CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207318Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA:	207318
Related IND:	68384
Generic Name:	Pimavanserin
Trade Name:	Nuplazid®
Strength:	20 mg Immediate Release Tablet
Sponsor:	Acadia
Indication:	Parkinson Disease Psychosis
Submission Type:	Original NDA- NME
Priority Classification:	Priority
Submission Date:	9/01/15
OCP Division:	DCP1
OND Division:	DPP
Review Team:	Kofi Kumi, Di Zhou, Kevin Krudys, Hao Zhu

Background

Pimavanserin is metabolized by CYP3A4. The sponsor did not conduct a dedicated study that evaluated the effect of CYP3A4 inducers on the exposure of Pimavanserin when the inducers are co-administered with CYP3A4 inducers. However, the sponsor conducted a population pharmacokinetic (PopPK) analysis that evaluated the effect of inducers on the clearance of pimavanserin.

The results of the PopPK analysis suggested that when you pooled all patients who took an inducer (N=15) compared to those who did not take inducer or inhibitor (N= 312) in the Phase 3 safety and efficacy trials (Studies ACP-103- 012, 014, 020), no relationship between inducers and apparent clearance of pimavanserin was observed. However, PopPK analysis using data from only patients in the pivotal safety and efficacy (ACP-103-020) who took inducers (N=6) compared to those who did not take no inducer or inhibitor (N=70) showed an effect on clearance (p=0.033) of pimavanserin. Clearance of Pimavanserin increased in these patients (Figure 1).

Reviewer Comment

To address the issue of the probability of decreased exposure to pimavanserin when it is administered with CYP3A4 inducer, a statement is included in the proposed label stating that when pimavanserin is taken with CYP3A4 inducers, exposures may decrease and an increase in pimavanserin dose may be needed. Frequent monitoring for efficacy is recommended.

Since a maximum dose cannot be recommended based on the PopPK analysis and the concern that there may be decrease in exposure which could lead to reduction in efficacy when

pimavanserin is taken with CYP3A4 inducer, a study to evaluate the effect of strong CYP3A4 inducer is being recommended as a Phase IV Commitment. This will inform the recommendation for a maximum dose to be taken when pimavanserin is co-administered with CYP3A4 inducer if a dose adjustment is needed.

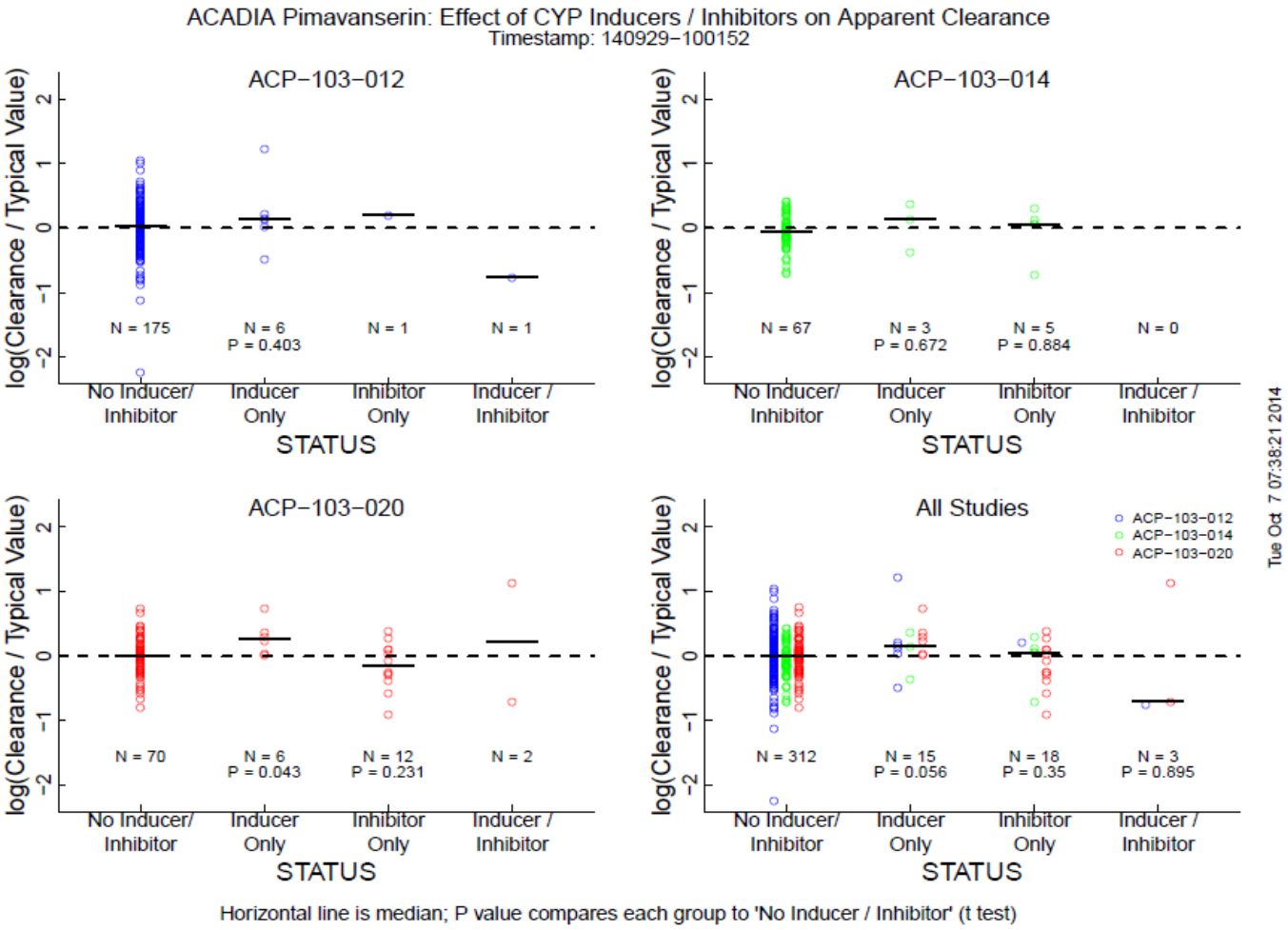
PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☒ PMC ☐ PMR	Magnitude of change in exposure when pimavanserin is co-administered with strong CYP3A4 inducers	Pimavanserin is metabolized by CYP3A4. Coadministration of CYP3A4 inducer would result in a decrease in the exposure to pimavanserin which could lead to reduced efficacy	(b) (4)

/s/: Kofi A. Kumi, Ph.D., Clinical Pharmacology Reviewer

RD/FT Initialed by: Hao Zhu, Ph.D., Team Leader, Clinical Pharmacology

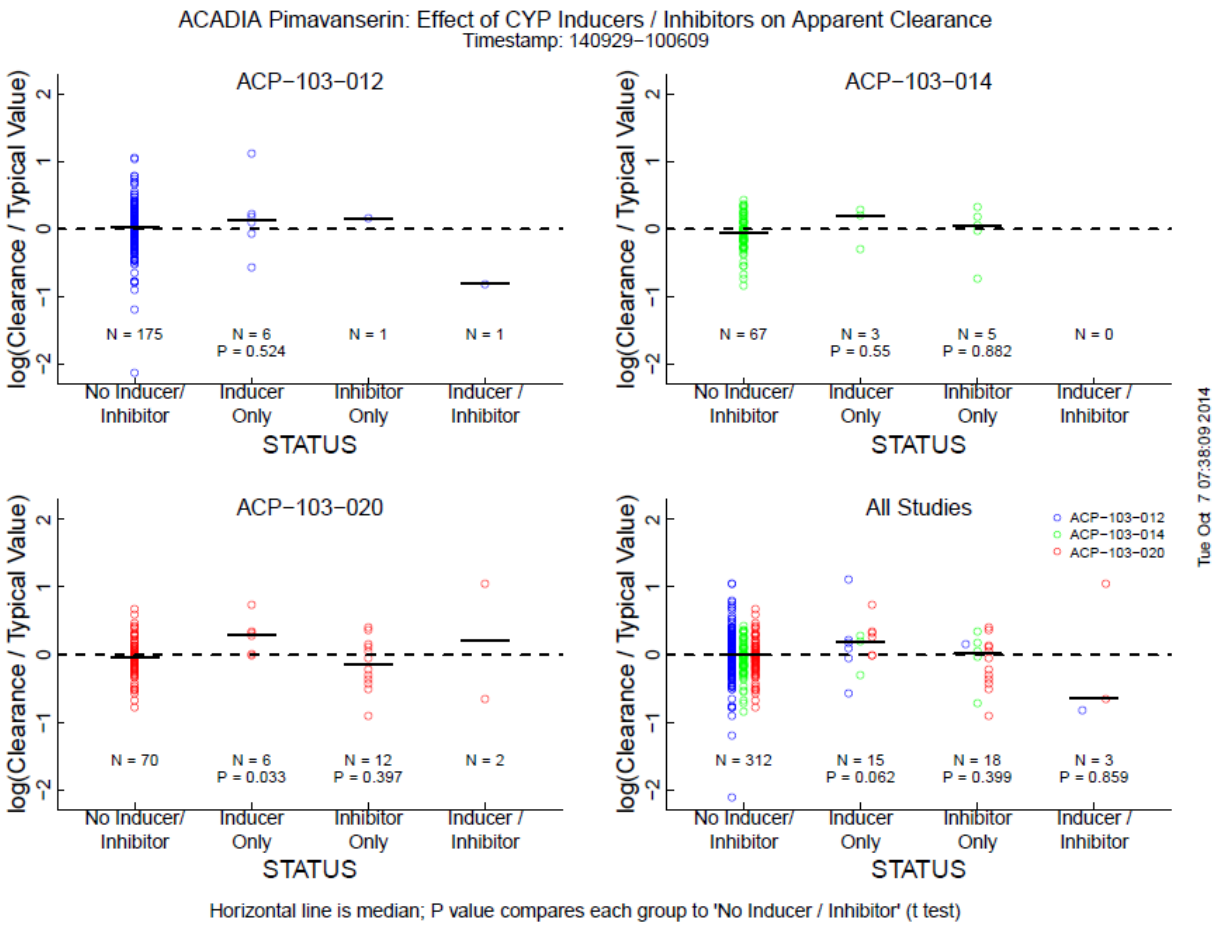
FT Initialed by: Mehul Mehta, Ph.D., Division Director, DCP1/OCP

Attachment: Figure 1



Appendix 11.21. Studies ACP-103-012, ACP-103-014, ACP-103-020: Evaluation of Drug-Drug Interaction for Optimal Model with Covariates Height and Age

Source: Sponsor's Population Pharmacokinetic analysis report



Appendix 11.22. Studies ACP-103-012, ACP-103-014, ACP-103-020: Evaluation of Drug-Drug Interaction for Optimal Model with Covariates Height and Creatinine Clearance

Source: Sponsor's Population Pharmacokinetic Report

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/s/

KOFI A KUMI
04/27/2016

HAO ZHU
04/27/2016

MEHUL U MEHTA
04/27/2016

Clinical Pharmacology Review

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1.0 Executive Summary

The sponsor submitted an original New Drug Application (NDA) for Pimavanserin Tartrate tablets for the treatment of Psychosis associated with Parkinson's disease (PDP). Pimavanserin currently holds a breakthrough designation and is under priority review. There is currently no approved drug for the treatment of PDP. However, clozapine, an atypical antipsychotic, is reported to have shown efficacy in PDP patients in a randomized, PDP trial and is used off-label. Quetiapine, another atypical antipsychotic, is also used off-label to treat PDP patients. Pimavanserin is a selective and potent serotonin 5-HT2A receptor inverse agonist. Pimavanserin Tartrate has been developed as 20 mg (17 mg pimavanserin) immediate release solid oral dosage formulation. A once-daily oral dose of 40 mg pimavanserin tartrate (34 mg pimavanserin) is the intended dose for the treatment of PDP and will be administered as 2 of the 20 mg strength. The clinical development program included four placebo-controlled studies in subjects with PDP which were conducted to evaluate the safety and efficacy of pimavanserin at once-daily doses of 10, 20, 40 or 60 mg over a 4-6 week treatment period. The submission contained one pivotal Phase 3 safety and efficacy trial in PDP patients. The pivotal trial (ACP-103-020) was a placebo-controlled, double-blind study that evaluated the safety and efficacy of 40 mg of Pimavanserin tartrate versus placebo in patients with psychosis associated with Parkinson's disease. Nine pharmacokinetic studies, population pharmacokinetic and exposure-response analysis reports, 3 Pharmacodynamic studies and 31 in vitro studies were included in the submission. The pharmacokinetic studies included a relative bioavailability, food effect, mass balance, single and multiple doses, drug-drug interaction studies. The proposed commercial drug product and Phase 3 clinical trial material are the same except for product identifiers (tablet deboss impression) (b) (4) The key issues addressed in this review are 1) whether exposure-response relationships for efficacy and safety support the proposed dosing regimen of 40 mg Pimavanserin tartrate (34 mg pimavanserin) daily, 2) Recommendations for appropriate use of the formulation, 3) Recommendations for dosing in patients with renal and hepatic impairment, 4) Recommendations for dosing with strong inhibitors of CYP 3A4 and 5) whether pimavanserin prolong the QT/QTc interval. The Office of Clinical Pharmacology (OCP) key findings are summarized as follows:

- The proposed dosing regimen of 40 mg Pimavanserin tartrate once daily is acceptable
- Pimavanserin Tartrate can be taken with or without food. Pimavanserin Tartrate immediate release tablets can be crushed for immediate use.
- Pimavanserin dose should be reduced to one-half the recommended dose when co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir). Ketoconazole increased Pimavanserin Cmax and AUC by 1.5- and 3- fold, respectively

- No dose adjustment is recommended for patients with mild or moderate renal impairment. Pimavanserin is not recommended to be used in patients with severe renal impairment (CrCl < 30 mL/min).

- Pimavanserin is not recommended to be used in patients with hepatic impairment. Pimavanserin is eliminated via hepatic metabolism but the effect of hepatic impairment on its exposure has not been studied.

- Dose adjustment is not recommended based on weight, height, age and gender. Population pharmacokinetic analysis did not indicate significant difference in exposure in these covariates.

- Pimavanserin is expected to increase the QT/QTc interval by about 8 ms at the 40 mg dose with a 90% CI of 6.4 ms to 9.1ms.

Below are the general pharmacokinetics and biopharmaceutics features of Pimavanserin.

- Relative bioavailability of Pimavanserin Tartrate with pimavanserin oral solution as a reference is 99.7%.

- The proposed commercial Pimavanserin tartrate 20 mg tablets and the Phase 3 clinical trial materials are the same except for product identifiers (tablet deboss impression) (b) (4)

- Pimavanserin pharmacokinetics is proportional to dose between 20 and 300 mg after single dose administration.

- The elimination half-life of pimavanserin and its active metabolite, AC-279 are about 57 and 200 hours, respectively. Accumulation ratio was between 3.5 and 5.8.

- AC-279 accounts for approximately 5% of administered dose circulating in plasma.

- Protein binding is about 91 -97% and approximately less than 2% is excreted in urine or feces as the unchanged compound.

- Pimavanserin is a substrate of CYP3A, but not an inducer of major CYP enzymes.

- Pimavanserin is neither a substrate nor inhibitor of OATP1B1 or OATP1B3, P-gp, BCRP, OCT2, OAT1, OAT3

- AC-279 is not expected to have inhibitory or induction effect of major CYP enzymes.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information submitted in NDA 207318 and there are no significant issues with Clinical Pharmacology aspect of pimavanserin application and would support approval of pimavanserin. However due to concern about acceptability of the risk to benefit ratio, OCP would defer to the Medical Team's decision on the approvability or non-approvability of pimavanserin for the treatment of psychosis associated with Parkinson's Disease. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendations and Comments
Overall	☐ Yes ☐ No ☒ NA	Pending labeling and medical's risk and benefit assessment.
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	One pivotal safety and efficacy trial in combination with 1 other safety and efficacy study
Proposed dose for general PDP patient population	☒ Yes ☐ No ☐ NA	The proposed starting dose of 40 mg daily

Proposed dose adjustment in specific patients or patients with co-medications	☒ Yes ☐ No ☐ NA	Recommendations: Pimavanserin dose should be reduced to one-half when co-administered with CYP3A4 strong inhibitors (e.g. ketoconazole, ritonavir). (b) (4) Not recommended for patients with hepatic impairment Dose adjustment in mild and moderate renal impaired patients is not recommended. Pimavanserin is not recommended for patients with severe renal impairment (CrCl < 30 mL/min). Because a dedicated study has not been conducted (b) (4) (b) (4)
Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	The to-be-marketing and clinical trial formulations are the same except for product identifiers (tablet deboss impression) (b) (4)
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor.

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1.2 Post Marketing Studies

Office of Clinical Pharmacology proposes the following post-marketing requirements

PMC or PMR	Key Drug Development Question	Rationale	Design Summary
PMR	Is dose adjustment needed for Hepatic Impaired Patients	Pimavanserin is primary eliminated by hepatic metabolism. Therefore, hepatic impairment could affect the exposure levels of pimavanserin	(b) (4)

			(b) (4)
PMR	Is dose adjustment needed for severe renal impairment patients	Pimavanserin is eliminated primary by hepatic metabolism. However, the existing data appear to suggest certain level of exposure increase in patients with severe renal impairment. Therefore, evaluation of whether severe renal impairment affects the elimination of pimavanserin would enable recommendation of dose adjustments, if any, in this patient population	

1.3 Labeling Recommendations

Pimavanserin dose should be reduced to one-half the recommended dose when co-administered with CYP3A4 strong inhibitors (e.g. ketoconazole, ritonavir).

Not recommended for patients with hepatic impairment because studies have not been conducted in this patient population

Dose adjustment is not recommended in patients with mild or moderate renal impairment. Pimavanserin is not recommended for patients with severe renal impairment (CrCl < 30 mL/min) because studies have not been conducted in this patient population.

Pimavanserin Tartrate can be administered with or without food

1.4 Summary of Clinical Pharmacology and Biopharmaceutic Findings

Pimavanserin is a selective, potent serotonin 5-HT2A receptor inverse agonist. Pimavanserin Tartrate has been developed as a solid oral dosage form (immediate release tablet) for once-daily dosing in humans.

Biopharmaceutics

The relative bioavailability of pimavanserin after administration of Pimavanserin Tartrate oral tablet with Pimavanserin oral solution as a reference is about 99.7%. Administration of Pimavanserin Tartrate with food (55 g fat, 33 g protein, and 58 g carbohydrate) did not have a significant effect on pimavanserin exposure, but median Tmax was prolonged by about 4 hours. The difference in median Tmax is not expected to be clinically relevant.

Table 1: Statistical analyses of pharmacokinetic parameters

Treatment	Cmax (ng/mL)		AUC 0-∞ (ng*h/mL)		AUC 0-z (ng*h/mL)	
	Ratio (%)	90% CI	Ratio (%)	90% CI	Ratio (%)	90% CI
Tablet Fasted/ Solution	110.5	100.5-121.4	99.7	90.9–109.4	101	92.7–110.1
Tablet Fed/ Tablet Fasted	91.1	82.9-100.1	108.3	98.7–118.0	108.1	99.2–117.9

Source: Study ACP-103-001

The proposed commercial pimavanserin tartrate 20 mg tablets (containing 17 mg of pimavanserin base) and the Phase 3 clinical trial materials are the same except for product identifiers (tablet deboss impression) (b) (4)

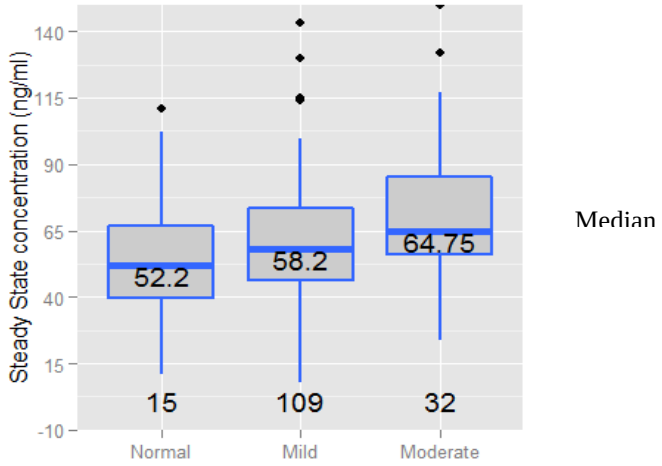
Effect of Intrinsic Factors

Renal: The effect of renal impairment on the pharmacokinetics of pimavanserin has not been studied. Evaluation of exposure in renal impaired patients who participated in the pivotal efficacy and safety study indicated there is not a clinically relevant difference in exposure between patients with mild and moderate renal impaired patients and those who did not have renal impairment (Figure 1). Furthermore, most patients enrolled in the clinical studies had mild

or moderate renal impairment, so most of the safety database is in a population with some degree of renal impairment.

Univariate comparison of steady state plasma concentration of normal population versus mild or moderate renal impaired population showed there are a 10% increase in mild and 20% increase in moderate renal impaired patients

Figure 1: Steady-State Pimavanserin Concentration in Different Groups of Renal Function in North American subjects



The change of pimavanserin concentration in patients with severe renal impairment is unclear at present. Mechanistically, we do not expect a substantial increase in pimavanserin exposure in severe renal impaired patients because pimavanserin is primarily metabolized by CYP3A4 and less than 1% of pimavaserin, which is likely readily absorbed, was identified in urine. However, Figure 1 suggested a correlation between decrease in renal function and increase in pimavanserin exposure. Population PK analysis also identified a relationship between creatinine clearance and pimavanserin clearance. Consistent with the observed trend, approximately 50% increase in pimavanserin exposure as compared to the mild renal impairment patients (Table 2) has been observed in limited patients (n=4) with borderline severe renal impairment (patients' creatinine clearance levels are slightly below 30 mL/min). This level of change in exposure, even though from patients with better renal function than that of a typical severe renal impairment patient, is approaching the general threshold for potential dosage adjustment with the caveat that the observed data are associated with uncertainty due to factors such as limited samples size.

It should be noted that the patient population is elderly with late stage Parkinson's disease and with a short expected life span (a few months to 1 to 2 years). There is a potential for confusion and sedation in this general patient population. For this patient population with severe renal impairment, the internal environment is expected to be further compromised (e.g., electrolyte imbalance). The existing data appear to suggest some concerning safety signals, such as higher mortality rate, QTc interval prolongation, etc. associated with the treatment of pimavanserin in mild to moderate renal impairment patients. In severe renal impairment patients, the safety profile may be worsening due to changes in internal environment and we do not have sufficient

experience in this population. Therefore, in severe renal impaired patients, until additional data on exposure are available, it is prudent not to use pimavanserin in severe renal patients.

Table 2

Pimavanserin Steady State Concentration in patients with severe renal impairment in the clinical safety and efficacy trials

Subject ID	Study	Dose (mg)	CrCl (Cockcroft-Gault) [mL/min]	Steady State Concentration Normalized to 40 mg (ng/mL)
003-003	012	10	23	74
026-101	012	10	29	84
129-005	012	10	28	112
314-104	020	40	26	85
Mean from severe RI Patients				89

Hepatic: Since the effect of hepatic impairment has not been studied and mass balance studies indicated metabolism is the major route for elimination, the use of pimavanserin in hepatic impaired patients is not recommended.

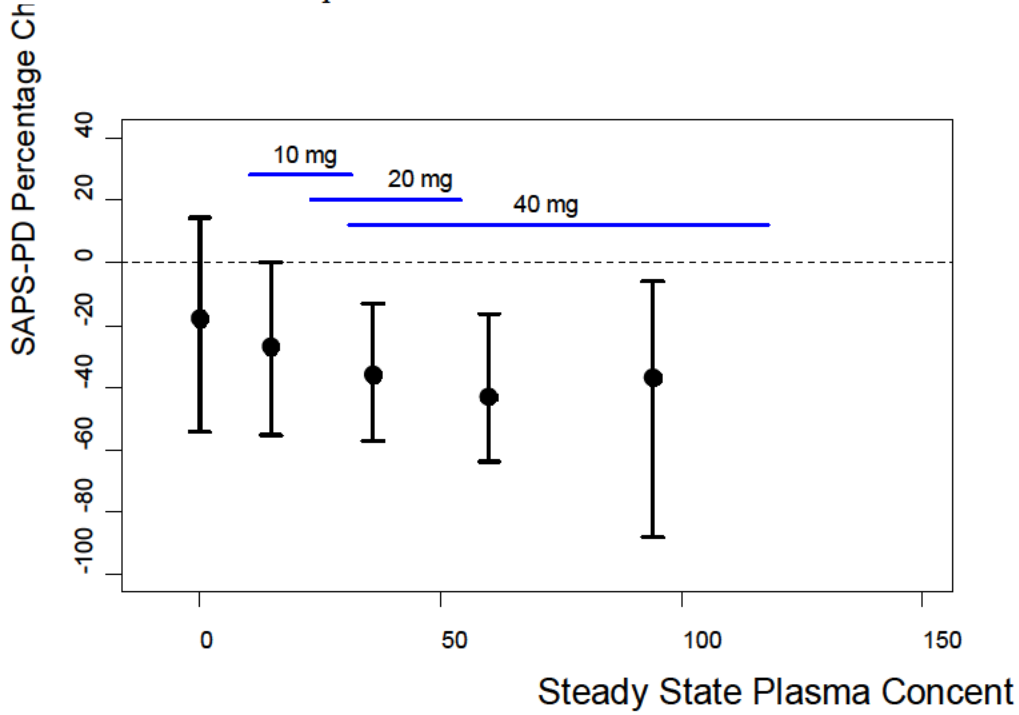
Effect of Extrinsic Factors (Drug-Drug Interactions)
Cytochrome P450 (CYP) 3A4 is the major enzyme responsible for the biotransformation of pimavanserin. Ketoconazole increased plasma Cmax of pimavanserin approximately 1.5-fold and increased AUC (0-∞) by about 3-fold. Dose adjustment to ½ the recommended dose based on the available strength is suggested.

Exposure-Response (E-R)

E-R relationship showed that the sponsor's proposed dose of 40mg QD has greater percentage change from baseline in SAPS-PD score compared with lower doses (10 mg QD, 20 mg QD). Final results were generalized as SAPS-PD percentage change from baseline (Figure 2). Based on the available data, further increase in the dose to levels greater than 40 mg appear unlikely to result in an increase in efficacy.

The four kinds of adverse event (hallucinations, confusion, edema, and gait disturbance) were not found to be correlated pimavanserin concentration. The two System Organ Class (SOC) with the highest incidence of Treatment Emergent Adverse Events (TEAE) were nervous system and psychiatric disorders. The most common nervous system TEAEs were dizziness, headache, and somnolence. Within the psychiatric disorders SOC, confusional state, hallucination, and insomnia were the most common adverse events reported. Within the gastrointestinal disorders SOC, the incidences of TEAEs of nausea, constipation, and diarrhea were the most common.

Figure 2: SAPS-PD Percentage Change from Baseline vs. Steady State Plasma Concentration at 6 Weeks in North American Population



Vertical line and label in X axis represent cutoff of four exposure quartiles; points and error bar represent median and 25%-75% percentiles of the observed percentage change from baseline in placebo group and each exposure quartile; blue horizontal lines and label on the top represent 5%-95% percentile of steady state plasma concentration at each dose level. Dashed line represents no change compared with baseline SAPS-PD score. (N_{pl}=150, N_{10mg}=50, N_{20mg}=15, N_{40mg}=109)

An increase of about 8 ms in the QT/QTc interval is expected at 40 mg pimavanserin with a 90% CI of 6.4 ms to 9.1ms. Sponsor included doses of 20 mg and 80 mg in their thorough QT study, but not a 40 mg dose. Pimavanserin 20 mg had no clinically meaningful effect on the QTc interval. The point estimates were 6.6 ms and the upper bound of the CI did not exceed 10.0 ms. Pimavanserin 80 mg dose was associated with a time-matched maximal mean corrected QT interval (QTcI) increase of 10.7 ms and an upper CI of 13 ms. Pimavanserin 40 mg was predicted to prolong the QTc with a mean of 7.8 and an upper 90% CI of 9.1 ms.

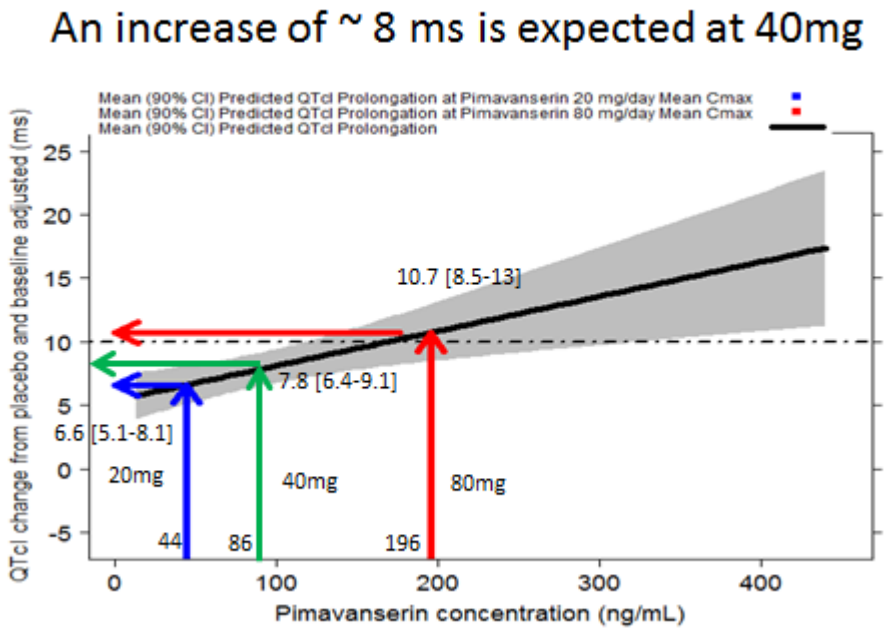


Figure 3: A single regression linear model was used to describe the data.

Absorption, Distribution, Metabolism and Excretion (ADME)

Absorption

- Extensively absorbed (>98%) after oral administration
- Relative BA (tablet to solution): 99.7%
- Tmax: 6 hours
- Dose proportional between 20 to 300 mg
- No significant effect of food

Distribution

- Protein Binding: 91% - 97%
- Volume of Distribution: 2021L

Metabolism

- CYP3A4/5 major enzyme involved in metabolism
- Metabolized to N-Desmethyl pimavanserin (AC-279), active metabolite and other minor metabolites

Excretion

- Metabolism primary route of elimination
- Low levels of unchanged pimavanserin excreted in urine (0.55%) or feces (1.53%)
- Primary excreted via feces
- Approximately 46% (mean 45.5% ± 4.5%) of radioactive dose excreted in feces and 23% (mean 23.1 ±3.3%) excreted in urine.
- Terminal T ½ is about 57 hours for pimavanserin and 200 hours for active metabolite, AC-279

2.0 Question Based Review (QBR)

2.1 General Attributes

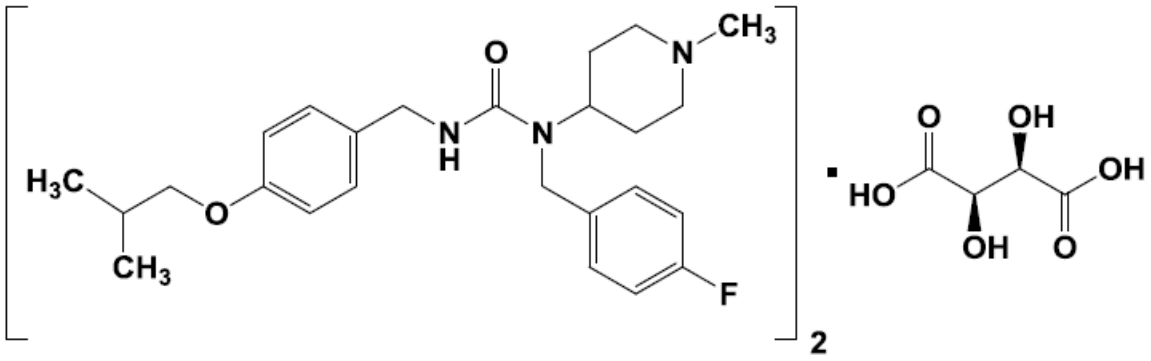
2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The sponsor submitted an original New Drug Application (NDA) for Pimavanserin Tartrate tablets for the treatment of Psychosis associated with Parkinson's disease (PDP). Pimavanserin has a breakthrough therapy designation. In April 2013, FDA agreed with the sponsor that an NDA would be accepted for filing on the basis of data from a single, strongly positive study (ACP-103-020) with supportive safety and efficacy data from earlier trials. Pimavanserin is a selective and potent serotonin 5-HT2A receptor inverse agonist. Pimavanserin has been developed as a solid oral dosage form (immediate release tablet) for once-daily dosing in humans. A once-daily oral dose of 40 mg pimavanserin tartrate (34 mg pimavanserin base) is the intended dose for the treatment of PDP. Its safety and tolerability have been evaluated in 23 completed or ongoing clinical trials and its efficacy evaluated in patients with PDP. Four placebo-controlled studies in subjects with PDP have been conducted to evaluate the safety and efficacy of pimavanserin at once-daily doses of 10, 20, 40 or 60 mg over a 4-6 week treatment period. The submission contained one pivotal Phase 3 safety and efficacy trial in PDP patients. The pharmacokinetics of pimavanserin was evaluated in healthy subjects as well as patients in 9 studies and population pharmacokinetic and exposure-response analysis reports. In addition, Pharmacodynamic studies evaluating effect of pimavanserin on QTc and PET studies and 31 in vitro studies evaluating protein binding, Cytochrome P450 (CYP) inhibition, induction and drug transporters were included in the submission. The proposed commercial drug product and Phase 3 clinical trial materials are the same except for product identifiers (tablet deboss impression) (b) (4)

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Pimavanserin is the active moiety of the tartrate salt with the chemical name of urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-{[4-(2-methylpropoxy)phenyl] methyl}, (*2R*,*3R*)-2,3-dihydroxybutanedioate

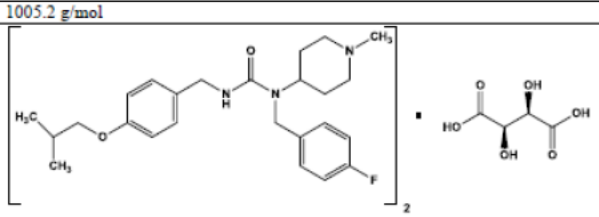
Figure 4: Structure of Pimavanserin Tartrate



$(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$ (pimavanserin tartrate) M.W.: 1005.20

The molecular weight of pimavanserin is 427.55
Source: Clinical Pharmacology Summary Aid

Table 3: Physicochemical Properties of Pimavanserin Tartrate

USAN:	Pimavanserin tartrate	
Chemical Name(s)	Urea, *N*-[(4-fluorophenyl) methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1)	
CAS Registry No.	706782-28-7	
Molecular Formula	$(C_{25}H_{34}FN_3O_2)_2.C_4H_6O_6$	
Formula Weight	1005.2 g/mol	
Structural Formula	 (427.55 g/mol free base)$_2$ • (150.09 g/mol tartaric acid) = 1005.20 g/mol tartrate salt	
Appearance	White to off-white powder	
Melting Range by DSC	Onset between (b) (4)	
pKa	8.6	
Log D	1.4 at pH 4.0; >3.0 at pH 7.4	
Log P	4.67 (calculated)	
Solubility	Solvent	Pimavanserin tartrate solubility[a]
	Water	Freely soluble
	(b) (4)	
	(b) (4)	
	[a]Solubility description follows current USP	
	(b) (4)	

Source: Summary of Biopharmaceutics and Analytical Methods

The sponsor states that Pimavanserin tartrate drug substance is a highly soluble and highly permeable compound which meets the criteria for BCS class (b) (4) An evaluation of BCS classification was not officially requested; hence, an evaluation has not been conducted. The following table contains the qualitative and quantitative composition of the proposed commercial tablet.

Table 4: Composition of Pimavanserin Tablet, 17 mg

Component	Function	Quality Standard	Quantity Per Tablet		
			mg/Tablet	% w/w (b) (4)	% w/w (Coated Tablets)
					(b) (4)
Pimavanserin tartrate	Active ingredient	In-house	20.0[a]		
(b) (4			(b) (4		
microcrystalline cellulose					
Pregelatinized starch					
Magnesium stearate					
(b) (4					
Film Coated Tablet					
					(b) (4)
					(b) (4)
Total for Coated Tablet					

NF: National Formulary; USP: United States Pharmacopeia; NA: Not applicable

[a] 20 mg of pimavanserin tartrate salt is equivalent to 17 mg of pimavanserin free base.

(b) (4)

Source: Clinical Pharmacology Summary Aid

2.1.3 What are the proposed mechanism (s) of action and therapeutic indication(s)?

The precise mechanism(s) by which pimavanserin exerts its antipsychotic effect is unknown but results of *in vitro* studies suggest that the principal mechanism of action is through selective inverse agonist of the serotonin 5-HT2A receptor subtype. Pimavanserin's only other activity is as an inverse agonist at 5-HT2C receptors, but at much lower potency. Pimavanserin is reported not to bind to dopaminergic, histaminergic, adrenergic, or muscarinic receptors. Pimavanserin is reported to have little to no activity at other G-protein coupled receptors (GPCRs), in contrast to other available antipsychotic drugs (APDs).

2.1.4 What are the proposed dosage and route of administration?

Pimavanserin is intended for oral administration. The recommended dose of pimavanserin is 34 mg (equivalent to 40 mg pimavanserin tartrate), taken as two 17 mg strength tablets once daily. Pimavanserin can be administered with or without food, and without prior titration. (b) (4)

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

There are currently no FDA-approved drugs for PDP. Clozapine is the only atypical antipsychotic (ADP) that is reported to have shown efficacy in randomized, placebo controlled studies of PDP but it is not approved for this indication. It is reported that atypical APDs quetiapine and clozapine are often prescribed off-label to treat PDP.

2.2 General Clinical Pharmacology

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

The use of pimavanserin for the treatment of Parkinson's Disease Psychosis (PDP) was studied in one (1) pivotal Phase 3 (ACP-103-020) trial that evaluated the efficacy, tolerability and safety of 40 mg pimavanserin versus placebo and 3 other Phase 2 and 3 (ACP-103-006, ACP-103-012, ACP-103-014) placebo-controlled trials in subjects with PDP evaluating safety and efficacy of pimavanserin at once-daily doses of 10, 20, 40, or 60 mg over a 4-6 week treatment period. Clinical pharmacology studies including pharmacokinetic (PK) characterization, effect of extrinsic factors (e.g. ketoconazole, carbidopa/levodopa), and thorough QT study were conducted. (b) (4)

2.2.2 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The sponsor reported that a variety of endpoints were collected to assess the potential utility of pimavanserin in the treatment of PDP. These variables included the following clinical rating scales: the Scale for the Assessment of Positive Symptoms (SAPS) (items from the hallucination [H] and delusion [D] domains only), the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III (measuring Activities of Daily Living and Motor Symptoms, respectively), the Clinical Global Impression – Severity (CGI-S) and Improvement (CGI-I) scales and the Scales for Outcomes in Parkinson's disease – Sleep (SCOPA-Sleep, including nighttime sleep and daytime wakefulness subscales).

The sponsor reported that the SAPS and specifically the combined score of the hallucinations and delusions domains was originally selected as the primary measure of efficacy in early Phase III studies of pimavanserin. The selection of these domains was based on their relevance to the positive symptoms of psychosis common in PDP, high inter-rater reliability, and utility (as demonstrated in the Phase II ACP-103-006 study) for assessing effects of treatment on the frequency and severity of hallucinations and delusions in the PDP population. Importantly, the SAPS also had precedence in the US Parkinson Study Group (US PSG) trial of clozapine in PDP. At a meeting in June 2006, the Agency did not object in principle to the use of the hallucinations and delusions domains of the SAPS as the primary measure of antipsychotic efficacy for pivotal studies (refer to medical review for Agency's evaluation)

The sponsor stated that in Study ACP-103-020, subjects were interviewed using the full 20-item SAPS-H+D scale; however, the primary analysis was re-designed to measure response on only a subset of the items reflective of the symptoms expressed in PDP (9 items; hallucinations: auditory, voices conversing, somatic/tactile, visual and global; delusions: persecutory, jealousy,

reference and global). This SAPS-PD measure was assessed in the ACP-103-020 study by independent blinded raters and the results were supported by highly significant results on the original 20-item SAPS-H+D measure. The CGI-I and CGI-S were secondary efficacy endpoints assessed by medically-qualified site staff blind to the SAPS scores.

2.2.3 What were the design features of the pivotal efficacy and safety trial?

The pivotal study was a Phase III trial of treatment with pimavanserin 40 mg or placebo once daily for 6 weeks at sites in North America (US and Canada). This was a randomized, double-blind, placebo-controlled, outpatient study that evaluated the safety and efficacy of pimavanserin 40 mg compared to placebo in the treatment of PDP for 6 weeks (42 days). The study included a 2-week screening period, baseline (before randomization on Day 1), 6 weeks of double-blind treatment, and 4 weeks of safety follow-up. On Day 1, subjects were randomized to receive pimavanserin 40 mg or placebo (1:1 ratio within each center). During the treatment period, additional study visits occurred on Days 15, 29, and 43 (or early termination) (±3 days per visit). All subjects were required to attend a follow-up visit on Day 71 (±3 days) except for those who entered the extension study on Day 43 (end of double-blind treatment). Subjects were to ingest a single oral dose of study drug once daily (2 tablets per dose). The first dose of study drug was administered at the study center in the presence of center personnel. During the remainder of the treatment period, subjects ingested study drug as outpatients, except for Days 15 and 29 when study drug was administered at the study center after safety assessments were completed and a pharmacokinetic (PK) blood sample was collected. The last dose of study drug was taken by the subject at home on Day 42. The primary efficacy endpoint was the mean change from baseline to Day 43 in the PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD). Safety and efficacy assessments were conducted at all scheduled study visits. Blood samples for determination of plasma pimavanserin concentrations were obtained predose on Days 1, 15, and 29, and on Day 43. The planned sample size was 200 subjects (100 per treatment). Overall, 199 subjects were randomized to double-blind treatment (placebo, n=94; pimavanserin 40 mg, n=105), 198 in the safety analysis set (placebo, n=94; pimavanserin 40 mg, n=104). The following table summarizes the study design and efficacy measures for studies

Table 5: Study Design and Efficacy Measures for Placebo-Controlled and Open-Label Studies of Pimavanserin in PDP

Study ID	Phase	Number of Study Centers (Locations)	Study Dates, Status	Study Objectives	Study and Control Drugs Dose, Route, Regimen[a]	# Subjects Expected/Enrolled & Enrolled/Completed by Arm[b]	Duration	Sex M/F Median Age (Range) ITT or Eval[b]	Efficacy Measures (Primary in bold where applicable)	Post Baseline Visits where Efficacy Assessed[g]
Placebo-Controlled Double-Blind Studies										
-020 CSR Narrative	III	NA: 54 (US: 52, Canada: 2)	8/2010 to 10/2012 Completed	Efficacy, safety	40 mg placebo QD	200/199 40 mg: 105/89 (95/89) PBO: 94/87 (90/87)	6 weeks	116 M/69 F 72.0 years (53-90)	**SAPS-PD** SAPS-H+D, SAPS-H, -D, CGI-S, CGI-I, SCOPA-Sleep, CBS	Days 15, 29, 43
-012 CSR Narrative	IIb/III	NA (US): 34 Europe: 26 India: 13	6/2007 to 7/2009 Completed	Efficacy, safety	10 mg 40 mg placebo QD	280/298 10 mg: 101/85 (98/85) 40 mg: 99/83 (92/82) PBO: 98/91 (97/91)	6 weeks	181 M/106 F 70.0 years (40-87)	**SAPS-H+D** SAPS-H, -D, CGI-S, CGI-I, SCOPA-Sleep CBS, NMSS	Days 8, 15, 29, 42
-014 CSR Narrative	IIb/III	NA (US): 18 Europe: 21	3/2008 to 12/2009 Early-Terminated	Efficacy, safety	10 mg 20 mg placebo QD	279/123 10 mg: 42/38 (38/37) 20 mg: 41/35 (41/35) PBO: 40/32 (38/32)	6 weeks	74 M/43 F 72.0 years (53-90)		
-006 CSR Narrative	II	NA (US): 15	3/2004 to 12/2005 Completed	Exploratory efficacy, safety	20-40-60 mg (flexible) placebo QD	60/60 PIM: 29/20 (28/20) PBO: 31/24 (31/24)	4 weeks	45 M/14 F 70.0 years (46-90)	SAPS-H+D, SAPS-H, -D, CGI-S, CGI-I	Days 8, 15, 28 (SAPS on D28 only)

Table 6: Study Design and Efficacy Measures for Placebo-Controlled and Open-Label Studies of pimavanserin in PDP (Continued)

Study ID	Phase	Number of Study Centers (Locations)	Study Dates, Status	Study Objectives	Study and Control Drugs Dose, Route, Regimen[a]	# Subjects Expected/Enrolled & Enrolled/Completed by Arm[b]	Duration	Sex M/F Median Age (Range) ITT or Eval[b]	Efficacy Measures (Primary in bold where applicable)	Post Baseline Visits where Efficacy Assessed[g]
Long-term Open-Label Studies										
-015[c] CSR Narrative	III	NA: 67 Europe: 35 India: 12	7/2007 Ongoing	Long-term safety	40 mg QD	456 entered 348 withdrawn 108 ongoing	Chronic (Longest single duration 67.5 mos)[d]	281 M/175 F 71.0 years (40-90)	SAPS-H+D, SAPS-H, -D CGI-S, CGI-I CBS	Months 1, 3, 6, 9, 12 & every 6 months thereafter (SAPS at Month 1 only)
-010[e] CSR Narrative	II	NA (US): 13	11/2004 to 5/2013 Completed	Long-term safety	20 mg 40 mg 60 mg QD	38 entered 38 withdrawn[f]	Chronic (Longest single duration >8 yrs)	28 M/10 F 70.5 years (50-90)	CGI-S	Week 2, Months 1, 2, 3 and every 3 months thereafter

Abbreviations: CBS=Caregiver Burden Scale; CGI-I=Clinical Global Impression - Improvement; CGI-S=Clinical Global Impression - Severity; F=female; M=male; NA=North America; NMSS=Non-Motor Symptoms Score; PBO=placebo; PIM=pimavanserin; QD=once daily; SAPS=Scale for the Assessment of Positive Symptoms; SAPS-H+D=SAPS-Hallucinations and SAPS-Delusions subscales; SAPS-PD=SAPS in Parkinson's disease

Note: Studies are listed in order of importance and as presented in subsequent ISE sections.

[a] All studies used oral administration of study drugs as tablets.

[b] ITT population for the 4 placebo-controlled trials, evaluable population for the 2 extension trials.

[c] Included patients who rolled over after completing 6 weeks of double-blind, placebo-controlled treatment in Studies -020, -012, or -014. The analyses of Study -015 presented in the ISE included data up to Extension Week 96 for all patients. Subjects can remain on study for as long as they are considered by the Investigator to be deriving benefit (and until pimavanserin becomes commercially available).

[d] Except for the subject who rolled over from -010 (who has now continued beyond 9 years total treatment), the longest duration at the cutoff date was 67.5 months.

[e] Included patients who rolled over from Phase II Study -006. The analyses include data up to Extension Week 96 for all patients.

[f] Excluded 1 subject from -004 (PD dyskinesia study) who was not confirmed to have PDP and rolled into -010.

[g] Subjects in both the -012 and -020 studies received 42 days of treatment. The end-of-treatment visit was referred to as Day 42 in -012 and Day 43 in -020.

Source: Sponsor's Clinical Overview

2.2.4 What are the evidences of efficacy provided by the sponsor in support of the application?

The following table contains the results of the safety and efficacy trials based on the sponsor's analysis. Refer to FDA review for Agency's analysis and conclusions.

Table 7: Summary of Efficacy in Study ACP-103-020 at Day 43: All Scales, Domains or Other Item Clusters

Endpoint	Measure	Rater	Source Table[a]	Population - Analysis[b]	LSM Treat-ment Δ[c]	95% Confidence Intervals	p-value
ANTIPSYCHOTIC EFFICACY							
Primary	SAPS-PD	Independent (Central)	14.2.1.1.1	ITT – MMRM	-3.06	(-4.91, -1.20)	0.001
		Independent (Central)	14.2.1.1.5	PP – MMRM	-3.18	(-5.07, -1.28)	0.001
		Independent (Central)	14.2.1.1.2	ITT - LOCF	-2.91	(-4.75, -1.07)	0.002
		Independent (Central)	14.2.1.1.3	ITT - WOCF	-2.78	(-4.63, -0.93)	0.003
		Independent (Central)	14.2.1.1.4	All rand - WOCF/BOCF	-2.36	(-4.12, -0.61)	0.008
Supportive	SAPS-PD % Change	Independent (Central)	14.2.3.3.1	ITT - MMRM	-23.1%	(-36%, -10%)	0.001
	SAPS-PD Responder	Independent (Central)	14.2.3.20.1	ITT - CMH	20.63%	(7.05%, 34.21%)[d]	0.004[e]
	SAPS H+D	Independent (Central)	14.2.3.5.1	ITT - MMRM	-3.37	(-5.40, -1.35)	0.001
	SAPS H+D % Change	Independent (Central)	14.2.3.4.1	ITT - MMRM	-23.5%	(-37%, -10%)	0.001
	GSAPS-H+D	Independent (Central)	14.2.3.6.1	ITT - MMRM	-0.93	(-1.65, -0.21)	0.012
	SAPS-H	Independent (Central)	14.2.3.7.1	ITT - MMRM	-2.08	(-3.46, -0.71)	0.003
	SAPS-D	Independent (Central)	14.2.3.8.1	ITT - MMRM	-1.16	(-2.22, -0.10)	0.033
Secondary	CGI-I	Investigator	14.2.2.3.1	ITT - MMRM	-0.67	(-1.06, -0.27)	0.001
	CGI-I Responder	Investigator	14.2.2.4.1	ITT - Chi-square	23.3%	(9.3, 37.2)	0.002
	CGI-S	Investigator	14.2.2.2.1	ITT - MMRM	-0.58	(-0.92, -0.25)	0.001
OTHER EFFICACY							
Exploratory	SCOPA-Night	Investigator	14.2.3.1.1	ITT - MMRM	-0.93	(-1.84, -0.02)	0.045
	SCOPA-Day Wake	Investigator	14.2.3.1.5	ITT - MMRM	-1.22	(-2.17, -0.27)	0.012
	Caregiver Burden	Caregiver	14.2.3.2.1	ITT - MMRM	-4.34	(-7.00, -1.67)	0.002
	Caregiver Burden – Categ	Caregiver	14.2.3.2.3	ITT - CMH	N/A	N/A	0.004

Abbreviations: ANCOVA=analysis of covariance; BOCF=baseline-observation-carried-forward; CMH=Cochran-Mantel-Haenszel test; GSAPS-H+D=sum of the global items for the H and D domains; LOCF=last-observation-carried-forward; LSM=least squares mean; MMRM=mixed model repeated measures analysis; OC=observed cases; SAPS-PD=sum of 9-item PD-adapted SAPS; SAPS-D=sum of 13 items for D domain; SAPS-H=sum of 7 items for H domain; SAPS-H+D=sum of 20 items for H and D domains, WOCF=worst-observation-carried-forward

[a] Source tables in ACP-103-020 CSR

[b] MMRM refers to OC MMRM analyses; ANCOVA was used for all LOCF, WOCF, and BOCF imputation methods

[c] LSM treatment Δ (or adjusted difference in responders) = pimavanserin minus placebo

[d] Adjusted proportion difference using weighting scheme of CMH and stratified Wald 95% confidence interval

[e] P-value was from a CMH test stratified by baseline SAPS-PD severity.

Source: Sponsor's Clinical Overview

The sponsor reported that pimavanserin 40 mg was statistically more efficacious than placebo in decreasing the frequency and severity of hallucinations and delusions in subjects with PDP as measured by the SAPS-PD primary analysis as well as all supportive variables and sensitivity analyses. The least squares (LS) mean change in SAPS-PD score from baseline to Day 43 showed a 5.79-point improvement at Day 43 for pimavanserin 40 mg compared to a 2.73-point improvement for placebo, a treatment difference of 3.06 points (p=0.001; effect size 0.50). Importantly, treatment effect was seen for both hallucinations and delusions as demonstrated by statistically significant improvements in the separate SAPS H and D domain scores. Refer to medical review for Agency's conclusions.

2.2.5 Exposure-Response

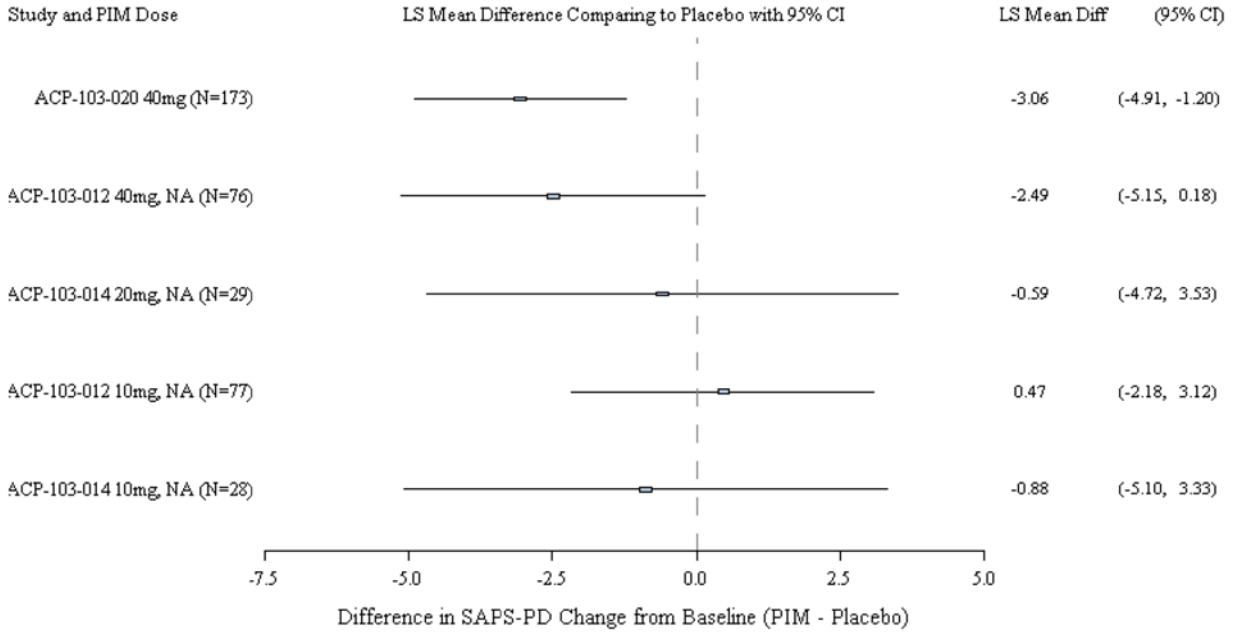
2.2.5.1 Is the proposed once daily dose of 40 mg pimavanserin tartrate, by the sponsor, appropriate for major Parkinson's Disease Psychosis (PDP) patients?

Yes, the proposed 40mg QD dose is reasonable. Pivotal phase III clinical trial ACP-103-020 showed significant antipsychotic efficacy at the 40 mg dose in patients with Parkinson's disease psychosis (PDP) as measured using the 9-item SAPS-PD scale. In the second supportive clinical trial ACP-103-012, there was an observation of a 42% response rate in the placebo group and no significant superior antipsychotic efficacy achieved at 40 mg dose compared with placebo group. Data reanalysis within the North American Region appeared to reduce the placebo response, as it appeared that the non- North American region had an unusually high percentage of responders (Figure 5). Notably, centralized ratings were used in evaluation of primary measure in US population. Based on this retrospective analysis of ACP-103-012, the Sponsor modified the protocol for ACP-103-020 to address the high placebo response. Thus we think it is reasonable to exclude all non-north American individuals in our pooled exposure-response (E-R) analysis.

Our exposure–response analysis was conducted with North American data pooled together from Studies ACP-103-012, ACP-103-104 and ACP-103-020 (Figure 6). E-R relationship showed that the sponsor's proposed dose of 40mg QD has greater percentage change from baseline in SAPS-PD score compared with lower doses (10 mg QD, 20 mg QD). Final results were generalized as SAPS-PD percentage change from baseline in Figure 6. Based on the available data, further increase in the dose to levels greater than 40 mg appear unlikely to result in an increase in efficacy.

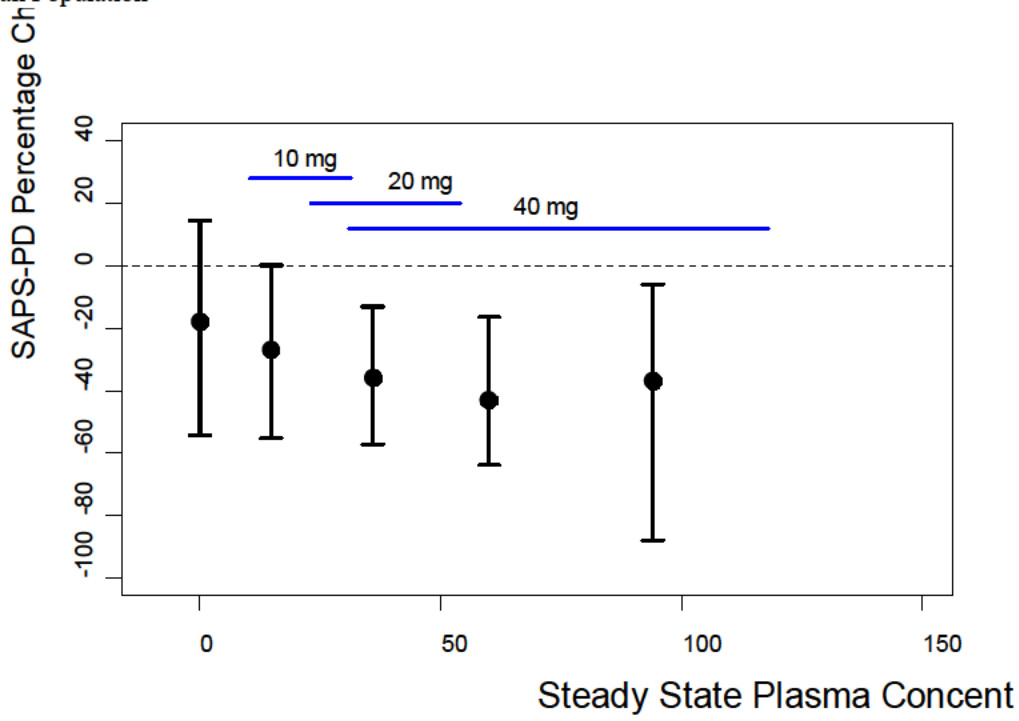
The four kinds of adverse event (hallucinations, confusion, edema, and gait disturbance) were not found to be correlated pimavanserin concentration.

Figure 5: Dose Selection: SAPS-PD Score Change from Baseline at 6W in North American Population



Source: Pharmacometric Review

Figure 6: SAPS-PD Percentage Change from Baseline vs. Steady State Plasma Concentration at 6 Weeks in North American Population

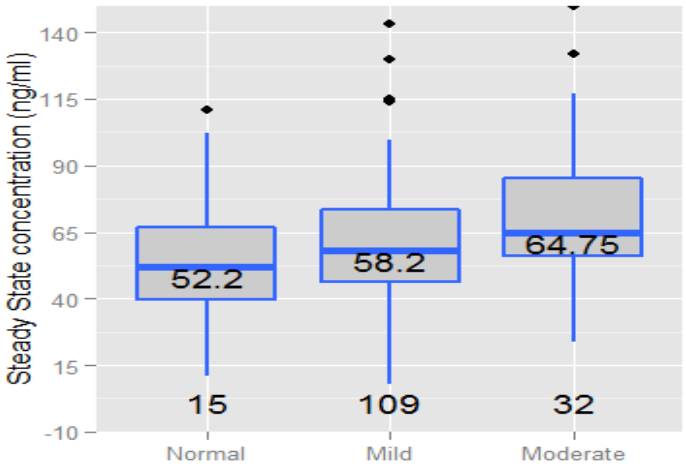


Source: Pharmacometric review

2.2.5.2 Is dose adjustment needed for renal impaired populations?

No, dose adjustment is not needed for mild or moderate renal impaired population. Univariate comparison of steady state plasma concentration of normal population versus mild or moderate renal impaired population showed there are a 10% increase in mild and 20% increase in moderate renal impaired patients (Figure 7). Although our population PK model shows that creatinine clearance is a significant covariate for apparent clearance, the effect is small and in line with observed concentrations. Furthermore, since ~23% (mean 23.1 ± 3.3%) of radioactive drug was excreted in urine and 46% (mean 45.5 ± 4.5%) of the radioactive drug was excreted in feces, the main elimination pathway for pimavanserin is metabolism. Furthermore, we note from figure 7 that most patients enrolled in the clinical program had mild or moderate renal impairment, so most of the safety database is in this population. Thus, no dose adjustment is needed for mild or moderate renal impaired patients However, pimavanserin is not recommended to be used in severe renal impaired patients.

Figure 7: Steady-State Pimavanserin Concentration in Different Groups of Renal Function



Note: Three studies ACP-103-012, ACP-103-104 and ACP-103-020 were pooled together and only the 40 mg dosing regimen is included. Trough plasma concentration observation at day 29 for each individual was used as steady state concentration. Steady state concentration in each renal function level was compared in box plot. Renal function level is determined by creatinine clearance. Median concentration in normal population (CRCL>=90) and mild (CRCL: 60-89) or moderate (CRCL: 30-59) renal impaired population were labeled. Number in the bottom indicated N number in each group.

The change of pimavanserin concentration in patients with severe renal impairment is unclear at present. Mechanistically, we do not expect a substantial increase in pimavanserin exposure in severe renal impaired patients because pimavanserin is primarily metabolized by CYP3A4 and less than 1% of pimavanserin which is likely readily absorbed, was identified in urine. However, Figure 1 suggested a correlation between decrease in renal function and increase in pimavanserin exposure. A relationship was also identified in the population PK analysis. Consistent with the observed trend, approximately 50% increase in pimavanserin exposure as compared to the mild renal impairment patients (Table 2) has been observed in limited patients (n=4) with borderline severe renal impairment (patients' creatinine clearance levels are slightly below 30 mL/min). This level of change in exposure, even though from patients with better renal function than that of a typical severe renal impairment patient, is approaching the general threshold for potential dosage adjustment with the caveat that the observed data are associated with uncertainty due to factors such as limited samples size.

It should be noted that the patient population is elderly with late stage Parkinson's disease and with a short expected life span (a few months to 1 to 2 years). There is a potential for confusion and sedation in this general patient population. For this patient population with severe renal impairment, the internal environment is expected to be further compromised (e.g., electrolyte imbalance). The existing data appear to suggest some concerning safety signals, such as higher mortality rate, QTc interval prolongation, etc. associated with the treatment of pimavanserin in mild to moderate renal impairment patients. In severe renal impairment patients, the safety profile may be worsening due to changes in internal environment and we do not have sufficient experience in this population. Therefore, in severe renal impaired patients, until additional data on exposure are available, it is prudent to not use pimavanserin in severe renal patients.

2.2.5.3 Does pimavanserin prolong the QT or QTc interval?

Yes, an increase of about 8 ms is expected at 40 mg pimavanserin with a CI of 6.4 ms to 9.1ms. Sponsor included doses of 20 mg and 80 mg in their thorough QT study, but not a 40 mg dose. Pimavanserin 20 mg had no clinically meaningful effect on the QTc interval. The point estimates were 6.6 ms and the upper bound of the CI did not exceed 10.0 ms. Pimavanserin 80 mg dose was associated with a time-matched maximal mean corrected QT interval (QTcI) increase of 10.7 ms and an upper CI of 13 ms. Pimavanserin 40 mg was predicted to prolong the QTc with a mean of 7.8 and an upper 90% CI of 9.1 ms. For further details, refer to the QT-IRT review by Dr. Zhang (10/27/2015).

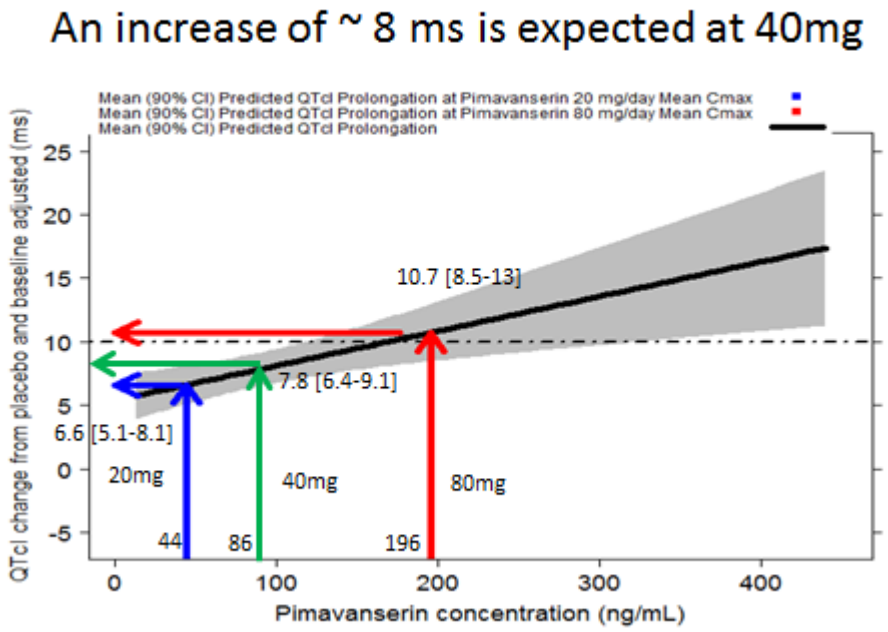


Figure 8: A single regression linear model was used to describe the data.

2.3 General Pharmacokinetics

2.3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Yes the active moieties have been appropriately determined and measured. Pimavanserin and its significant circulating metabolite AC-279, have been identified in plasma and measured using validated liquid chromatography-tandem mass spectrometric (LC-MS/MS). The method provided accuracy, precision, selectivity, sensitivity, and reproducibility in the determination of

pimavanserin and its metabolite (AC-279) in human plasma and/or urine. Incurred Sample Reanalysis (ISR) was not conducted; however, this was not a recommendation in the Agency's published guidance on analytical methods when the studies were conducted.

2.3.2 What is the proposed metabolic scheme and enzymes involved in the metabolism of pimavanserin?

Pimavanserin is extensively metabolized after oral administration via phase I and II pathways including hydroxylation, dehydrogenation, *N*-demethylation, *N*-dealkylation, *O*-dealkylation, *N*-oxygenation followed by *O*-methylation and *O*-glucuronidation. All primary metabolites are formed from the activity of 3 enzyme systems: cytochrome P450 (CYP) 3A4, flavin monooxygenase (FMO), and hydrolytic enzymes. The following figure and table contain the proposed metabolic pathway and identity of the metabolites, respectively.

Figure 9: Proposed biotransformation pathway for Pimavanserin (ACP-103)

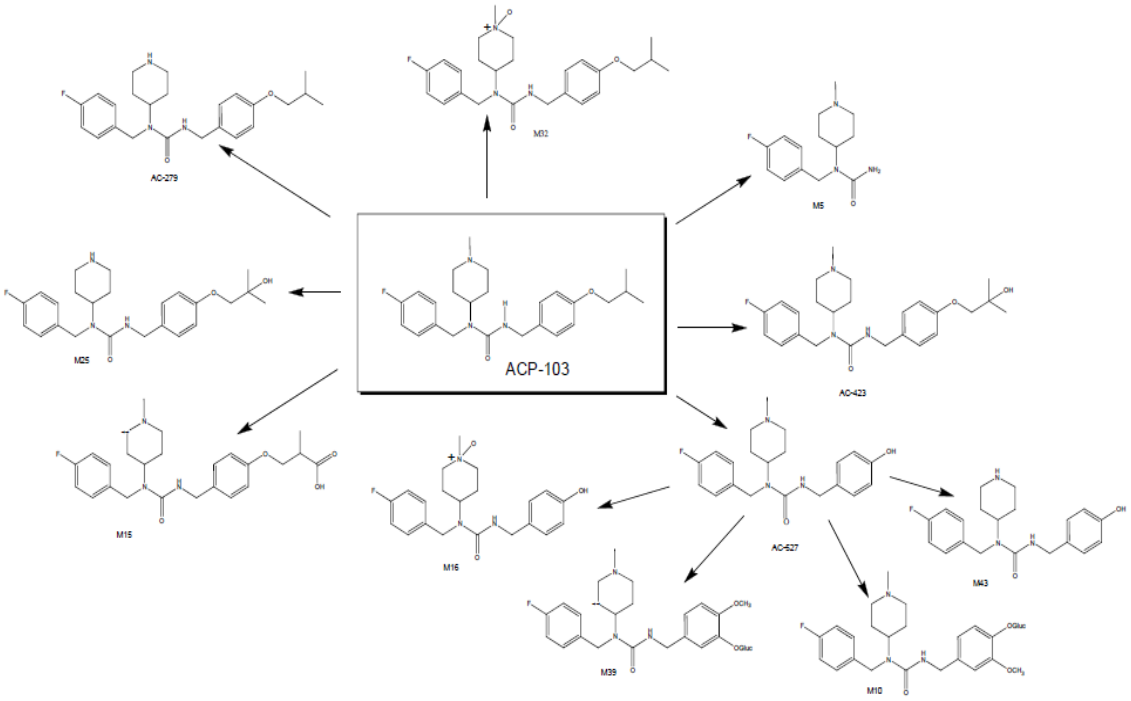


Table 8: Percent of sample radioactivity as [^{14}C]-ACP-103 or metabolites of [14C]-ACP-103 in pooled plasma after administration of a single 40-mg (100-µCi) oral dose of [14C]-ACP-103 to male human subjects

Peak Identification	Retention Time (Minutes)	Proposed Identification	Percent of Sample Radioactivity Collection Time (Hours) 1	2	4	6	9	12	16	24
M1	2.50-2.75	Unknown	14.43	11.11	8.75	11.50	7.31	5.08	5.56	8.32
M6	23.00-23.50	Unknown	ND	ND	2.92	3.84	1.54	ND	ND	ND
M38	25.50-26.00	Unknown	4.52	3.74	7.32	4.71	7.10	2.80	7.67	ND
M10	26.25	Gluc-271336+CH_3	ND	ND	ND	ND	ND	3.86	ND	ND
M39	27.00-27.50	Gluc-271337+CH_3	10.67	3.35	ND	4.85	ND	3.56	3.04	ND
M40	28.75-29.75	Unknown	ND	1.92	4.90	4.54	5.10	7.50	2.52	4.57
M41	30.75	Unknown	ND	ND	ND	ND	ND	ND	4.10	ND
M16	31.25-32.00	AC-271377	11.62	8.62	4.24	4.88	3.88	ND	1.72	ND
M18	34.50-34.75	AC-527	7.60	4.79	ND	3.19	ND	ND	ND	ND
M44A	39.75-40.50	Unknown	ND	3.07	ND	5.95	1.32	ND	ND	ND
M26	43.00-47.00	AC-423[a]	4.01	2.97	3.58	2.44	2.95	2.80	3.25	1.66
M31	52.00-52.75	Unknown	4.16	ND	3.80	3.36	ND	ND	ND	ND
M48	53.50-53.75	Unknown	5.56	4.89	ND	ND	ND	ND	ND	ND
M33	62.25-62.50	AC-279	ND	1.63	ND	ND	ND	7.80	4.91	7.89
Parent	63.00-63.25	ACP-103[b]	4.52	4.60	10.18	10.88	27.66	33.26	23.77	29.90
M35	64.00-64.25	Unknown	ND	2.78	2.97	ND	ND	4.92	3.71	4.19
M36	65.50-65.75	Unknown	4.75	6.90	7.54	3.81	6.99	7.50	7.29	9.91
		Total	71.8	60.4	56.2	64.0	63.9	79.1	67.5	66.4

ND Peak not detected or less the 3% of the run.
a AC-423 radioactivity area was estimated based on LC/MS analysis data, since there was no discrete peak in AC-423 elution area due to low radioactivity in samples.
b The retention time of 4 and 9 hours is 62.25 minutes.
Note: If a metabolite detected at one time point represented >3% of the radioactivity, then the metabolite was reported for all time points, even when it represented <3% of the radioactivity, for consistency in tracking.

Source: Sponsor's Clinical Pharmacology Summary

Table 9: Primary Sites of Pimavanserin Metabolism

Reaction Leading to Metabolite Formation	**Abbreviated Name of Resultant Metabolite**	**ACADIA Code for Resultant Metabolite**
N-Demethylation of the piperidine nitrogen	*N*-Desmethyl-PIM	AC-279 (AC-260279)
O-Dealkylation (loss of *iso*-butyl side chain)	*O*-Desalkyl-PIM	AC-527 (AC-090680)
N-Oxygenation (*N*-oxide formation)	PIM-*N*-oxide	AC-285 (AC-260285)
N-Dealkylation at the urea nitrogen	*N*-Desalkyl-PIM	AC-249 (AC-271249)
ω-Hydroxylation of the *iso*-butyl side chain	ω-Hydroxy-PIM	AC-236[1] (AC-260236)
(ω-1)-Hydroxylation of the *iso*-butyl side chain	(ω-1)-Hydroxy-PIM	AC-423 (AC-260423)
Exo-Dehydrogenation of the *iso*-butyl side chain	*Exo*-Dehydro-PIM	AC-356 (AC-271356)
Endo-Dehydrogenation of the *iso*-butyl side chain	*Endo*-Dehydro-PIM	M62.4[2]
Ortho-Aromatic hydroxylation of the substituted phenol	*ortho*-Hydroxy-PIM	AC-620 (AC-260620)
Dehydrogenation followed by cyclization	Bicyclic-PIM	AC-035 (AC-272035)

[1] Also known as AC-627 (AC-271627).
[2] *Endo*-dehydro-PIM is the only primary metabolite that was not synthesized or purified. It was not detectable in plasma by radiometric HPLC analysis.
Source: Sponsor's Clinical Pharmacology Summary

2.3.3 What are the PK characteristics of the Pimavanserin?

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

Pharmacokinetic parameters for pimavanserin have been determined in healthy subjects at single doses ranging from 20 to 300 mg and multiple doses up to 150 mg for 14 days. Absorption of pimavanserin occurs with a median Tmax of 6 h (range 4-24 h) and was generally unaffected by dose. Relative bioavailability of the tablet formulation to solution was 99.7%. The apparent elimination half-life of pimavanserin is about 57 hours. A dose proportional increase in Cmax and AUC(0-∞) of pimavanserin with escalation of pimavanserin tartrate oral dose from 20 to 300 mg was observed based on the power model analysis. The following figures and table demonstrate the dose proportional increase.

Figure 10: Individual and mean Cmax of ACP-103 in human subjects after single oral administration of ACP-103 doses of 20 mg, 50 mg, 100 mg, 200 mg, and 300 mg (n=4 in all groups).

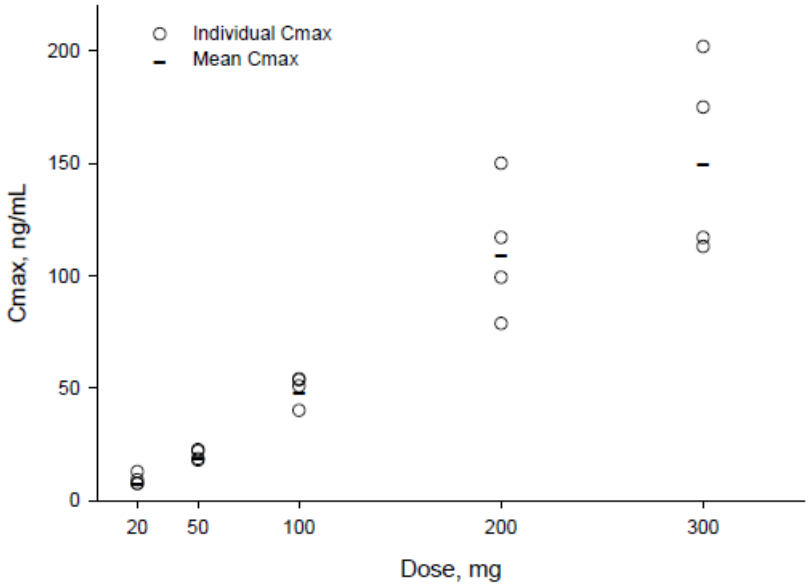


Figure 11: Individual and mean AUC (0-∞) of pimavanserin in human subjects after single oral administration of pimavanserin doses of 20 mg, 50 mg, 100 mg, 200 mg, and 300 mg (n=4 in all groups).

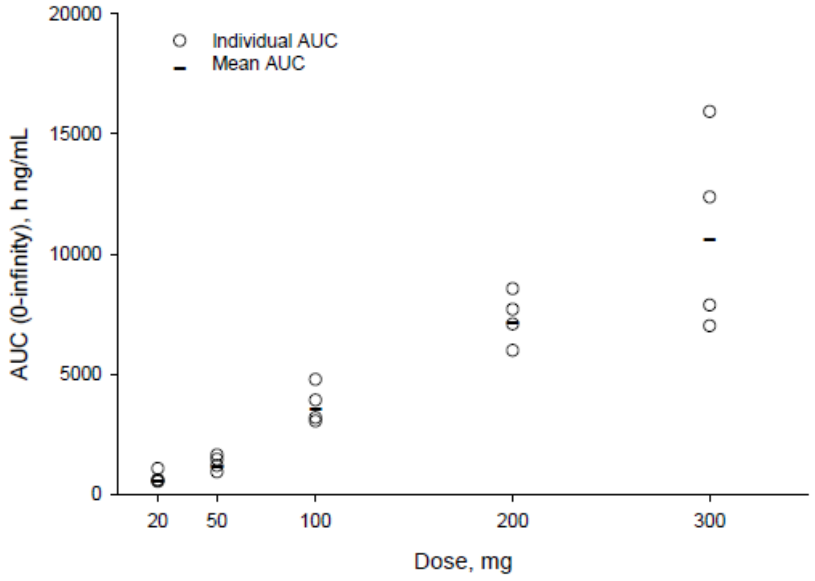


Table 10: Summary of Dose Proportionality Analysis (Power model)

Parameter (unit)	Intercept			Slope		
	Estimate	SE	95% CI	Estimate	SE	95% CI
AUCinf (ng*h/mL)	3.2766	0.2975	(2.6515, 3.9016)	1.0495	0.0646	(0.9138, 1.1852)
Cmax (ng/mL)	-1.0539	0.2337	(-1.5449,-0.5629)	1.0680	0.0507	(0.9614, 1.1746)

Table11: Summary of Pharmacokinetic Data for Pimavanserin Following Single Doses (20 mg to 300 mg) in Healthy Subjects

Study Number (Dosing Schedule) *Population*	Dose [mg] (N)	Day	PK Parameter Mean (SD)				
			C_{max} [ng/mL]	T_{max} [h] Median (Min, Max)	$AUC_{0\text{-}inf}$ [ng-h/mL]	CL/F [L/h]	$t_{1/2}$ [h]
ACP-103-001[a] (I) (Single Dose) *Healthy subjects*	20 (4)	1	9.25 (2.5)	6 (6,6)	706 (253)	26.0 (7.0)	57.0 (12)
	50 (4)	1	20.3 (2.4)	6 (6,9)	1315 (309)	33.9 (8.6)	53.0 (4.8)
	100 (4)	1	49.7 (6.5)	6 (6,9)	3742 (794)	23.5 (4.6)	58.3 (5.6)
	200 (4)	1	111 (30)	6 (6,6)	7335 (1079)	23.6 (3.6)	55.4 (13)
	300 (4)	1	152 (44)	6 (6,6)	10798 (4146)	26.4 (9.6)	53.5 (7.6)
ACP-103-001[a] (II) (Single Dose) *Healthy subjects*	100 (8)	1	51.4 (8.0)	6 (6,12)	3847 (622)	26.6 (4.0)	60.0 (9.0)
	100[b] (8)	1	57.0 (10)	6 (6,6)	3871 (858)	26.8 (5.2)	57.9 (7.6)
	100[b] Fed (8)	1	52.2 (11)	11 (6,24)	4269 (1278)	25.3 (7.2)	56.8 (9.7)
ACP-103-009 (Single Dose) *Healthy subjects*	100 (18)	1	42.1 (10)	12			
ACP-103-016[c] (Single Dose) *Healthy subjects*	40 (6)	1	19.2 (2.2)	9 (9,16)	1392 (280)	29.7 (6.0)	51.4 (6.7)
ACP-103-023[d] (Single Dose) *Healthy subjects*	40 (19)	1	17.11 (3.8)	9 (6,16)	1257 (464)	36.2 (15)	58.2 (13)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero to infinity; CL/F, oral clearance; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum observed plasma concentration; t, time postdose; $t_{½}$, terminal half-life

[a] ACP-103-001 was a 2-part study: I = dose range finding; II = food effects. Oral dosing was replaced with nasogastric dosing due to subjective local intolerance of oral solution, starting with 100 mg pimavanserin.

[b] Dose administered as tablet, both fasted and fed.

[c] ACP-103-016 data are derived from a mass balance study that also included radioactivity analyses.

[d] Data indicated are for Day 1 Pimavanserin alone, single dose.

Source: Sponsor's Summary of Clinical Pharmacology

Table 12: Pharmacokinetic Parameters of Pimavanserin and its Major Pharmacologically-Active Metabolite AC-279 following Single Oral Administration of Pimavanserin (40 mg)

Parameter (Unit)	Pimavanserin Mean ± SD[a] N=19	AC-279 Mean ± SD[a] N=19
$AUC_{0\text{-}t}$ (ng-h/mL)	1224 ± 433	747 ± 160
$AUC_{0\text{-}inf}$ (ng-h/mL)	1257 ± 464	1108 ± 257
C_{max} (ng/mL)	17.1 ± 3.8	4.0 ± 1.0
T_{max} (h)	9.00	36
$t_{½}$ (h)	58.2 ± 13.2	199.6 ± 64.7
CL/F (L/h)	36.2 ± 15.3	-
V_z/F (L)	2836 ± 650	-

[a] Mean (±SD), except for T_{max} which is shown as median

Source: Study AC-103-023

The elimination half-life of AC-279 is approximately 200 hours.

Multiple Dose Pharmacokinetics

After multiple dose daily administration, steady state is achieved by day 14. Pimavanserin demonstrated dose-proportional pharmacokinetics following multiple dosing over the 50- to 150-mg dose range studied. Pimavanserin accumulated over time after daily administration for

14 days. Steady state Cmax and AUC0-24 values were around 3- to 5-fold greater following multiple dosing for 14 days. Over the 24-hour steady-state collection interval, urinary recovery was less than 3% for pimavanserin and 7% for its active metabolite, AC-279. The elimination half-life of AC-279 is ~200 hours.

Table 13: Descriptive Statistics for Pimavanserin Pharmacokinetics at Steady State (Day 14)

Group	Statistic	Cmax,ss (ng/mL)	Tmax,ss (h)	Cmin,ss (ng/mL)	Tmin,ss (h)	Cavg,ss (ng/mL)	AUC(0-24),ss (ng*h/mL)	Lambda_z (1/h)	t1/2,ss (h)	CLpo,ss (L/h)	%Fluc [a]	AR [b]	Cmax Ratio [c]
50 mg	N	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	92.88	7.000	60.65	8.503	76.55	1838.7	0.01358	54.59	25.15	41.90	5.208	4.683
	SD	31.31	1.549	18.93	12.027	28.23	680.7	0.00312	18.52	6.75	2.21	2.870	2.526
	CV (%)	33.7	22.1	31.2	141.4	36.9	37.0	23.0	33.9	26.8	5.3	55.1	53.9
	Minimum	69.6	6.00	46.2	0.00	55.5	1332	0.00755	42.8	13.5	39.7	2.90	2.76
	Median	82.1	6.00	55.6	1.51	66.6	1597	0.0147	47.4	26.7	41.6	4.31	3.85
	Maximum	153	9.00	97.2	24.00	131	3153	0.0162	91.8	31.9	45.2	10.8	9.62
100 mg	N	5	5	5	5	5	5	4	4	5	5	5	5
	Mean	193.4	6.600	120.3	0.600	158.2	3804.6	0.01217	60.09	22.82	46.44	5.038	4.674
	SD	27.6	1.342	18.8	0.548	24.9	598.5	0.00342	14.98	3.70	10.33	0.464	0.586
	CV (%)	14.3	20.3	15.6	91.3	15.8	15.7	28.1	24.9	16.2	22.2	9.2	12.5
	Minimum	160	6.00	98.6	0.00	124	2987	0.00927	41.0	18.2	33.9	4.34	4.15
	Median	190	6.00	118	1.00	159	3821	0.0113	62.3	22.3	46.9	5.04	4.59
	Maximum	229	9.00	150	1.00	194	4668	0.0169	74.8	28.5	61.5	5.51	5.58
150 mg	N	4	4	4	4	4	4	4	4	4	4	4	4
	Mean	247.5	5.500	151.3	6.000	195.0	4680.3	0.01445	47.99	27.55	49.40	3.695	3.503
	SD	35.0	1.000	21.4	12.000	22.4	548.9	0.00037	1.29	3.25	5.32	0.660	0.653
	CV (%)	14.2	18.2	14.1	200.0	11.5	11.7	2.6	2.7	11.8	10.8	17.9	18.7
	Minimum	212	4.00	131	0.00	172	4123	0.0142	46.1	24.3	42.9	2.98	2.93
	Median	242	6.00	149	0.00	195	4673	0.0143	48.5	27.5	50.4	3.75	3.41
	Maximum	294	6.00	176	24.00	218	5252	0.0150	48.9	31.0	54.0	4.30	4.27

[a] %Fluc=percent fluctuation, calculated as (Cmax,ss-Cmin,ss)/Cavg,ss*100.
[b] AR=accumulation ratio, calculated as AUC(0-24),ss/AUC(0-24).
[c] Cmax Ratio=Cmax,ss/Cmax.

Source: Study ACP-103-002

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

No substantial differences exist between the pharmacokinetics of pimavanserin in healthy and in patients with Parkinson's disease. Pharmacokinetic parameters for metabolite AC-279 were determined in healthy subjects only; no data is available in Parkinson's disease patients.

Table 14: Pharmacokinetic Parameters for Pimavanserin in Healthy and Parkinson's Disease Subjects

Study Number (Dosing Schedule) *Population*	Dose [mg] (N)	Day	C_{max} [ng/mL]	AUC_{0-24h} [ng-h/mL]	Ct[a]	T_{max} [h] Med	CL/F
ACP-103-002 (QD x 14 days) *Healthy subjects*	100 (6)	1	43.2 (12.8)	792 (14.5)	-	6 (38.7)	-
	100 (5)	14	193 (14.3)	3805 (15.7)	120 (15.6)	6 (20.3)	22.8 (16.2)
ACP-103-005 (QD x 14 days) *Parkinson's disease subjects*	100 (4)	1	43.7 (24.4)	762 (25.7)	-	11 (61.0)	-
	100 (4)	14	143 (9.7)	2920 (12.4)	97.2 (26.8)	9 (27.2)	29.4 (11.5)

[a] Pre-dose; CV% is indicated in parentheses

Source: Clinical Pharmacology Summary

A population PK analysis was conducted using data from six clinical trials in which pimavanserin was administered orally in healthy subjects and in subjects with Parkinson's disease who did not have psychosis and in subjects with PDP. The analysis indicated that there is no significant difference between the pharmacokinetics in healthy subjects and the target population.

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

Intersubject variability (CV%) of PK parameters from both single and multiple dosing studies was generally less than 50% in healthy volunteers and PD subjects.

2.3.3.4 What are the characteristics of drug absorption?

In vitro studies in Caco-2 cells indicated pimavanserin is a highly permeable and in addition the compound is also highly soluble. Refer to Office of Pharmaceutical Quality (OPQ)- Biopharm review for detail evaluation of the permeability and solubility of pimavanserin.

The human mass balance study indicated a low level of pimavanserin in feces (< 2%), suggesting pimavanserin maybe extensively absorbed from the intestine (> 98%). Absorption of pimavanserin occurs with a median Tmax of 6 h (range 4-24 h) and was generally unaffected by dose. The relative bioavailability of the tablet formulation with solution as reference is about 99.7%. Ingestion of a high-fat meal had no significant effect on rate (Cmax) and extent (AUC) of pimavanserin exposure. The formulation of the tablet used in the food effect studies is different from the proposed to be marketed formulation. However, [redacted] (b) (4) the differences in formulation is not like to be clinically meaningful.

2.3.3.5 What are the characteristics of drug distribution?

Pimavanserin is highly bound to plasma proteins ranging from 91% to 97% in humans. The blood-to-plasma ratio was 1.80, 1.55 and 1.51 at 0.05, 0.2 and 1 μM pimavanserin, suggesting there is little or no concentration-dependent partitioning of pimavanserin into red blood cells. The apparent volume of distribution of pimavanserin in humans was estimated to be approximately 2021.41L.

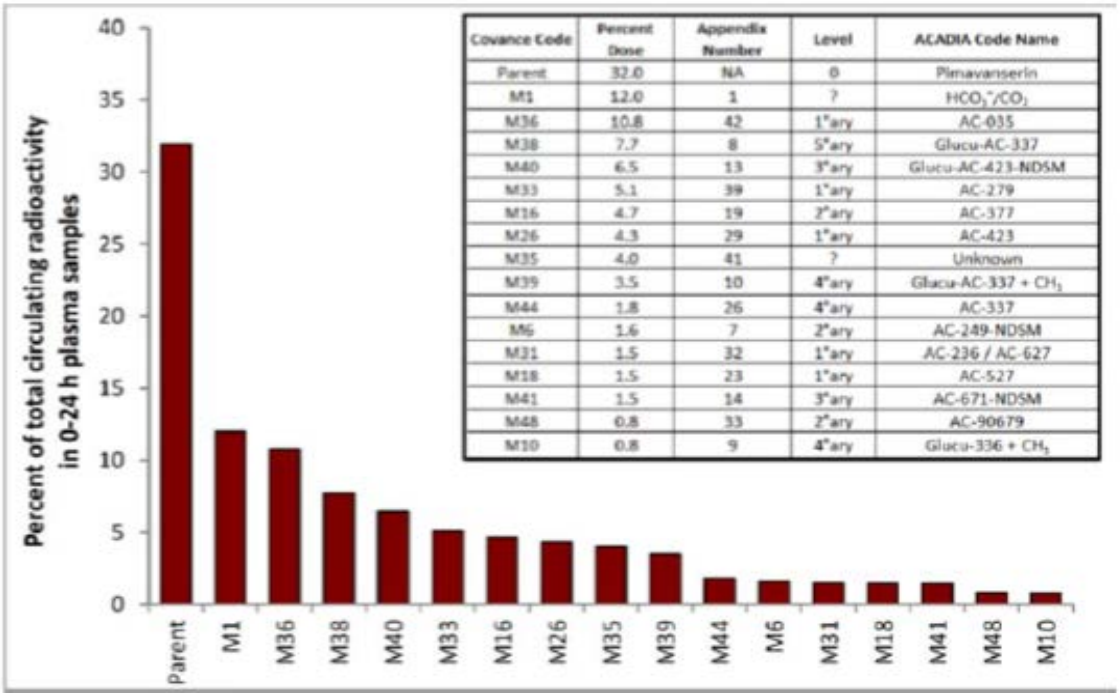
2.3.3.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

In the mass balance study conducted in humans low levels (<2% of dose) of unchanged pimavanserin are eliminated in urine (0.55%) and feces (1.53%), indicating that metabolism is the major route of elimination and that pimavanserin is principally eliminated via feces. Approximately 46% (mean 45.5 ± 4.5%) of the radioactive dose was excreted in feces and ~23% (mean 23.1 ± 3.3%) was excreted in urine.

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

Pimavanserin accounted for 32% of circulating drug-derived material. Metabolites represent approximately two-thirds of circulating drug-derived material. In addition to the unchanged pimavanserin, a total of 39 metabolites were detected by both radiometric HPLC and LC-MS/MS. With the exception of M1 and AC-279, all of the metabolite AUC values were <10% of the circulating radioactivity (total circulating drug-derived material) and <25% of parent AUC. M1 was putatively identified as radioactive carbon dioxide/bicarbonate (released from the radioactive urea moiety).

Figure 12: Human Plasma Metabolites as a Percentage of Circulating Drug-Derived Material (Total Radioactivity) in 0-24 Hour Plasma Samples Following Oral Dosing



Covance Code	Percent Dose	Appendix Number	Level	ACADIA Code Name
Parent	32.0	NA	0	Pimavanserin
M1	12.0	1	?	HCO_3^-/CO_2
M36	10.8	42	1°ary	AC-035
M38	7.7	8	5°ary	Glucu-AC-337
M40	6.5	13	3°ary	Glucu-AC-423-NDSM
M33	5.1	39	1°ary	AC-279
M16	4.7	19	2°ary	AC-377
M26	4.3	29	1°ary	AC-423
M35	4.0	41	?	Unknown
M39	3.5	10	4°ary	Glucu-AC-337 + CH_2
M44	1.8	26	4°ary	AC-337
M6	1.6	7	2°ary	AC-249-NDSM
M31	1.5	32	1°ary	AC-236 / AC-627
M18	1.5	23	1°ary	AC-527
M41	1.5	14	3°ary	AC-671-NDSM
M48	0.8	33	2°ary	AC-90679
M10	0.8	9	4°ary	Glucu-336 + CH_2

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

There is no evidence that enterohepatic recirculation takes place for pimavanserin. No double peak phenomenon was observed in PK studies for pimavanserin administered under conditions either with food intake or without.

2.3.3.9 What are the characteristics of drug excretion in urine?
Low levels of unchanged pimavanserin are eliminated in both urine (0.55%) and feces (1.53%). However, approximately 46% of the radioactive dose of pimavanserin was excreted in feces and about 23% was excreted in urine through the last collection interval (20 days) at which point cumulative excretion had reached a plateau. The renal clearance was approximately 2.01 L/h in healthy subjects.

Table 15: Summary of Mean (SD) Pharmacokinetic Parameter Data for [$_{14}$C]-Pimavanserin Total radioactivity in Urine and Feces

Parameter[1]	Units	Urine	Feces
$A_{eu(0-t)}$	mg	9.02 (1.31)	NA
$A_{ef(0-t)}$	mg	NA	17.7 (1.8)
%Excreted	%	23.1 (3.3)	45.5 (4.5)
CL_R	L/h	2.01 (0.326)	NA

Abbreviations: $A_{ef(0-t)}$, amount of drug excreted in the feces over the sampling interval of 0 to last measurable fecal contribution; $A_{eu(0-t)}$, amount of drug excreted in the urine over the sampling interval of 0 to last measurable urine contribution; CL_R, renal clearance from blood/plasma; %Excreted, percent excreted in the feces or urine; NA, not applicable; SD, standard deviation

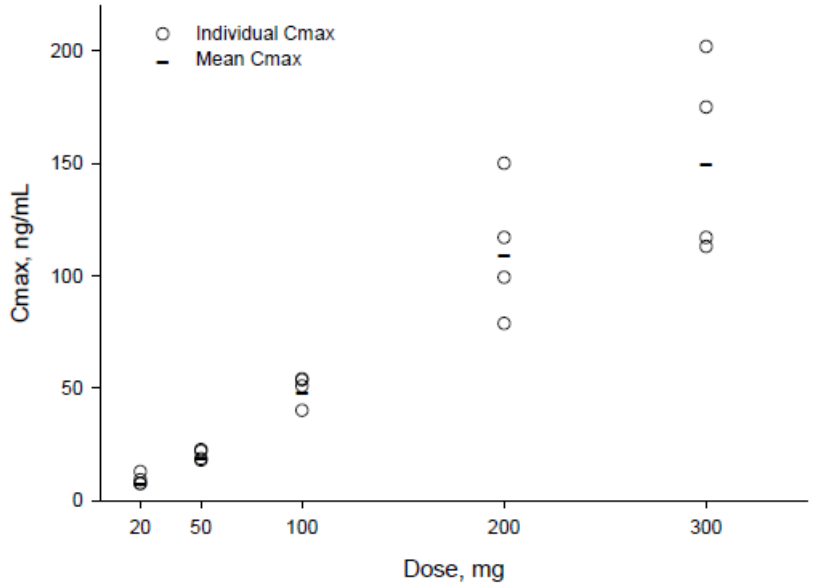
[1] Mean (SD)

Source: Study ACP-103-016

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

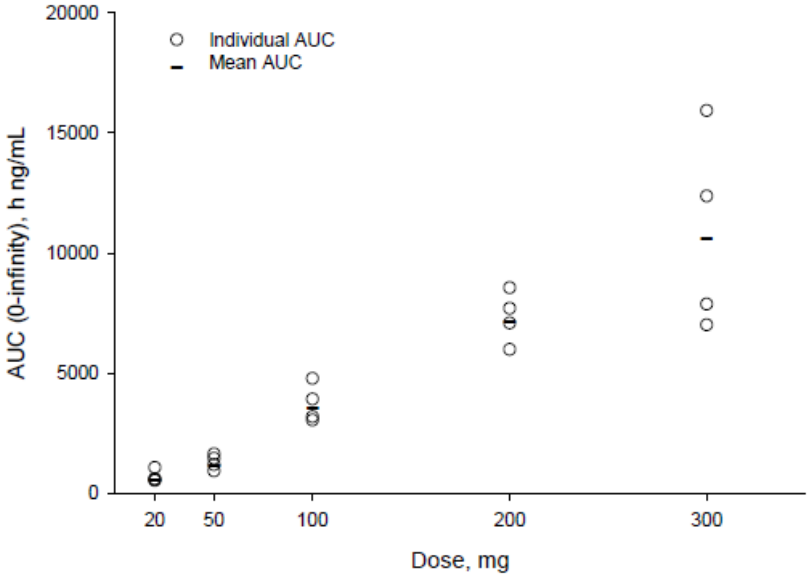
Mean Cmax and AUC(0-∞) increased dose proportionally over the dose range from 20 mg to 300 mg after single dose administration. After single- (Day 1) and multiple- (Day 14) dose administration of 50, 100 or 150 mg pimavanserin in healthy volunteers, pharmacokinetics of pimavanserin were dose-proportional.

Figure 12: Individual and mean Cmax of pimavanserin in human subjects after single oral administration of ACP-103 doses of 20 mg, 50 mg, 100 mg, 200 mg, and 300 mg (n=4 in all groups).



Source: Study ACP-103-001

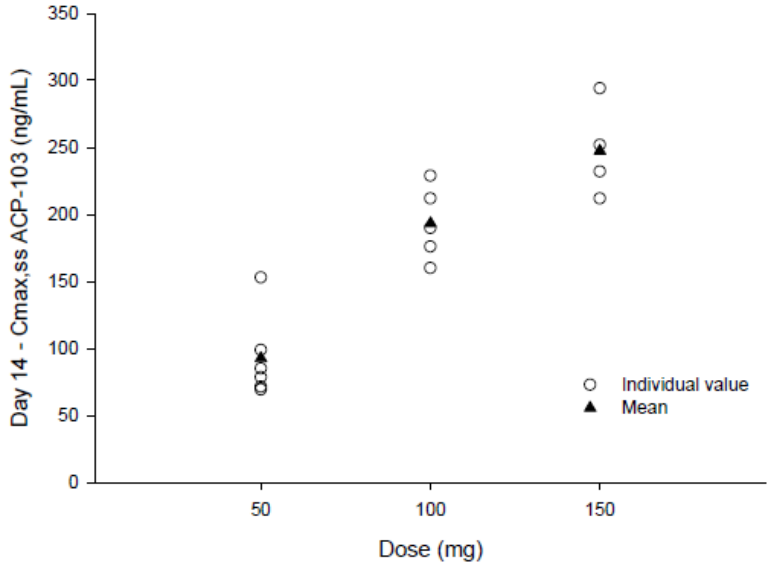
Figure 13: Individual and mean AUC (0-∞) of pimavanserin in human subjects after single oral administration of ACP-103 doses of 20 mg, 50 mg, 100 mg, 200 mg, and 300 mg (n=4 in all groups).



Source: Study ACP-103-001

Figure 14: Individual and mean Cmax,ss values of pimavanserin in human subjects after oral administration of ACP-103 doses of 50 mg , 100 mg, and 150 mg on Day 14.

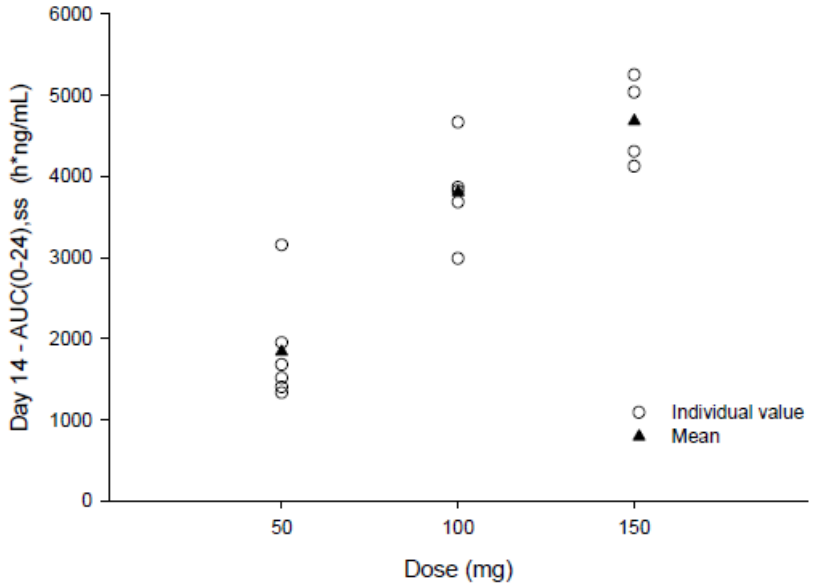
Multiple dose Day 14: 50 mg (n=6), 100 mg (n=5), and 150 mg (n=4)



Source: Study ACP-103-002

Figure 15: Individual and mean AUC(0-τ),ss values of pimavanserin in human subjects after oral administration of ACP-103 doses of 50 mg, 100 mg, and 150 mg on Day 14.

Multiple dose Day 14: 50 mg (n=6), 100 mg (n=5), and 150 mg (n=4)



Source: Study ACP-103-002

Power model analysis supported the observation that pimavanserin exhibit dose linearity. The following power model was used to assess dose linearity: Log (Parameter) = a + b * log (dose) Where 'a' is the intercept and 'b' is the slope. Linearity was assessed based on whether 95% confidence intervals constructed for the estimate of 'b' included a value of 1.0. The following tables contain the results of the power model analysis.

Table 16: Summary of Dose Proportionality Analysis (Power model) After Single Dose Administration

Parameter (unit)	Intercept			Slope		
	Estimate	SE	95% CI	Estimate	SE	95% CI
AUCinf (ng*h/mL)	3.2766	0.2975	(2.6515, 3.9016)	1.0495	0.0646	(0.9138, 1.1852)
Cmax (ng/mL)	-1.0539	0.2337	(-1.5449,-0.5629)	1.0680	0.0507	(0.9614, 1.1746)

Table 17: Summary of Dose Proportionality Analysis (Power model) After Multiple Dose Administration

Parameter (unit)	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)
Cmax (ng/mL)	-1.2084	0.3535	(-1.9578,-0.4590)	1.0841	0.0780	(0.9187, 1.2495)
Cmax,ss (ng/mL)	0.7785	0.5513	(-0.4125, 1.9696)	0.9554	0.1236	(0.6883, 1.2225)
Cmin,ss (ng/mL)	0.6214	0.5279	(-0.5190, 1.7617)	0.8875	0.1184	(0.6318, 1.1432)
Cavg,ss (ng/mL)	0.6878	0.5906	(-0.5882, 1.9637)	0.9284	0.1324	(0.6422, 1.2145)

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

There is no evidence of a circadian rhythm based on the pharmacokinetics of pimavanserin.

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

Accumulation of pimavanserin is consistent with its long half-life and was measured following multiple doses (14 days) both in healthy volunteers and Parkinson's Disease subjects. In healthy volunteers, the mean Cmax,ss to Cmax ratio was 4.3, 4.5 and 3.5 for 50 mg, 100 mg and 150 mg pimavanserin, respectively. The mean AUC(0-τ),ss to AUC(0-τ) ratio was 4.7, 4.8, and 3.7 for 50 mg, 100 mg and 150 mg pimavanserin, respectively. In Parkinson's subjects the mean Cmax,ss to Cmax ratio was 4.8 and 3.5 for 25 mg and 100 mg pimavanserin, respectively. The mean AUC(0-τ),ss to AUC(0-τ) ratio was 5.8 and 4.1 for 25 mg and 100 mg pimavanserin, respectively.

2.3.4 Intrinsic Factors

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

The effect of renal and hepatic impairment on the pharmacokinetics of pimavanserin has not been studied. Although formal pharmacokinetic analyses on the target population have not been performed, steady-state predose data suggest no differences in exposure were noted among PD patients and healthy volunteers. In a population pharmacokinetic analysis, the findings suggest that dosing of pimavanserin should not be adjusted based on body weight or height. Similarly, the effects of age on systemic exposure are relatively small and should not affect dosing. Evaluation of exposure in renal impaired patients who participated in the pivotal efficacy and safety study indicated there is not a clinically relevant difference in exposure between patients

with mild and moderate renal impaired patients and those who did not have renal impairment. (See figure 7). Since the effect of hepatic impairment has not been studied, the use of pimavanserin in hepatic impaired patients is not recommended.

2..3.4.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Since the effect of hepatic impairment has not been studied, the use of pimavanserin in hepatic impaired patients is not recommended. Based on population pharmacokinetic analyses, dosing of pimavanserin should not be adjusted based on body weight, height, and age

2.3.4.3 Does genetic variation impact exposure and/or response?

The sponsor did not evaluate the impact of genetic variation on exposure and/or response.

2.3.5 *Extrinsic Factors*

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

Pimavanserin was evaluated *in vitro* as a substrate for CYP and FMO enzymes and selected drug transporters, as an inducer of CYP enzymes, and as an inhibitor of 7 CYP enzymes and 7 drug transporters. AC-279 (*N*-desmethyl-pimavanserin) was evaluated as a substrate for selected transporters, as an inducer of CYP enzymes, and as an inhibitor of 7 CYP enzymes and 7 drug transporters. CYP3A4/5 is the major enzyme responsible for the metabolic clearance of pimavanserin. Pimavanserin is not a substrate for the efflux transporters P-gp and BCRP or the hepatic uptake transporters OATP1B1 and OATP1B3.

The *in vitro* studies of pimavanserin and its active metabolite AC-279 identified no perpetrator potential other than weak inhibition of intestinal CYP3A4/5 by pimavanserin and weak induction of CYP3A4/5 by AC-279, which were shown in a subsequent clinical interaction study with midazolam to be over-predictions. Accordingly, pimavanserin is not expected to affect the pharmacokinetics of concomitant drugs due to CYP inhibition, CYP induction or transporter inhibition

2.3.5.2 Is the drug a substrate of CYP enzymes?

CYP3A4 is the major enzyme responsible for the biotransformation of pimavanserin

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

Pimavanserin or its active metabolite AC-279 caused no significant inhibition of any of the 7 CYP enzymes examined. Pimavanserin and its active metabolite AC-279 (*N*-desmethylpimavanserin) were evaluated *in vitro* as reversible and irreversible inhibitors of the 7

major drug-metabolizing CYP enzymes in HLM: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and CYP3A4/5, and as inducers of CYP1A2, CYP2B6 and CYP3A4/5 mRNA levels in 3 preparations of cultured human hepatocytes. Results showed that pimavanserin may be a potential inhibitor of intestinal CYP3A4/5 *in vitro*, but this was shown in vivo not to be clinically relevant in a clinical study with midazolam. Results showed that AC-279 may be a potential inducer of CYP3A4/5 *in vitro*, but this was shown not to be clinically significant in a clinical study with midazolam.

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

Pimavanserin was evaluated as a substrate for the efflux transporters P-gp, BCRP, OATP1B1 and OATP1B3. Pimavanserin was evaluated as a potential inhibitor of 7 drug transporters: P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2. AC-279 was evaluated as a substrate for the efflux transporters P-gp and BCRP. It was also evaluated as a potential inhibitor of 7 drug transporters. Pimavanserin and AC-279 were both weak inhibitors of various transporters but none of the *Ratios* or *R* values of [inhibitor]/IC50 exceed FDA cutoff values, suggesting that neither pimavanserin nor AC-279 will cause clinically relevant inhibition of any of the 7 transporters examined.

Table 16: Summary of Results of the Transporter Inhibition Studies with Pimavanserin and AC-279

Transporter Type *FDA Ratio Cutoff*	**Transporter**	**Pimavanserin**		**AC-279**	
		IC_{50}[a]	***Ratio*** [b]	**IC_{50}[a]**	***Ratio*** [b]
Intestinal efflux *Ratio* ≥10	**P-gp**	34.6 µM	9.2	Not applicable for metabolites	
	BCRP	43.8 µM	7.3		
Intracellular efflux *Ratio* ≥0.1	**P-gp**	34.6 µM	0.007	46.5 µM	0.002
	BCRP	43.8 µM	0.006	17.9 µM	0.006
Hepatic uptake *Ratio* ≥0.1	**OATP1B1**	133 µM	0.002	27.3 µM	0.004
	OATP1B3	43 µM	0.006	127 µM	0.001
Hepatic uptake *R-value* ≥1.25	**OATP1B1**	133 µM	1.002	Not applicable for metabolites	
	OATP1B3	43 µM	1.007		
Renal uptake *Ratio* ≥0.1	**OAT1**	No inhibition observed		81.7 µM	0.001
	OAT3	No inhibition observed		40.5 µM	0.001
	OCT2	No inhibition observed		No inhibition observed	

[a] As recommended by the FDA, IC_{50} values are based on the nominal concentration of pimavanserin or AC-279.
[b] *Ratios* are based on [inhibitor]/IC_{50} where the inhibitor concentration is one of the following: intestinal concentration of pimavanserin (I_2 = dose/250 mL = 318 µM) for intestinal efflux transporters; total (bound + unbound) C_{max} at steady state (I_1 = 0.25 µM for pimavanserin and 0.11 µM for AC-279) for intracellular efflux transporter and hepatic uptake transporters, or unbound C_{max} at steady state (I = 0.0125 µM for pimavanserin and 0.0055 µM for AC-279) for renal transporters. For inhibition of hepatic uptake transporters by pimavanserin following oral dosing, *R* values were based on total C_{max} at the inlet to the liver ($[I]_{in,max}$ = 5.56 µM for pimavanserin).

Source: Clinical Pharmacology Summary

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

In vitro reaction phenotyping studies identified CYP3A4/5 as the major enzyme responsible for the metabolic clearance of pimavanserin. A clinical interaction study to evaluate the effects of ketoconazole, a strong inhibitor of CYP3A4/5, on the PK of pimavanserin was conducted. The study showed that inhibition of CYP3A4/5 by ketoconazole increased plasma Cmax of pimavanserin approximately 1.5-fold and increased AUC(0-∞) by about 3-fold. Dose adjustment to ½ the recommended dose is suggested. Food does not significantly affect the exposure (Cmax and AUC) of pimavanserin.

2.3.5.6 What are the drug-drug interactions?

2.3.5.6.1 Is Drug of interest impacted by co-administered other drugs?

Ketoconazole increased pimavanserin plasma Cmax of pimavanserin approximately 1.5-fold and increased AUC(0-∞) by about 3-fold. Dose adjustment to ½ the recommended dose is suggested. The following table contains the results of from the study.

Table 17: Effects of Ketoconazole, a Strong CYP3A4/5 Inhibitor, on the Pharmacokinetics of Pimavanserin

Parameter (Unit)	Pimavanserin Alone[a]	Pimavanserin w/Ketoconazole[b]	Ratio of Treatment Means (Pimavanserin + Ketoconazole/Pimavanserin Alone)	
	N=19	N=19	N=19	
Statistic	Mean ± SD[c]	Mean ± SD[c]	Ratio of Geometric Means	90% CI (LCL, UCL)
AUC_{0-t} (ng-h/mL)	1224 ± 433	3415 ± 768	2.872	2.665, 3.096
AUC_{0-inf} (ng-h/mL)	1257 ± 464	3783 ± 912	3.092	2.665, 3.096
C_{max} (ng/mL)	17.1 ± 3.8	25.1 ± 5.5	1.466	1.406, 1.528
T_{max} (h)	9.00	9.00	-	-
t½ (h)	58.2 ± 13.2	89.2 ± 25.4	-	-
CL/F (L/h)	36.2 ± 15.3	11.5 ± 4.3	-	-
V_z/F (L)	2836 ± 650	1397 ± 364	-	-

Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the concentration-time curve from time t of the last quantifiable concentration; CI, confidence interval; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; LCL, lower confidence limit; SD, standard deviation; t½, terminal elimination half-life; T_{max}, time to maximum plasma concentration; UCL, upper confidence limit; V_z/F, apparent volume of distribution

A 2-sided paired t-test was performed on the natural log-transformed pimavanserin AUC_{0-t}, AUC_{0-inf}, and C_{max} at the alpha level of 0.05.

[a] 40 mg pimavanserin single dose on Day 1

[b] 40 mg pimavanserin single dose with ketoconazole 400 mg once daily on Days 15-28

[c] Mean (±SD), except for T_{max} which is shown as median

Source: Study ACP-103-023 and Clinical Pharmacology Summary

2.3.5.6.2 Does Drug of interest impact other co-administered drugs?

Co-administration of midazolam, a probed drug for CYP3A4, with pimavanserin did not affect the pharmacokinetics of midazolam.

Based on *in vitro* findings, a clinical drug interaction study was conducted with midazolam, a sensitive *in vivo* probe drug for CYP3A4/5. The results show that, contrary to the *in vitro* predictions, dosing with pimavanserin for 1, 18 or 38 days had no significant effect on the PK of midazolam.

Table 18: Geometric Mean Ratios and 90% Confidence Intervals for AUC and Cmax of Midazolam

Ratio	Parameter	n	Ratio of Geometric Means (%)	90% CI (LCL) [a]	90% CI (UCL) [a]
Day 3/Day 1	Ln-transformed AUC_{0-inf}	24	103.15	96.14	110.67
	Ln-transformed AUC_{0-t}	24	102.64	95.39	110.44
	Ln-transformed C_{max}	24	107.52	98.83	116.98
Day 20/Day 1	Ln-transformed AUC_{0-inf}	19	95.27	87.87	103.29
	Ln-transformed AUC_{0-t}	19	94.09	86.44	102.42
	Ln-transformed C_{max}	19	95.49	86.05	105.97
Day 40/Day 1	Ln-transformed AUC_{0-inf}	18	86.05	76.33	97.02
	Ln-transformed AUC_{0-t}	18	83.95	74.27	94.88
	Ln-transformed C_{max}	18	105.63	91.79	121.56

Note: [a] LCL = lower confidence limit; UCL = upper confidence limit

Co-administration of carbidopa/levodopa (Sinemet) with pimavanserin did not affect the pharmacokinetics of levodopa. Because a significant portion of subjects in the pimavanserin clinical efficacy trials was concomitantly receiving carbidopa/levodopa, a study was conducted to assess the pharmacokinetics of levodopa when carbidopa/levodopa (Sinemet) was taken with pimavanserin. Comparison of levodopa PK parameters between treatments showed no statistically significant differences; the 90% CIs fell within 80% to 125%, indicating that co-administration of 40 mg pimavanserin with immediate-release carbidopa/levodopa has no significant effect on levodopa exposure

Table 19: Effects of Coadministering Pimavanserin with Carbidopa/Levodopa on the Pharmacokinetics of Levodopa

Parameter[a]	N	Ratio of Geometric Means	90% CI (LCL, UCL)	p-Value
AUC_{0-tau}	18	0.966	0.934, 0.999	<0.001
$C_{max(ss)}$	18	0.925	0.798, 1.072	0.053
$C_{min(ss)}$	18	0.980	0.864, 1.110	0.006

Abbreviations: AUC_{0-tau}, area under the concentration-time curve over the morning dose interval; CI, confidence interval; $C_{max,ss}$, maximum observed plasma concentration, steady state; $C_{min,ss}$, minimum observed plasma concentration at steady state; LCL, lower confidence limit; UCL, upper confidence limit

[a] All parameters were natural log-transformed

Source: Study ACP-103-024 and Clinical Pharmacology Summary

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

No. Pimavanserin is indicated as a monotherapy for PDP.

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

There is no known mechanistic basis for pharmacodynamics drug-drug interactions. The sponsor stated that the most frequent concomitant medications not indicated for motor function used in the target population are represented in the following table

Table 19: Most Frequent (≥5% of Subjects) Concomitant Medications Not Indicated for Motor Function in the PDP Placebo-controlled 6-week Studies

Preferred Term	Placebo (N=231) n (%)	PIM 10 mg (N=140) n (%)	PIM 20 mg (N=41) n (%)	PIM 40 mg (N=202) n (%)	All PIM (N=383) n (%)	Total (N=614) n (%)
Overall	202 (87.4)	108 (77.1)	38 (92.7)	176 (87.1)	322 (84.1)	524 (85.3)
Acetylsalicylic acid	69 (29.9)	27 (19.3)	12 (29.3)	66 (32.7)	105 (27.4)	174 (28.3)
Rivastigmine	36 (15.6)	11 (7.9)	7 (17.1)	31 (15.3)	49 (12.8)	85 (13.8)
Simvastatin	31 (13.4)	13 (9.3)	5 (12.2)	28 (13.9)	46 (12.0)	77 (12.5)
Multivitamins	38 (16.5)	11 (7.9)	4 (9.8)	26 (12.9)	41 (10.7)	79 (12.9)
Paracetamol	18 (7.8)	10 (7.1)	4 (9.8)	25 (12.4)	39 (10.2)	57 (9.3)
Clonazepam	31 (13.4)	8 (5.7)	8 (19.5)	22 (10.9)	38 (9.9)	69 (11.2)
Levothyroxine	21 (9.1)	12 (8.6)	2 (4.9)	20 (9.9)	34 (8.9)	55 (9.0)
Docusate	23 (10.0)	12 (8.6)	4 (9.8)	17 (8.4)	33 (8.6)	56 (9.1)
Omeprazole	27 (11.7)	10 (7.1)	4 (9.8)	19 (9.4)	33 (8.6)	60 (9.8)
Donepezil	23 (10.0)	6 (4.3)	6 (14.6)	20 (9.9)	32 (8.4)	55 (9.0)
Macrogol	22 (9.5)	5 (3.6)	2 (4.9)	23 (11.4)	30 (7.8)	52 (8.5)
Escitalopram	17 (7.4)	6 (4.3)	6 (14.6)	16 (7.9)	28 (7.3)	45 (7.3)
Vitamin D NOS	20 (8.7)	3 (2.1)	2 (4.9)	23 (11.4)	28 (7.3)	48 (7.8)
Ubidecarenone	11 (4.8)	11 (7.9)	5 (12.2)	10 (5.0)	26 (6.8)	37 (6.0)
Alprazolam	13 (5.6)	4 (2.9)	7 (17.1)	14 (6.9)	25 (6.5)	38 (6.2)
Fusosemide	21 (9.1)	9 (6.4)	1 (2.4)	15 (7.4)	25 (6.5)	46 (7.5)
Ibuprofen	21 (9.1)	8 (5.7)	0 (0.0)	17 (8.4)	25 (6.5)	46 (7.5)
Metoprolol	30 (13.0)	9 (6.4)	2 (4.9)	14 (6.9)	25 (6.5)	55 (9.0)
Cyanocobalamin	21 (9.1)	5 (3.6)	3 (7.3)	16 (7.9)	24 (6.3)	45 (7.3)
Lisinopril	18 (7.8)	2 (1.4)	2 (4.9)	19 (9.4)	23 (6.0)	41 (6.7)
Finasteride	9 (3.9)	7 (5.0)	2 (4.9)	13 (6.4)	22 (5.7)	31 (5.0)
Ascorbic acid	16 (6.9)	7 (5.0)	2 (4.9)	11 (5.4)	20 (5.2)	36 (5.9)
Atorvastatin	11 (4.8)	4 (2.9)	1 (2.4)	15 (7.4)	20 (5.2)	31 (5.0)
Folic acid	7 (3.0)	6 (4.3)	2 (4.9)	12 (5.9)	20 (5.2)	27 (4.4)
Potassium	17 (7.4)	5 (3.6)	1 (2.4)	14 (6.9)	20 (5.2)	37 (6.0)

Source: ISS, Table PDP6 1-4.5
Note: The 2013 March version of the WHO Drug Dictionary (WHODD) was used to code medications. WHO ATC Class was from ATC level 3.
The summary table was displayed in descending order of frequency based on the 'All PIM' group.
Note: ≥5% of subjects in 'All PIM' group.

Source: Clinical Pharmacology Aid

2.4 General Biopharmaceutics

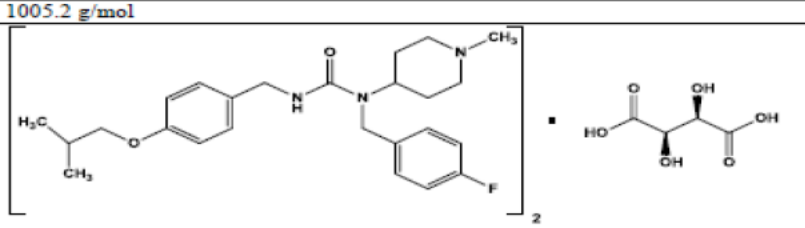
2.4.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

An official determination was not made during this review because a formal request was not included in the application. Refer to Biopharmaceutics review for further comments. (b) (4)

(b) (4)

The sponsor states that the dissolution profile data indicate that ≥ (b) (4)% of the pimavanserin label claim (17 mg per tablet) is released within 15 minutes (b) (4)
Refer to Biopharmaceutics review for details of Dissolution data and information on BCS classification.

Table 20: Physicochemical Properties of Pimavanserin Tartrate

USAN:	Pimavanserin tartrate	
Chemical Name(s)	Urea, *N*-[(4-fluorophenyl) methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1)	
CAS Registry No.	706782-28-7	
Molecular Formula	$(C_{25}H_{34}FN_3O_2)_2.C_4H_6O_6$	
Formula Weight	1005.2 g/mol	
Structural Formula	 (427.55 g/mol free base)$_2$ • (150.09 g/mol tartaric acid) = 1005.20 g/mol tartrate salt	
Appearance	White to off-white powder	
Melting Range by DSC	Onset between (b) (4)	
pKa	8.6	
Log D	1.4 at pH 4.0; >3.0 at pH 7.4	
Log P	4.67 (calculated)	
Solubility	Solvent	Pimavanserin tartrate solubility[a]
	Water	Freely soluble
	(b) (4)	
	(b) (4)	
[a]Solubility description follows current USP.		
	(b) (4)	

Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods

2.4.2 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

The proposed commercial pimavanserin 17 mg tablets (containing 20 mg of pimavanserin tartrate) and the Phase 3 clinical trial materials are the same except for product identifiers (tablet deboss impression) (b) (4)

The composition of Pimavanserin TBM and the Clinical Trial Formulations are provided in the following table.

Table 21: Clinical and Proposed Commercial Pimavanserin Formulations

Development Phase	Formulation Phase 1 and Phase 2				Formulation Phase 3[a]		Commercial
Formulation / Ingredients	(b) (4)		Tablet		Tablet		Tablet
			5 mg[b,c]	20 mg[b,d]	5 mg[b,c]	20 mg[b,d]	20 mg[b,d]
Pimavanserin tartrate (drug substance)				(b) (4)			(b) (4)
(b) (4)							
Microcrystalline cellulose, NF							
(b) (4)							
Pregelatinized Starch, NF							
Magnesium stearate, NF							
(b) (4)							
Clinical trial protocol	ACP-103-001 ACP-103-003 ACP-103-011 ACP-103-016	ACP-103-002 ACP-103-008 ACP-103-010	ACP-103-005	ACP-103-001 ACP-103-004 ACP-103-005 ACP-103-006 ACP-103-007 ACP-103-009 ACP-103-010	ACP-103-012 ACP-103-014	ACP-103-010 ACP-103-012 ACP-103-014 ACP-103-015 ACP-103-017 ACP-103-018 ACP-103-019 ACP-103-020 ACP-103-023 ACP-103-024 ACP-103-027 ACP-103-029	NA

NA = Not Applicable

a The 20 mg Phase 3 formulation was also used in NDA-enabling Phase 1 and Phase 2 clinical studies.

b (b) (4)

c

d 20 mg of pimavanserin tartrate corresponds to 17 mg of pimavanserin free base.

e (b) (4)

f

g

h

The pharmacokinetic parameters for the (b) (4) and immediate-release tablet formulation were comparable

Table 22: Analysis of Variance for Pharmacokinetic Parameters: Pimavanserin Tartrate Tablet versus Solution

Parameters	Arithmetic Mean Solution Fasted	Arithmetic Mean Tablet Fasted	Geometric LS Mean Tablet Fasted	Geometric LS Mean Solution Fasted	Tablet Fasted/ Solution Fasted Ratio (%)	90% CI	p-value
C_{max} (ng/mL)	51.4	57.0	56.1	50.8	110.5	100.5-121.4	0.0851
AUC_{0-t} (ng-h/mL)	3517.1	3578.8	3520.4	3486.4	101.0	92.7-110.1	0.8454
AUC_{inf} (ng-h/mL)	3847.4	3870.9	3795.0	3805.5	99.7	90.9-109.4	0.9590

Reference: Study ACP-103-001 Table 7
AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to the last measurable plasma concentration-time point
AUC_{inf}: Area under the plasma concentration-time curve from time 0 to infinity (extrapolated)
C_{max}: Maximum plasma concentration

Source: Clinical Pharmacology Summary Aid

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

The PK properties of pimavanserin are not significantly affected by food, except for an increase in median Tmax (6 h fasted vs 10.5 h fed). The 90% CIs were within the 80% – 125% interval when comparing the absence of food effect on pimavanserin pharmacokinetics.

It must be noted that the formulation used in the food effect study is different from the proposed commercial formulation. However, based on the high degree of absorption , the relative bioavailability with solution as reference of 99.7%, the reported solubility pimavanserin and dissolution characteristics of the drug product, (b) (4) it is expected that the difference in formulation used in the food effect study and the proposed TBM formulation would not be clinically meaningful.

Table 23: Analyses of Variance for Pimavanserin Pharmacokinetic Parameters: Fed versus Fasted

Parameters	Arithmetic Mean Tablet Fed	Arithmetic Mean Tablet Fasted	Geometric LS Mean Tablet Fed	Geometric LS Mean Tablet Fasted	Tablet Fed/ Tablet Fasted Ratio (%)	90% CI	*p*-value
C_{max} (ng/mL)	52.2	57.0	51.1	56.1	91.1	82.9-100.1	0.1033
AUC_{0-t} (ng*h/mL)	3929.6	3578.8	3806.8	3520.4	108.1	99.2-117.9	0.1319
AUC_{inf} (ng*h/mL)	4269.1	3870.9	4108.3	3795.0	108.3	98.7-118.8	0.1550

Reference: Study ACP-103-001 Table 7
AUC_{0-t}: Area under the plasma concentration-time curve from time 0 to last measurable plasma concentration-time point
AUC_{0-} Area under the plasma concentration-time curve from time 0 to infinity (extrapolated)
C_{max}: Maximum plasma concentration

Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods

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

Only one strength, 20 mg pimavanserin (17 mg active moiety) is being proposed to-be marketed. The proposed dose is 40 mg (34 mg active moiety) to be given as 2 of the 20 mg (17 mg active moiety) strength.

2.5 Analytical Methods

2.5.1 What bioanalytical methods are used to assess concentrations of Pimavanserin and its metabolite, AC-279 (N-desmethyl pimavanserin) and is the validation complete and acceptable?

Three methods using high performance liquid chromatography-tandem mass spectrometric (LC-MS/MS) have been validated for the quantitative determination of pimavanserin concentrations in heparinized human plasma samples. One of these methods also includes the quantification of pimavanserin' s major circulating N-desmethyl- pimavanserin metabolite, AC-279

Table 24: Bioanalytical Method Validation and Validation Summary*

Analyte	Validation Report Reference	Issue Date	Clinical Study	Matrix	Validation Summary
ACP-103 (concentrations reflect the free base form of pimavanserin)	(b) (4) Study BA020036 Appendix 1 ACP103-P1A	March 11, 2003 Report revision 1: August 24, 2004 Report Revision 2: May 11, 2006	ACP-103-001; ACP-103-002; ACP-103-005; ACP-103-006 (Aptuit); ACP-103-007 (Aptuit); ACP-103-009; ACP-103-011	Human plasma containing sodium heparin	Range: 0.500 to 500 ng/mL Inter-batch mean accuracy and precision of QCs: accuracy 104.80 to 108.13%, precision 3.30 to 4.05% Intra-batch accuracy and precision (range 0.50-376 ng/mL): accuracy 102.40 to 110.00%, precision 2.57 to 5.07%.
ACP-103 (concentrations reflect the tartrate salt of pimavanserin unless noted)	(b) (4) Study (b) (4) S06-166	June 18, 2007; amended June 29, 2007 to correct an error in the status of run 2 (accepted to rejected) Amendment 2 October 21, 2013 to change footnote on the reference standards table (pg. 6)	ACP-103-008; ACP-103-010; ACP-103-012; ACP-103-014; ACP-103-016; ACP-103-018; ACP-103-020;	Human plasma containing lithium heparin; ACP-103-008, ACP-103-018 used sodium heparin	Range: 0.100 to 100 ng/mL Intra-Assay Accuracy (%Bias): -2.8 to 18.0%** Intra-Assay Precision (%CV): 3.8 to 5.7% Inter-Assay Accuracy (%Bias): -1.3 to 6.0% Inter-Assay Precision (%CV): 0.0 to 10.3%
ACP-103 (concentrations reflect the free base form of pimavanserin)	(b) (4) Study (b) (4) S13-082	September 18, 2014; amended September 8, 2014 to correct to clarify details regarding reference materials	ACP-103-023 ACP-103-027 ACP-103-029	Human plasma containing lithium heparin	Range: 0.100 to 100 ng/mL Intra-Assay Accuracy (%Bias): 3.0 to 10.0% (LLOQ) and 1.0 to 8.3% (Low-High) Intra-Assay Precision (%CV): 2.1 to 4.1% (LLOQ) and 1.2 to 4.6% (Low-High) Inter-Assay Accuracy (%Bias): 7.0% (LLOQ) and 3.9 to 7.0% (Low-High) Inter-Assay Precision (%CV): 3.3% (LLOQ) and 0.0 to 2.3% (Low-High)

*All methods are LC-MS/MS methods and were fully validated (see NDA Section 5.3.1.4 for method validation reports)
** Values >15.0% are for LLOQ QC

Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods.

The analytical methods are acceptable.

2.5.2 Which metabolites have been selected for analysis and why?

AC-279 is the only major circulating metabolite of pimavanserin that is of interest. It is pharmacologically active and has similar receptor activity to pimavanserin. Pimavanserin is extensively metabolized; however, of the 42 human metabolites, only two, AC-279 (*N*-desmethyl-pimavanserin) and M1, were 25% or greater of parent AUC and/or greater than 10% of the total circulating drug-derived material AUC. Chromatographic profile of M1 and radioactive bicarbonate ($H^{14}CO_3^-$), strongly suggest CO_2 is the highly polar metabolite M1 and therefore MIST and DDI considerations are irrelevant.

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

The total plasma concentrations of pimavanserin and the major metabolite AC-279 have been measured in clinical studies. Protein binding did not vary with drug concentration.

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

The range and fitting of the standard curve, lower and upper limits of quantitation for each bioanalytical method used to measure pimavanserin and AC-279 levels in plasma is provided in the table below. The performance of the assay method was evaluated and the assay met all acceptance criteria prior to sample analysis.

Table 25: Bioanalytical Methods: Range and Fitting of Standard Curve, Lower and Upper Limits of Quantitation

Analytical Validation Report	Standard Curve Range	Curve Fitting	LLOQ	ULOQ
(b) (4) 2002-1093-BIO	Pimavanserin: 0.5 - 500 ng/mL (for 100 µL of heparinized human plasma)	Weighted (1/x) linear regression based on analyte:IS peak area ratios on Watson LIMS System (Version 6.1.1)	0.5 ng/mL	500 ng/mL
(b) (4) R07-035	Pimavanserin: 0.100 - 100 ng/mL (for 150 µL human plasma, lithium heparin)	Linear $1/x^2$	0.1 ng/mL	100 ng/mL
(b) (4) R13-082	Pimavanserin: 0.100 - 100 ng/mL (for 200 µL human plasma, lithium heparin) AC-279: 0.500 - 500 ng/mL (for 200 µL human plasma, lithium heparin)	Pimavanserin: Quadratic $1/x^2$ AC-279: Quadratic $1/x^2$	PIM: 0.1 ng/mL AC-279: 0.5 ng/mL	PIM: 100 ng/mL AC-279: 500 ng/mL

IS, Internal Standard; LLOQ, lower limit of quantitation; ULOQ, upper limit of quantitation; PIM, pimavanserin

Source: Clinical Pharmacology Summary Aid

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

The range of the standard curve(s), lower and upper limits of quantification, lower limit of detection, and accuracy and precision at these limits from the individual analytical validation reports are given in the following tables

Table 26: Analytical Performance of Pimavanserin Calibration Standards in Heparinized Human Plasma (Study (b) (4)-2002-1093-BIO)

	Concentrations (ng/mL)						
	0.500	1.00	10.0	50.0	100	250	500
Mean	0.495	0.986	10.3	50.5	98.9	248	503
SD	0.0404	0.0192	0.343	1.2	4.49	14.1	24.7
%CV	8.16	1.95	3.33	2.38	4.54	5.69	4.91
%Theoretical	99.0	98.6	103.0	101.0	98.9	99.2	100.6
%Bias	-1.0	-1.4	3.0	1.0	-1.1	-0.8	0.6
N	6	6	6	5	6	6	6

Source: Clinical Pharmacology Summary Aid

Table 27: Analytical Performance of Pimavanserin Calibration Standards in Heparinized Human Plasma (Study (b) (4) R07-035)

	Concentrations (ng/mL)							
	0.100	**0.200**	**0.400**	**2.00**	**10.0**	**50.0**	**80.0**	**100**
Mean	0.0996	0.201	0.404	1.95	10.1	51.7	80.3	95.8
SD	0.00677	0.0112	0.0182	0.0647	0.514	2.80	3.99	6.41
%CV	6.8	5.6	4.5	3.3	5.1	5.4	5.0	6.7
%Bias	-0.4	0.5	1.0	-2.5	1.0	3.4	0.4	-4.2
n	6	6	6	5	6	6	6	6

Source: Clinical Pharmacology Summary Aid

Table 28: Analytical Performance of Pimavanserin Calibration Standards in Heparinized Human Plasma (Study (b) (4) R13-082)

	Concentrations (ng/mL)							
	0.500	**1.00**	**5.00**	**25.00**	**100**	**300**	**450**	**500**
Mean	0.507	0.965	5.15	24.9	101	285	456	522
SD	0.0156	0.0315	0.157	0.610	4.90	15.8	26.6	38.9
%CV	3.1	3.3	3.0	2.4	4.9	5.5	5.8	7.5
%Bias	1.4	-3.5	3.0	-0.4	1.0	-5.0	1.3	4.4
n	6	6	6	6	6	6	6	6

Source: Clinical Pharmacology Summary Aid

Table 29: Analytical Performance of AC-279 Calibration Standards in Heparinized Human Plasma (Study (b) (4) R13-082)

	Concentrations (ng/mL)							
	0.500	**1.00**	**5.00**	**25.00**	**100**	**300**	**450**	**500**
Mean	0.507	0.965	5.15	24.9	101	285	456	522
SD	0.0156	0.0315	0.157	0.610	4.90	15.8	26.6	38.9
%CV	3.1	3.3	3.0	2.4	4.9	5.5	5.8	7.5
%Bias	1.4	-3.5	3.0	-0.4	1.0	-5.0	1.3	4.4
n	6	6	6	6	6	6	6	6

Source: Clinical Pharmacology Summary Aid

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

Stability data are provided in the following tables

Table 30: Sample Stability – Pimavanserin (Study (b) (4)-2002-1093-BIO)

Condition	Time Period
Freeze thaw stability at –70°C in polypropylene tubes in heparinized human plasma	At least 4 cycles
Heparinized human plasma at room temperature (~21°C)	At least 24 hours
Autosampler (storage at ~5°C)	At least 8 days
Stock Solutions at ~4°C	At least 28 days
Working Stock Solutions at –20°C	At least 31 days
Working Standard Solutions at –20°C	At least 57 days
Working Standard Solutions at room temperature (~21°C)	At least 24 hours
Working internal standard solutions at room temperature (~21°C)	At least 22 hours

Source: Clinical Pharmacology Summary Aid

Table 31: Sample Stability – Pimavanserin (Study (b) (4)R07-035)

Condition	Time Period
Freeze / Thaw Stability in Matrix	5 cycles
Stability in Matrix at room temperature	5 hours
Short Term Stability in Matrix at -20°C	27 days
Long Term Stability in Matrix at -20°C and -70°C for calibration range of 0.500 to 500 ng/mL	392 Days
Stock Solution Stability at room temperature (in DMF)	7 hours
Standard Solution Stability at room temperature (acetonitrile:water, 50:50 v/v)	6 hours
Stock Solution Stability at 1 to 8°C (in DMF)	133 days
Reinjection reproducibility at room temperature	98 hours

Source: Clinical Pharmacology Summary Aid

Table 32: Sample Stability – Pimavanserin (Study (b) (4)R13-082)

Condition	Time Period
Freeze / Thaw Stability in Matrix	4 cycles
Stability in Matrix at room temperature	6 hours
Long Term Stability in Matrix at -20 °C	7 days
Long Term Stability in Matrix at -70 °C	49 Days
Stock Solution Stability at room temperature (in DMF)	6 hours
Standard Solution Stability at room temperature (acetonitrile:water, 50:50 v/v)	6 hours
Stock Solution Stability at 5 °C (in DMF)	133 days
Reinjection reproducibility at room temperature	173 hours

Source: Clinical Pharmacology Summary Aid

Table 33: Sample Stability – AC-279 (Study (b) (4) R13-082)

Condition	Time Period
Freeze / Thaw Stability in Matrix	4 cycles
Stability in Matrix at room temperature	6 hours
Long Term Stability in Matrix at -20 °C	7 days
Long Term Stability in Matrix at -70 °C	49 Days
Stock Solution Stability at room temperature (in DMF)	6 hours
Standard Solution Stability at room temperature (acetonitrile:water, 50:50 v/v)	6 hours
Stock Solution Stability at 5°C (in DMF)	235 days
Reinjection reproducibility at room temperature	173 hours

Source: Clinical Pharmacology Summary Aid

3. Appendix

3.1 Pharmacometric Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Do exposure-response relationships for efficacy and safety support a 40 mg dose regimen of pimavanserin in patients with Parkinson's disease psychosis?

Yes, the proposed 40mg QD dose is reasonable. Pivotal phase III clinical trial ACP-103-020 showed significant antipsychotic efficacy at the 40 mg dose in patients with Parkinson's disease psychosis (PDP) as measured using the 9-item SAPS-PD scale. In the second supportive clinical trial ACP-103-012, there was an observation of a 42% response rate in the placebo group and no significant superior antipsychotic efficacy achieved at 40 mg dose compared with placebo group. Data reanalysis within the North American Region appeared to reduce the placebo response, as it appeared that the non-North American region had an unusually high percentage of responders. **(Figure 2)**. Notably, centralized ratings were used in evaluation of primary measure in US population. Based on this retrospective analysis of ACP-103-012, the Sponsor modified the protocol for ACP-103-020 to address the high placebo response. Thus we think it is reasonable to exclude all non-north American individuals in our pooled exposure-response (E-R) analysis.

Our exposure–response analysis was conducted with North American data pooled together from Studies ACP-103-012, ACP-103-104 and ACP-103-020 **(Figure 1)**. E-R relationship showed that the sponsor's proposed dose of 40mg QD has greater percentage change from baseline in SAPS-PD score compared with lower doses (10 mg QD, 20 mg QD). Final results were generalized as SAPS-PD percentage change from baseline in **Figure 1**. Based on the available data, further increase in the dose to levels greater than 40 mg appear unlikely to result in an increase in efficacy.

The four kinds of adverse event (hallucinations, confusion, edema, and gait disturbance) were not found to be correlated pimavanserin concentration.

Figure1. SAPS-PD Percentage Change from Baseline vs. Steady State Plasma Concentration at 6 Weeks in North American Population

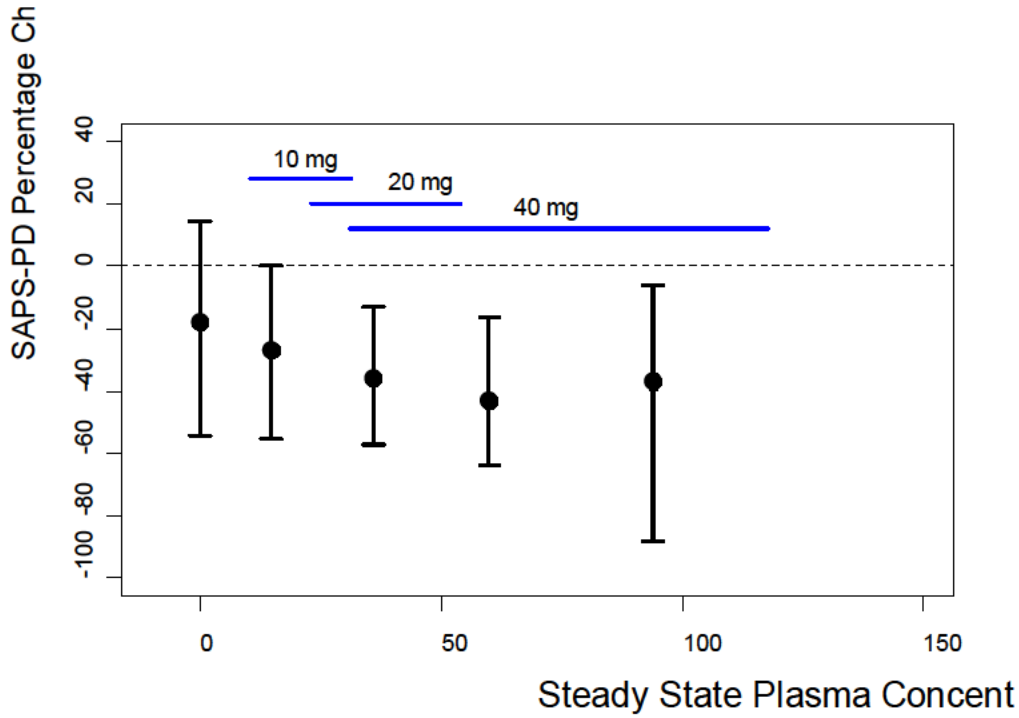


Figure 1: Vertical line and label in X axis represent cutoff of four exposure quartiles; points and error bar represent median and 25%-75% percentiles of the observed percentage change from baseline in placebo group and each exposure quartile; blue horizontal lines and label on the top represent 5%-95% percentile of steady state plasma concentration at each dose level. Dashed line represents no change compared with baseline SAPS-PD score. (N_{pl}=150, N_{10mg}=50, N_{20mg}=15, N_{40mg}=109)

Figure 2. Justification for Excluding Non-North American subjects

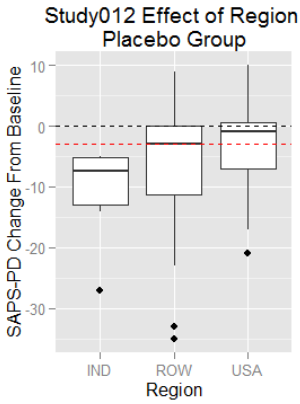


Figure 2: In study ACP-103-012, SAPS-PD change from baseline score were compared in different regions within placebo group. Black dash line represents no change from baseline. Red Dash line represents change in score that the sponsor proposed as clinically significant (CFB=-3). Left: (N_{IND}=10, N_{ROW}=44, N_{USA}=43).

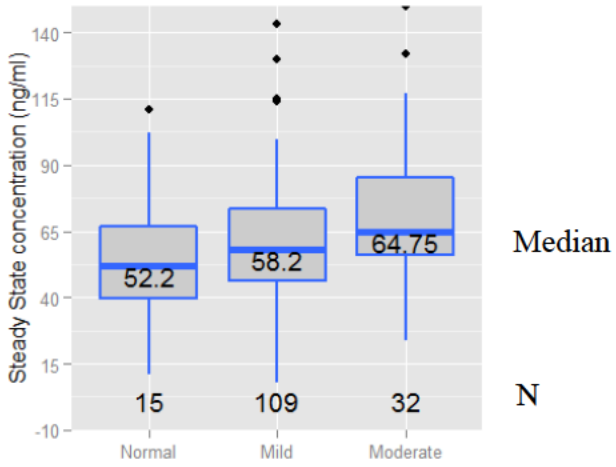
1.1.2 Is dose adjustment needed for renal impaired populations?

No, dose adjustment is not needed for mild or moderate renal impaired population. Univariate comparison of steady state plasma concentration of normal, mild and moderate renal impaired populations is illustrated in **Figure 3**. It is important to note from **Figure 3** that most patients enrolled in the clinical program had mild or moderate renal impairment, so most of the safety database is in patients with some degree of renal dysfunction. This also suggests that when comparing concentration in patients with moderate renal impairment, the most appropriate comparator is the mild renal impairment group, rather than patients with normal renal function. This comparison yields a modest increase in patients with moderate renal impairment of ~10%. Although population PK modeling also shows that creatinine clearance is a significant covariate for apparent clearance, the effect is small and in line with observed concentrations. Furthermore, since ~23% of radioactive drug was excreted in urine and 46% of the radioactive drug was excreted in feces, the main elimination pathway for pimavanserin is metabolism. For all of these reasons, no dose adjustment is needed in these populations.

There is insufficient data to accurately project the expected pimavanserin concentrations in patients with severe renal impairment. There was only one patient in the clinical program who can be clearly categorized as having severe renal impairment. This individual's 40 mg dose-normalized steady state concentration was 74 ng/ml, which is consistent with the moderate renal impairment group in **Figure 3.** Although we would not a priori expect an increase in this population, there is PK data from patients suggesting a positive relationship between creatinine clearance and pimavanserin exposure. Given this uncertainty, it might seem appealing to recommend a lower starting dose (i.e., 20 mg) in patients with severe renal impairment and allow them to titrate to the 40 mg dose, but in the absence of a both an exposure-response relationship for safety and a clear definition of a 'responder' it is unclear how physicians would titrate patients in practice. It may also turn out that there is no increase in exposure in patients with severe renal impairment, which would make titration unnecessary. (b) (4)

[redacted]

Figure3. Steady-State Pimavanserin Concentration in Different Groups of Renal Function



Note: Three studies ACP-103-012, ACP-103-104 and ACP-103-020 were pooled together and only the 40 mg dosing regimen is included. Trough plasma concentration observation at day 29 for each individual was used as steady state concentration. Steady state concentration in each renal function level was compared in box plot. Renal function level is determined by creatinine clearance. Median concentration in normal population (CRCL>=90) and mild (CRCL: 60-89) or moderate (CRCL: 30-59) renal impaired population were labeled. Number in the bottom indicated N number in each group.

Does this drug prolong the QT/QTc Interval?

Yes, an increase of about 8 ms is expected at 40 mg pimavanserin with a CI of 6.4 ms to 9.1ms. (**Figure 4)**. Sponsor included doses of 20 mg and 80 mg in their thorough QT study, but not a 40 mg dose. Pimavanserin 20 mg had no clinically meaningful effect on the QTc interval. The point estimates were 6.6 ms and the upper bound of the CI did not exceed 10.0 ms. Pimavanserin 80 mg dose was associated with a time-matched maximal mean corrected QT interval (QTcI) increase of 10.7 ms and an upper CI of 13 ms. Pimavanserin 40 mg was predicted to prolong the QTc with a mean of 7.8 and an upper 90% CI of 9.1 ms. For further details, refer to the QT-IRT review by Dr. Zhang (10/27/2015).

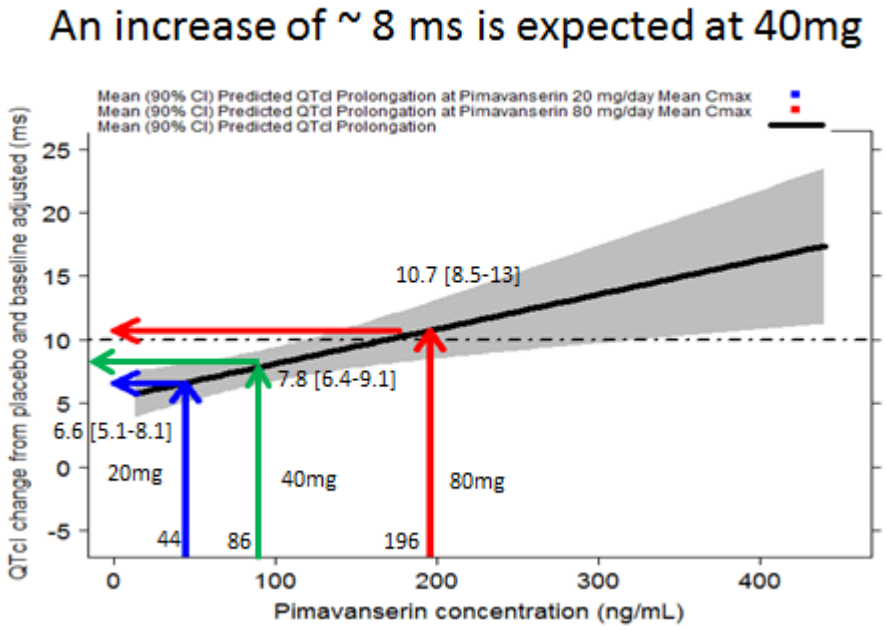


Figure 4: A single regression linear model was used to describe the data.

1.2 Recommendations

The sponsor's proposed dosing regimen of 40 mg appears reasonable.

2 PERTINENT REGULATORY BACKGROUND

Pimavanserin is a new molecular entity, characterized as a serotonin-selective, inverse agonist that preferentially targets the 5-HT2A receptor subtype. It has been developed for the treatment of psychosis associated with Parkinson's disease under IND 68384 and currently holds breakthrough therapy designation. There is currently no approved product for this indication. A pre-NDA meeting was held with the Sponsor on June 2, 2014, where DPM commented that the Sponsor's population PK approach seemed reasonable and encouraged the Sponsor to also perform exposure-response analysis for safety.

3 RESULTS OF SPONSOR'S ANALYSIS

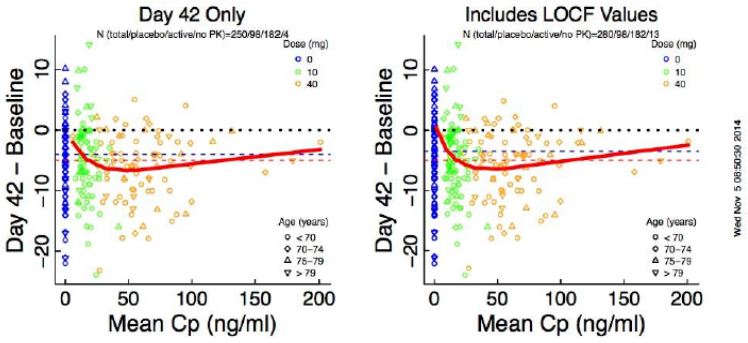
3.1 Exposure Response Analysis

Exposure-response analysis for SAPS-PD in individual phase III studies **(Figure 5)** and pooled phase III studies **(Figure 6)** were conducted using graphical methods. Mean plasma concentration (C_p) was defined as 0 in placebo patients and calculated as the mean plasma level on the day of the SAPS measurement for those patients receiving pimavanserin. Day 42 SAPS-PD score minus the baseline value was used as the response variable. A smoother was used to show trends in the data. **Table 1** summarizes the database used by the Sponsor. Two analyses were included: one limited to patients who had Day 42/Day 43 data and the other including LOCF values.

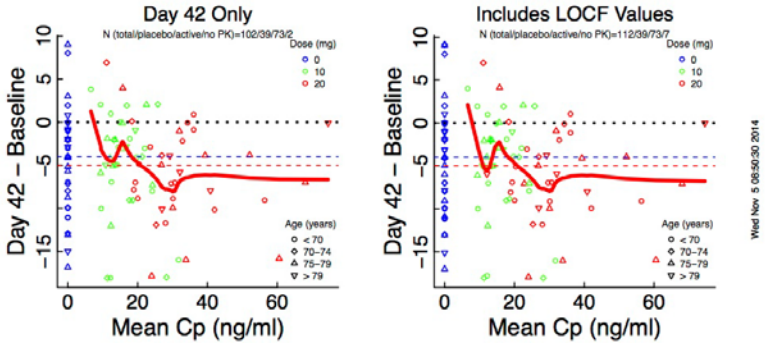
Table 1: Subjects Include in Sponsor's Analysis

Study	Placebo	Pimavanserin With Both PK + SAPS Data	Pimavanserin Without Both PK + SAPS Data
ACP-103-012	98	183	13
ACP-103-014	39	73	7
ACP-103-020	94	90	14
Pooled	231	346	34

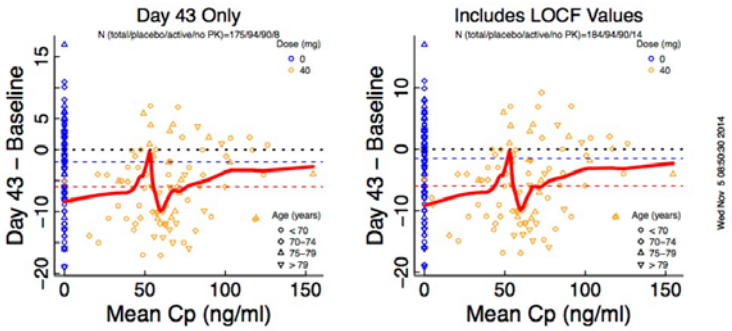
Source: Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: SAPS Section 4



Exposure-Response Analysis for the 9-Item SAPS-PD Primary Analysis for Study **ACP-103-012**



Exposure-Response Analysis for the 9-Item SAPS-PD Primary Analysis for Study **ACP-103-014**

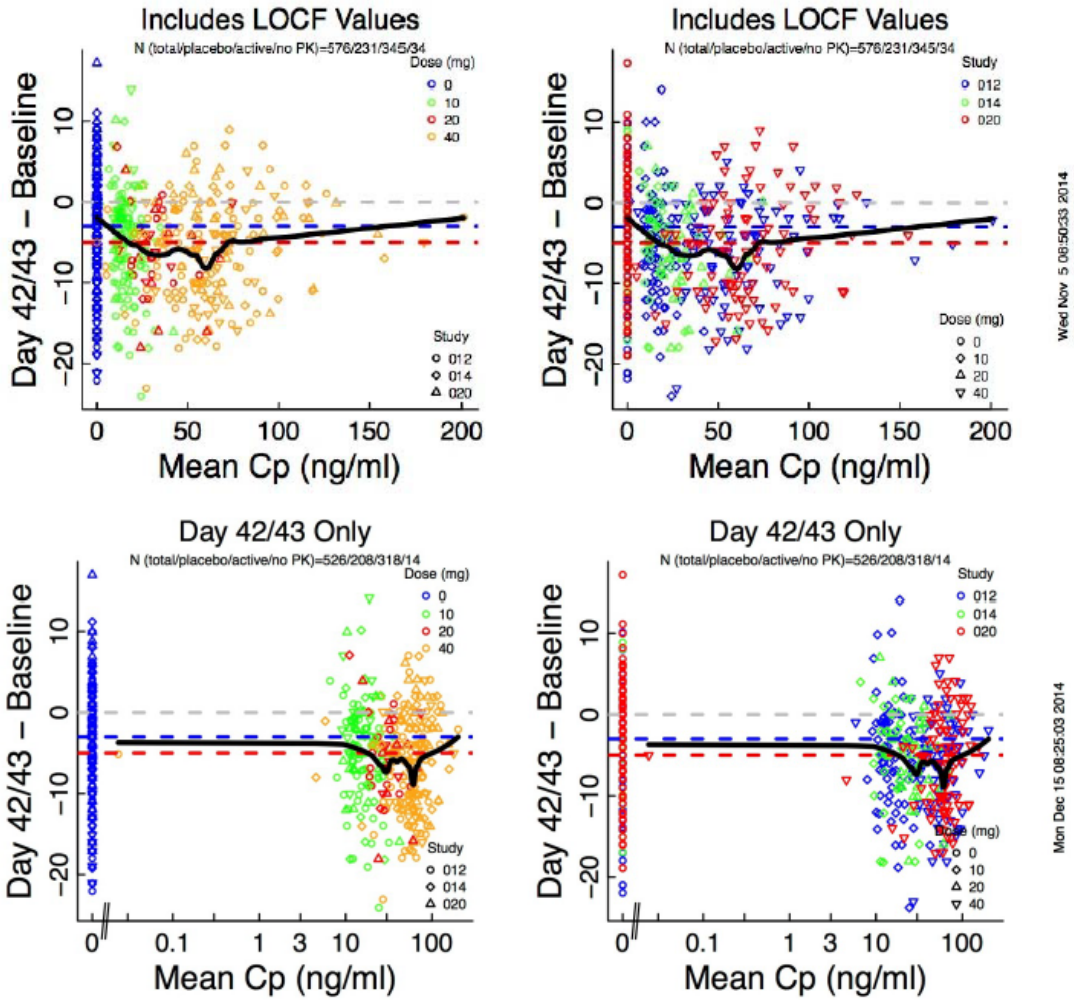


Exposure-Response Analysis for the 9-Item SAPS-PD Primary Analysis for Study **ACP-103-020**

Source: Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: SAPS Section 4.1

Figure5: Exposure Response Analysis for Individual Phase III studies

The x-axis is Mean Cp, the y-axis is the difference between the Day 42 value and baseline. The left panel includes only subjects for whom a value was obtained at Nominal Day 42; the right panel includes LOCF values. Colors distinguish doses; symbols distinguish age groups. The thick red line is a smoother (Supersmoother®). Horizontal lines appear at 0 (dotted, no change); placebo median (dashed, blue); and pimavanserin median (dashed, red). "N" indicates the number of data points displayed; "No PK" indicates subjects omitted because there was not a Mean Cp value that corresponded to the SAPS measurements.



Source: Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: SAPS Section 4.1

Figure 6. Result for Pooled Analysis of All studies
Exposure-Response Analysis for the 9-Item SAPS-PD Primary Analysis for the Pooled Analysis of Three Phase 3 Studies. The x-axis is Mean Cp (top panels: linear scale; bottom panels: log scale, with an axis break for the placebo group), the y-axis is the difference between the Day 42/43 value and baseline. All panels include LOCF values. Colors or symbols distinguish doses/studies. The thick black line is a smoother (Supersmoother®). Horizontal lines appear at 0 (dashed, no change); placebo median (dashed, blue); and pimavanserin median (dashed, red). "N" indicates the number of data points displayed; "No PK" indicates the number of subjects omitted because there was not a Mean Cp value that corresponded to the SAPS measurements.

The shaded text below is taken directly from the Sponsor's conclusions:

An exposure-response analysis for SAPS consistently demonstrated that pimavanserin improved the response to the primary outcome measure, the 9-item SAPS-PD score compared to placebo. Age did not appear to influence the response to pimavanserin.

The results of Study ACP-103-020 appeared to differ from those of the other studies: in ACP-103-020, the response was flat at all Mean Cp ranges (but improved compared to placebo) whereas, in the other studies, increasing Mean Cp was associated with an improved response. A likely explanation is that the only pimavanserin dose in ACP-103-020 was 40 mg; as a result, there were few subjects with low Mean Cp values associated with the 10- and 20-mg doses in the other studies.

Several analyses demonstrated a plateau effect: Mean Cp > 60-70 ng/mL yielded no further improvement (and, in some instances, a small worsening at higher Mean Cp, although the number of subjects in that range was relatively small). These findings support ACADIA's selection of an optimal dose and demonstrate that larger doses (with commensurate higher Mean Cp values) would not likely benefit subjects.

Reviewer's Comments:

The Sponsor's analysis does not take into account the differential placebo response in non-North American patients, nor does it take into account the potential impact of baseline SAPS-PD. The observation of a worsening at higher pimavanserin exposure is unlikely to be a true effect and is more likely due to an over-interpretation of the smooth line.

3.2 Pop-PK model

The Sponsor's population pharmacokinetic analysis was performed in three stages based on the population: healthy subjects, patients with Parkinson's Disease (PD) who did not have psychosis, and in subjects with Parkinson's Disease with psychosis. A summary of the clinical trials included in the analysis is displayed in **Table 2**.

Table 2: Summary of clinical trials used in Sponsor's population pharmacokinetic analysis

Study	Design	Formulation	Dose Levels (mg)	Sampling	Population
ACP-103-001 Part 1	Single ascending dose	Solution	20, 50, 100, 200, 300	Extensive	Healthy subjects
ACP-103-001 Part 2	Food effect (*vs.* solution)	Solution, Tablet	100	Extensive	Healthy subjects
ACP-103-002	Multiple ascending dose (14 daily doses)	Capsules	50, 100, 150	Extensive	Healthy subjects
ACP-103-005	Multiple dose (14 daily doses)	Tablet	25, 100	Extensive	Parkinson's without psychosis
ACP-103-012	Steady state	Tablet	10, 40	Sparse	Parkinson's with psychosis
ACP-103-014	Steady state	Tablet	10, 20	Sparse	Parkinson's with psychosis
ACP-103-020	Steady state	Tablet	40	Sparse	Parkinson's with psychosis

(Source: Sponsor's Population Pharmacokinetic Report, Table 25, Page 28)

Stage 1 Results: Healthy Subjects

The Sponsor's first population model included data from only healthy subjects who received three formulations (solution, tablets and capsules) and had extensive sampling. The goal of the analysis was to identify the structural model, test for dose linearity and examine the effects of formulation and food on absorption. The Sponsor determined that a one-compartment model with allometric scaling of systemic parameters fit the data well. The only covariates included in this model were to describe formulation and fed status on absorption. The rate of absorption was approximately two-fold slower for tablet/fed but did not differ by formulation in fasted subjects. The absorption lag differed by formulation. Parameter estimates for the optimal model are displayed in **Table 3**.

Tabel 3: Pop-PK Parameters (Healthy Subjects)

Parameter	Typical Value	Inter-Individual Variability*
Apparent Clearance (L / day)	$590.217 \bullet (WT\dagger / 76)^{0.75}$	0.2289
Apparent Distribution Volume (L)	$1850.09 \bullet (WT\dagger / 76)$	0.1367
Solution, Fasting (ACP-103-001)		
Absorption rate (/ day)	11.3852	0.4871
Absorption lag (days)	0.0138273	0.3639
Tablets, Fasting (ACP-103-001)		
Absorption rate relative to solution	1.0	—‡
Absorption lag relative to solution	2.12119	—‡
F relative to solution	1.0	—‡
Tablets, High-Fat Meal (ACP-103-001)		
Absorption rate relative to solution	0.539504	—‡
Absorption lag relative to solution	0.593178	—‡
F relative to solution	1.0	—‡
Capsule, Fasting§ (ACP-103-002)		
Absorption rate relative to solution	1.0	—‡
Absorption lag relative to solution	1.97881	—‡
F relative to solution	1.0	—‡

*Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.
† WT is weight in kg; 76 is the median weight.
‡ Inter-individual variability was not permitted for this term.
§ Subjects fasted prior to dosing on days of intense pharmacokinetic sampling. On days in which trough samples were obtained, those samples were obtained 30 minutes after completion of breakfast.

OMEGA #	Applies to THETA	Variance	Square Root Variance	Correlation
1	Clearance/F	0.052382	0.2289	—
2	V/F	0.0186984	0.1367	—
1 / 2	—		—	0.5222
6	Absorption Rate	0.237311	0.4871	—
7	Absorption Lag	0.132428	0.3639	—
6 / 7	—		—	0.3423

Description	Variance	Square Root Variance
Proportional Component of Error	0.0297791	0.1726
Additive Component of Error	0.126781	0.3561

Source: Tables 1 to Table 3 in Sponsor's Population Pharmacokinetic Report

Stage 2 Results: Patients with Parkinson's Disease without Psychosis

The one study in this patient population (ACP-103-005) included extensive sampling in eight patients. The Sponsor chose this study as a second stage of the analysis to confirm the structural model and to estimate absorption rate and lag in a patient population with similar demographics as the target population. A one-compartment model with allometric scaling of systemic parameters was found to best fit the data. No other covariates were incorporated into the model. Parameter estimates for the optimal model are displayed in **Table 4.**

Tabel 4: Pop-PK Parameters (Patients with Parkisnon's Disease without Psychiosis)

Parameter	Typical Value	Inter-Individual Variability*
Apparent Clearance (L / day)	$550.715 \cdot (WT\dagger/75)^{0.75}$	0.3347
Apparent Distribution Volume (L)	$1897.0 \cdot WT\dagger/75$	0.1390
Absorption rate (/ day)	7.43222	0.5442
Absorption lag (days)	0.0707227	0.33399

*Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.
† WT is weight in kg; 75 is the median weight

OMEGA #	Applies to THETA	Variance	Square Root Variance	Correlation
1	Clearance/F	0.112001	0.3347	—
2	V/F	0.0193273	0.139	—
1 / 2	—	—	—	0.7567
5	Absorption Rate	0.296114	0.5442	—
6	Absorption Lag	0.115511	0.3399	—
5 / 6	—	—	—	< -0.99

Description	Variance	Square Root Variance
Proportional Component of Error	0.0142411	0.1193
Additive Component of Error	0.491917	0.7014

Source: Tables 7 to Table 9 in Sponsor's Population Pharmacokinetic Report

Stage 3 Results: Patients with Parkinson's Disease with Psychosis
Trough samples in the target population from Studies ACP-103-012, ACP-103-014 and ACP-103-020 were included in this analysis. Typical values for absorption rate and absorption lag were fixed to the values obtained in Stage 2. A one-compartment model was used as the structural model. As opposed to models in Stage 1 and Stage 2, parameters were not normalized for weight. The covariates in **Table 5** were considered for inclusion in the model.

Table 5: Covariates for Population Pharmacokinetic Model

Demographic / Morphometric Covariates	Coding
Subject ID	ID used in dataset
Age	Years
Gender	Male = 1; Female = 2
Weight	kg
Height	cm
BMI	kg/m^2
BSA	body surface area, calculated using the Mosteller equation (6)
Lean body mass	kg, calculated using Hume's equation (7)
Race	White/Caucasian = 1; Black/African-American = 2; 3 = Asian; 5 = mixed; 99 = other (includes Iranian [ACP-103-005; N = 1], Hispanic [ACP-103-12; N = 4])
Ethnicity (Hispanic)	No = 1; Yes = 2

Laboratory Values	Coding
Albumin	gm/L
Alkaline phosphatase	IU/L
ALT (SGOT)	IU/L
AST (SGPT)	IU/L
Total bilirubin	µM/L
Serum creatinine	µM/L
Creatinine clearance	Calculated using the Cockcroft-Gault (2), MDRD (3), and CPK-EPI (4) equations (the latter two based on serum creatinine, weight, age, gender, and race)

Source: Pages 45-46 in Sponsor's Population Pharmacokinetic Report

The following covariates appeared to be related to apparent clearance (in order of descending statistical significance): height, lean body mass, age, gender, and creatinine clearance. The Sponsor evaluated various combinations of these covariates and ultimately selected two final models. In the

first model, apparent clearance increased with height and decreased with age. In the second, apparent clearance increased with height and increased with creatinine clearance (assessed by CKD-EPI). Although the minimum value of the objective function was lower with the second model, the Sponsor claimed that the inclusion of creatinine clearance is physiologically unrealistic. Parameter estimates for the first model are displayed in **Table 6**.

Tabel 6: Pop-PK Parameters with Height and Age Affecting Apparent Clearance in Stage 3

Parameter	Typical Value	Standard Error	Inter-Individual Variability*
HeightFactor†	1 + 0.00851 • (HT – 168)	0.0023664	—¶
AgeFactor‡	1 – 0.007558 • (AGE – 71)	0.0027419	—¶
Apparent Clearance (L / day)	587.093 • HeightFactor • AgeFactor	13.8812	0.3911
Apparent Distribution Volume (L)	2021.41	264.149	0.5319
Absorption rate (/ day)§	7.4322	—	—¶
Absorption lag (days)§	0.0707	—	—¶

*Calculated as sqrt($omega^2$) where $omega^2$ is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.
† HT is weight in cm; 168 is the median height.
‡ AGE is age in years; 71 is the median age.
§ These terms (obtained from Table 7) are fixed to the values obtained from Analysis Stage 2.
¶ Inter-individual variability was not permitted for these terms.

OMEGA #	Applies to THETA	Variance	Square Root Variance	Correlation
1	Clearance/F	0.152987	0.3911	—
2	V/F	0.282902	0.5319	—
1 / 2	—	—	—	0.2399

Description	Variance	Square Root Variance
Proportional Component of Error	0.0185967	0.1364
Additive Component of Error	30.7264	5.543

Source: Tables 13-15 in Sponsor's Population Pharmacokinetic Report

Parameter estimates for the second model with height and renal function as covariates are displayed in **Table 7**

Tabel 7: Pop-PK Parameters with Height and Creatinine Clearance Affecting Apparent Clearance in Stage 3

Parameter	Typical Value	Standard Error	Inter-Individual Variability*
HeightFactor	1 + 0.00853 • (HT – 168)	0.00232139	—
CrClFactor	1 + 0. 00486 • (CrCl – 72)	0.00159841	—
Apparent Clearance (L / day)	588.814 • HeightFactor • CrClFactor	13.6891	0.3869
Apparent Distribution Volume (L)	2007.17	235.536	0.5391
Absorption rate (/ day)§	7.4322	—	—
Absorption lag (days)§	0.0707	—	—

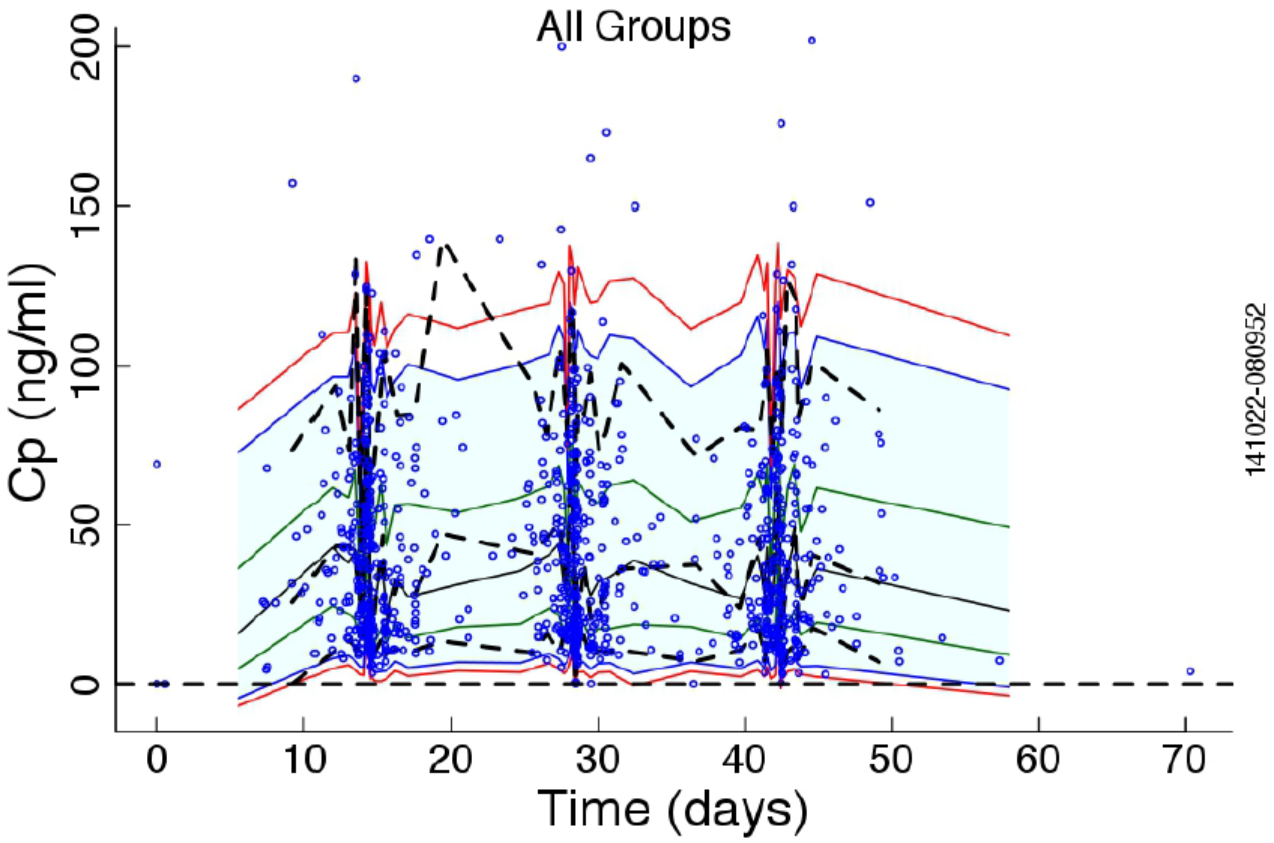
*Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.
† HT is weight in cm; 168 is the median height.
‡ CrCl is creatinine clearance (calculated with the CKD-EPI equation) in ml/min/1.73 m^2; 72 is the median value for creatinine clearance.
§ These terms (obtained from **Table 7**) were fixed.

OMEGA #	Applies to THETA	Variance	Square Root Variance	Correlation
1	Clearance/F	0.14969	0.3869	—
2	V/F	0.290604	0.5391	—
1 / 2	—	—	—	0.2251

Description	Variance	Square Root Variance
Proportional Component of Error	0.0186217	0.1365
Additive Component of Error	30.689	5.54

The visual predictive check for the final model with height and age as covariates is presented in **Figure 7**. Model qualification also included evaluation of likelihood profiles and boostrap analysis.

Figure 7: Visual Predictive Check for the Final Model with Covariates of Height and Age on Clearance



Source: Figure 22, Page 71 of Sponsor's Population Pharmacokinetic Report.

The Sponsor concludes that at the anticipated pimavanserin clinical dose of 40 mg, mean plasma concentration at steady state for the typical subject will be 68.1 or 67.9 ng/ml based on the two models. Because of the significant degree of accumulation at steady state, peak and trough values will differ minimally from these values. Daily AUC for the 40-mg dose will be 1635 or 1630 ng/ml • hours, also based on the two final models.

According to the Sponsor, their findings suggest that dosing of pimavanserin should not be adjusted based on bodyweight or height. Similarly, the effects of age and renal function on systemic exposure are relatively small and can probably be ignored in dosing in these populations.

Reviewer's Comments:

The Sponsor's model appears to provide a reasonable fit to the data. On the other hand, it is a bit contradictory that the Sponsor casts doubt on creatinine clearance as a covariate for clearance due to physiologic reasoning yet is willing to accept height as a covariate. We also do not see a compelling reason why data from all three stages could not be pooled in one population pharmacokinetic analysis. To address some of these concerns and to further probe the robustness of the Sponsor's conclusions, the reviewers performed an independent analysis.

3.3 Pimavanserin Exposure-Response for Safety

Introduction: Sponsor submitted exposure-response analysis for four adverse effects: hallucination, confusion, edema, and gait disturbance.

Method:. A daily mean plasma concentration was estimated by the Sponsor's Pop-PK model. Individuals without PK analysis were excluded. Adverse event after their final dose were excluded. For each adverse event, values for mean plasma concentration were extracted and corresponding percentile rank was determined. Placebo subjects were not involved in ranking.

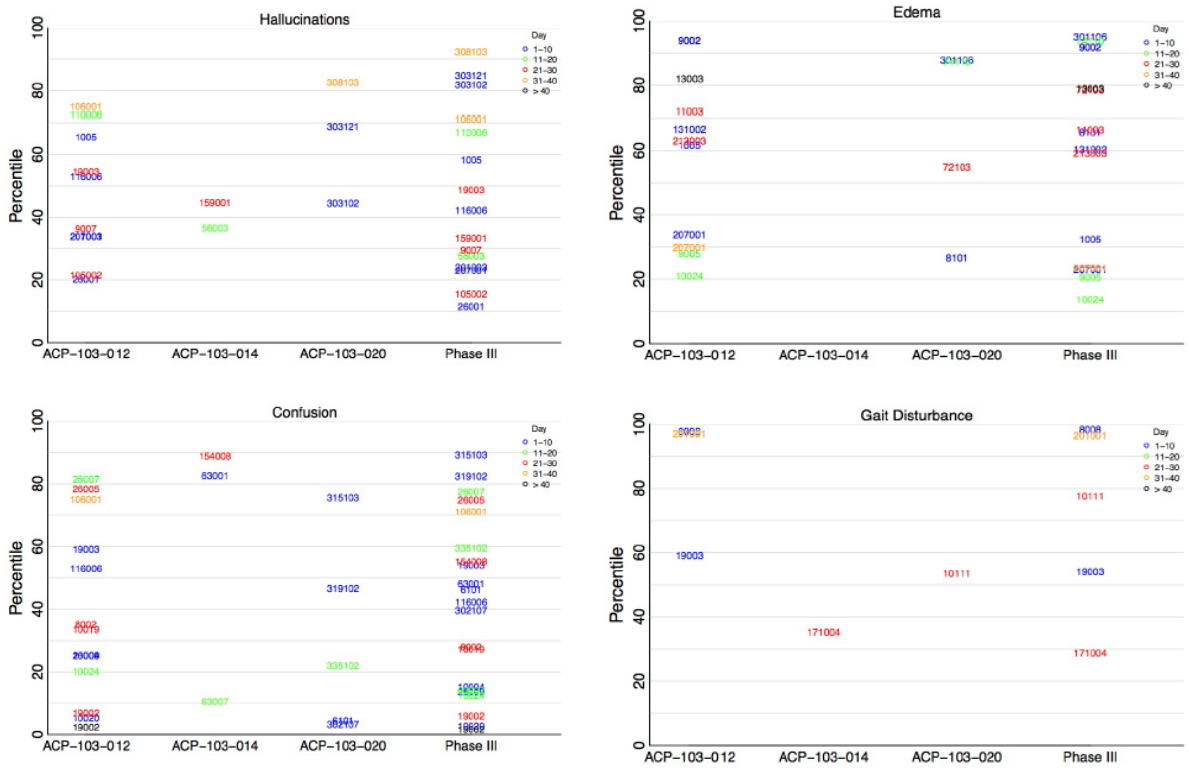


Figure 8: Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: Adverse Events

Source: Exposure-Response Analysis for Pimavanserin in Phase 3 Studies: Adverse Events Page 16-17

Sponsor's Conclusion: There was no evidence that any of the adverse events were associated with a cluster of high (or low) mean Cp values.

Reviewer's Comments: We agree with the Sponsor that these four adverse reactions do not appear to be related to pimavanserin exposure.

4. REVIEWER'S ANALYSIS

3.4 Introduction

In the current submission, the sponsor performed exposure-response analysis of SAPS-PD Score Change from Baseline at 6 weeks in individual studies or pooled studies of study ACP-103-012, ACP-103-014 and ACP-103-020 . We performed analysis to justify exclusion of non-north American population **(Figure 2)**, and to establish an exposure-response relationship within the North American population **(Figure 1)**.

3.5 Objectives

The analysis objective is to explore the relationship between pimavanserin exposure and the primary efficacy endpoint, SASP-PD score at week 6 to support dosing regimen selection.

Taking advantage of the Pop-PK model, the effect of renal function on exposure was also assessed

3.5.1 Data Sets

Data sets used are summarized in Table 8.

Table 8. Exposure Response Analysis Data Sets

Study Number	Name	Link to EDR
Exposure Response Analysis Data Sets		
ACP-103-012	012-adqs-saps.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\ER Efficacy\ 012-adqs-saps.csv
ACP-103-014	014-adqs-saps.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\ER Efficacy\ 014-adqs-saps.csv
ACP-103-020	020-adqs-saps.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\ER Efficacy\ 020-adqs-saps.csv
Mean Cp values of all studies	acadia-meancpvalues-2014-10-05.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\ER Efficacy\ acadia-meancpvalues-2014-10-05.csv
Pop-PK Data Set		
Combined overall PK dataset	stage_all.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan

3.5.2 Software

- NONMEN (Version 7.2, ICON Development Solutions)
- R (3.0.3. Insightful Inc.)
- Pirana 2.9.0 (Pirana Software & Consulting BV 2014)

3.6 Results

3.6.1 Exposure-Response Analysis

An exploratory graphical analysis was conducting. Data from studies ACP-103-012, ACP-103-104 and ACP-103-020 were pooled together and non-North American individuals were excluded (226 non-north American individuals out of 589 total numbers in three studies). In addition 39 individuals were excluded due to lack of PK data or early trial termination. Finally 324 individuals were included for in the plot. In exposure-response exploration, estimated mean plasma concentration value at day 29 is used as steady state plasma concentration and percent change from baseline in SAPS-PD score is used as response. The results are summarized in **Figure 1**. Parametric models were developed to describe the relationship, but none provided an adequate fit to the data. The results should be interpreted with caution but do suggest that the percent change from baseline in SAPS-PD score increases with dose but reaches a plateau near the 40 mg dose.

Pop- PK model:

Method:

Data from three stages of the sponsor's analysis were merged together and analyzed. Six studies are involved: two in healthy subjects (Studies ACP-103-001, ACP-103-002), one in subjects with Parkinson's Disease who did not have psychosis (Studies ACP-103-005), and three in subjects with Parkinson's Disease with psychosis (Studies ACP-103-012, ACP-103-014, ACP-103-020).

Result:

A one-compartment model fit the data well. Parameter estimates are displayed in **Table 9**. Body weight was found as covariate of volume of distribution. Lean body mass and creatinine clearance were added as apparent clearance covariates. According to the model, apparent clearance increases with an increase of creatinine clearance. For example, a normal patient with creatinine clearance of 90 ml/min/1.73 m^2 has estimated apparent clearance of 637.47 L/day, mild renal impaired patient with creatinine of 60 ml/min/1.73 m^2 has estimated apparent clearance of 550.44 L/day and moderate renal impaired patient with creatinine of 30 ml/min/1.73 m^2 has estimated apparent clearance of 428.29 L/day.

A side by side comparison of FDA PK model and sponsor's 3 stage PK model parameters were shown in **Table 10**. There are no major differences in model parameters other than covariates **Table 10**. In FDA POP-PK model, body weight was found as a covariate of volume of distribution. Lean body mass and creatinine clearance were added as apparent clearance covariates. Age **(mod8)**, weight **(mod18)**, gender **(mod19)** and race **(mod24)** were not found to be significant covariates for apparent clearance. Population and individual diagnosis plot were shown in **Figure 9** and **Figure 10**.

Table 9. Pop-PK Final Parameter Report

Theta	Description	Estimate	FIX	SE	RSE	95%CI	ΔOFV
1	CL/F	588	-	11.9	2%	[564.67 , 611.32]	
2	V/F	2090	-	56.4	2.7%	[1979.45 , 2200.54]	
5	Absorption Rate	10.9	-	0.926	8.5%	[9.08 , 12.71]	
6	Absorption Lag	0.0268	-	0.0016	5.9%	[0.024 ,0.03]	
7	WT~V [1]	0.483	-	0.165	34.2%	[0.16 , 0.806]	-7.299
9	LBM~CL [2]	0.444	-	0.123	27.7%	[0.203 , 0.685]	-13.554
14	CrCl (CPD-EPI)~CL [3]	0.362	-	0.0887	24.5%	[0.188 , 0.536]	-23.876
Omega							
1,1	IIV of CL/F	0.149					
2,2	IIV of V1/F	0.036					
3,3	IIV of KA	0.33					
4,4	IIV of ALAG	0.0309					
Sigma							
1,1	Proportional component of error	0.0175					
2,2	Additive component of error	16					

1, SCALEV = (WT / 72.5)** THETA(7)
2, LBMFCT = (LBM/50.7)**THETA(9)
3, CKDFCT = (GFRCKDEPI/72)** THETA(14)

V/F = THETA(2) * SCALEV * EXP(ETA(2))
CL/F = THETA(1) *LBMFCT DFCT * CKDFCT * EXP(ETA(1))

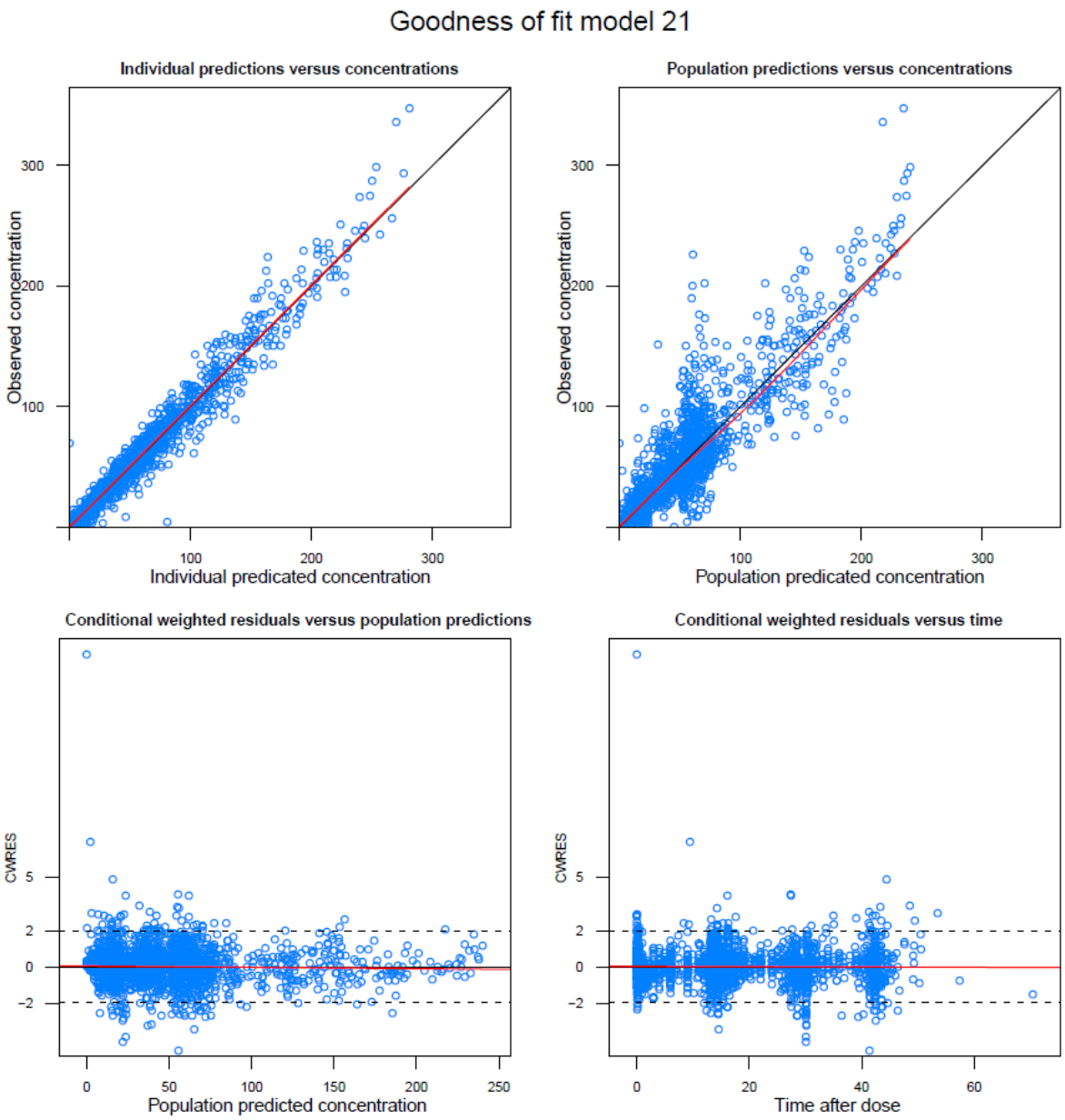


Figure 9: PoP-PK model Goodness of Fit Plots

Individual Plot Goodness of Fit (Representative)

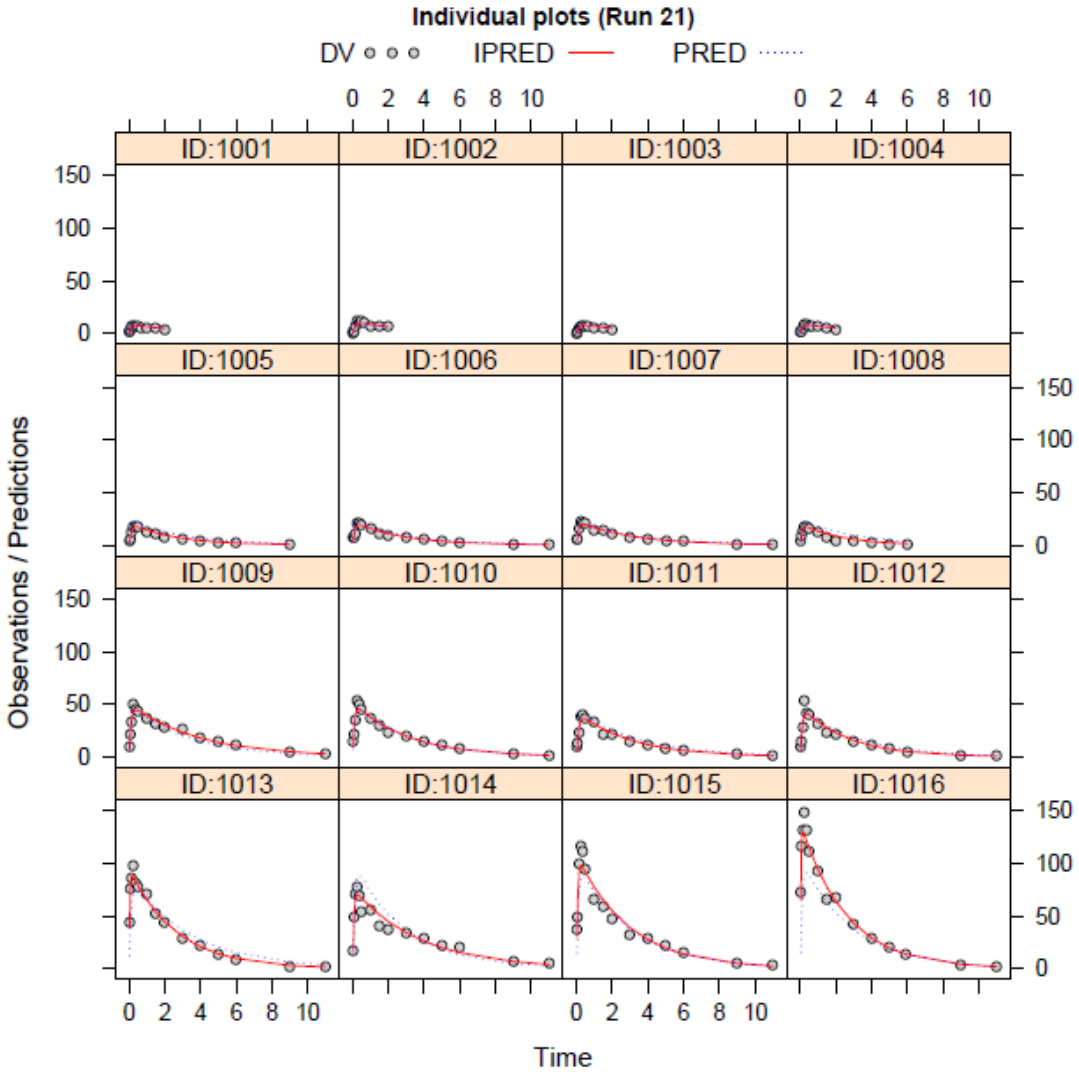


Figure 10: Individual Diagnosis Plot (3-1)

Individual Plot Goodness of Fit (Representative)

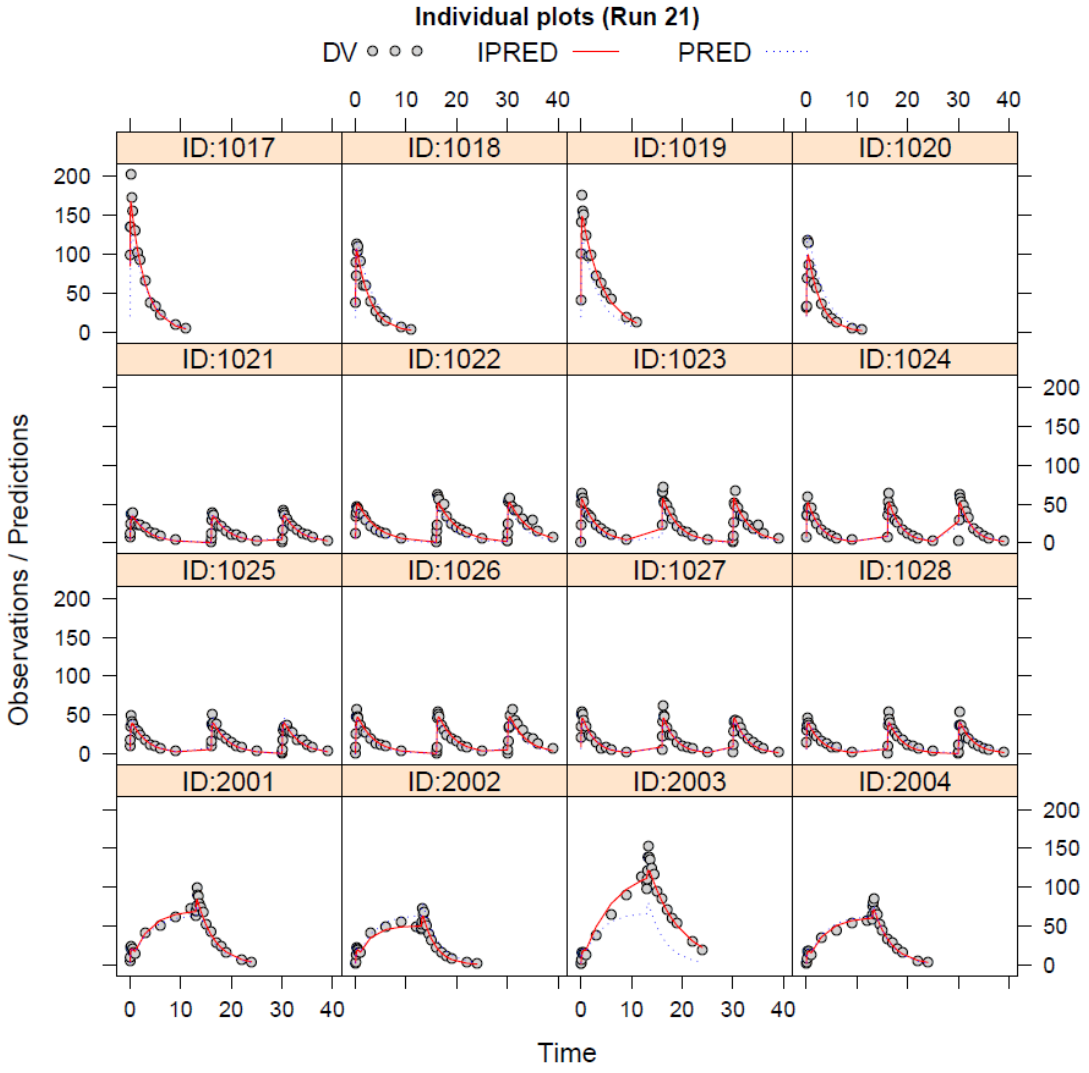


Figure 10: Individual Diagnosis Plot (3-2)

Individual Plot Goodness of Fit (Representative)

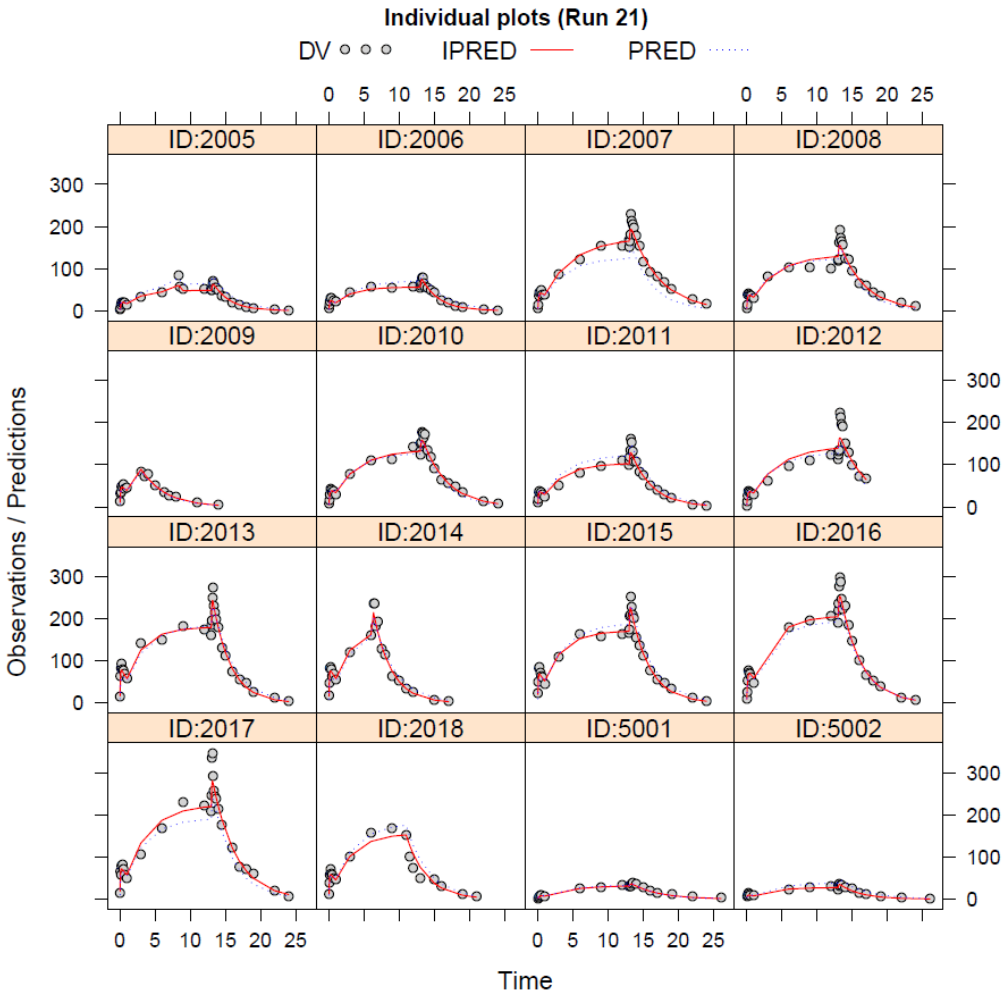


Figure 10: Individual Diagnosis Plot (3-3)

Table 10. Comparison of FDA developed Pop-PK Model with Sponsor'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

Listing of Analyses Codes and Output Files

Pop-PK		
21.mod	Final pop-pk model imput file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan\
21.lst	Final pop-pk model output file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan\
21_GOF.pdf	Mod21 goodness of Fit diagnosis Plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan\pirana_reports
21_ind_plots.pdf	Mod21Individual Goodness of Fit Diagnosis Plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan\pirana_reports
24.mod	Test effect of race on apparent clearance	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan\
24.lst	Mod24 Output	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan\
Combined overall PK dataset	Pop-PK dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pimavanserin_NDA 207318_LZ\FDA Analysis_Yuan\PPK\PPK programs\PPK_combined_Yuan

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