive Check by Ketoconazole Treatment

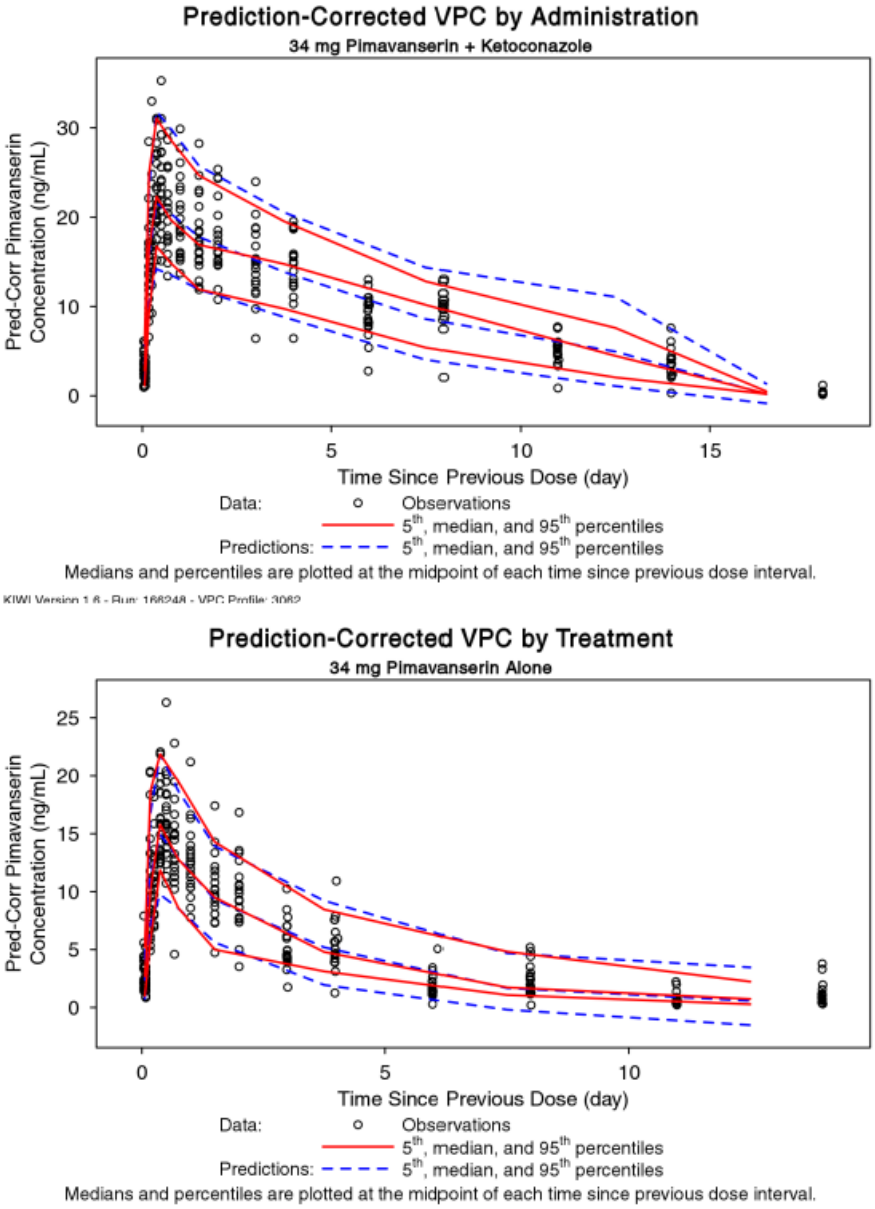
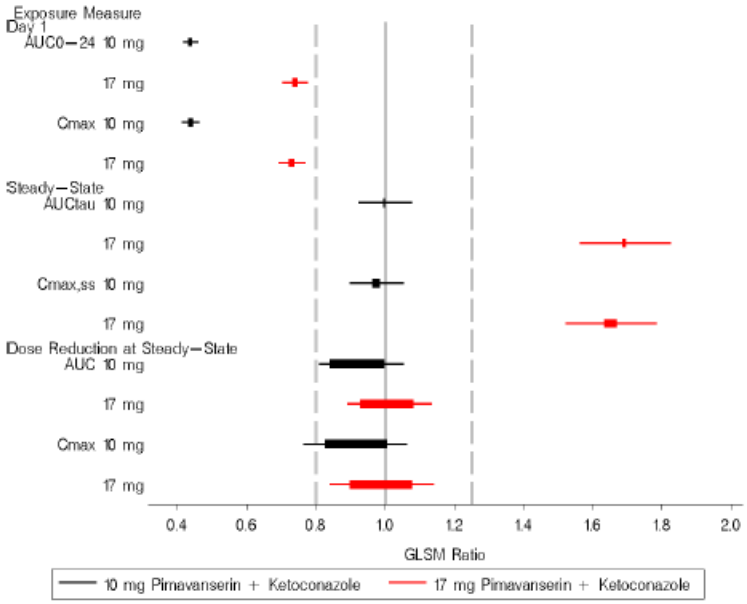


Figure 6 Geometric Least Squares Mean Ratios With Corresponding 90% Confidence Intervals: Statistical Analysis of Treatment With and Without Ketoconazole (Bioequivalence Results From Simulated Clinical Trials)



Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; AUC_{tau}, area under the concentration-time curve from the time of drug administration (time 0) to the end of the dosing interval, τ; C_{max}, maximum observed drug concentration; $C_{max,ss}$, maximum observed drug concentration at steady state; GLSM, geometric least squares mean.
Note: Day 1: Reference treatment is single dose 34 mg pimavanserin; Test treatment is single dose 10 mg or 17 mg pimavanserin + ketoconazole; Number of trials = 500; Number of subjects per trial = 150.
Note: Steady State: Reference treatment is steady-state 34 mg pimavanserin; Test treatment is steady-state 10 mg or 17 mg pimavanserin + ketoconazole; Number of trials = 500; Number of subjects per trial = 150.
Note: Dose Reduction at Steady-State: Reference treatment is 34 mg pimavanserin alone dosed to presumed steady state; Test treatment is first dose 10 or 17 mg pimavanserin + ketoconazole after switching from 34 mg pimavanserin at presumed steady state; Number of trials = 500; Number of subjects per trial = 12. AUC is AUC_{tau} for reference treatment and AUC_{0-24} for test treatment; C_{max} is $C_{max,ss}$ for reference treatment and C_{max} for test treatment.
Dashed gray lines represent the bioequivalence criteria limits of 0.8 and 1.25.
For each parameter, horizontal bars mark the minimum lower confidence limit and maximum upper confidence limit for the ratio; vertical bars represent the range of ratio point estimates.

22.4.3 Summary of Bioanalytical Method Validation

Study ACP-103-023

Analyte		ACP-103	AC-260279
Method		LC/MS/MS	LC/MS/MS
Matrix		Plasma	Plasma
Calibration	Range	0.100 – 100 ng/mL	0.500 – 500 ng/mL
	#Conc	8	8
	%CV	2.2 – 3.7	2.4 – 7.5
	%Bias	-4.0 – 4.0	-5.0 – 4.4
	R2	0.9970 – 0.9991	0.9972 – 0.9979

Quality Control	Range	0.100 – 80 ng/mL	0.500 – 400 ng/mL
	#Conc	5	5
	%CV	0.0 – 2.3	0.0 – 3.2
	%Bias	3.9 – 7.0	1.0 – 4.7
Performance		Acceptable	Acceptable

22.4.4 Office of Study Integrity and Surveillance (OSIS) Bioequivalence Site Inspection Report

MEMORANDUM

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

DATE: 12/1/2017

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210793

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below and the outcome of the inspections was classified as No Action Indicated (NAI). OSIS is notifying the review division that a dosing error was observed at Vince and Associates under the previously inspected BLA 761039. The clinical investigator (Dr. Martin Kankam, M.D., Ph.D.) who conducted the clinical portion of the study under BLA 761039 is the same investigator conducting the clinical portion of the current study.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Vince & Associates Clinical Research	10103 Metcalf Avenue, Overland Park, KS.
Analytical	(b) (4)	

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/s/

SHILA S NKAH
12/01/2017

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JASMEET K KALSI
06/27/2018

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06/27/2018
Clinical Reviewer: NDA 207318, S-003

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06/28/2018

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06/28/2018

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	210793
Supporting document/s:	SDN 1
Applicant's letter date:	8/31/17
CDER stamp date:	8/31/17
Product:	Nuplazid (pimavanserin) 34 mg capsule
Indication:	Treatment of hallucinations and delusions associated with Parkinson's disease psychosis
Applicant:	Acadia Pharmaceuticals, Inc.
Review Division:	Psychiatry Products
Reviewer:	Amy M. Avila, PhD
Supervisor/Team Leader:	Aisar Atrakchi, PhD
Division Director:	Mitchell Mathis, MD
Project Manager:	Jasmeet (Mona) Kalsi, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210793 are owned by Acadia or are data for which Acadia has obtained a written right of reference.
Any information or data necessary for approval of NDA 210793 that Acadia does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210793.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Acadia Pharmaceuticals has submitted a new NDA for a new dosage form of pimavanserin, a 34 mg capsule. NUPLAZID® (pimavanserin) 17 mg tablets was approved on April 29, 2016 under NDA 207318 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis to be administered as two 17 mg tablets for a maximum daily dose of 34 mg.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted.

1.3 Recommendations

1.3.1 Approvability

The NDA is approvable from a nonclinical standpoint.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

None for nonclinical

2 Drug Information

2.1 Drug

CAS Registry Number: 706782-28-7

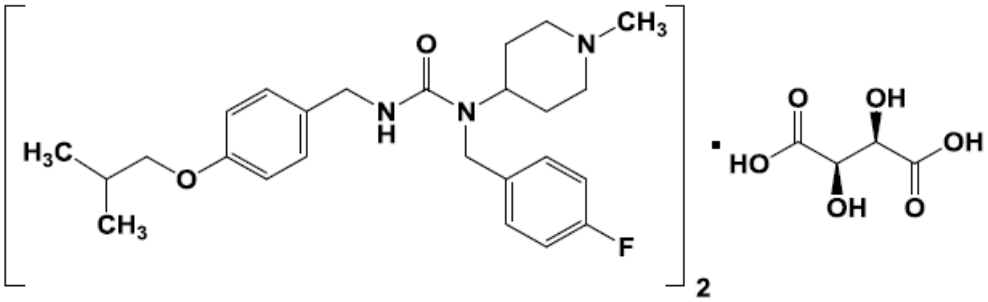
Generic Name: Pimavanserin tartrate

Code Name: ACP-103

Chemical Name: Urea, N-[(4-fluorophenyl) methyl]-N-(1-methyl-4-piperidinyl)-N'-[[4-(2-methylpropoxy)phenyl]methyl]-,(2R,3R)-2,3-dihydroxybutanedioate (2:1)

Molecular Formula/Molecular Weight: $(C_{25}H_{34}FN_3O_2)2{\cdot}C_4H_6O_6$ (pimavanserin tartrate): 1000.5 g/mol; $C_{25}H_{34}FN_3O_2$ (pimavanserin): 427.55 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Atypical antipsychotic (Serotonin receptor 2A (5-HT2A) inverse agonist)

2.2 Relevant INDs, NDAs, BLAs and DMFs

The Applicant is cross-referencing NDA 207318 for Nuplazid (pimavanserin) 17 mg tablets that was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis on April 29, 2016.

2.3 Drug Formulation

Table 2.3.P.1–1 Composition of Pimavanserin Capsules, 34 mg

Component	Function	Quality Standard	Quantity Per Capsule	
			mg/Capsule	% w/w
Pimavanserin tartrate	Active ingredient	In-house	40.0[a]	40.0
Microcrystalline cellulose	(b) (4)			
Magnesium stearate				
				(b) (4)
HPMC capsule shell	(b) (4)	In-house		(b) (4)
Total				

NF = National Formulary; NA = Not applicable

[a] 40 mg of pimavanserin tartrate salt is equivalent to 34 mg of pimavanserin free base.

[b] Typical average weight of an empty capsule shell is indicated. HPMC capsule shells are composed of hypromellose (HPMC), titanium dioxide, yellow iron oxide, FD&C blue #1, and black iron oxide.

[Excerpted from Quality Overall Summary section of NDA submission.]

2.4 Comments on Novel Excipients

There are no novel excipients. The 34 mg capsules contain inactive ingredients that are a subset of the same ingredients present in the 17 mg tablets, with the addition of an HPMC capsule shell.

2.5 Comments on Impurities/Degradants of Concern

The same drug substance will be used to manufacture the 34 mg capsules. The proposed specifications for impurities and degradation products in the 34 mg capsules

are the same as those for the approved 17 mg tablets. There are no new impurities or degradation products in the 34 mg capsules compared to the approved 17 mg tablets. Therefore, there are no concerns from a nonclinical standpoint regarding impurities/degradants in the 34 mg capsules. Refer to the nonclinical review of the 17 mg tablets from the original NDA 207318.

Degradation Products (b) (4)	The proposed acceptance criterion of NMT (b) (4)% w/w for (b) (4) in drug product specification takes into account the potential amount of (b) (4) present in the drug product at release and potential growth in (b) (4) amount over proposed shelf life.
Each Individual unspecified	An acceptance criterion of NMT (b) (4)% w/w for each individual unspecified degradation product is consistent with the identification threshold permitted in the ICH Q3B(R2) guideline based for a drug product with daily dose of 34 mg.
Total Specified and Unspecified	The proposed acceptance criterion of NMT (b) (4)% w/w for total specified and unspecified impurities is based on the acceptance criteria of NMT (b) (4)% w/w for (b) (4) and (b) (4)% w/w for individual unspecified degradation product.

[Excerpted from the Quality Overall Summary section of NDA submission.]

2.6 Proposed Clinical Population and Dosing Regimen

The clinical population for the 34 mg capsules of Nuplazid is the same as that for the approved 17 mg tablets: patients with Parkinson's disease psychosis (for the treatment of hallucinations and delusions).
Recommended dose is a single 34 mg capsule taken orally once daily, without titration.

3 Studies Submitted

No nonclinical studies were submitted with this application.

11 Integrated Summary and Safety Evaluation

This NDA is for the introduction of a new immediate release, solid oral dosage form of Nuplazid, specifically, a capsule containing 34 mg of pimavanserin (equivalent to 40 mg pimavanserin tartrate).
No nonclinical studies were submitted, or recommended from the Division, to support the safety of the 34 mg capsules. There are no safety concerns, from a nonclinical standpoint, with the 34 mg capsules of Nuplazid (pimavanserin tartrate).

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/s/

AMY M AVILA
04/11/2018

AISAR H ATRAKCHI
04/11/2018